The Construction of Carbon-Heteroatom Bonds (C-X; X = N, O, S) Under Metal-Free Conditions to Access Useful Heterocyclic Scaffolds

A thesis

Submitted in partial fulfilment of the requirements

of the degree of

Doctor of Philosophy

By

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Dedicated to My Son

&

My Wife

भारतीय विज्ञान शिक्षा एवं अनुसंधान संस्थान, पुणे
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CERTIFICATE

Certified that the work incorporated in this thesis entitled **"*The Construction of Carbon-Heteroatom Bonds (C-X; X = N, O, S) Under Metal-Free Conditions to Access Useful Heterocyclic Scaffolds*"** submitted by Mr. Vikas V. Khade was carried out by the candidate, under my supervision. The work presented here or any part of it has not been included in any other thesis submitted previously for the award of any degree or diploma from any other university or institution.

Date: 30/06/2022,
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DECLARATION

I declare that this written submission represents my own ideas in my own words and where other's ideas have been included; I have adequately cited and referenced the original source. I also declare that I have adhered to all academic honesty and integrity principles and have not misrepresented or fabricated or falsified any idea/ data/ fact/ source in my submission. I understand that violation of the above will be cause for disciplinary action by the Institute and can also evoke penal action from the sources which have thus not been properly cited or from whom proper permission has not been taken when needed.

Date: 30/06/2022 **Mr. Vikas V. Khade**

Pune **ID: 20163426**

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Vikas V. Khade

CONTENT

Abbreviations

Å	Angstrom
Ar	Aryl/heteroaryl
BHT	Dibutylhydroxytoluene
Bn	Benzyl
Boc	di-*tert*-butyl dicarbonate
BocNHOTs	*tert*-butyl (tosyloxy)carbamate
bpy	(2,2'-bipyridyl)
br	Broad
Cbz	Benzyl carbamate
CFL	Compact fluorescent lamps
CPS	Count per seconds
CV	Cyclic voltammetry
° C	Degree celsius
δ	Chemical shift
d	Doublet
DABCO	1,4-Diazabicyclo[2.2.2]octane
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	N,N'-Dicyclohexylcarbodiimide
DCE	Dichloroethane
DCM	Dichloromethane
DEE	1,2-diethoxyethane
DIPEA	N,N-diisopropyl methyl amine
DMAP	4-(Dimethylamino)pyridine
DMDA	N,N-dimethyl ethylene diamine
DMDO	Dimethyldioxirane

DME	Dimethyl carbonate
DMF	N,N-dimethyl formamide
DMS	Dimethyl sulfide
DMSO	Dimethyl sulfoxide
eh	2-Ethyl haxanoate
Equiv.	Equivalent
ESI TOF	Electrospray ionization time-of-flight
Et	Ethyl
EtOAc	Ethyl acetate
EY	Eosin Y
g	Gram
HRMS	High-resolution mass spectrometry
hv	Photochemical
Hz	Hertz
i-Pr	Isopropyl
J	Coupling constant
λ_{max}	Wavelength
LEDs	Light-emitting diode
m-CPBA	meta-Chlorobenzoic acid
m	Multiplate
M	Molar
MBH	Morita Baylis Hillman
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
Mes-Acr-MeClO_4	9-mesityl-10-methylacridinium perchlorate
mg	Milli gram
MHz	Megahertz
mL	Milli litter

mM	Milli molar
mmol	Milli mole
MMPP	Magnesium monoperoxyphthalate hexahydrate
MP	Melting point
MS	Molecular sieves
mV/S	Milli volt per second
NBS	N-bromosuccinimide
NCE	New chemical entities
NCS	N-chlorosuccinimide
nm	Nanometer
NMR	Nuclear magnetic resonance
NR	No reaction
OAc	Acetate
ONf	Nonafluorobutanesulfonate
OTf	Trifluoromethanesulfonate
p	Para
p-BrBn	4-Bromo benzyl
PivOH	Pivalic acid
p-MeBn	4-Methyl benzyl
p-TsOH	*p*-Toluenesulfonic acid
Ph	Phenyl
q	Quartet
QN	Quinuclidine
RB	Round bottom flask
Rf	Retardation factor
r.t.	Room temperature
s	Singlet
SCE	Standard calomel electrode
SET	Single-electron transfer

t	Triplet
t-amyl	*tert*-Amyl
t-Bu	*tert*-Butyl
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl)
TFA	Trifluoroacetic acid
TFDO	Methyl(trifluoromethyl)dioxirane
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
TMS	Trimethylsilane
TPP	2,4,6-Triphenylpyrelium-tetraborate
TsCl	Tosyl chloride
μM	Micromolar
UV	Ultraviolet
V	Volt
W	Watt

SYNOPSIS

The thesis entitled ***"The Construction of Carbon-Heteroatom Bonds (C-X; X = N, O, S) Under Metal-Free Conditions to Access Useful Heterocyclic Scaffolds"*** consists of five chapters.

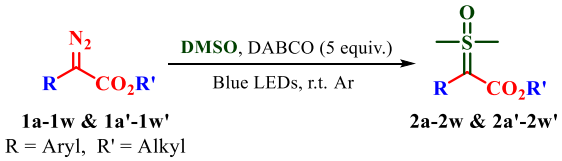
Chapter 1: ***A Brief Overview of Carbon-Heteroatom Bond Forming Reactions to Access Heterocyclic Scaffolds***

The construction of heterocyclic scaffolds via carbon-heteroatom bond (C-X; X = N, O, S) forming reactions is one of the significant and important transformations in organic synthesis. Many heterocyclic scaffolds and natural products have been synthesized relying on numerous carbon-heteroatom bond forming strategies. Many natural products, polymers, materials and pharmaceutical ingredients have heterocyclic cores in their structures. Over the years, many strategies have been developed to construct the carbon-heteroatom bonds to synthesize heterocyclic frameworks. Some of the representative carbon-heteroatom bond forming reactions have been highlighted in this chapter.

Chapter 2: ***DABCO-Mediated One-Pot Synthesis of Sulfoxonium Ylides from Diazo Compounds Under Blue Light Conditions***

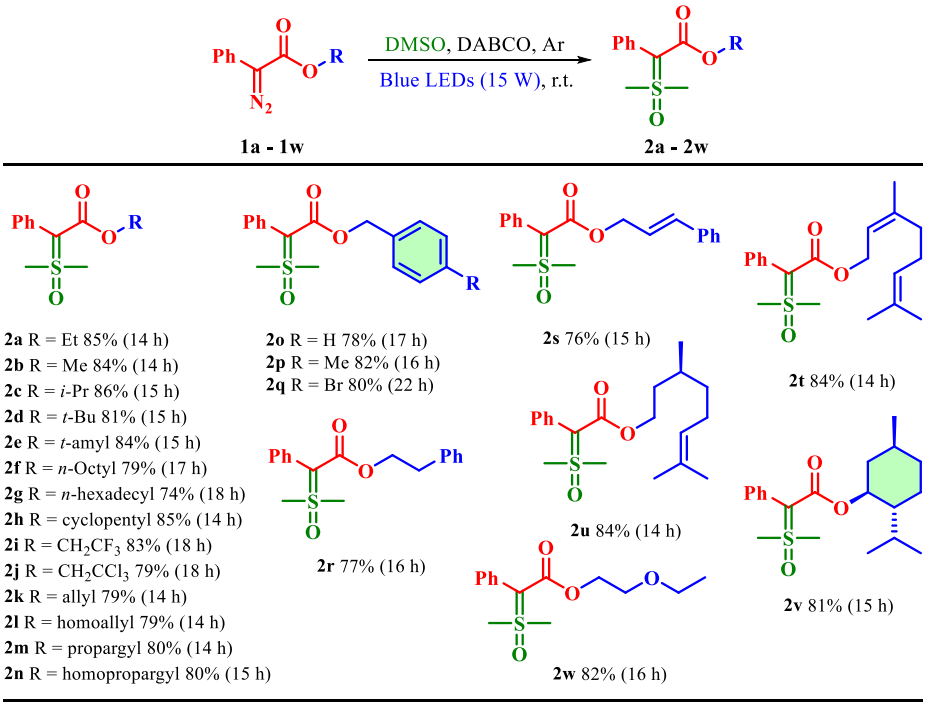
This chapter describes the development of a synthetic protocol to access sulfoxonium ylides starting from α-aryl-α-diazo esters under visible light conditions via C–S construction. Sulfoxonium ylides are the carbene precursors and they are also surrogates of diazo compounds. Sulfoxonium ylides have been employed in many synthetic transformations to access a diverse range of organic compounds and compounds of biological importance on an industrial scale as well. There are many methods for the synthesis of sulfoxonium ylides. However, the synthesis of sulfoxonium ylides under metal-free, mild and visible light conditions are seldom reported in the literature. In this regard, the development of a new synthetic strategy to access the sulfoxonium ylides under practical reaction conditions using a clean energy source is highly desirable. In view of this, we have developed a synthetic protocol to access sulfoxonium ylides starting from α-aryl-α-diazo acetates in the presence of DABCO under visible light conditions in very good yields (Scheme 2.1).

The chapter briefly gives an overview of the importance of sulfoxonium ylides and some of the selected approaches for the synthesis of the same.



Scheme 2.1 Synthesis of sulfoxonium ylides

After exhaustive screening and optimization, we have developed a synthetic strategy to access sulfoxonium ylides **2** starting from α-phenyl-α-diazo ethyl ester **1**, using DABCO (5 equiv.), in dry DMSO as a neat solvent as well as a reagent, blue LED (15 W) under inert atmosphere at room temperature (monitored).

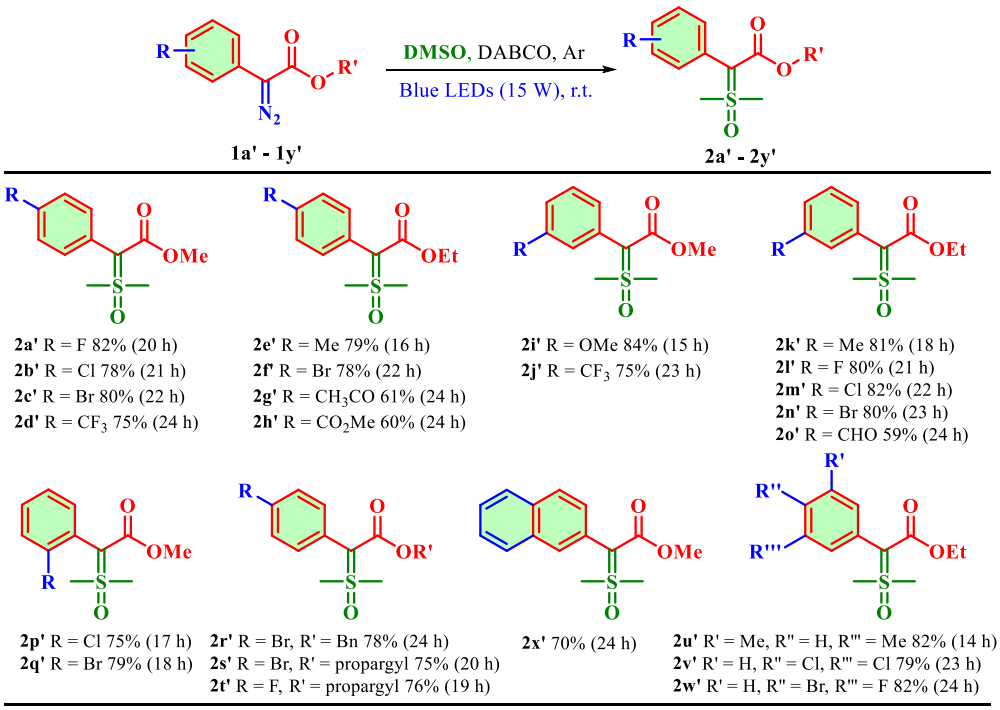


Reaction condition: (0.2 mmol) **1**, (0.5 mmol) DABCO, (1 mL) DMSO, (15 W) Blue LED, r.t.-reaction temperature was monitored, under Argon

Scheme 2.2 Substrate scope of sulfoxonium ylides

Having optimized reaction conditions, we explored the substrate scope for the synthesis of various sulfoxonium ylides by varying ester moiety as well as aryl group in the α-aryl-α-diazo esters **1** so as to generalize the protocol for wider utility. To begin with, we treated different α-phenyl-α-diazo esters (**1a-1w**, having different ester groups) under optimized reaction conditions

to afford the corresponding sulfoxonium ylides **2a-2w** in good to very good yields (up to 86%, Scheme 2.2). α-Phenyl-α-diazo esters having electro-donating as well electron-withdrawing ester groups worked smoothly under optimized reaction conditions. Even α-aryl-α-diazo esters having multiple bonds at the ester part reacted well under the optimized reaction conditions to afford the corresponding sulfoxonium ylides **2k-2n** in very good yields and we did not observe any intramolecular cyclopropanation/cyclopropenation type of products.



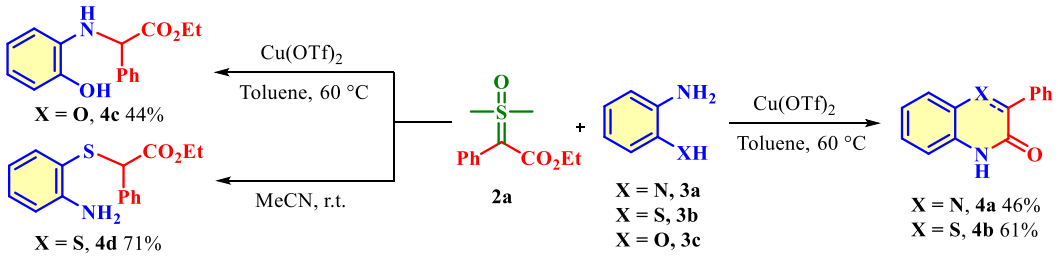
Reaction condition: (0.2 mmol) **1**, (0.5 mmol) DABCO, (1 mL) DMSO, Blue LED (15 W), r.t.-reaction temperature was monitored, under Argon

Scheme 2.3 Substrate scope of sulfoxonium ylides

Encouraged by the initial success of the synthesis of sulfoxonium ylides by varying ester groups, we then explored the reactivity of different α-aryl-α-diazo esters having varied aryl groups as well as ester's part under the optimized reaction conditions to afford the corresponding sulfoxonium ylides **2a'-2x'** in good to very good yields (up to 84%, Scheme 2.3). α-Aryl-α-diazo esters having aryl group substituted with different electron-deactivating groups, electron-withdrawing groups and electron-donating groups at the *ortho*, *meta* and *para* positions reacted smoothly with DMSO under optimized reaction conditions to furnish the corresponding sulfoxonium ylides in very good yields (Scheme 2.3). Also, α-aryl-α-diazo esters having keto and

aldehyde moieties (**1g' and 1o'**) also furnished the corresponding desired products (**2g'** and **2o'**) in moderate yields.

We further carried out a series of control experiments to have an insight into the mechanism. Based on the experimental results we observed that reaction did not involve any radical intermediate. It has been proposed that an unstable electrophilic carbene intermediate generated *in situ* reacts with DABCO to form a negatively charged reactive carbanionic intermediate that further reacts with DMSO to form another intermediate that eventually breaks down to form the sulfoxonium ylide. The protocol also proved to be practical in the gram-scale synthesis of sulfoxonium ylides **2a** in good yield (82%). For the wider utility of this protocol, the sulfoxonium ylide **2a** has been further utilized for the synthesis of different heterocycles and precursors of biologically active compounds following the literature procedures (**4a-4d,** Scheme 2.3).

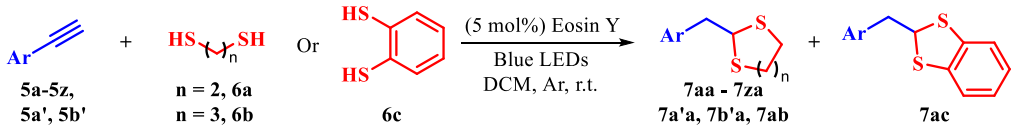


Scheme 2.3 Utility of sulfoxonium ylide **2a**

In conclusion, we have developed a protocol for the synthesis of sulfoxonium ylides starting from α-aryl-α-diazoacetates and DMSO in presence of DABCO under blue light irradiation via C–S bond construction. The protocol proved to be easy, practical and relies on visible light under metal-free conditions to furnish different sulfoxonium ylides. This method explored the use of easily accessible and less expensive DABCO and DMSO as reagents under clean energy such as visible light. This protocol also proved to be practical on a gram-scale quantity. These sulfoxonium ylides have also been utilized for the synthesis of useful precursors of biologically active compounds via C–S, C–N bonds formation.

Chapter 3: *Blue Light Promoted Direct Synthesis of 1,3-Dithiolanes from Terminal Aromatic Alkynes*

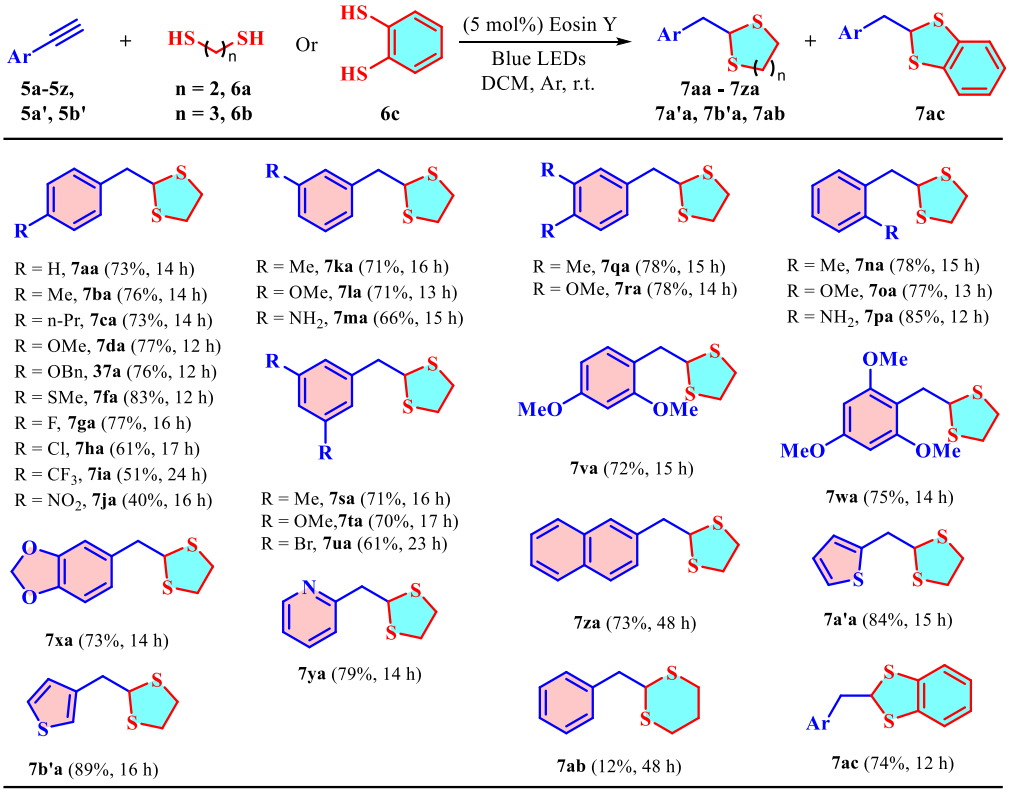
This chapter discloses the development of a synthetic protocol for the direct regioselective dihydrothionation of aromatic/heteroaromatic terminal alkynes with dithiols under visible light irradiation conditions to access useful 1,3-thiolanes in very good yields via two C–S bond formation (Scheme 3.1).



Scheme 3.1: Synthesis of 1,3-dithioacetals

Cyclic thioacetal is a very useful synthetic precursor and it has been employed as protecting groups of carbonyl compounds as well as for umpolung reactivity as an acyl anion equivalent for different useful transformations to access many organic compounds, bioactive compounds and even many pharmaceuticals. In view of this, many synthetic procedures have been developed for the synthesis of thioacetals over the years. The direct synthesis of cyclic thioacetals via dihydrothionation of an alkyne using dithiols is synthetically challenging as there are anticipated competitive reactions such as Markovnikov, anti-Markovnikov addition and the issue of control of stereoselectivity. There are not many procedures to access dithioacetals starting from alkynes to the best of our knowledge. In this regard, we planned to explore the synthesis of cyclic thioacetals starting from terminal alkynes and dithiols via regioselective dihydrothionation under milder and sustainable reaction conditions using visible light. This chapter gives a brief account of some of the selected synthetic procedures to access cyclic thioacetals starting from terminal alkynes. After careful and systematic screening, we optimized the reaction conditions to access cyclic thioacetals **7** starting from aromatic as well as heteroaromatic terminal alkynes **5** (1 equiv.), 1,2-ethane dithiol **6** (1 equiv.), Eosin Y (5 mol%) as an organophotocatalyst in DCM solvent under the irradiation of blue light (30 W, Blue LEDs) while maintaining the inert atmosphere at room temperature (Scheme 3.1). Having optimized reaction conditions, we further explored the substrate scope to synthesize various 1,3-dithiolanes. The various aromatic/heteroaromatic terminal alkynes containing electron-donating, electron-withdrawing as

well as electron-deactivating groups on the aryl moiety reacted smoothly under optimized reaction conditions to afford the corresponding cyclic thioacetals (**7aa-7za**, **7a'a-7b'a, 7ab**) in good to excellent yields (up to 89%, Scheme 3.2).



Reaction conditions: **5** (1 equiv.), **6** (1 equiv.), Eosin Y (5 mol%), dry and degassed DCM (2 mL), blue LEDs (30 W), r.t., under Argon

Scheme 3.2 The substrate scope of dithioacetals

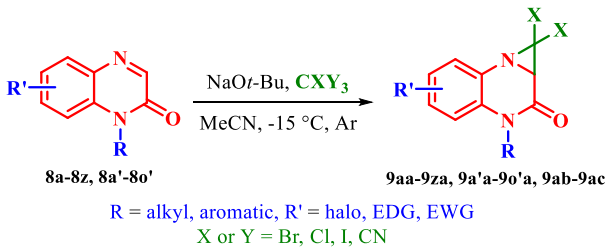
We observed that terminal alkynes having disubstituted as well as trisubstituted aryl group reacted smoothly under the optimized reaction conditions to afford the corresponding 1,3-dithiolanes. Even, the aromatic dithiol such as benzene-1,2-dithiol reacted with phenylacetylene under optimum reaction conditions to afford the corresponding cyclic thioacetal **7ac** in good yield (Scheme 3.2). The protocol proved to be scalable on gram quantity to afford the corresponding 1,3-dithiolane **7aa** in good yield (73%). In order to have an insight into the reaction mechanism, we carried out a series of control experiments, cyclic voltammetric and the Stern-Volmer studies. Based on these results we proposed that the initial reaction of terminal alkyne **5** and 1,2-ethane dithiol **6a** leads to the formation an anti-Markovnikov-type intermediate (vinyl tethered thiol) and this intermediate eventually reacts with the excited photocatalyst Eosin

Y (EY*) to form a radical intermediate. This would further undergo cyclization followed by a SET process with reduced EY* to form the corresponding desired cyclic thioacetal (after the proton abstraction and regenerating the ground state photocatalyst EY* to EY).

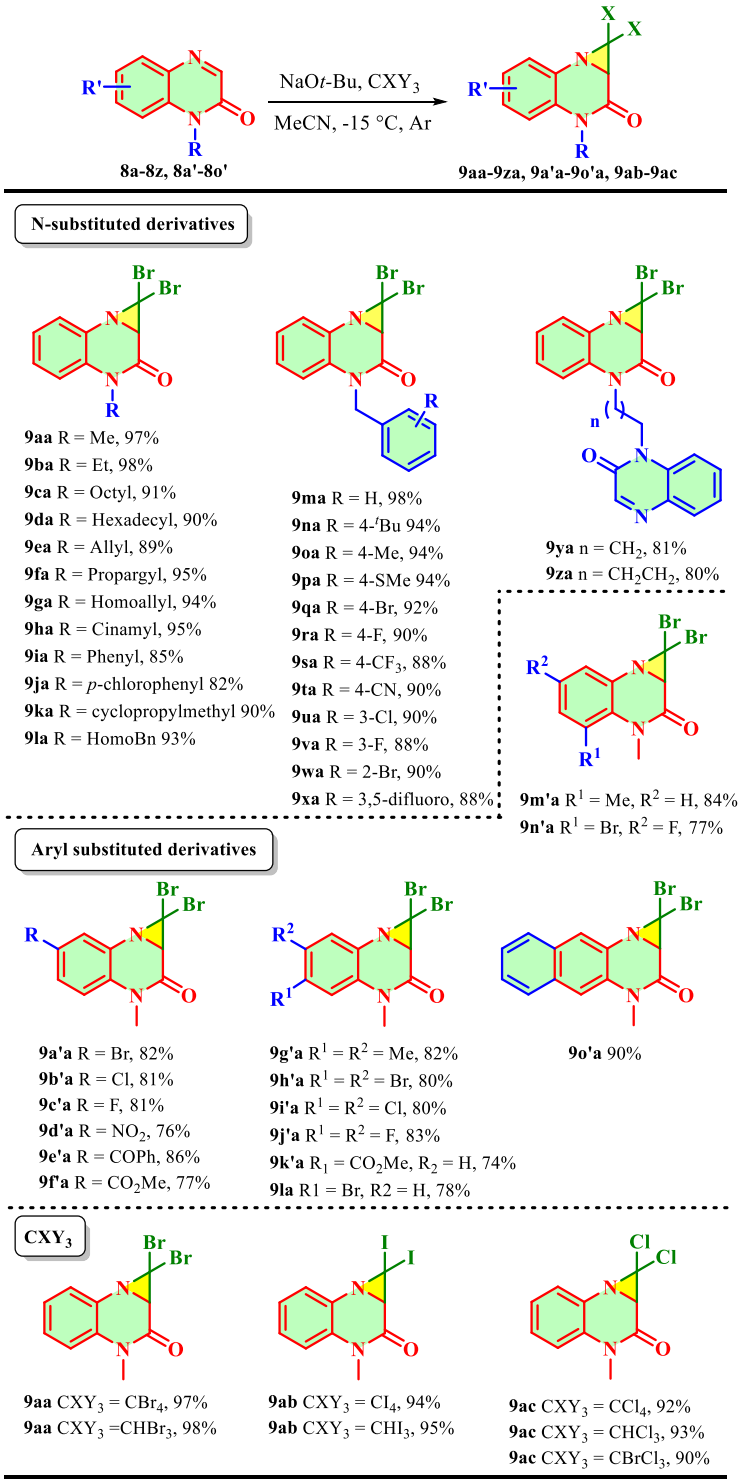
In summary, we have successfully demonstrated a regioselective dihydrothionation of aromatic as well as heteroaromatic terminal alkynes using 1,2-ethane dithiol in presence of Eosin Y as a photocatalyst under visible light irradiation. The protocol proved to be very practical and easy under metal-free conditions and relied on clean energy source such as visible light to drive the reaction for the construction of thioacetal via two C–S bond formation. A wide range of terminal alkynes reacted smoothly under the conditions to afford various cyclic 1,3-dithiolanes in very good yields. The plausible reaction mechanism of this transformation has been proposed based on a series of control experiments, Stern-Volmer plot and cyclic voltammetric studies.

Chapter 4: ***An Access to Strenuous Fused Dihalo-Aziridino Quinoxalinone via C3-H Functionalization followed by Tandem Cyclization of Quinoxalinone***

This chapter presents a methodology to access strenuous, fused dihalo-aziridino quinoxalinone via C3-H functionalization of quinoxalinone followed by tandem cyclization using carbon tetrabromide and sodium *tert*-butoxide (Scheme 4.1). Fused dihalo-aziridino quinoxalinone is a novel heterocyclic scaffold and is constructed via the formation of C–C and C–N bonds. It is well known that quinoxalinone is a very useful and versatile framework that allows a great possibility for the functionalization and modification to offer various quinoxalinone derivatives during the drug discovery process. This chapter gives a brief overview on the importance of quinoxalinone and its derivatives. Owing to the importance of the C3-H functionalization of quinoxalinone, this chapter highlights some of the selected examples of C3-H functionalization of quinoxalin-2(1*H*)-one.



Scheme 4.1: Synthesis of fused aziridino quinoxalinones.

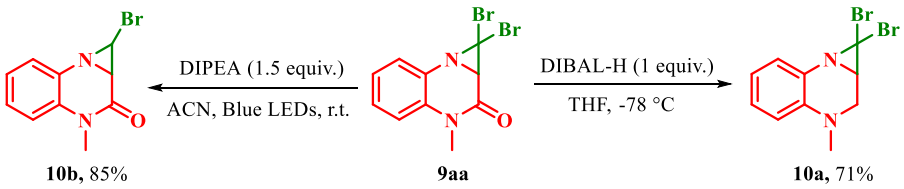


Reaction condition: **8a** (0.2 mmol), NaO^{t}Bu (0.4 mmol), CXY_3 (0.4 mmol), dry MeCN (2 mL), under Argon, at -15 °C)

Scheme 4.2 Substrate scope of fused dihalo-aziridino quinoxalinones

Looking at the versatility of quinoxalin-2(1*H*)-one as well as aziridine frameworks and also by considering the importance of *N*-heterocyclic fused quinoxalin-2(1*H*)-one we planned to explore the synthesis of aziridine fused quinoxalin-2(1*H*)-ones (Scheme 4.1). Based on the exhaustive screening 1-methyl quinoxalin-2(1*H*)-one **8a** (1 equiv.), CBr_4 or CX_4 (2 equiv.), sodium *tert*-butoxide (2 equiv.), in MeCN under an inert atmosphere at -15 °C proved to be the optimum reaction conditions to afford the desired dihalo-aziridino 1-methyl quinoxalinone derivatives **9a**.

Having obtained the optimized reaction condition, we explored the substrate scope to synthesize different aziridine fused quinoxalin-2(1*H*)-ones and different haloforms, carbon tetrahalides. Under the optimized reaction conditions, various *N*-substituted quinoxalin-2(1*H*)-ones (having different protecting groups on N) reacted smoothly with CBr_4 under the optimized reaction conditions to afford the corresponding desired fused dibromo-aziridino quinoxalinones (**9aa-9za)** in excellent yields (up to 98%, Scheme 4.2). All the quinoxalin-2(1*H*)-one derivatives with different *N*-protecting groups tolerated the reaction conditions to afford the desired products. Similarly, electron-donating, deactivating and withdrawing groups did not have any impact on the outcome of the yields of products. In order to evaluate the substrate scope further, we treated quinoxalinones having different substitutions on aryl moiety with CBr_4 under the optimized reaction conditions to obtain the corresponding products fused dibromo-aziridino quinoxalinones (**9a'a-9o'a**) in excellent yields (up to 86%, Scheme 4.2). Later, we explored the reaction of *N*-methyl quinoxalin-2(1*H*)-one with different haloforms, carbon tetrahalides under the optimized reaction conditions to afford the corresponding fused dihalo-aziridino quinoxalinones (**9aa, 9ab, 9ac**) in excellent yields (up to 98%, Table 4.1). The protocol also proved to be scalable on a gram scale to afford the corresponding product **9aa** in excellent yield (91%).



10b, 85% **9aa** **10a,** 71%

Scheme 4.3 Utility of **9aa** for accessing useful compounds

In order to extend the utility of the product **9aa** and for the wider applicability of the protocol we have explored the regioselective and chemoselective reduction of **9aa** by using DIPEA under

visible light irradiation (Blue LED) to afford the corresponding bromo-aziridino-heterocycles **10b** in very good yield (85%, Scheme 4.3). We also employed the fused dibromo-aziridino quinoxalinone **9aa** for amide reduction using DIBAL-H to afford the corresponding fused piperazine derivative **10a** in good yield (71%, Scheme 4.3).

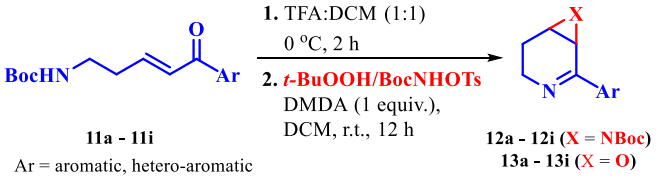
Based on a series of control experimental observations we proposed that carbon tetrabromide upon treatment with sodium *tert*-butoxide forms an unstable carbanion reactive intermediate (Br_3C^-) that further attacks the *N*-methyl quinoxalin-2(1*H*)-one **7a** to form negatively charged species (salt) that would intramolecularly attack the bromine attached to β-carbon to furnish the fused dibromo-aziridino-quinoxalinone **9aa**.

In summary, we have explored the synthesis of novel, strenuous fused dihalo-aziridino-quinoxalinone heterocyclic scaffolds under simple and practical conditions using easily available reagents. Later, we have also shown that protocol is scalable on gram quantity. A wide range of fused dihalo-aziridino quinoxalinones have been synthesized starting from quinoxalinones and carbon tetrahalides via C–C and C–N bond formation. We have also carried out a few control experiments to validate the mechanism of this transformation. Fused dihalo-aziridino quinoxalinones have been also employed for further transformations to access useful compounds.

Chapter 5: ***An Access to Aziridino-Fused Piperid-1-enes and Epoxy-Fused Piperid-1-enes Starting from δ-Amino Enones***

This chapter presents a novel strategy to access aziridino fused piperid-1-enes and epoxy fused piperid-1-enes starting from δ-amino enones using DMDA and BocNHOTs or *t*-BuOOH respectively. Fused bicyclic piperidine derivatives are known to possess potent bioactivities and these core scaffolds have been explored as potential bioactive templates for different targets. Interestingly, some of the fused heterocycles are also known as energy materials due to their steric as well as angle strain. It is well known that minor modifications in the piperidine core can result in interesting properties. Owing to the importance of these scaffolds, efforts have been made to construct epoxy-fused piperidines and aziridino-fused piperidines in the literature. In this regard, we became interested in building these frameworks by looking at the available literature and our expertise in the research field. This chapter presents an overview of the importance of these fused bicyclic piperidines and some of the synthetic strategies. We observed that relatively

a very few protocols are available for the synthesis of aziridino fused piperidines in comparison to the epoxy fused piperidines. Considering the importance of these fused bicyclic piperidines we developed a novel synthetic strategy to access aziridino fused piperid-1-enes and epoxy fused piperid-1-enes starting from δ-amino enones using DMDA and BocNHOTs or *t*-BuOOH respectively (Scheme 5.1).

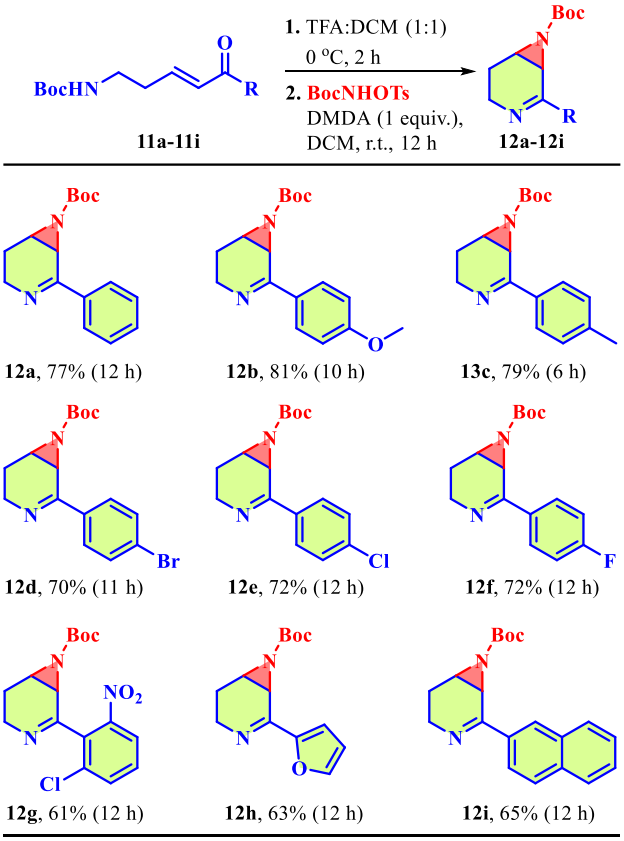


Scheme 5.1 Synthesis of derivatives of 3,4-epoxy and 3,4-aziridino piperid-1-enes

Based on our systematic screening we optimized the reaction of **11a** (1 equiv.) treated with TFA: DCM (v/v 1:1) for deprotection of the Boc group and the corresponding TFA salt of δ-amino-enone [**I]** (used further without purification), treated with BocNHOTs (1.5 equiv.) in presence of DMDA (1 equiv.) in the DCM solvent at room temperature to obtain the aziridino fused piperid-1-enes **12a.**

Having obtained the optimum reaction conditions, we further explored the substrate scope of tandem aziridination-cyclization by using various aromatic amino enones (**11a-11i**). All the *N*-protected amino enones were synthesized by following the literature procedure. The *N*-protected amino enones were subjected to deprotection to obtain the corresponding TFA salt of δ-amino enones and were further used for the next steps without any purification. All TFA salt of δ-amino enones having aromatic as well heteroaromatic moieties underwent facile tandem aziridination-cyclization in presence of BocNHOTs under standard reaction conditions to afford the corresponding 2-aryl-3,4-aziridino piperid-1-enes (**12a-12i**) in moderate to excellent yields (Scheme 5.2). The various electron-donating, electron-withdrawing, and electron-deactivated groups on the aryl part of δ-amino enones reacted smoothly under standard reaction conditions. The heteroaromatic, as well as highly aromatic group-containing δ-amino enones, also afforded their corresponding products (**12h-12i**) in good yields (Scheme 5.2). The molecular structure of compound **12e** was unambiguously confirmed by single-crystal X-ray analysis. All these

aziridine fused bicyclic piperid-1-enes have been synthesized starting from *N*-protected enones in one pot following two steps.

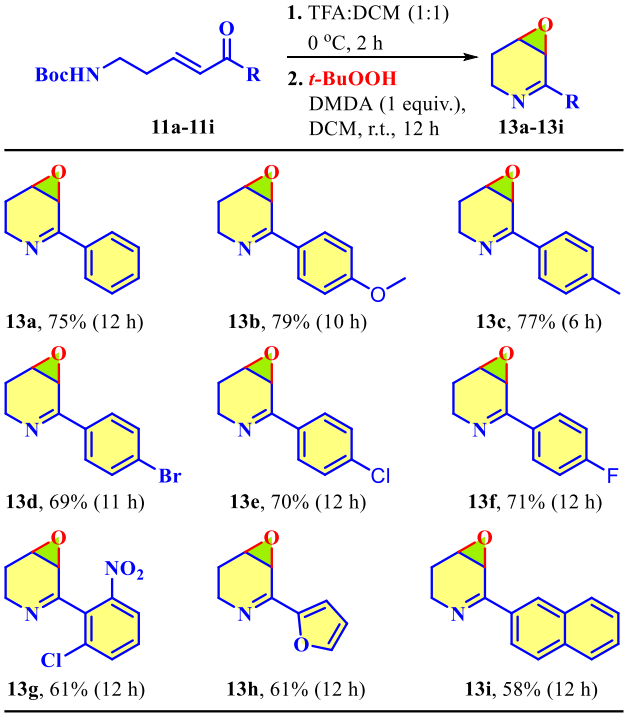


Reaction condition: Enones **11a** was deprotected by TFA:DCM (1:1) then the resulting amino enone **I** was used directly without purification. Enone [**I]** (1 equiv. based on the stoichiometry of **11a**), BocNHOTs (1.1 equiv.), DMDA (1 equiv.), DCM (2 mL), r.t., 12 h

Scheme 5.2 Tandem aziridination and cyclization

Encouraged by the initial success, we further extended this strategy to explore the tandem epoxidation-cyclization. In view of this different aromatic amino enones (**11a-11i**) were treated with TFA to obtain TFA salt of δ-amino enones and were explored for the tandem epoxidation-cyclization reaction without further purification. The reaction of TFA salt of δ-amino-enone [**I]**, DMDA (1 equiv.), *t*-BuOOH (1.1 equiv.) in DCM as solvent at room temperature proved to be the optimum reaction conditions to access the corresponding epoxy fused piperid-1-enes **13a**. Different δ-amino-enones (**11a-11c**) having electron-donating groups such as methoxy and methyl on aryl moiety reacted easily under optimized reaction conditions to afford the corresponding epoxy fused bicyclic piperid-1-enes (2-aryl-3,4-epoxy piperid-1-enes) (**13a-13c**) in moderate to good yields (Scheme 5.3). Also, δ-amino-enones (**11d-11g**) contain electron

deactivating groups such as bromo, chloro, fluoro and electron-withdrawing groups such as nitro on aryl moiety also well reacted under the optimized reaction conditions to afford the corresponding desired products (**13d-13g**) in good yields (Scheme 5.3). Interestingly, δ-amino-enones having heteroaromatic and highly aromatic moieties transformed to afford the corresponding desired products (**13h-13i**) in moderate yields.



Reaction condition: Enones **11a** was deprotected by TFA:DCM (1:1) then the resulting amino enone [**I**] was used directly without purification. Enone [**I**] (1 equiv. based on the stoichiometry of **11a**), *t*-BuOOH (1.1 equiv.), DMDA (1 equiv.), DCM (2 mL), r.t., 12 h)

Scheme 5.3 Tandem epoxidation and cyclization

Based on the previous studies on aziridination reaction the probable mechanistic pathway was proposed for tandem aziridination/epoxidation-cyclization sequence. TFA salt of δ-amino enone upon treatment with DMDA forms a *trans*-imine intermediate. This would further isomerise to form a kinetically stable *cis*-imine isomer intermediate that eventually cyclizes to form a dehydro piperidene intermediate. This intermediate would be attacked by relatively nucleophilic reagent BocNHOTs via Michael addition followed by intramolecular aziridination as well as by the elimination of the tosyl group to form the final desired aziridine fused piperid-1-ene product.

In summary, we have developed a novel, regioselective, mild organocatalytic protocol for the synthesis of fused *N*-heterocyclic compounds (1-aryl-3,4-aziridino piperid-1-ene and 1-aryl-3,4-epoxy piperid-1-ene) starting from TFA salt of δ-amino enones and BocNHOTs/*t*-BuOOH in presence of DMDA. This protocol tolerated a wide variety of aromatic/heteroaromatic δ-amino-enones under the optimized reaction conditions to access fused N-heterocyclic scaffold via C–N and C–O bond construction. This protocol may find wider applications in organic synthesis due to the importance of fused bicyclic piperidine cores in natural products and pharmaceuticals.

List of Publications

1 Shiv Pal, Meghna A Manae, **Vikas V. Khade**, Shabana Khan*. “Reactivity of N-heterocyclic carbene, 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene, towards heavier halogens (Br_2 and I_2)” *J. Indian Chem. Soc.*, **2018**, *95*, 765-770.

2 Nilanjana Sen, Shiv Pal, **Vikas V. Khade**, Shabana Khan* “Cyclic Four-Membered Stanna Thio and Seleno Compounds from 2-Aminopyridinato Stannylenes” *Eur. J. Inorg. Chem.,* **2019**, 4450-4454.

3 **Vikas V. Khade**, Archana S. Thube, Prakash K. Warghude, Ramakrishna G Bhat* “DABCO mediated one-pot synthesis of sulfoxonium ylides under blue LED”. *Tetrahedron Lett.,* **2021**, *77,* 153258-153262.

4 **Vikas V. Khade**, Archana S. Thube, Pankaj D. Dharpure, Ramakrishna G. Bhat*. Direct synthesis of 1,3-dithiolanes from terminal alkynes via visible light photoredox catalysis. *Org. Biomol. Chem.*, **2022**, *20*, 1315-1319.

5 Pankaj D. Dharpure, Mousami Bhehara, **Vikas V. Khade**, Archana S. Thube, Ramakrishna G. Bhat* A direct access to thiocyano-thioesters from cyclic thioacetals via photoredox catalysis: an introduction of two functional groups in one-pot. *Org. Lett.* **2022**, 24, 6919-6924.

6 **Vikas V. Khade**, Archana S. Thube, Anindita Bahumik, Ramakrishna G. Bhat*. An Access to strenuous fused dihalo-aziridino quinoxalinone via C3-H functionalization followed by tandem cyclization of quinoxalinone. **Manuscript communicated**.

7 **Vikas V. Khade,** Tushar M. Khopade, Ramakrishna G. Bhat* An access to aziridino fused piperid-1-enes and epoxy fused piperid-1-enes starting from δ-amino enones. **Manuscript under preparation**.

A Brief Overview of Carbon-Heteroatom Bond Forming Reactions to Access Heterocyclic Scaffolds

1

1.1 Abstract

The construction of heterocyclic scaffolds through a carbon-heteroatom bond (C–N, C–O, C–S) forming reactions have gained significant attention in organic synthesis over the years. The construction of carbon-heteroatom bonds is of great interest to building biologically active compounds, natural products, various polymers and materials. Various novel strategies have been developed to construct the carbon-heteroatom bonds to access heterocyclic scaffolds and some of the selected carbon-heteroatom bond forming reactions have been highlighted in this chapter.

1.2 Introduction

Various heterocyclic compounds have significant importance in pharmaceutical as well as in synthetic organic chemistry due to their bioactivity and reactivity.[1] Most of these heterocyclic compounds contain nitrogen, sulfur and/or oxygen atoms in their core scaffolds. Mostly these biologically active compounds, natural products, agrochemicals and some of the valuable materials utilized in material chemistry have any of the heteroatom bonds or all the heteroatom bonds (C–N, C–O, and C–S bonds) in their structures. There has been a great effort over the century to build cyclic scaffolds via the construction of carbon-heteroatom bonds using various strategies. Three-membered fused heterocycles (aziridines, epoxides) are found in many useful compounds and they are also precursors as well as intermediates for the synthesis of many important compounds due to their steric strain and inherent reactivity.[2] Even though they have steric strain and inherent reactivity, they are widely present in many natural products and pharmaceuticals and they have also been utilized as reactive partners in many synthetic transformations.[1,2] Various organic compounds containing C–N or C–O or C–S or having all these carbon-heteroatom bonds are known for potent biological activity (Fig. 1.1). Piperidine

core containing alkaloids such as isopelletierine[3] (contains C–N bond) is derived from the root-bark of the pomegranate, while (*S*)-anabasine[4] (contains C–N bond) is an alkaloid having pyridine and piperidine units and is found in tobacco tree and it is utilized as insecticides in agrochemicals. The compounds having *β*-lactam core such as penicillin G[5] (contains both C–N and C–S bonds) and clavulanic acid[6] (contains both C–N and C–O bonds) and are known for their antibiotic activity. The three-membered and strained nitrogen-containing Mitomycin C[7] (contains C–N bond) and Ficellomycin[8] (contains C–N bond) show antitumor and antibiotic activity respectively. (+)-Tagetitoxin[9] (contains C–O and C–S bonds) is known for preferentially inhibiting the eukaryotic RNA polymerase III.

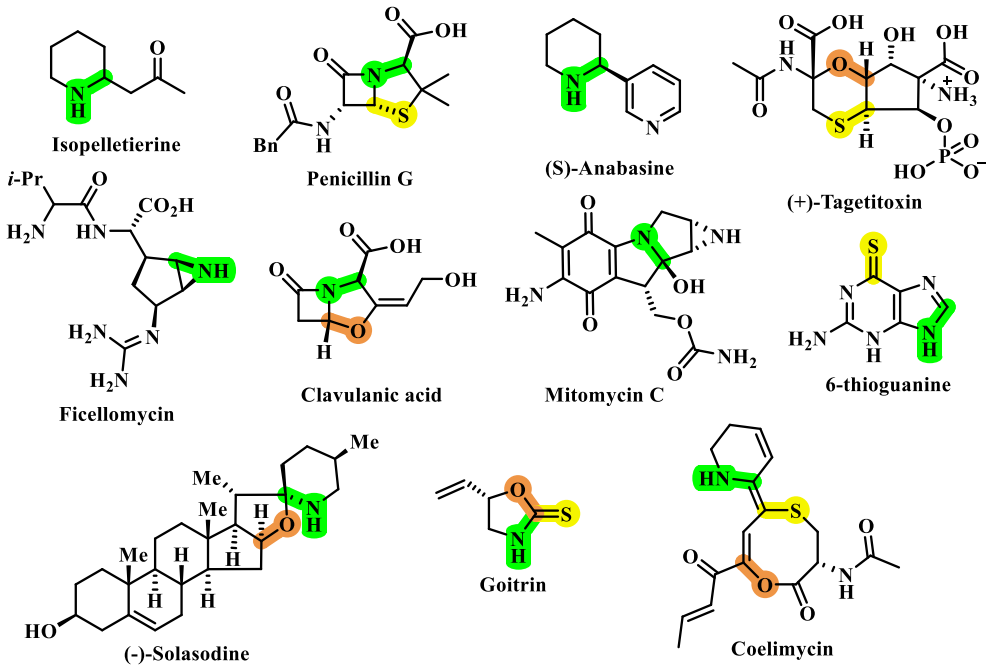


Figure 1.1 Representative natural products having C–N, C–S, C–O and C=S bonds in their cyclic framework

Goitrin[10] (contains C–O, C–N and C=S bonds) and is known to reduce the production of thyroxine (thyroid hormones). Coelimycin[11] (contains C–S, C–O and C–N bonds) is believed to be the earliest, coloured specialized metabolite that is synthesized during the life cycle of the model organism *Streptomyces coelicolor*. Solasodine[12] (contains C–N and C–O bonds) is known for its diuretic, anticancer, antifungal, cardiotonic, antispermatogenetic, antiandrogenic, immunomodulatory, antipyretic activities and is also known to elicit effects on the central

nervous system. 6-thioguanine[13] (contains C–N and C=S bonds) has been explored as a medicine to treat acute myeloid leukemia, acute lymphocytic leukemia, and chronic myeloid leukemia.

Undoubtedly, many natural and synthetic cyclic heterocyclic compounds having multiple carbon-heteroatom bonds in their core scaffolds modulate many chemical, physical and biological properties. Undoubtedly, aiming to develop synthetic strategies for accessing carbon-heteroatom bonds (C–N, C–O, and C–S bonds) to construct a heterocyclic framework is very important and essential from a synthetic and medicinal chemistry point of view. This introductory chapter gives a brief account of carbon-heteroatom bond-forming reactions using different synthetic strategies at room temperature to access useful scaffolds. This chapter is mainly divided into three parts highlighting C–N, C–O and C–S bond-forming strategies

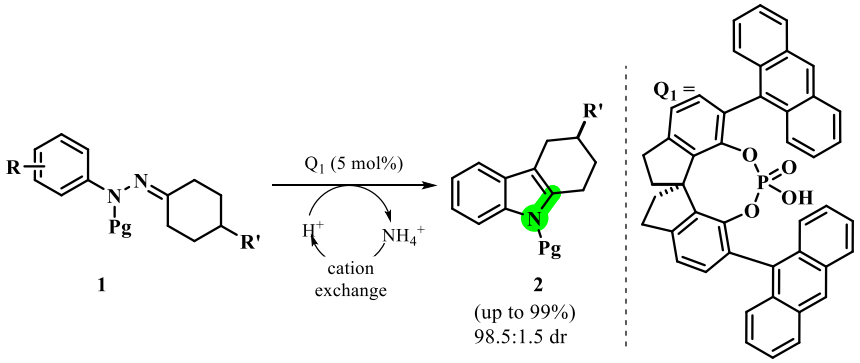
1.3 C–N bond containing cyclic scaffold

It is very well known that nitrogen-containing compounds have special importance due to their potent and diverse biological activities and they are also present in various natural products, pharmaceuticals and agrochemicals.[1e-f] Obviously, to build a nitrogen heterocyclic scaffold, the construction of the C–N bond is one of the key steps.[14]

Despite significant advancements in developing various strategies for the C–N bond construction there still exists a lot of challenges to developing newer strategies that are easy to handle, more practical, economical and sustainable in nature. Some of the selected C–N bond-forming strategies to construct nitrogen heterocyclic compounds have been highlighted.

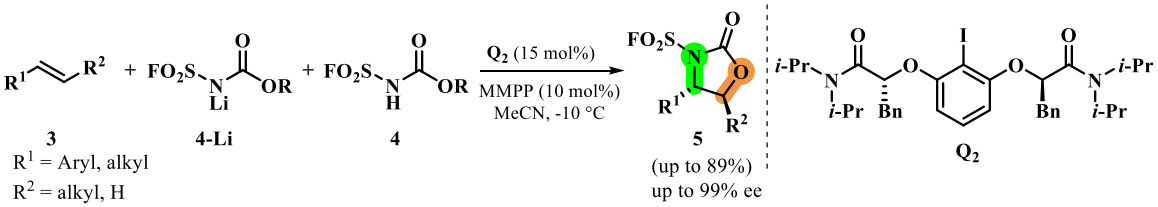
1.3.1 Organocatalyzed cyclization

Different organocatalysts have been explored for different stereoselective transformations and the organocatalysts are known to drive the reactions via ionic or covalent interactions.[15] List and coworkers have explored the non-covalent organocatalysis using novel spirocyclic chiral phosphoric acid **Q_1** to catalyse the reaction of 4-substituted cyclohexanone-derived phenylhydrazones **1** to obtain useful 3-substituted tetrahydrocarbazoles **2** in excellent yields (Scheme 1.1).[16]



Scheme 1.1. Non-covalent organocatalyzed synthesis of tetrahydrocarbazoles

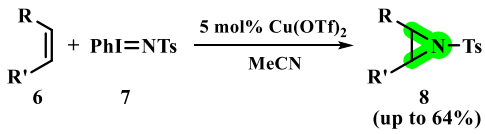
Recently, Hashimoto and coworkers have reported the synthesis of *trans*-oxazolidinone **5** relying on the construction of C–N and C–O bonds via catalytic enantioselective intermolecular oxyamination of alkenes **3,** lithium amide **4** (and alkyl (fluorosulfonyl)carbamate **4**, in presence of organoiodine(I/III) catalyst **Q2** in very good yields and excellent enantioselectivity (Scheme 1.2).[17]



Scheme 1.2 Oxyamination of alkenes via covalent organocatalysis

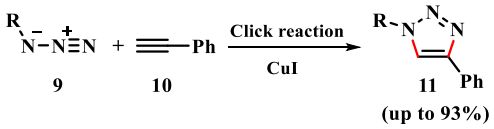
1.3.2 Metal-mediated cycloaddition

C–N bond construction has been also achieved via metal catalysis. Cycloaddition (2+1) of simple mono/di-substituted alkene **6** and *N*-tosyliminobenzyliodinane **7** has been explored under copper catalysis to access the corresponding aziridine derivatives **8** in moderate yields (up to 64%, Scheme 1.3). It has been proposed that $Cu(OTf)_2$, forms an organometallic complex with **7** and acts as one centered synthon for the cycloaddition reaction while alkene **6** acts as a two-centered synthon.[18]



Scheme 1.3 Metal catalyzed [2+1] cycloaddition to access aziridines

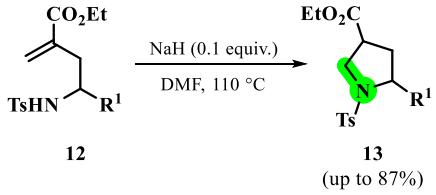
One well-known reaction is the copper-catalyzed azide-alkyne cycloaddition (CuAAC) or click chemistry that effectively constructs two C–N bonds in one pot using azides **9** and alkynes **10** to furnish the triazoles **11** in excellent yields (Scheme 1.4). This strategy is widely utilized, reliable, and straightforward to make C–N bonds. Easily accessible copper iodide as a catalyst is known to catalyze this simple [3+2] cycloaddition reaction between alkyl/aryl azide **9** and alkyne **10**.[19]



Scheme 1.4 Copper catalyzed [3+2] cycloaddition

1.3.3 Nucleophilic cyclization

The nucleophilic cyclization strategy relies on the generation of a nucleophile in presence of a base that further undergoes intramolecular as well as intermolecular cyclization depending on the type and nature of substrates. Ichikawa *et. al* have reported an intramolecular cyclization of *N*-homoallylsulfonamides **12** using strong base sodium hydride at an elevated temperature (110 °C) to afford the corresponding pyrrolidine derivative in very good yields (up to 87%, Scheme 1.5).[20] It has been proposed that *N*-homoallylsulfonamides **12** undergoes cyclization via the generation of nucleophilic anionic intermediate that cyclizes via Michael addition to form the corresponding pyrrolidine **13.**

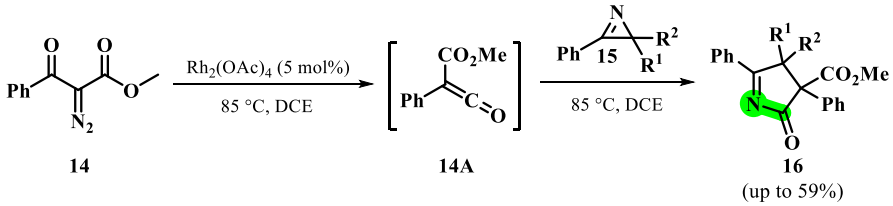


Scheme 1.5 Base-mediated nucleophilic intramolecular cyclization

1.3.4 Ring expansion

The C–N bond has also been constructed via a ring expansion strategy to access *N*-heterocyclic scaffold. Novikov and coworkers have demonstrated that methyl 2-diazo-3-(4-methoxyphenyl)-3-oxopropanoate have **14** upon treatment with rhodium acetate dimer (5 mol%**)** as a catalyst forms ketene intermediate **14A**. This *in situ* generated intermediate upon treatment with *2H*-

azirine **15** under heating condition (85 °C) affords the corresponding *1H*-pyrrol-2(3*H*)-ones **16** via the ring expansion albeit in moderate yields. (Scheme 1.6)[21]

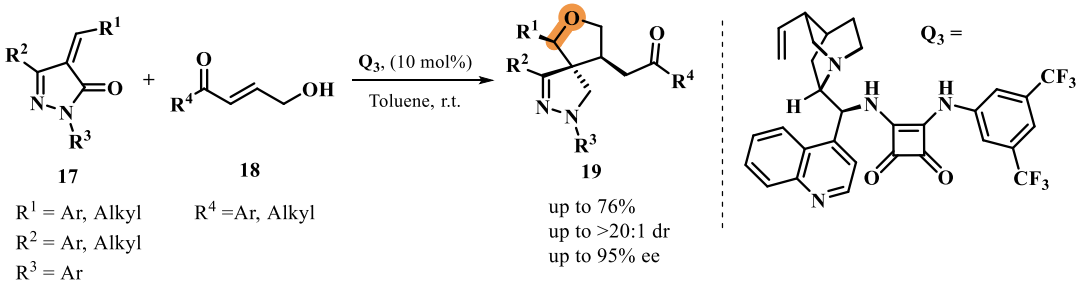


Scheme 1.6 Ring expansion strategy to access *N*-heterocyclic scaffold

1.4 C–O bond containing cyclic scaffolds

There are many oxygen containing compounds such as epoxides, oxetanes, etc. are widely utilized as reagents or useful synthetic precursors to access valuable compounds via ring-opening or ring expansion reactions.[1c-d, 22] Some of the compounds such as tetrahydrofuran and tetrahydropyran, dioxanes are well utilized as solvents as well as reagents[23a] and ligands.[23b]. There are multiple drugs, natural products, agrochemicals and materials that contain cyclic ether as a key motif at specific positions.[1c-d] Owing to the importance of oxygen-containing heterocycles many methods have been developed for the construction of the C–O bond. Some of the methodologies for the construction of C–O bonds to access cyclic scaffolds have been discussed.

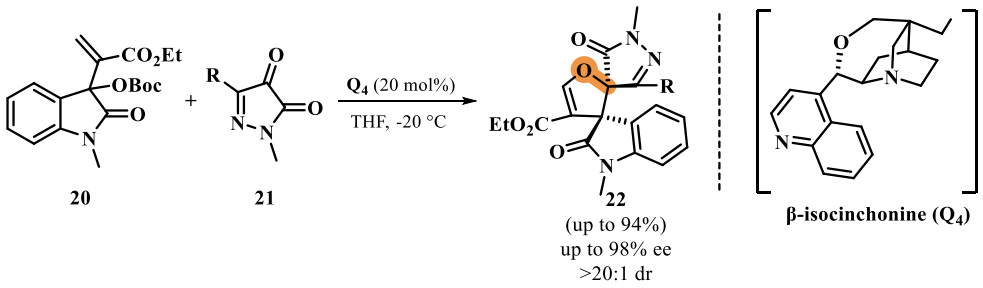
1.4.1 Organocatalytic cyclization



Scheme 1.7 Synthesis of spiro-tetrahydrofuran-pyrazolones via C–O bond formation

S. C. Pan and coworkers have reported the first diastereo- and enantio-selective synthesis of spiro-tetrahydrofuran-pyrazolones via organocatalytic asymmetric oxa-Michael/Michael cascade reaction between γ-hydroxyenones **18** and unsaturated pyrazolones **17** (Scheme 1.7).[24] They

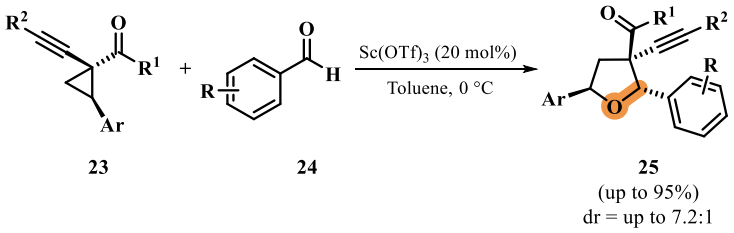
utilized the squaramide-based organocatalysts **Q3** for the construction of spiro compounds **19** via C–O bond formation in very good yield and enantioselectivity.



Scheme 1.8 Organocatalytic cyclization to access spiro compound via C–O bond formation

Bhat and coworkers have reported the highly enantioselective and diastereoselective synthesis of spiro-oxindole dihydrofuran fused pyrazolones. They utilized the pyrazolone 4,5-diones **21** and Morita Baylis Hilmann (MBH) adduct derived from isatin **20** in presence of β-isocinchonine (**Q4**) organocatalyst to access spirooxindole dihydrofuran fused pyrazolones **22** in very good yields and very high enantioselectivity via (3+2) cycloaddition (Scheme 1.8).[25] In this strategy C–O bond formation paved the way for the formation of the spiro compound.

1.4.2 Metal catalyzed cycloaddition

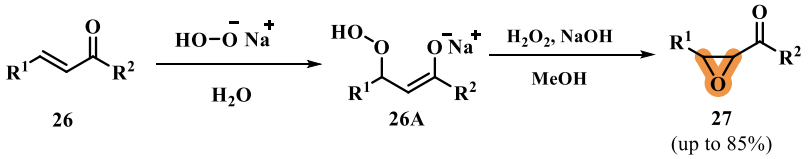


Scheme 1.9 Synthesis of 2,5-trans-tetrahydrofuran derivatives

Metal catalysis has been well established for the construction of C–O bond in literature. Wang and coworkers reported the formal intermolecular [3+2] cycloaddition reaction of alkynylcyclopropane ketones **23** with electron-rich aromatic aldehydes **24** to afford the corresponding 2,5-trans-tetrahydrofuran derivatives **25** via scandium catalysis in excellent yields with very good diastereoselectivity (Scheme 1.9).[26]

1.4.3 Nucleophilic cyclization

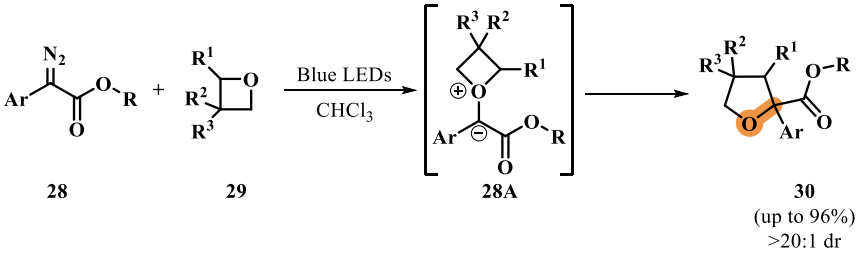
Manchanayakage and coworkers have disclosed the protocol to access substituted epoxides **27** starting from chalcones **26** under oxidizing reaction conditions. The H_2O_2 under alkaline condition (NaOH) attacks (nucleophilic) on the chalcones **26** to form the corresponding substituted epoxide derivatives **27** via the hydroperoxide-enolate intermediate **26A**. This intermediate **26A** undergoes intramolecular cyclization to furnish desired epoxide **27** via the construction of two C–O bonds (Scheme 1.10).[27]



Scheme 1.10 Cyclopropanation of chalcones

1.4.4 Ring expansion

Oxetanes **29** are saturated oxygen atom containing heterocycles and have steric and angle strain. Due to these properties, they are very reactive and hence explored in various transformations. Oxetane derivative **29** upon treatment with α-phenyl-α-diazo ethyl ester **28** under the visible light irradiation undergoes ring expansion reaction via an intermediate **28A** to form corresponding five-membered oxolane (or THF) derivatives **30** in excellent yields with excellent diastereoselectivity.[28]

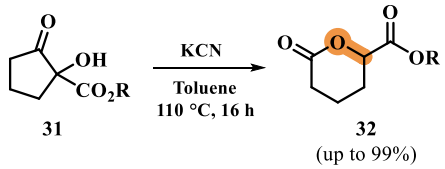


Scheme 1.11 Synthesis of tetrahydrofuran derivatives under visible light conditions

1.4.5 Lactonization

Lactonization is one of the useful organic transformations that relied on C–O bond formation leading to cyclization. It is an important step for the synthesis of butenolides, phthalides, 5,6-

dihydropyran-2-ones and 3,4-dihydropyran-2-ones and these compounds are key motifs in biologically active compounds as well as in many natural products.[29]



Scheme 1.12 Synthesis of tetrahydro-2*H*-pyran-2-one

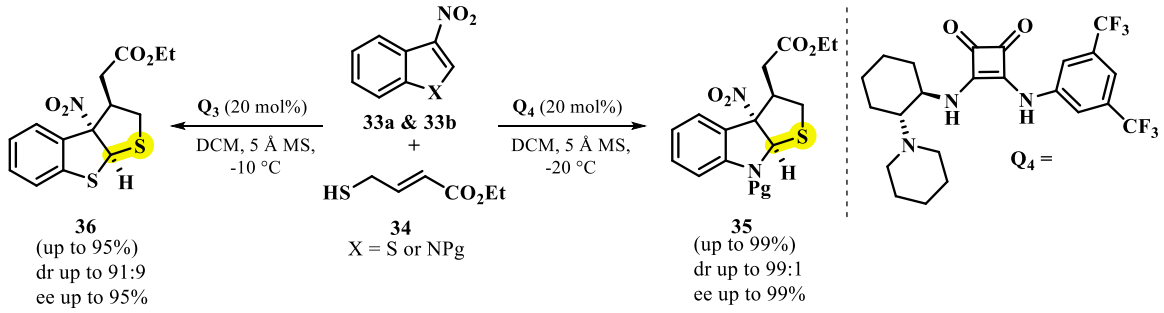
δ-Valerolactone **32** has been synthesized starting from cyclic α-hydroxy-β-oxoesters **31** in presence of the catalytic amount of potassium cyanide in toluene under reflux conditions (up to 99%, Scheme 1.12).[29] The reaction is believed to undergo via retro-Dieckmann condensation followed by lactonization.

1.5 C–S bond containing cyclic scaffolds

Like oxa-heterocycles, cyclic thioether containing natural products and pharmaceuticals are plenty in numbers. Many of these sulfur containing compounds exhibit potent biological activities and pharmacological properties. Many important drugs have sulfur atom in the form of C–S bond. Some of the drugs contain cyclic thioether moiety in the form of thiirane, thietane, thiolane, and thiane core.[1a-1b] Some of the protocols for accessing thioethers derivatives via C–S bond formation have been mentioned here.

1.5.1 Organocatalytic cyclization

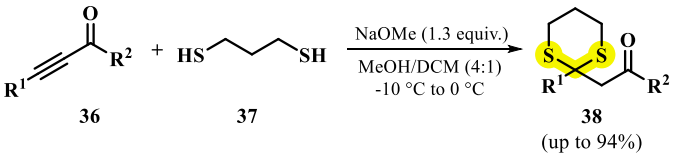
Yuan and coworkers have developed a protocol for the dearomatization of 3-nitroindoles **33a** and 3-nitrobenzothiophenes **33b** using 4-mercapto-2-butenoate **34** in presence of squaramide based oragnocatalyst **Q4** to afford the corresponding tetrahydrothiopheneindolines **35** or tetrahydrothiophenebenzothiophenes **36** in excellent yields with excellent enantioselectivity (Scheme 1.13).[30] They reported the first example of thiol-triggered catalytic asymmetric dearomatization of 3-nitroindoles and 3-nitrobenzothiophenes successfully.



Scheme 1.13 Asymmetric dearomatization of 3-nitroindoles and 3-nitrobenzothiophenes

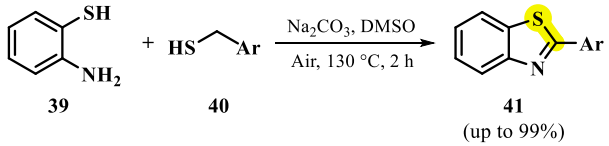
1.5.3 Nucleophilic cyclization

Ley and coworkers have reported the synthesis of 1,3-dithiane derivatives **38** via the double conjugation addition of 1,3-propanedithiol **37** to propargylic ketones, esters and aldehydes **36** under basic conditions at low temperature in excellent yields (up to 94%, Scheme 1.14). These masked 1,3-dicarbonyl systems can be converted to a range of functionalized oxygen and sulfur-containing heterocycles that can be used in natural product synthesis.[32]



Scheme 1.14 Synthesis of 1,3-cyclic dithioacetals

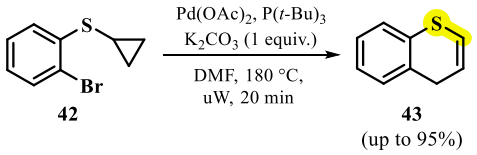
Zhang *et. al* have reported the benzyl thiol **40** promoted direct dehydrogenative cyclization strategy with 2-aminothiphenol **39** to access benzo[*d*]thiazole derivatives **41** under elevated reaction conditions in excellent yields (Scheme 1.15). This protocol has been proved to be applicable for a wide variety of 2-amino thiophenols as well as benzyl thiols under metal-free conditions.[33]



Scheme 1.15 Synthesis benzothiazole

1.5.4 Ring expansion

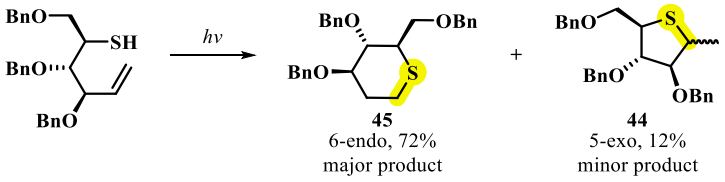
Kaim, Grimaud and coworkers have described the synthesis of thiochromenes **43** via ring opening of cyclopropane-substituted thioethers **42** under palladium catalysis and microwave reaction condition (180 °C) in excellent yields (Scheme 1.16).[34] It has been proposed that cyclopropane-substituted thioethers **42** undergo oxidative addition with palladium catalyst followed by the thiol assisted ring opening to insert into palladium to result in ring expansion and subsequent reductive elimination resulting in thiochromenes **43**.



Scheme 1.16 Ring expansion to access thiochromenes

1.5.6 Radical cyclization access cyclic thioethers

Scanlan and coworkers have disclosed the synthesis of thiosugars such as **45** and **44** starting from thiol substrate having δ-terminal alkene **43** under the irradiation of UV light (Scheme 1.26).[35] It has been proposed that thiyl radical generated from **43** upon UV-light irradiation undergoes cyclization either through 6-endo-trig and 5-exo-trig to form the corresponding compounds **45** and **44**.



Scheme 1.17 Radical cyclization of thiols

1.6 Conclusions

In summary the chapter has highlighted the various carbon-heteroatom bond-forming reactions to access useful heterocyclic scaffolds. Different synthetic strategies for the construction of C–N, C–O and C–S bonds have been presented to show the importance of the carbon-heteroatom bond

forming reactions. In spite of many synthetic strategies for the construction of C–X (X = N, O, S) bonds, the development of novel synthetic strategies under mild, practical and sustainable reaction conditions are highly desirable.

Our lab has been focussing on the synthesis of useful and bioactive scaffolds via the development of novel synthetic strategies for the construction C–X (X = N, O, S) bonds using different fields of organic synthesis.[36,37,38] Owing to the importance of C–X bond formation we aimed to develop newer synthetic protocols to construct carbon-heteroatom bonds (C–X; X = N, O, S) so as to access useful organic compounds under sustainable, metal-free and ambient reaction conditions. The efforts toward the development of C–X (X = N, O, S) bond-forming strategies using different synthetic approaches to build useful scaffolds have been presented in the subsequent chapters.

1.7 References

1 K. A. Scott, J. T. Njardarson, *Top. Curr. Chem., 2018,* **376**, 5; (b) R. J. Cremlyn, *An Introduction to Organosulfur Chemistry*, John Wiley & Sons, Chichester, **1996**; (c) J. Cossy, A. Guérinot. *Adv. Heterocycl. Chem.*, **2016**, *119*, 107; (d) S. Meng, G.-L. Tang, H.-X. Pan. *ChemBioChem*, **2018**, *19*, 2002-2022; (e) J. A. Joule, *Natural Products Containing Nitrogen Heterocycles-Some Highlights 1990-2015. In Advances in Heterocyclic Chemistry*; Elsevier Ltd, 2016; Vol. 119, pp 81-106; (f) M. M. Heravi, V. Zadsirjan**.** *RSC Adv.*, **2020**, *10*, 44247-44311.

2 L. Degennaro, P. Trinchera, R. Luisi, *Chem. Rev.*, **2014**, *114*, 7881-7929; (b) Y. Zhu, Q. Wang, R. G. Cornwall, Y. Shi, *Chem. Rev.*, **2014**, *114*, 8199-8256.

3 (a) J. A. King, V. Hofmann, F. H. McMillan. *J. Org. Chem.*, **1951**, *16*, 1100-1110; (b) M.-G. A. Shvekhgeimer. *Russ. Chem. Rev.*, **1998**, *67*, 1031-1060.

4 (a) R. H. Linnell. *J. Am. Chem. Soc.* **1954**, *76*, 1391-1393; (b) A. A. M. Habib, M. M. A. Hassan, F. J. Muhtadi. *J. Pharm. Pharmac.*, **1974**, *26*, 838

5 (a) D. D. Dexter J. M. van der Veen. *J. Chem. Soc., Perkin Trans. 1*, **1978**, 185-190; (b) Q. Liu, Y. Li, W. Li, X. Liang, C. Zhang, H. Liu. *ACS Sustainable Chem. Eng.*, **2016**, *4*, 609-615.

6 (a) A. K. MacKenzie, N. J. Kershaw, H. Hernandez, C. V. Robinson, C. J. Schofield, I. Andersson. B*iochemistry*, **2007**, *46*, 1523-1533; (b) E. G. de Andrade, M. de S. C. Silva,

R. B. Haga, V. C. Santos, A. Pessoa Jr., C. de O. R.-Yagui, *Biotechnol. Appl. Biochem.*, **2011**, *58*, 103-108.

7 (a) V.-S. Li, D. Choi, Z. Wang, L. S. Jimenez, M.-S. Tang, H. Kohn. *J. Am. Chem. Soc.*, **1996**, *118*, 2326-2331; (b) M. H. Mashatookia, B. G.-Choobar. *Phys. Chem. Chem. Phys.*, **2022**, *24*, 6639-6654.

8 (a) F. Reusser. *Biochemistry*, **1977**, *16*, 3406-3412; (b) J. F. Abel, H. Agbo, H. Zhang, S. Moria, C. M. H. Watanabe. *Nat. Prod. Rep.*, **2011**, *28*, 693-704.

9 (a) A. E. Aliev, K. Karu, R. E. Mitchellb M. J. Portera. *Org. Biomol. Chem.*, **2016**, *14*, 238-245; (b) C. He, H. Chu, T. P. Stratton, D. Kossler, K. J. Eberle, D. T. Flood, P. S. Baran. *J. Am. Chem. Soc.*, **2020**, *142*, 13683-13688.

10 (a) J. Lüthy, B. Carden, U. Friederich, M. Bachmann. *Experientia*, 1984, **40,** 452-453; (b) M. A. Greer. *J. Am. Chem. Soc.* **1956**, *78*, 1260-1261.

11 (a) J. P. G.-Escribano, L. Song, D. J. Fox, V. Yeo, M. J. Bibb, G. L. Challis. *Chem. Sci.*, **2012**, *3*, 2716-2720; (b) B. Bednarz, M. Kotowska, K. J. Pawlik. *Appl. Microbiol. Biotechnol.*, **2019**, *103*, 6423-6434.

12 (a) L. H. Briggs, R. P. Newbold, N. E. Stace. *J. Chem. Soc.*, **1942**, 3-12; (b) L. I. Brutko, *Chem. Nat. Compd*., **1966**, *2*, 363.

13 (a) G. B. Elion, G. H. Hitchings. *J. Am. Chem. Soc.*, **1955**, *77*, 1676; (b) A. Ono, T. Atsugi, M. Goto, H. Saneyoshi, T. Tomori, K. Seio, T. Dairakuc, J. Kondo. *RSC Adv.*, **2019**, *9*, 22859-22862.

14 (a) J. Bariwalab, E. V. der Eycken. *Chem. Soc. Rev.*, **2013**, *42*, 9283-9303; (b) R. Hili, A. K. Yudin. *Nat. Chem. Biol.*, **2006**, *2*, 284-287.

15 (a) B. List. *Chem. Rev.* **2007**, *107*, 5413-5415; (b) D. W. C. MacMillan. *Nature*, **2008**, *455*, 304-308.

16 (a) S. Müller, M. J. Webber, B. List, *J. Am. Chem. Soc.*, **2011**, *133*, 18534-18537.

17 C. Wata, T. Hashimoto. *J. Am. Chem. Soc.*, **2021**, *143*, 1745-1751.

18 D. A. Evans, M. T. Bilodeau, M. M. Faul, *J. Am. Chem. Soc*., **1994**, *116*, 2742-2753.

19 J. E. Hein, V. V. Fokin. *Chem. Soc. Rev.*, **2010**, *39*, 1302–1315.

20 J. Ichikawa, G. Lapointea, Y. Iwaia, *Chem. Commun*., **2007**, 2698-2700.

21 N. V. Rostovsky, M. S. Novikov, A. F. Khlebnikov, D. S. Yufit. *Chem. Heterocycl. Compd.*, **2017**, *53*, 985-988.

22 J. A. Bull, R. A. Croft, O. A. Davis, R. Doran, K. F. Morgan. *Chem. Rev.*, **2016**, *116*, 12150-12233.

23 (a) Z. Yang, M. L. Stivanin, I. D. Jurberg, R. M. Koenigs, *Chem. Soc. Rev.*, **2020**, *49*, 6833-6847; (b) R. M. Peltzer, O. Eisenstein, A. Nova, M. Cascella. *J. Phys. Chem. B*, **2017**, *121*, 4226-4237.

24 B. Mondal, R. Maity, S. C. Pan. *J. Org. Chem.*, **2018**, *83*, 8645-8654.

25 P. K. Warghude, A. S. Sabale, R. G. Bhat, *Org. Biomol. Chem.*, **2020**, *18*, 1794-1799.

26 C. Zhang, M. Xu, J. Ren, Z. Wang. *Eur. J. Org. Chem.*, **2016**, 2467-2478.

27 D. Ngo, M. Kalala, V. Hogan, R. Manchanayakage. *Tetrahedron Lett.*, **2014**, *55*, 4496-4500.

28 S. Jana, Z. Yang, C. Pei, X. Xu, R. M. Koenigs. *Chem. Sci.*, **2019**, *10*, 10129-10134.

29 D. Kieslich, J. Christoffers. *Org. Lett.*, **2021**, *23*, 953-957.

30 X.-M. Chen, C.-W. Lei, D.-F. Yue, J.-Q. Zhao, Z.-H. Wang, X.-M. Zhang, X.-Y. Xu, W.-C. Yuan. *Org. Lett.*, **2019**, *21*, 5452-5456.

31 (a) J.-Q. Zhang, F. Tong, B.-B. Sun, W.-T. Fan, J.-B. Chen, D. Hu, X.-W. Wang. *J. Org. Chem.*, **2018**, *83*, 2882; (b) Q. Cheng, F. Zhang, Y. Cai, Y.-L. Guo, S. L. You. *Angew. Chem., Int. Ed.*, **2018**, *57*, 2134; (c) J.-Q. Zhao, M.-Q. Zhou, Z.-J. Wu, Z.-H. Wang, D.-F. Yue, X.-Y. Xu, X.-M. Zhang, W.-C. Yuan. *Org. Lett.*, **2015**, *17*, 2238.

32 M. J. Gaunt, H. F. Sneddon, P. R. Hewitt, P. Orsini, D. F. Hook, S. V. Ley. *Org. Biomol. Chem.*, **2003**, *1*, 15-16.

33 J. L. Zhang, M. J. Qiao, L. Chen, Y. B. Dong, C. K. Jiao, S. Q. Liao, Y. J. Wu. *Org. Chem. Front.*, **2019**, *6*, 2844.

34 S. Ponra, A. Nyadanu, N. Pan, E. M.-Lurin, A. Savy, M. Vitale, L. E. Kaim, L. Grimaud. *Org. Process Res. Dev.*, **2020**, 24, *5*, 827-834.

35 E. M. Scanlan, V. Corcé, A. Malone. *Molecules*, **2014**, *19*, 19137-19151.

36 For C–N bond construction see (a) A. R. Mohite, P. R. Sultane, R. G. Bhat. *Tetrahedron Lett.*, **2012**, *53*, 30-35; (b) A. R. Mohite, R. G. Bhat. *J. Org. Chem.*, **2012**, *77*, 5423-5428; (c) P. R. Sultane, A. R. Mohite, R. G. Bhat, *Tetrahedron Lett.*, **2012**, *53*, 5856-5858; (d) P. R. Sultane, R. G. Bhat. *J. Org. Chem.*, **2012**, *77*, 11349-11354; (e) L.V.R. Babu Syamala, R. G. Bhat. *Tetrahedron Lett.*, **2017**, *58*, 4836-4840; (f) T. M. Khopade, P. K. Warghude, A. D. Sonawane, R. G. Bhat. *Org. Biomol. Chem.*, **2019**, *17*, 561-566.

37 For C–O bond construction see (a) T. B. Mete, T. M. Khopade, R. G. Bhat. *Tetrahedron Lett.*, **2017**, *58*, 2822-2825; (b) T. M. Khopade, A. D. Sonawane, S. J. Arora, R. G. Bhat. *Adv. Synth. Catal.*, **2017**, *359*, 3905-3910; (c) D. Laha, R. G. Bhat, *Asian J. Org. Chem.*, **2020**, *9*, 918-921.

38 For C–S bond construction see (a) T. B. Mete, T. M. Khopade, R. G. Bhat. *Tetrahedron Lett.*, **2017**, *58*, 415-418; (b) P. D. Dharpure, A. Bhowmick, P. K. Warghude, R. G. Bhat. *Tetrahedron Lett.*, **2020**, *61*, 151407.

DABCO-Mediated One-Pot Synthesis of Sulfoxonium Ylides from Diazo Compounds Under Blue Light Conditions

2

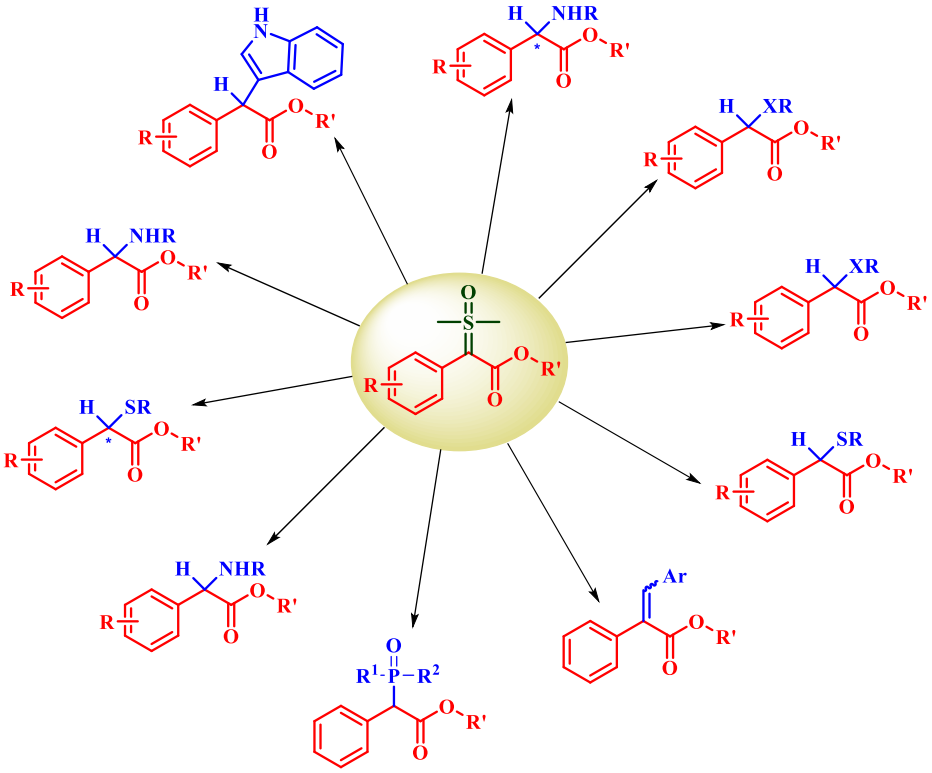
2.1 Abstract:

This chapter presents a visible light promoted and DABCO-mediated metal-free, synthesis of sulfoxonium ylides starting from diazo compounds at ambient temperature. This protocol explored the reactivity of DMSO and α-aryl-α-diazo esters in presence of DABCO under the irradiation of blue LEDs. The protocol proved to be practical and demonstrated the synthesis of different varieties of sulfoxonium ylide derivatives in good to excellent yields. The utility of this protocol has been demonstrated on gram-scale synthesis as well as late-stage modification has been explored via C–S and C–N bond constructing strategy to access few precursors of biologically active compounds. This straightforward and practical method provides an alternative route for the synthesis of useful sulfoxonium ylides starting from α-aryl-α-diazo acetates under mild reaction conditions using a clean energy source such as visible light.

2.2 Introduction

The ylides are very important and useful class of reactive intermediates and have been explored in various synthetic organic transformations due to their versatility.[1] Among different ylides, the reactivity of sulfur ylides as well as sulfoxonium ylides are very useful reactive intermediates and they have been explored for their unique reactivity in organic synthesis. Sulfoxonium ylides are the carbene precursors and they act as useful surrogates of diazo compounds due to their thermal stability and ease of handling.[2] Furthermore, sulfoxonium ylides have also been greatly utilized in the synthesis of many useful organic compounds and biologically active molecules on an industrial scale.[3,4] The α-aryl-α-ester derived sulfoxonium ylides have been employed in different racemic as well as asymmetric S–H, O–H, N–H, and P–H insertion types of reactions.[5,6] Sulfoxonium ylides have been explored for the synthesis of trisubstituted alkene and C-3

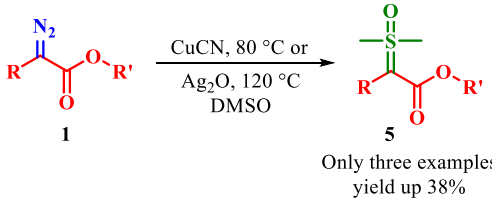
functionalization of indole derivatives[7] (See Scheme 2.1). Interestingly, the synthesis of α-aryl-α-ester sulfoxonium ylides have been explored very rarely. Despite its synthetic potential and wider utility, the development of synthetic protocols to access α-aryl-α-ester sulfoxonium ylides have received limited attention in the literature.[5c,5d,8,9,10,28] The design and development of newer synthetic strategies to access α-aryl-α-ester sulfoxonium ylides under sustainable and mild reaction conditions are desirable and necessary.



Scheme 2.1 Utility of sulfoxonium ylides

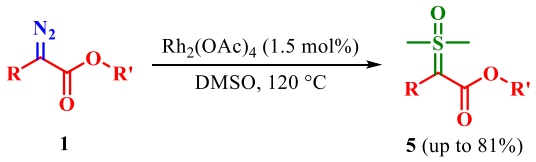
2.3 Previous approaches for the synthesis of sulfoxonium ylides

In 1970, Dost *et al.*, developed the synthesis of α-aryl-α-ester sulfoxonium ylides **5** starting from diazo esters **1** using copper cyanide or silver oxide as metal-based catalysts under heating conditions (80 °C for CuCN and 120 °C for Ag_2O) with limited substrate scope (only three derivatives) (see scheme 2.2).[8]



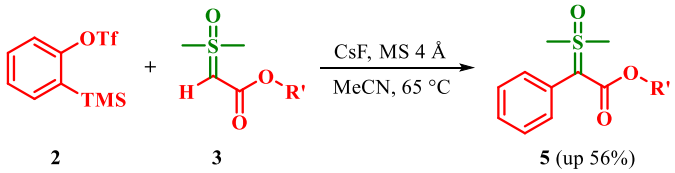
Scheme 2.2 Copper or Silver mediated synthesis of sulfoxonium ylides

In 2016, Dias *et al.*, have improvised the previous synthesis reported by Dost *et al.*,[8] and achieved the broader substrate scope by employing $Rh_2(OAc)_4$ as a catalyst under the heating condition to access sulfoxonium ylides **5** from diazo esters **1** in good yields (120 °C, up to 81 %, Scheme 2.3).[5c]



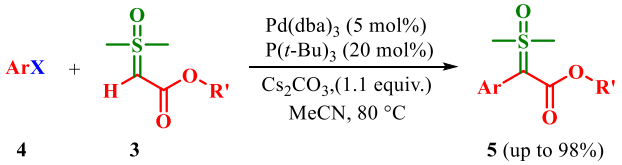
Scheme 2.3 Rhodium-based synthesis of sulfoxonium ylides.

Later, in 2018 Taloro *et al.*, have successfully employed mono-substituted sulfoxonium ylide **3** along with reactive aryne precursor **2** for the synthesis of the α-aryl-α-ester sulfoxonium ylides in good to very good yields (up to 56 %, Scheme 2.4).[9]



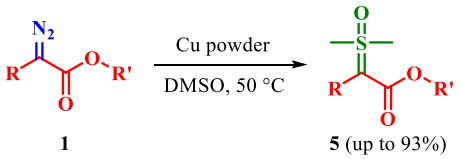
Scheme 2.4 Synthesis of sulfoxonium ylides from reactive aryne precursor

Later, in 2019 Christopher *et al.*, have disclosed a report on the synthesis of sulfoxonium ylides **5** by employing the palladium catalyst (5 mol%) for realizing the coupling reaction between α-ester sulfoxonium ylides **3** and (hetero) aryl iodides/ bromides/ triflates under heating conditions in presence phosphine ligands and base at an elevated temperature (80 °C) in good to very good yields (up to 98 %, Scheme 2.5).[10]



Scheme 2.5 Synthesis of sulfoxonium ylides through coupling reaction.

Very recently in 2020, Ramakrishna *et al.*, have disclosed a protocol for the synthesis of α-aryl-α-ester sulfoxonium ylides **5** from diazo esters **1** using copper powder in DMSO under heating conditions in good to very good yields (70 °C, see Scheme 2.6).[5d]



Scheme 2.6 Copper mediated synthesis of sulfoxonium ylides.

Though these protocols gave access to sulfoxonium ylides, these methods relied on transition metal catalysts/reagents, additional expensive reagents/ligands, additives, harsh reaction conditions with elevated temperature, longer reaction time, and in some cases limited substrate scopes limiting their wider applicability.

In the year 2018, Davies and coworkers for the first time systematically studied the UV-visible spectroscopic properties as well as the reactivity of α-aryl-α-diazo esters **1** under the irradiation of visible light conditions at room temperature.[11] This has led to the understanding of the behaviors of α-aryl-α-diazo esters **1** under visible light conditions. Many researchers have further utilized the α-aryl-α-diazo esters under visible light conditions for executing the (2+1) cycloaddition reactions with various derivatives of styrene,[11] alkynes,[12] benzenes[13], cyclooctatetraene, and (poly-) unsaturated carbocycles[14], indoles[15] at room temperature. It has been observed that the ylides obtained from the α-aryl-α-diazo esters **1** under visible light (Blue LEDs) usually undergo sigmatropic rearrangement (1,2- as well as 2,3-sigmatropic rearrangement) easily.[12,16a-16d] Many researchers have elegantly explored the intramolecular and intermolecular C–H bond insertions into the reactive diazo compounds for accessing useful compounds.[12,17] It has been successfully demonstrated that N–H,[12,18] O–H,[12] S–H,[19,20] and Si–H

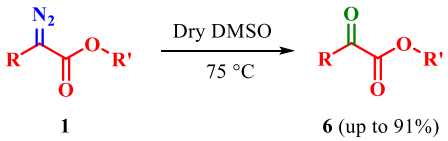
insertion on different α-aryl-α-diazo ester compounds under visible light reaction conditions at room temperature. Even the relatively less nucleophilic fluorinated alcohols have undergone O–H insertion with α-aryl-α-diazo esters via photoinduced proton transfer under visible light irradiation.[21]

Earlier research articles have described that α-aryl-α-diazo esters upon irradiation with visible light generate unstable and highly electrophilic carbene and this carbene can be trapped by a nucleophilic reagent.[22] Owing to the importance of sulfoxonium ylides and growing interest in visible light-mediated reactions, we planned to explore the reactivity of *in situ* generated carbene intermediate by trapping it with dimethyl sulfoxide (DMSO) to afford either sulfoxonium ylides or α-ketoesters. We hypothesized that DMSO may attack the carbene intermediate either through the nucleophilic attack of a lone pair of sulfur and/or through the oxygen of DMSO to afford corresponding sulfoxonium ylides or α-ketoesters respectively. In spite of some of the recent advancements in the synthesis of sulfoxonium ylides, however, there are various drawbacks to overcome especially some of the pertinent issues such as harsh reaction conditions, elevated reaction temperature, and the use of transition metal reagents. In this regard, the design and development of a protocol that is practically convenient, and user-friendly to access sulfoxonium ylides are highly desirable. Herein, in this chapter, we present the DABCO-mediated direct synthesis of different sulfoxonium ylides starting from α-aryl-α-diazo esters under visible light irradiation at room temperature.

2.4 Results and Discussion

In order to validate our assumption, we commenced with a model reaction of α-phenyl-α-diazo ethyl acetate **1a** as a model substrate along with DMSO (10 equiv.) in DCM (1 mL) as solvent under irradiation with blue LEDs. Gratifyingly, the reaction afforded the desired sulfoxonium ylide **5a** albeit in poor yield (12%) along with the corresponding α-phenyl-α-keto ethyl acetate **6** (6% yield) under the blue light irradiation at room temperature for 12 h (See Table 2.1. Entry 1). Encouraged by this initial primary result, we planned to optimize the reaction further to synthesize the sulfoxonium ylide **5a** exclusively in a higher yield. In this regard, to begin with, we screened various percentages of DMSO in DCM solvent (20-50 equiv. and neat). Interestingly, we observed that neat DMSO as a solvent while maintaining the initial reaction

conditions afforded the corresponding sulfoxonium ylide **5a** in moderate yield (60%) however along with α-phenyl-α-keto ethyl acetate **6** as a side product in 35% yield (Table 2.1. Entries 2-4). In order to examine the effect of dissolved oxygen if any, we degassed the reaction mixture by freeze–pump thaw method.[23] To our surprise we observed a slight enhancement in the yield of sulfoxonium ylide **5a** along with α-ketoester **6** (Table 2.1, entry 5). It is well known that the DMSO is a very hygroscopic solvent and the complete removal of water, as well as dissolved oxygen, may not be an easy task and practical. It's also well documented in the literature by Stoltz and coworkers[24] that DMSO can also attack the reactive α-aryl-α-diazo esters **1** (at *in situ* generated carbene) through the nucleophilic attack of lone pair of oxygen) under thermal conditions to furnish the corresponding α-phenyl-α-keto esters **6** along with the expulsion of dimethyl sulfide (DMS) as a by-product (Scheme 2.7). We have done experiments repeated times and observed the reaction afforded the sulfoxonium ylides **5a** and keto ester **6** along with DMS as a by-product under blue light conditions (See Scheme 2.10d). The formation of DMS as a by-product was further confirmed by olfactory analysis as well as by recording the HRMS of the reaction mixture (see Experimental section, page no. 48)



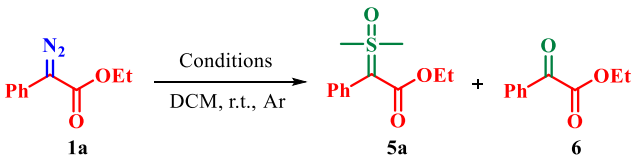
1 **6** (up to 91%)

Scheme 2.7 Synthesis of α-phenyl-α-keto esters

In order to overcome some of these pertinent practical problems during the sulfoxonium ylide synthesis and to increase the yield of **5a**, we planned to optimize the reaction further by screening different additives that have the intrinsic ability to quench the dissolved singlet oxygen and/or that are relatively more nucleophilic with respect to DMSO to control or arrest the reactivity of unstable carbene. In this regard, we screened different additives such as biphenyl, sodium azide, and DABCO while maintaining the initially standardized reaction condition. We observed that among all the additives DABCO (5 Equiv.) proved to be more efficient afford the sulfoxonium ylide **5a** in good yield and we did not observe the corresponding α-ketoester **6** (79%, See table 2.1 entries 6-8).[23] We also notice that further reduction in the amount of DABCO led to a decrease in the yields of sulfoxonium ylide **5a** and interestingly, this also afforded the

corresponding α-phenyl-α-keto ester **6** in higher yield along with the formation of azine and dimerized side products (Table 2.1 Entries 9-10).

Table 2.1 Optimization of reaction conditions[a]



1a 5a 6

Entry	Light source	Additives (equiv.)	Time (h)	Yield (%)[b] **6**	**5a**
1.	Blue LED	-	14	10	3
2.[c]	Blue LED	-	14	12	6
3.[d]	Blue LED	-	14	15	8
4.[e]	Blue LED	-	14	60	35
5.[f]	Blue LED	-	14	63	35
6.[e]	Blue LED	Biphenyl (5)	16	55	15
7.[e]	Blue LED	Sodium azide (5)	72	-	5
8.[e]	**Blue LED**	**DABCO (5)**	**14**	**79**	-
9.[e]	Blue LED	DABCO (4)	14	73	9
10.[e]	Blue LED	DABCO (3)	14	68	19
11.	Blue LED	DMAP (5)	24	52	18
12.	Blue LED	DBU (5)	36	70	-
13.	Blue LED	Et_3N (5)	48	55	25
14.	Blue LED	QN (5)	48	50	20
15.	UV light	DMAP (5)	48	-	5
16.	Green LED	DMAP (5)	72	5	3
17.[g]	-	DMAP (5)	72	-	-
18.	-	DMAP (5)	72	-	-
19.[h]	Blue LED	DMAP (5)	24	-	39
20.[i]	Blue LED	DMAP (5)	24	-	5

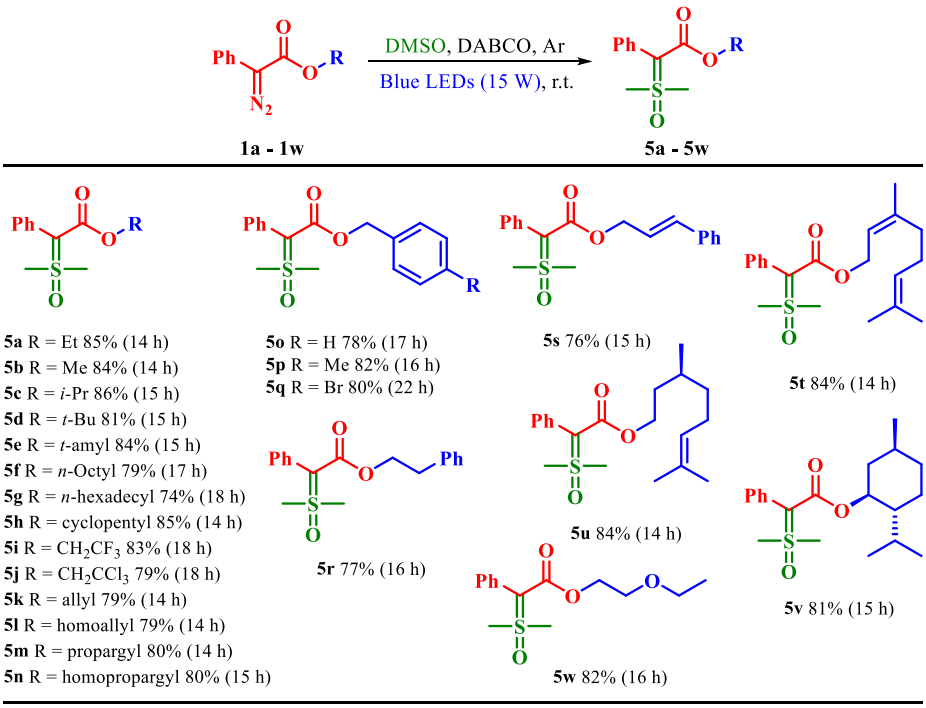
Reaction condition: [a]0.2 mmol of **1a** in 10 equivalent of **DMSO** in 1 mL **DCM** solvent at room temperature, Blue LED (15 W), [b]Isolated yield of **2a** and **6**, [c]20 equivalent of DMSO, [d]50 equivalent of DMSO, [e]Neat DMSO solvent instead of DCM, [f]reaction mixture was degassed by freeze-pump thaw method. [g]at 45 °C, [h]Under the oxygen balloon, [i]1:1 DMSO and H_2O, Green LED (15 W)

To verify whether or not DABCO plays any other important role as a nucleophilic base during the course of this transformation, we screened a few different tertiary amines. α-Phenyl-α-diazo ethyl acetate **1a** and DMSO on treatment with DMAP (5 equivalent) under irradiation of blue light (15 W) afforded the corresponding desired product **5a** along with the α-phenyl-α-keto ester

6 (Table 2.1, entry 11). It is also noteworthy to highlight that the DBU as an additive exclusively furnished the desired product in 70% yield though in relatively long reaction time under the blue light irradiation (36 h, Table 2.1, entry 12). While reaction in presence of additives such as quinuclidine and triethylamine furnished the mixture of **5a** and **6** (Table 2.1, entries 13, 14). Interestingly, the reaction of **1a** under UV as well as green light irradiation while maintaining other reaction conditions did not prove to be beneficial (Table 2.1 entries 15, 16). While the reaction of **1a** in absence of light (dark condition) and also at elevated temperature did not work (Table 2.1 entries 17, 18). These results indicated that visible blue light is very essential for smooth transformation. While the reaction of **1a** in presence of an oxygen atmosphere afforded the corresponding keto ester **6** and the reaction with water (50% in DMSO) did not furnish the desired product **5a** and afforded a trace amount of **6** (Table 2.1. Entries 19, 20). We observed that the usage of DABCO and blue LED (15 W) are beneficial to obtain the desired product **5a** exclusively. Based on our exhaustive as well systematic screening, α-phenyl-α-diazo ethyl acetate **1a**, DABCO (5 equiv.), in dry DMSO as neat solvent and as a reagent, blue LED (15 W) under inert atmosphere at room temperature (monitored) proved to be the optimum reaction condition to synthesize the sulfoxonium ylide **5a**.

Having obtained the optimized reaction conditions, we set out for the synthesis of various sulfoxonium ylides by varying ester moiety as well as aryl group in the α-aryl-α-diazo esters to generalize the protocol for wider utility. The reaction of α-phenyl-α-diazo methyl acetate **1b** under the optimized reaction conditions afforded the corresponding sulfoxonium ylide **5b** in very good yield (84% Scheme 2.8). While the α-phenyl-α-diazo esters having secondary, tertiary alkyl groups on the ester part such as *iso*-propyl, *tert*-butyl, and *tert*-amyl have reacted smoothly under the reaction conditions to afford the corresponding products **5c**, **5d**, and **5e** in very good yields and we did not observe any intramolecular C–H insertion type of the products which otherwise are known to react under blue light conditions (Scheme 2.8).[5a] The α-phenyl-α-diazo esters containing long-chain alkyl groups such as *n*-octyl as well as *n*-hexadecyl reacted smoothly under the optimized reaction conditions to give the corresponding sulfoxonium ylides **5f** and **5g** in good yields. These products are very interesting as they have a polar head group and a non-polar tail part. The α-phenyl-α-diazo esters containing the cyclopentyl group also reacted well under the reaction conditions to afford the sulfoxonium ylide **5h** in very good yield. We also observed that α-phenyl-α-diazo esters having electron-withdrawing groups such as 1,1,1-

trifluoroethyl and 1,1,1-trichloroethyl groups reacted under the optimized reaction conditions to afford the corresponding sulfoxonium ylides **5i** and **5j** in very good yields (Scheme 2.8). It is very important to highlight those α-phenyl-α-diazo esters having multiple bonds at the ester part reacted smoothly to afford the corresponding sulfoxonium ylides **5k-5n** in very good yields and we did not observe any intramolecular cyclopropanation/cyclopropenation products.[25] The α-phenyl-α-diazo benzyl esters containing benzyl group with electron-donating groups as well as electron-deactivating group substituent at the para position in ester part reacted with DMSO smoothly under optimized reaction conditions to afford respective sulfoxonium ylides (**5o-5q, 5r**) in very good yields (up to 82%).



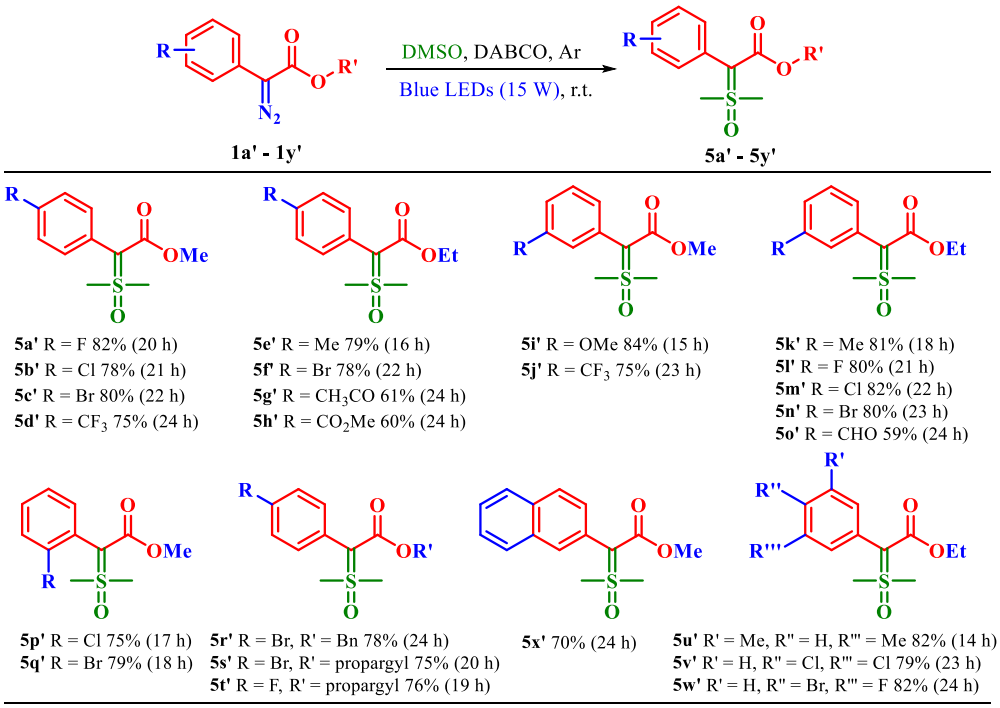
Reaction condition: **1** (0.2 mmol), DMSO (1 mL), DABCO (1 mmol), Blue LED (15 W), Under argon, r.t.

Scheme 2.8 Substrate scope and synthesis of different sulfoxonium ylides

α-Phenyl-α-diazo benzyl ester with a nucleophilic olefin (cinnamyl group) **1s** reacted with DMSO under the reaction conditions afforded the corresponding sulfoxonium ylide **5s** in very good yield (76%) and we did not observe any side product emanated from intramolecular cyclopropanation.[25] α-Phenyl-α-diazo esters prepared from naturally occurring chiral alcohols [(–)-citronellol, (–)-menthol and nerol] reacted smoothly with DMSO to afford the corresponding sulfoxonium ylides (**5t-5v**) in very good yields (Scheme 2.8). The diazo substrate derived from

ethoxy ethanol **1w** also underwent a facile transformation to afford the sulfoxonium ylide **5w** in very good yield.

Encouraged by the initial success of the synthesis of sulfoxonium ylides by varying the ester parts, we became interested to explore the reactivity of different α-aryl-α-diazo esters having varied aryl groups as well as esters (**1a'-1c', 1f', 1l'-1n', 1p'-1q'**) under the optimized reaction conditions (Scheme 2.9). α-Aryl-α-diazo esters containing aryl groups having different electron deactivating groups such as fluoro, chloro, and bromo at the *ortho*, *meta*, and *para* positions reacted smoothly with DMSO under optimized reaction conditions to furnish the corresponding sulfoxonium ylides in very good yields (**5a'-5c', 5f', 5l'-5n', 5p'-5q'**) (Scheme 2.9). While the α-aryl-α-diazo esters having an aryl group substituted with an electron-withdrawing group (**1d', 1h', 1j',** and **1o'**) reacted with DMSO to furnish the corresponding sulfoxonium ylides (**5d', 5h', 5j',** and **5o'**) in moderate to good yields (Scheme 2.9).

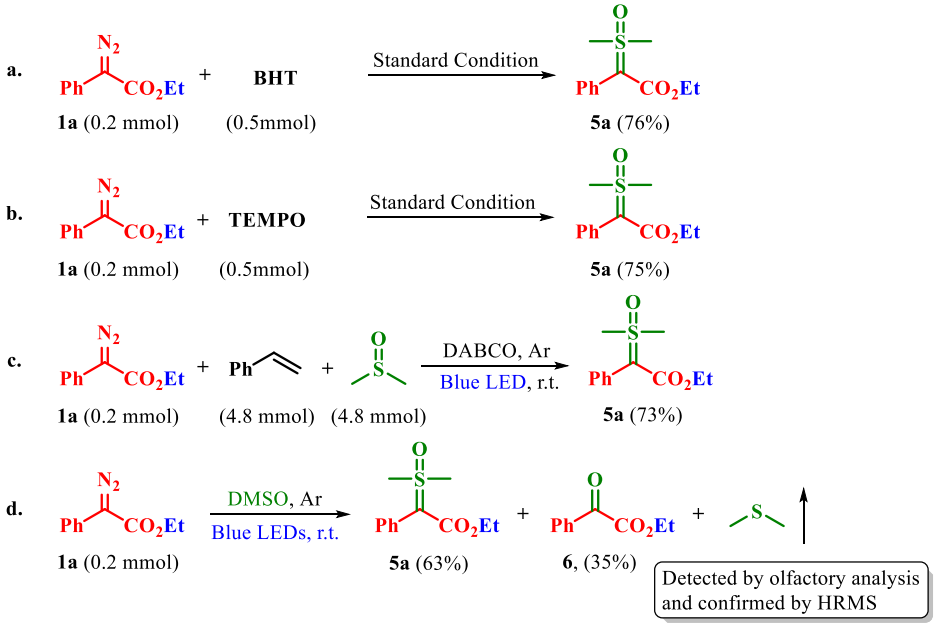


Reaction condition: **1** (0.2 mmol), DMSO (1 mL), DABCO (1 mmol), Blue LED (15 W), Under argon, r.t.

Scheme 2.9 Synthesis of sulfoxonium ylides

Also, α-aryl-α-diazo esters having keto and aldehyde moiety at the phenyl ring (**1g' and 1o'**) afforded the corresponding desired products (**5g'** and **5o'**) in moderate yields. α-Aryl-α-diazo

esters having an aryl group substituted with electron-donating groups (**1e'** and **1i)** gave the corresponding sulfoxonium ylides (**5e'**, **5i'**) in very good yields. While the α-aryl-α-diazo benzyl/propargyl esters with deactivating substituents on the aryl group reacted smoothly with DMSO to afford the desired products (**5r'-5t'**) in very good yields. The α-aryl-α-diazo esters (**1u'-5w'**) with disubstituted aryl moiety also furnished the corresponding sulfoxonium ylides (**5u'-5w')** in very good yields. The diazo compound containing the naphthyl moiety also gave the corresponding sulfoxonium ylide **5x'** in 70% yield (Scheme 2.9).

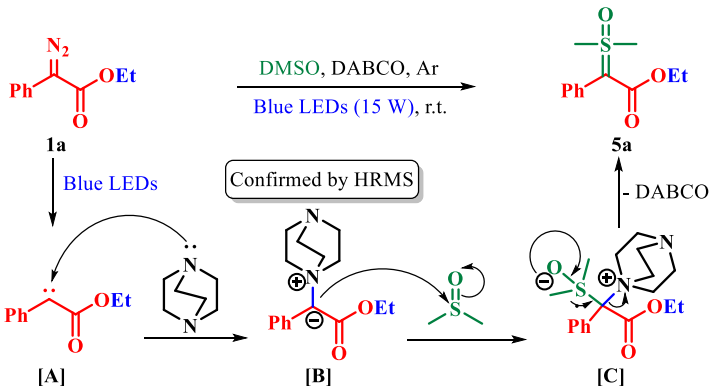


Scheme 2.10 A series of control experiments

To understand the reaction mechanism in-depth and to propose a plausible mechanistic pathway we performed a series of control experiments. To begin with, we carried out reactions of **1a** with DMSO in presence of radical scavengers such as BHT (2.5 equiv.) as well as TEMPO (2.5 equiv.) under the optimized reaction conditions (Scheme 2.10). We observed that these reactions worked well to afford the desired product **5a** in good yields and there was no inhibition. These results indicated that radical intermediate may not be involved in the pathway (Scheme 2.10a and 2.10b). Later, we carried out a reaction of α-phenyl-α-diazo ethyl acetate **1a** in presence of equimolar DMSO and styrene under the optimized reaction conditions. We observed that substrate **1a** selectively reacted with DMSO to afford the desired sulfoxonium ylide **5a** (73% yield), while the relatively nucleophilic styrene did not react with **1a** (Scheme 2.10c). and we did

not observe any cyclopropanation product. As discussed earlier, we observed that the reaction afforded the sulfoxonium ylides **5a** and keto ester **6** along with DMS as a by-product under blue light conditions (Scheme 2.10d). These results showed that DMSO is reacting with carbene through nucleophilic sulfur.

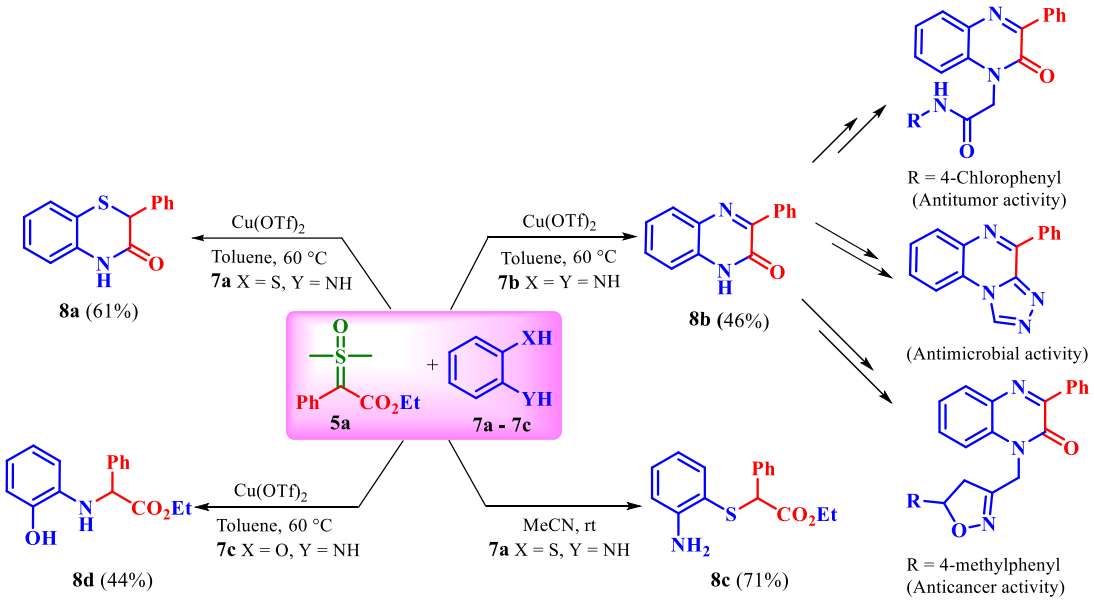
Based on our experimental observations, control experiments and preceding literature,[11-22] we have depicted a plausible reaction mechanism (Scheme 2.11). Initially, the α-phenyl-α-diazo ethyl acetate **1a** upon irradiation with visible light (blue LED) at room temperature forms a highly reactive unstable electrophilic carbene intermediate [**A**] *in situ* subsequently expulsion of stable dinitrogen. Further this intermediate [**A**] reacts with DABCO to give the corresponding negatively charged carbanionic reactive intermediate [**B**] (supported by the HMRS, page no. 48). Later this carbanion of this intermediate [**B**] reacts with DMSO to give a sterically crowded as well as highly reactive (unstable) intermediate [**C**]. This intermediate subsequently breaks down to furnish the desired product **5a** and releases DABCO (Scheme 2.11). It is also evident that from the proposed mechanism that in principle catalytic amount of DABCO could have been sufficient for the desired transformation, however, as the carbene is generating continuously (under irradiation of blue light) and to arrest the side reaction and to quench the singlet oxygen, excess DABCO might have proved to be beneficial (Scheme 2.11).



Scheme 2.11 Plausible reaction mechanism

Further, the practicability of this method has been demonstrated on a gram-scale synthesis of **5a** in very good yield (82%, See experimental section, Page no. 44). We have also employed the sulfoxonium ylide **5a** for the synthesis of different useful compounds **8a-8d** that are very useful in many transformations. The compound **8b** is an important precursor and has been utilized for

the synthesis of biologically active compounds (see scheme 2.12).[26] The compound **5a** upon treatment with 2-amino thiophenol **7a** and o-phenylenediamine **7b** independently in the presence $Cu(OTf)_2$ in toluene at an elevated temperature (60 °C) furnished the useful compound **8a** in moderate yield (61%, via S–H insertion followed by the subsequent cyclization) and **8b** in modest yield (46%, via consecutive N–H insertion, cyclization followed by aerial oxidation). The reaction of **5a** and **7a** at room temperature furnished the corresponding S–H insertion product **8c** exclusively (71% yield). Later, we carried out the reaction of **5a** with 2-amino phenol **7c** in presence of $Cu(OTf)_2$ at an elevated temperature to furnish the corresponding N–H insertion product **8d** in modest yield (44%yield).



Scheme 2.12 Application of sulfoxonium ylide

2.5 Conclusions

In summary, DABCO-mediated synthesis of sulfoxonium ylides under blue light conditions and metal-free conditions has been demonstrated. This protocol proved to be practical and user-friendly and gave access to different sulfoxonium ylides via the C–S bond constructing strategy. The protocol relied on commercially viable DABCO and DMSO using a clean energy source such as visible light. The different diazo compounds containing electron-donating, -withdrawing, and -deactivating functional groups well tolerated the reaction conditions to afford the corresponding sulfoxonium ylides in very good yields. This protocol also proved to be practical

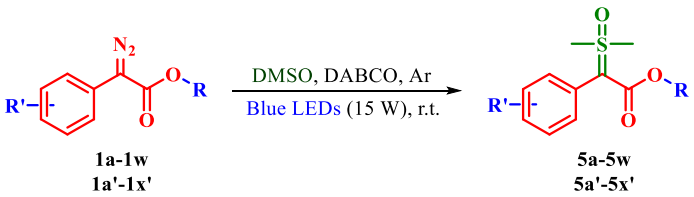
for the gram-scale synthesis of sulfoxonium ylides. These sulfoxonium ylides have also been utilized for the synthesis of useful precursors of biologically active compounds. This straightforward and practical method offers an alternative route to access very useful sulfoxonium ylides from α-aryl-α-diazoacetates.

2.6 Experimental Section

2.6.1 General

The required chemicals, reagents and solvents were purchased from commercial suppliers such as Sigma aldrich, Alfa aesar, Spectrochem, Avara, TCI, and local vendors. Further, they were used without any purification. The solvents were dried by using suitable drying agents and stored on molecular sieves. Thin-layer chromatography (TLC) was performed using silica gel 60 GF_{254} pre-coated aluminium-backed plates (2.5 mm). The visualization was accomplished by irradiation with UV light at 254 nm. The ninhydrin, vanillin, $KMnO_4$, PMA, DNP stains were utilized as staining reagents for product verifications. The column chromatography and preparative thin-layer chromatography (if needful) were performed for product purifications by using petroleum ether and ethyl acetate mixture. ^1H NMR spectra and $^{13}C\{^1H\}$ NMR spectra (proton decoupled) were recorded at 400 MHz, and 100 MHz (Bruker and Jeol) respectively. Chemical shifts (δ) are reported in ppm downfield from $CDCl_3$ (δ = 7.26 ppm) for ^1H NMR and relative to the central $CDCl_3$ resonance (δ = 77.16 ppm) for $^{13}C\{^1H\}$ NMR spectroscopy. The coupling constant (*J*) was reported in Hz and the proton couplings were described in singlet (s), doublet (d), triplet (t), quartet (q), multiplate (m), and broad (br). All the samples were analyzed by high-resolution mass spectrometry (HRMS) using ESI TOF. Melting points were measured using the BÜCHI M-560 melting point apparatus. All melting points were measured in open glass capillary and values are uncorrected.

2.6.2 General procedure A for the synthesis of (5a-5w) and (5a'-5x'):

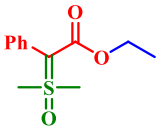


1a-1w
1a'-1x'

5a-5w
5a'-5x'

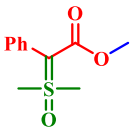
The 10 mL screw cap vial was charged with a magnetic stir bar, **1** (0.2 mmol), DABCO (0.5 mmol) and DMSO (1 mL) under an argon atmosphere. Then screw cap vial containing the reaction mixture was closed properly and kept under the irradiation of Blue LEDs (15 W) with constant stirring at r.t. (temperature was monitored) over 14 h. After the completion of the reaction (monitored by TLC), The DMSO was quenched with the ice-cold water and further, the aqueous layer was extracted with chloroform (10 mL x 3). The combined organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude product was further purified by column chromatography over silica gel using petroleum ether and ethyl acetate (30:70) to afford the corresponding sulfoxonium ylides (**5a-5w**, **5a'-5x'**).

Ethyl 2-(dimethyl(oxo)-λ^6-sulfaneylidene)-2-phenylacetate (5a):



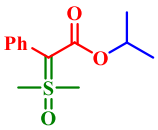
The **5a** was synthesized by following the general procedure **A**. White solid (40.7 mg 85% yield). *Rf* = 0.33 (petroleum ether/EtOAc 30:70), MP: (150.7-152.3 °C) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.21 (m, 5H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.39 (s, 6H), 1.18 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.4, 133.7, 132.7, 128.4, 127.0, 70.4, 59.0, 43.3, 14.9. HRMS (ESI) m/z: $[M+H]^+$ calculated for $[C_{12}H_{17}O_3S]^+$ 241.0893 found 241.0905.

Methyl 2-(dimethyl(oxo)-λ^6-sulfaneylidene)-2-phenylacetate (5b):



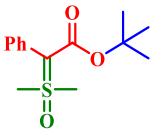
The **5b** was synthesized by following the general procedure **A**. White solid (38 mg 84% yield). *Rf* = 0.36 (petroleum ether/EtOAc 30:70), MP: (179-180.8 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 – 7.25 (m, 5H), 3.61 (s, 3H), 3.40 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 166.8, 133.8, 132.5, 128.6, 127.3, 70.3, 50.6, 43.2. HRMS (ESI) m/z: $[M+H]^+$ calculated for $[C_{11}H_{15}O_3S]^+$ 227.0736 found 227.0797.

Isopropyl 2-(dimethyl(oxo)-λ^6-sulfaneylidene)-2-phenylacetate (5c):



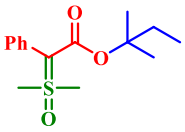
The **5c** was synthesized by following the general procedure **A**. White solid (43.6 mg 86% yield). *Rf* = 0.37 (petroleum ether/EtOAc 30:70), MP: (112-113.5 ℃). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.19 (m, 5H), 5.00 (hept, *J* = 6.3 Hz, 1H), 3.39 (s, 6H), 1.17 (d, *J* = 6.3 Hz, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.1, 133.6, 133.0, 128.3, 126.8, 70.6, 66.0, 43.5, 22.4. HRMS (ESI) m/z: $[M+H]^+$ calculated for $[C_{13}H_{19}O_3S]^+$ 255.1049 found 255.1059.

Tert-butyl 2-(dimethyl(oxo)-λ^6-sulfaneylidene)-2-phenylacetate (5d):



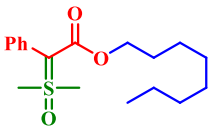
The **5d** was synthesized by following the general procedure **A**. White solid (43.5 mg 81% yield). *Rf* = 0.36 (petroleum ether/EtOAc 30:70), MP: (109.8-110.4 ℃). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.17 (m, 5H), 3.37 (s, 6H), 1.43 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.2, 133.6, 133.4, 128.2, 126.6, 79.0, 71.5, 43.6, 29.0. HRMS (ESI) m/z: $[M+H]^+$ calculated for $[C_{14}H_{21}O_3S]^+$ 269.1206 found 269.1223.

Tert-pentyl 2-(dimethyl(oxo)-λ^6-sulfaneylidene)-2-phenylacetate (5e):



The **5e** was synthesized by following the general procedure **A**. White solid (47.4 mg 84% yield). *Rf* = 0.37 (petroleum ether/EtOAc 30:70), MP: (78-79.1 ℃). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.17 (m, 5H), 3.38 (s, 6H), 1.70 (q, *J* = 7.5 Hz, 2H), 1.41 (s, 6H), 0.78 (t, *J* = 7.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.3, 133.6, 129.0, 128.2, 126.7, 81.3, 71.3, 43.5, 34.5, 26.4, 8.4. HRMS (ESI) m/z: $[M+H]^+$ calculated for $[C_{15}H_{23}O_3S]^+$ 283.1362 found 283.1365.

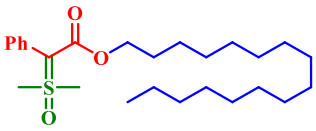
Octyl 2-(dimethyl(oxo)-λ^6-sulfaneylidene)-2-phenylacetate (5f):



The **5f** was synthesized by following the general procedure **A**. White solid (51.3 mg 79% yield). *Rf* = 0.31 (petroleum ether/EtOAc 30:70), MP: (80-81.1 ℃) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.20 (m, 5H), 4.02 (t, *J* = 6.7 Hz, 2H), 3.41 (s, 6H), 1.56 – 1.52 (m, 2H), 1.23 (s, 10H), 0.87 (t, *J* = 6.9 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.6, 133.7, 132.8, 128.4, 127.0, 70.3, 63.3, 43.4, 31.9, 29.3, 29.3, 29.2,

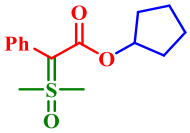
26.1, 22.8, 14.2. HRMS (ESI) m/z: $[M+H]^+$ calculated for $[C_{18}H_{29}O_3S]^+$ 325.1832 found 325.1837.

Hexadecyl 2-(dimethyl(oxo)-λ^6-sulfaneylidene)-2-phenylacetate (5g):



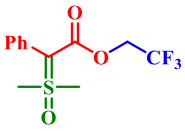
The **5g** was synthesized by following the general procedure **A**. White solid (65 mg 74% yield). *Rf* = 0.3 (petroleum ether/EtOAc 30:70), MP: (98.1-99.3 ℃) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.21 (m, 5H), 4.02 (t, *J* = 6.8 Hz, 2H), 3.41 (s, 6H), 1.56 – 1.52 (m, 2H), 1.32 – 1.19 (m, 26H), 0.88 (t, *J* = 6.9 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.6, 133.7, 132.7, 128.4, 127.0, 70.3, 63.3, 43.4, 32.1, 29.8, 29.8, 29.7, 29.5, 29.4, 29.2, 26.1, 22.8, 14.3. HRMS (ESI) m/z: $[M+H]^+$ calculated for $[C_{26}H_{45}O_3S]^+$ 437.3084 found 437.3087.

Cyclopentyl 2-(dimethyl(oxo)-λ^6-sulfaneylidene)-2-phenylacetate (5h):



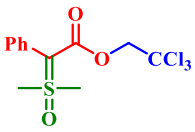
The **5h** was synthesized by following the general procedure **A**. White solid (47.5 mg 85% yield) *Rf* = 0.38 (petroleum ether/EtOAc 30:70), MP: (107.2-109 ℃). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.19 (m, 5H), 5.20 – 5.14 (m, 1H), 3.41 (s, 6H), 1.84 – 1.45 (m, 8H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.3, 133.5, 132.8, 128.8, 128.2, 126.8, 126.7, 75.5, 70.7, 43.5, 33.0, 23.8. HRMS (ESI) m/z: $[M+H]^+$ calculated for $[C_{15}H_{21}O_3S]^+$ 281.1206 found 281.1213.

2,2,2-trifluoroethyl 2-(dimethyl(oxo)-λ^6-sulfaneylidene)-2-phenylacetate (5i):



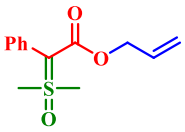
The **5i** was synthesized by following the general procedure **A**. White solid (48.9 mg 83% yield). *Rf* = 0.39 (petroleum ether/EtOAc 30:70), MP: (89.4-90.4 ℃) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.25 (m, 5H), 4.45 (dd, *J* = 16.8, 8.3 Hz, 2H), 3.41 (s, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 163.7, 133.7, 128.6, 127.6, 122.4, 71.1, 59.4, 59.1, 58.7, 58.3, 43.0. ^{19}F NMR (377 MHz, $CDCl_3$) δ -73.8. HRMS (ESI) m/z: $[M+H]^+$ calculated for $[C_{12}H_{14}F_3O_3S]^+$ 295.0610 found 295.0615.

2,2,2-trichloroethyl 2-(dimethyl(oxo)-λ^6-sulfaneylidene)-2-phenylacetate (5j):



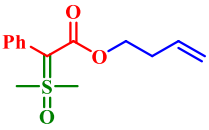
The **5j** was synthesized by following the general procedure **A**. White solid (54.5 mg 79% yield). *Rf* = 0.39 (petroleum ether/EtOAc 30:70), MP: (105.1-106.2) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.23 (m, 5H), 4.74 (s, 2H), 3.44 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 163.8, 133.8, 128.5, 127.5, 96.6, 77.2, 73.0, 71.2, 43.1. HRMS (ESI) m/z: $[M+H]^+$ calculated for $[C_{12}H_{14}Cl_3O_3S]^+$ 342.9724 found 342.9726.

Allyl 2-(dimethyl(oxo)-λ^6-sulfaneylidene)-2-phenylacetate (5k):



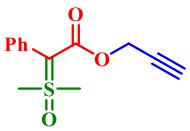
The **5k** was synthesized by following the general procedure **A**. White solid (40 mg 79% yield). *Rf* = 0.35 (petroleum ether/EtOAc 30:70), MP: (95.5-97.1 °C) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.23 (m, 5H), 5.93 – 5.82 (m, 1H), 5.16 (dd, *J* = 17.2, 1.5 Hz, 1H), 5.08 (dd, *J* = 10.5, 1.5 Hz, 1H), 4.55 (dd, *J* = 7.2, 5.7 Hz, 2H), 3.39 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.9, 133.8, 133.8, 132.5, 128.5, 127.2, 116.3, 70.5, 63.6, 43.2. HRMS (ESI) m/z: $[M+H]^+$ calculated for $[C_{13}H_{17}O_3S]^+$ 253.0898 found 253.0900.

But-3-en-1-yl 2-(dimethyl(oxo)-λ^6-sulfaneylidene)-2-phenylacetate (5l):



The **5l** was synthesized by following the general procedure **A**. White solid (42 mg 79% yield). *Rf* = 0.34 (petroleum ether/EtOAc 30:70), MP: (122.7-124.6 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.20 (m, 5H), 5.74 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H), 5.01 (dd, *J* = 13.6, 12.3 Hz, 2H), 4.09 (t, *J* = 6.7 Hz, 2H), 3.39 (s, 6H), 2.31 (q, *J* = 6.7 Hz, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.2, 134.9, 133.7, 132.6, 128.4, 127.0, 116.8, 70.5, 62.3, 43.3, 33.7. HRMS (ESI) m/z: $[M+H]^+$ calculated for $[C_{14}H_{19}O_3S]^+$ 267.1049 found 269.1054.

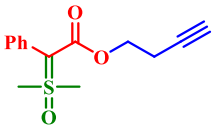
Prop-2-yn-1-yl 2-(dimethyl(oxo)-λ^6-sulfaneylidene)-2-phenylacetate (5m):



The **5m** was synthesized by following the general procedure **A**. White solid (40 mg 80% yield). *Rf* = 0.35 (petroleum ether/EtOAc 30:70), MP: (120.9-122.8 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.24 (m, 5H), 4.65 (d, *J* = 2.3 Hz,

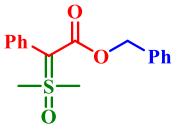
2H), 3.42 (s, 6H), 2.37 (t, *J* = 2.4 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 165.0, 133.8, 132.0, 128.6, 127.4, 79.6, 73.6, 70.7, 50.5, 43.3. HRMS (ESI) m/z: $[M+H]^+$ calculated for $[C_{13}H_{15}O_3S]^+$ 251.0736 found 251.0748.

But-3-yn-1-yl 2-(dimethyl(oxo)-λ^6-sulfaneylidene)-2-phenylacetate (5n):



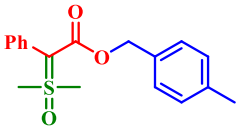
The **5n** was synthesized by following the general procedure **A**. White solid (42.4 mg 80% yield). *Rf* = 0.34 (petroleum ether/EtOAc 30:70), MP: (78-80.1 °C) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (dd, *J* = 3.4, 1.9 Hz, 4H), 7.26 (s, 1H), 4.17 (t, *J* = 6.9 Hz, 2H), 3.42 (s, 6H), 2.48 (td, *J* = 6.9, 2.6 Hz, 2H), 1.95 (t, *J* = 2.7 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 165.7, 133.7, 129.1, 128.5, 127.2, 81.2, 70.6, 69.6, 61.0, 43.4, 19.6. HRMS (ESI) m/z: $[M+H]^+$ calculated for $[C_{14}H_{17}O_3S]^+$ 265.0893 found 265.0892.

Benzyl 2-(dimethyl(oxo)-λ^6-sulfaneylidene)-2-phenylacetate (5o):



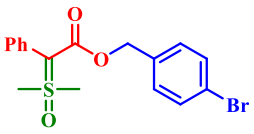
The **5o** was synthesized by following the general procedure **A**. White solid (47.2 mg 78% yield). *Rf* = 0.32 (petroleum ether/EtOAc 30:70), MP: (81-82.4 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.13 (m, 10H), 5.05 (s, 2H), 3.29 (s, 6H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 165.9, 137.8, 133.8, 132.5, 128.5, 128.3, 127.4, 127.2, 127.2, 70.7, 64.4, 43.2. HRMS (ESI) m/z: $[M+H]^+$ calculated for $[C_{17}H_{19}O_3S]^+$ 303.1049 found 303.1055.

4-methylbenzyl 2-(dimethyl(oxo)-λ^6-sulfaneylidene)-2-phenylacetate (5p):



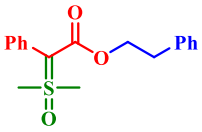
The **5p** was synthesized by following the general procedure **A**. White solid (52 mg 82% yield). *Rf* = 0.31 (petroleum ether/EtOAc 30:70), MP: (126-127.8 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.22 (m, 4H), 7.21 – 7.16 (m, 1H), 7.09 (d, *J* = 7.9 Hz, 2H), 7.03 (d, *J* = 7.9 Hz, 2H), 5.02 (s, 2H), 3.31 (s, 6H), 2.25 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 166.0, 137.1, 134.8, 133.8, 132.6, 129.1, 128.5, 127.5, 127.2, 70.6, 64.5, 43.3, 21.2. HRMS (ESI) m/z: $[M+H]^+$ calculated for $[C_{18}H_{21}O_3S]^+$ 317.1206 found 317.1206.

4-bromobenzyl 2-(dimethyl(oxo)-λ^6-sulfaneylidene)-2-phenylacetate (5q):



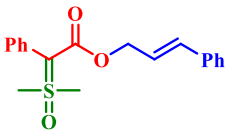
The **5q** was synthesized by following the general procedure **A**. White solid (61 mg 80% yield). *Rf* = 0.34 (petroleum ether/EtOAc 30:70), MP: (147.3-147.9 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.4 Hz, 2H), 7.34 – 7.26 (m, 5H), 7.11 (d, *J* = 8.1 Hz, 2H), 5.05 (s, 2H), 3.39 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.7, 137.0, 133.8, 132.4, 131.5, 129.0, 128.6, 127.4, 121.3, 70.8, 63.7, 43.2. HRMS (ESI) m/z: $[M+H]^+$ calculated for $[C_{17}H_{18}BrO_3S]^+$ 381.0155 found 381.0160.

Phenethyl 2-(dimethyl(oxo)-λ^6-sulfaneylidene)-2-phenylacetate (5r):



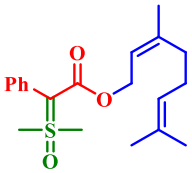
The **5r** was synthesized by following the general procedure **A**. White solid (48.7 mg 77% yield). *Rf* = 0.33 (petroleum ether/EtOAc 30:70), MP: (106.5-108.5 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.08 (m, 10H), 4.26 (t, *J* = 6.8 Hz, 2H), 3.35 (s, 6H), 2.86 (t, *J* = 6.8 Hz, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.2, 138.9, 133.9, 132.6, 129.3, 128.4, 128.3, 127.2, 126.3, 70.4, 63.8, 43.2, 35.7. HRMS (ESI) m/z: $[M+H]^+$ calculated for $[C_{18}H_{21}O_3S]^+$ 317.1206 found 317.1205.

Cinnamyl 2-(dimethyl(oxo)-λ^6-sulfaneylidene)-2-phenylacetate (5s):



The **5s** was synthesized by following the general procedure **A**. White solid (50 mg 76% yield). *Rf* = 0.35 (petroleum ether/EtOAc 30:70), MP: (113.7-115.3 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.10 (m, 10H), 6.44 (d, *J* = 15.9 Hz, 1H), 6.19 (dt, *J* = 15.9, 5.8 Hz, 1H), 4.65 (dd, *J* = 5.8, 1.3 Hz, 2H), 3.35 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.7, 136.6, 133.5, 132.2, 131.9, 128.3, 128.2, 127.4, 127.0, 126.3, 124.9, 70.3, 63.2, 43.0. HRMS (ESI) m/z: $[M+H]^+$ calculated for $[C_{19}H_{21}O_3S]^+$ 329.1206 found 329.1219.

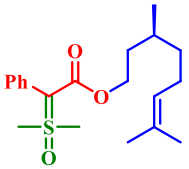
(Z)-3,7-dimethylocta-2,6-dien-1-yl 2-(dimethyl(oxo)-λ^6-sulfaneylidene)-2-phenylacetate (5t):



The **5t** was synthesized by following the general procedure **A**. White solid (58.5 mg 84% yield). *Rf* = 0.38 (petroleum ether/EtOAc 30:70), MP: (59.1-60.6 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.26 (m, 4H), 7.25 – 7.19 (m, 1H), 5.30 (t, *J* = 6.5 Hz, 1H), 5.06 (dt, *J* = 2.8, 1.4 Hz, 1H), 4.56 (dd, *J* = 6.8, 0.6 Hz, 2H),

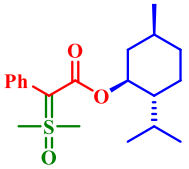
3.39 (s, 6H), 2.10 – 1.98 (m, 4H), 1.70 (d, *J* = 1.2 Hz, 3H), 1.65 (d, *J* = 0.8 Hz, 3H), 1.56 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 166.3, 140.3, 133.7, 132.7, 131.9, 128.4, 127.0, 124.0, 121.0, 77.2, 70.4, 59.9, 43.4, 32.3, 26.7, 25.8, 23.6, 17.8. HRMS (ESI) m/z: $[M+H]^+$ calculated for $[C_{20}H_{29}O_3S]^+$ 349.1832 found 349.1838.

(R)-3,7-dimethyloct-6-en-1-yl 2-(dimethyl(oxo)-λ^6-sulfaneylidene)-2-phenylacetate (5u):



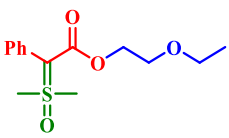
The **5u** was synthesized by following the general procedure **A**. White solid (58.9 mg 84% yield). *Rf* = 0.37 (petroleum ether/EtOAc 30:70), MP: (43.3-45.1 ℃). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.20 (m, 5H), 5.07 – 5.02 (m, 1H), 4.12 – 4.00 (m, 2H), 3.41 (s, 6H), 1.97 – 1.85 (m, 2H), 1.68 – 1.11 (m, 11H), 0.83 (d, *J* = 6.5 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 166.5, 133.7, 132.7, 131.2, 128.4, 127.0, 124.9, 70.4, 61.7, 43.3, 37.2, 36.0, 29.8, 25.8, 25.6, 19.5, 17.8. HRMS (ESI) m/z: $[M+H]^+$ calculated for $[C_{20}H_{31}O_3S]^+$ 351.1988 found 351.1998.

(1S,2R,5S)-2-isopropyl-5-methylcyclohexyl 2-(dimethyl(oxo)-λ^6-sulfaneylidene)-2-phenylacetate (5v):



The **5v** was synthesized by following the general procedure **A**. White solid (56.5 mg 81% yield). *Rf* = 0.33 (petroleum ether/EtOAc 30:70), MP: (132.5-134.7 ℃) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.18 (m, 5H), 4.62 (td, *J* = 10.8, 4.3 Hz, 1H), 3.39 (d, *J* = 17.4 Hz, 6H), 2.12 – 2.01 (m, 1H), 1.83 (dtd, *J* = 13.9, 6.9, 2.6 Hz, 1H), 1.66 – 1.55 (m, 2H), 1.51 – 1.38 (m, 1H), 1.27 – 1.14 (m, 1H), 1.08 – 0.98 (m, 1H), 0.98 – 0.90 (m, 1H), 0.89 – 0.72 (m, 10H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 166.2, 133.8, 132.9, 128.2, 126.9, 70.6, 47.3, 43.3, 41.7, 34.5, 31.6, 26.3, 23.7, 22.2, 20.9, 16.6. HRMS (ESI) m/z: $[M+H]^+$ calculated for $[C_{20}H_{31}O_3S]^+$ 351.1988 found 351.2000.

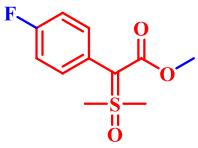
2-ethoxyethyl 2-(dimethyl(oxo)-λ^6-sulfaneylidene)-2-phenylacetate (5w):



The **5w** was synthesized by following the general procedure **A**. White solid (46.6 mg 82% yield). *Rf* = 0.39 (petroleum ether/EtOAc 30:70), MP: (76.0-78.1 ℃). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.22 (m, 5H), 4.20 (t, *J* = 5.0 Hz, 2H), 3.62 – 3.56 (m, 2H), 3.45 (dd, *J* = 8.7, 5.3 Hz, 2H), 3.40 (d, *J* = 1.4 Hz, 6H), 1.13 (t, *J* = 7.0 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 165.9, 133.7, 132.7, 128.4, 127.1, 70.5, 68.9,

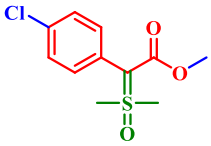
66.5, 62.5, 43.5, 15.3. HRMS (ESI) m/z: $[M+H]^+$ calculated for $[C_{14}H_{21}O_4S]^+$ 285.1155 found 285.1167.

Methyl 2-(dimethyl(oxo)-λ^6-sulfaneylidene)-2-(4-fluorophenyl)acetate (5a'):



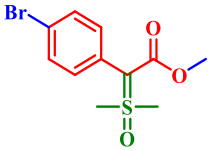
The **5a'** was synthesized by following the general procedure **A**. White solid (40 mg 82% yield). *Rf* = 0.31 (petroleum ether/EtOAc 30:70), MP: (119.2-111.1 ℃) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.22 (m, 2H), 7.04 – 6.97 (m, 2H), 3.60 (s, 3H), 3.40 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.7, 163.4, 161.0, 135.7, 135.6, 128.2, 115.6, 115.4, 68.7, 50.6, 43.3. ^{19}F NMR (377 MHz, $CDCl_3$) δ -114.9. HRMS (ESI) m/z: $[M+H]^+$ calculated for $[C_{11}H_{14}FO_3S]^+$ 245.0647 found 245.0644.

Methyl 2-(4-chlorophenyl)-2-(dimethyl(oxo)-λ^6-sulfaneylidene)acetate (5b'):



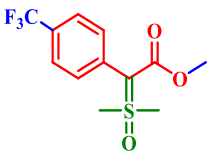
The **5b'** was synthesized by following the general procedure **A**. White solid (40.6 mg 78% yield). *Rf* = 0.31 (petroleum ether/EtOAc 30:70). MP: (168.2-169.9 ℃). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 3.61 (s, 3H), 3.43 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.5, 134.9, 133.1, 130.9, 128.7, 68.7, 50.6, 43.4. HRMS (ESI) m/z: $[M+H]^+$ calculated for $[C_{11}H_{14}ClO_3S]^+$ 261.0347 found 261.0344.

Methyl 2-(4-bromophenyl)-2-(dimethyl(oxo)-λ^6-sulfaneylidene)acetate (5c'):



The **5c'** was synthesized by following the general procedure **A**. White solid (49 mg 80% yield). *Rf* = 0.31 (petroleum ether/EtOAc 30:70). MP: (181.0-182.2 ℃). ^{1}H NMR (400 MHz, DMSO-D_6) δ 7.49 – 7.43 (m, 2H), 7.18 – 7.12 (m, 2H), 3.45 (s, 3H), 3.35 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-D_6) δ 164.8, 135.4, 132.9, 130.8, 119.4, 69.9, 49.6, 41.9. HRMS (ESI) m/z: $[M+H]^+$ calculated for $[C_{11}H_{14}BrO_3S]^+$ 304.9842 found 304.9848.

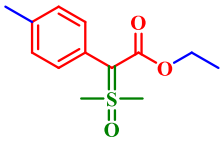
Methyl 2-(dimethyl(oxo)-λ^6-sulfaneylidene)-2-(4-(trifluoromethyl)phenyl)acetate (5d'):



The **5d'** was synthesized by following the general procedure **A**. White solid (44 mg 75% yield). *Rf* = 0.35 (petroleum ether/EtOAc 30:70). MP: (170.2-

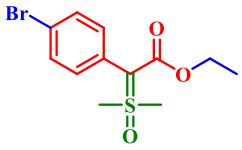
172.1 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.2 Hz, 2H), 7.42 (d, *J* = 8.1 Hz, 2H), 3.63 (s, 3H), 3.47 (s, 6H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 166.2, 136.4, 133.1, 128.5, 128.2, 125.8, 125.2, 125.1, 123.1, 120.4, 68.8, 50.7, 43.7. ^{19}F NMR (377 MHz, $CDCl_3$) δ -62.4. HRMS (ESI) m/z: $[M+H]^+$ calculated for $[C_{12}H_{14}F_3O_3S]^+$ 295.0610 found 295.0622.

Ethyl 2-(dimethyl(oxo)-λ^6-sulfaneylidene)-2-(p-tolyl)acetate (5e'):



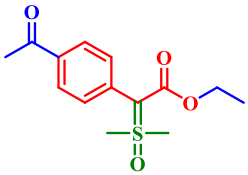
The **5e'** was synthesized by following the general procedure **A**. White solid (40 mg 79%). *Rf* = 0.33 (petroleum ether/EtOAc 30:70). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 – 7.15 (m, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.38 (s, 6H), 2.33 (s, 3H), 1.18 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 166.6, 136.9, 133.7, 129.5, 129.3, 70.0, 58.9, 43.2, 21.3, 14.9. HRMS (ESI) m/z: $[M+H]^+$ calculated for $[C_{13}H_{19}O_3S]^+$ 255.1049 found 255.1064.

Ethyl 2-(4-bromophenyl)-2-(dimethyl(oxo)-λ^6-sulfaneylidene)acetate (5f'):



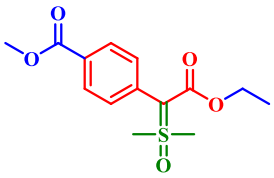
The **5f'** was synthesized by following the general procedure **A**. White solid (49.8 mg 78%). *Rf* = 0.33 (petroleum ether/EtOAc 30:70). MP: (181.0-182.2 °C) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.40 (m, 2H), 7.20 – 7.15 (m, 2H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.43 (s, 6H), 1.19 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 166.1, 135.0, 131.6, 131.5, 120.9, 68.8, 59.1, 43.6, 14.9. HRMS (ESI) m/z: $[M+H]^+$ calculated for $[C_{12}H_{16}BrO_3S]^+$ 318.9998 found 319.0002.

Ethyl 2-(4-acetylphenyl)-2-(dimethyl(oxo)-λ^6-sulfaneylidene)acetate (5g'):



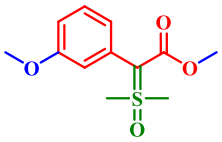
The **5g'** was synthesized by following the general procedure **A**. White solid (34.4 mg 61%). MP: (148.2-150.1 °C) *Rf* = 0.38 (petroleum ether/EtOAc 30:70). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.2 Hz, 2H), 7.41 (d, *J* = 8.1 Hz, 2H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.49 (s, 6H), 2.58 (s, 3H), 1.23 – 1.19 (m, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 197.9, 165.8, 138.2, 134.5, 132.3, 128.2, 69.48, 59.3, 43.9, 26.7, 14.8. HRMS (ESI) m/z: $[M+H]^+$ calculated for $[C_{14}H_{19}O_4S]^+$ 283.0999 found 283.1008.

Methyl 4-(1-(dimethyl(oxo)-λ^6-sulfaneylidene)-2-ethoxy-2-oxoethyl)benzoate (5h'):



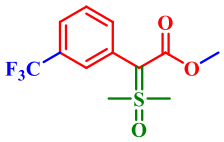
The **5h'** was synthesized by following the general procedure **A**. White solid (36 mg 60%). *Rf* = 0.39 (petroleum ether/EtOAc 30:70). MP: (122.8-124.6 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.3 Hz, 1H), 7.38 (d, *J* = 8.3 Hz, 1H), 4.10 (q, *J* = 7.1 Hz, 1H), 3.89 (s, 1H), 3.46 (s, 2H), 1.19 (t, *J* = 7.1 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.2, 165.8, 138.0, 132.3, 129.4, 127.6, 69.7, 59.2, 52.1, 43.8, 14.8. HRMS (ESI) m/z: $[M+H]^+$ calculated for $[C_{14}H_{19}O_5S]^+$ 299.0948 found 299.0952.

Methyl 2-(dimethyl(oxo)-λ^6-sulfaneylidene)-2-(3-methoxyphenyl)acetate (5i'):



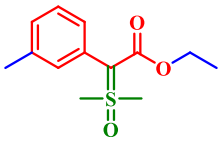
The **5i'** was synthesized by following the general procedure **A**. White solid (43 mg 84% yield) *Rf* = 0.26 (petroleum ether/EtOAc 30:70). MP: (121.5-123 °C) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.21 (m, 1H), 6.90 (d, *J* = 7.6 Hz, 1H), 6.87 (s, 1H), 6.83 (d, *J* = 8.3 Hz, 1H), 3.80 (s, 3H), 3.61 (s, 3H), 3.41 (s, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.8, 159.6, 133.8, 129.4, 126.2, 119.4, 113.0, 55.4, 50.7, 43.2. HRMS (ESI) m/z: $[M+H]^+$ calculated for $[C_{12}H_{17}O_4S]^+$ 257.0842 found 257.0850.

Methyl 2-(dimethyl(oxo)-λ^6-sulfaneylidene)-2-(3-(trifluoromethyl)phenyl)acetate (5j'):



The **5j'** was synthesized by following the general procedure **A**. White solid (44 mg 75%). *Rf* = 0.31 (petroleum ether/EtOAc 30:70). MP: (169.1-171.0 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (s, 1H), 7.50 – 7.46 (m, 2H), 7.41 (dd, *J* = 9.4, 5.8 Hz, 1H), 3.62 (s, 3H), 3.46 (s, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.3, 136.6, 133.2, 130.8, 130.5, 130.1, 130.0, 128.7, 125.6, 123.5, 123.5, 122.9, 68.5, 50.7, 43.6. ^{19}F NMR (377 MHz, $CDCl_3$) δ -72.4. HRMS (ESI) m/z: $[M+H]^+$ calculated for $[C_{12}H_{14}F_3O_3S]^+$ 295.0610 found 295.0612

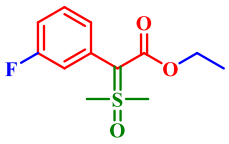
Ethyl 2-(dimethyl(oxo)-λ^6-sulfaneylidene)-2-(m-tolyl)acetate (5k'):



The **5k'** was synthesized following the general procedure **A**. White solid (41.3 mg 81% yield). *Rf* = 0.34 (petroleum ether/EtOAc 30:70). MP: (121.6-122.2 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 – 7.17 (m, 1H), 7.12 (s, 1H), 7.09 (d,

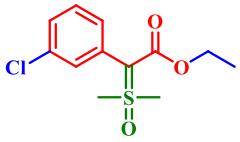
J = 7.9 Hz, 1H), 7.05 (d, *J* = 7.3 Hz, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.33 (s, 6H), 2.32 (s, 3H), 1.18 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 166.4, 137.9, 134.4, 132.5, 130.8, 128.3, 128.0, 70.5, 58.9, 43.3, 21.5, 14.9. HRMS (ESI) m/z: $[M+H]^+$ calculated for $[C_{13}H_{19}O_3S]^+$ 255.1049 found 255.1064.

Ethyl 2-(dimethyl(oxo)-λ^6-sulfaneylidene)-2-(3-fluorophenyl)acetate (5l'):



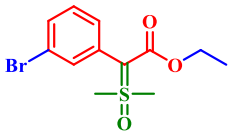
The **5l'** was synthesized by following the general procedure **A**. White solid (41.3 mg 80% yield). *Rf* = 0.38 (petroleum ether/EtOAc 30:70). MP: (127.2-128.8 °C) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (dt, *J* = 8.0, 4.1 Hz, 1H), 7.12 (d, *J* = 7.8 Hz, 1H), 7.09 – 7.04 (m, 1H), 6.99 – 6.93 (m, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.47 (s, 6H), 1.23 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 166.0, 163.8, 161.3, 134.8, 129.4, 129.3, 128.9, 120.2, 120.0, 113.8, 113.6, 69.4, 59.1, 43.5, 14.8. ^{19}F NMR (377 MHz, $CDCl_3$) δ -11.90. HRMS (ESI) m/z: $[M+H]^+$ calculated for $[C_{12}H_{16}FO_3S]^+$ 259.0799 found 259.0812.

Ethyl 2-(3-chlorophenyl)-2-(dimethyl(oxo)-λ^6-sulfaneylidene)acetate (5m'):



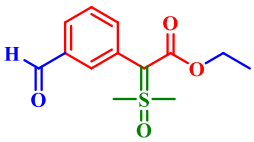
The **5m'** was synthesized by following the general procedure **A**. White solid (45 mg 82% yield). *Rf* = 0.38 (petroleum ether/EtOAc 30:70). MP: (82.1-84.1°C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (t, *J* = 1.7 Hz, 1H), 7.23 – 7.17 (m, 3H), 4.10 (q, *J* = 7.2 Hz, 2H), 3.43 (s, 6H), 1.20 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 166.0, 134.4, 133.8, 133.3, 131.5, 129.3, 126.9, 69.2, 59.2, 43.6, 14.8. HRMS (ESI) m/z: $[M+H]^+$ calculated for $[C_{12}H_{16}ClO_3S]^+$ 275.0503 found 275.0518.

Ethyl 2-(3-bromophenyl)-2-(dimethyl(oxo)-λ^6-sulfaneylidene)acetate (5n'):



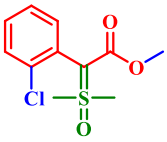
The **5n'** was synthesized by following the general procedure **A**. White solid (51 mg 80% yield). *Rf* = 0.38 (petroleum ether/EtOAc 30:70). MP: (42.3-45.2 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (t, *J* = 1.8 Hz, 1H), 7.33 (ddd, *J* = 7.9, 2.0, 1.2 Hz, 1H), 7.24 – 7.20 (m, 1H), 7.15 (t, *J* = 7.8 Hz, 1H), 4.08 (dt, m, 2H), 3.41 (s, 6H), 1.21 – 1.15 (m, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 166.0, 136.1, 134.7, 131.9, 129.7, 129.6, 122.0, 77.2, 69.2, 59.1, 43.5, 14.8. HRMS (ESI) m/z: $[M+H]^+$ calculated for $[C_{12}H_{16}BrO_3S]^+$ 319.9998 found 319.0009.

Ethyl 2-(dimethyl(oxo)-λ^6-sulfaneylidene)-2-(3-formylphenyl)acetate (5o'):



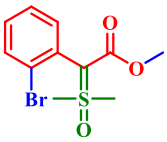
The **5o'** was synthesized by following the general procedure **A**. White solid (31.6 mg 59% yield). *Rf* = 0.30 (petroleum ether/EtOAc 30:70). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.98 (s, 1H), 7.80 (t, *J* = 1.6 Hz, 1H), 7.72 (dt, *J* = 7.6, 1.4 Hz, 1H), 7.57 (ddd, *J* = 7.7, 1.8, 1.3 Hz, 1H), 7.47 – 7.43 (m, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.46 (s, 6H), 1.19 (t, *J* =7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 192.6, 166.0, 139.3, 136.5, 134.8, 133.6, 128.8, 127.6, 68.2, 59.2, 43.8, 14.8. HRMS (ESI) m/z: $[M+H]^+$ calculated for $[C_{13}H_{17}O_4S]^+$ 269.0842 found 269.0857.

Methyl 2-(2-chlorophenyl)-2-(dimethyl(oxo)-λ^6-sulfaneylidene)acetate (5p'):



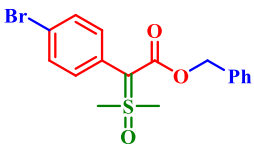
The **5p'** was synthesized by following the general procedure **A**. White solid (39 mg 75% yield). *Rf* = 0.29 (petroleum ether/EtOAc 30:70). MP: (153.2-154.2 ℃). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.38 (m, 2H), 7.26 – 7.22 (m, 2H), 3.63 (s, *J* = 28.3 Hz, 3H), 3.56 (s, 3H), 3.14 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.9, 139.2, 137.4, 131.0, 129.7, 127.1, 66.1, 50.7, 43.4, 41.5. HRMS (ESI) m/z: $[M+H]^+$ calculated for $[C_{11}H_{14}ClO_3S]^+$ 261.0347 found 261.03852.

Methyl 2-(2-bromophenyl)-2-(dimethyl(oxo)-λ^6-sulfaneylidene)acetate (5q'):



The **5q'** was synthesized by following the general procedure **A**. White solid (50.4 mg 79% yield). *Rf* = 0.30 (petroleum ether/EtOAc 30:70). MP: (168.2-168.9 ℃). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.44 (d, *J* = 7.0 Hz, 1H), 7.30 (td, *J* = 7.5, 1.3 Hz, 1H), 7.17 (td, *J* = 7.8, 1.8 Hz, 1H), 3.68 (s, 3H), 3.58 (s, 3H), 3.12 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.7, 137.3, 133.0, 131.4, 129.9, 127.8, 50.6, 43.4, 41.3. HRMS (ESI) m/z: $[M+H]^+$ calculated for $[C_{11}H_{14}BrO_3S]^+$ 304.9842 found 304.9848.

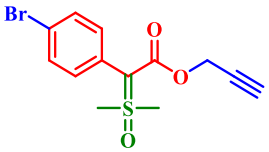
Benzyl 2-(4-bromophenyl)-2-(dimethyl(oxo)-λ^6-sulfaneylidene)acetate (5r'):



The **5r'** was synthesized by following the general procedure **A**. White solid (59.5 mg 78% yield). *Rf* = 0.38 (petroleum ether/EtOAc 30:70). MP: (107.0-108.9 ℃). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.4 Hz, 1H), 7.34 – 7.26 (m, 3H), 7.11 (d, *J* = 8.1 Hz, 1H), 5.05 (s, 1H), 3.39 (s, 3H). ^{13}C{^{1}H} NMR (100

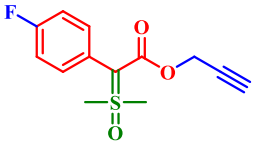
MHz, $CDCl_3$) δ 165.7, 137.0, 133.8, 132.4, 131.5, 129.0, 128.6, 127.4, 121.3, 70.8, 63.7, 43.2. HRMS (ESI) m/z: $[M+H]^+$ calculated for $[C_{17}H_{18}BrO_3S]^+$ 381.0155 found 381.0169.

Prop-2-yn-1-yl 2-(4-bromophenyl)-2-(dimethyl(oxo)-λ^6-sulfaneylidene)acetate (5s'):



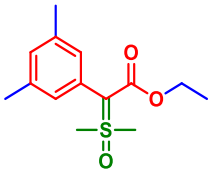
The **5s'** was synthesized by following the general procedure **A**. White solid (49.4 mg 75% yield). *Rf* = 0.38 (petroleum ether/EtOAc 30:70). MP: (164.2-166.3 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.42 (m, 2H), 7.22 – 7.16 (m, 2H), 4.65 (d, *J* = 2.2 Hz, 2H), 3.44 (s, 6H), 2.38 (t, *J* = 2.4 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 164.7, 135.2, 131.6, 130.9, 121.4, 79.4, 73.8, 60.5, 50.6, 43.5. HRMS (ESI) m/z: $[M+H]^+$ calculated for $[C_{13}H_{14}BrO_3S]^+$ 328.9842 found 328.9855.

Prop-2-yn-1-yl 2-(dimethyl(oxo)-λ^6-sulfaneylidene)-2-(4-fluorophenyl)acetate (5t'):



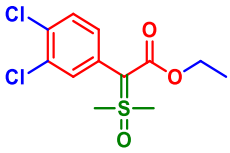
The **5t'** was synthesized by following the general procedure **A**. White solid (40.8 mg 76% yield). *Rf* = 0.35 (petroleum ether/EtOAc 30:70). MP: (148-149.6 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.26 (m, 2H), 7.04 – 6.98 (m, 2H), 4.64 (d, *J* = 1.9 Hz, 2H), 3.42 (s, 6H), 2.37 (t, *J* = 2.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 164.9, 163.5, 161.0, 135.7, 135.6, 127.6, 115.6, 115.4, 79.5, 73.7, 69.1, 50.5, 43.3. ^{19}F NMR (377 MHz, $CDCl_3$) δ -114.7. HRMS (ESI) m/z: $[M+H]^+$ calculated for $[C_{13}H_{14}FO_3S]^+$ 269.0642 found 269.0647.

Ethyl 2-(dimethyl(oxo)-λ^6-sulfaneylidene)-2-(3,5-dimethylphenyl)acetate (5u'):



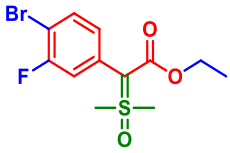
The **5u'** was synthesized by following the general procedure **A**. White solid (44 mg 82%) *Rf* = 0.39 (petroleum ether/EtOAc 30:70). MP: (79.6-81.6 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 6.92 (d, *J* = 0.4 Hz, 2H), 6.88 (s, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.38 (s, 6H), 2.28 (d, *J* = 0.5 Hz, 6H), 1.19 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.5, 137.8, 132.4, 131.6, 129.0, 70.6, 58.9, 43.3, 21.3, 14.9. HRMS (ESI) m/z: $[M+H]^+$ calculated for $[C_{14}H_{21}O_3S]^+$ 269.1206 found 269.1209.

Ethyl 2-(3,4-dichlorophenyl)-2-(dimethyl(oxo)-λ^6-sulfaneylidene)acetate (5v'):



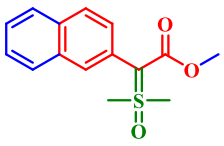
The **5v'** was synthesized by following the general procedure **A**. White solid (54 mg 79% yield). *Rf* = 0.32 (petroleum ether/EtOAc 30:70). MP: (117.9-120.1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 2.1 Hz, 1H), 7.34 (d, *J* = 8.3 Hz, 1H), 7.13 (dd, *J* = 8.3, 2.1 Hz, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.44 (s, 6H), 1.20 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.8, 134.8, 132.6, 132.5, 131.9, 130.5, 129.9, 67.8, 59.2, 43.7, 14.8. HRMS (ESI) m/z: $[M+H]^+$ calculated for $[C_{12}H_{15}Cl_2O_3S]^+$ 309.0113 found 309.0128.

Ethyl 2-(4-bromo-3-fluorophenyl)-2-(dimethyl(oxo)-λ^6-sulfaneylidene)acetate (5w'):



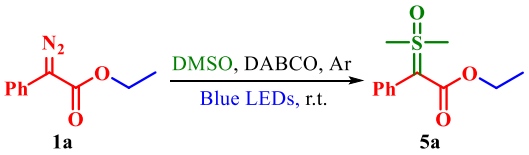
The **5w'** was synthesized by following the general procedure **A**. White solid (55.1 mg 82% yield). *Rf* = 0.32 (petroleum ether/EtOAc 30:70). MP: (136.1-138.0 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (t, *J* = 8.0 Hz, 1H), 7.09 (dd, *J* = 10.0, 2.0 Hz, 1H), 6.98 (dd, *J* = 8.3, 1.9 Hz, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.45 (s, *J* = 6.3 Hz, 6H), 1.20 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.7, 159.8, 157.4, 134.0, 133.9, 132.7, 129.8, 129.8, 121.0, 120.8, 107.0, 106.8, 68.2, 59.2, 43.7, 14.8. ^{19}F NMR (377 MHz, $CDCl_3$) δ -108.1. HRMS (ESI) m/z: $[M+H]^+$ calculated for $[C_{12}H_{15}BrFO_3S]^+$ 336.9904 found 336.9908.

Methyl 2-(dimethyl(oxo)-λ^6-sulfaneylidene)-2-(naphthalen-2-yl)acetate (5x'):



The **5x'** was synthesized by following the general procedure **A**. White solid (38.8 mg 70% yield). *Rf* = 0.4 (petroleum ether/EtOAc 30:70). MP: (145.8-147.6 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.78 (m, 4H), 7.47 – 7.44 (m, 2H), 7.41 (dd, *J* = 8.4, 1.8 Hz, 1H), 3.63 (s, 3H), 3.45 (s, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 163.2, 133.7, 133.7, 132.6, 132.2, 131.9, 130.1, 128.1, 127.7, 126.2, 77.2, 53.2, 50.7, 43.3. HRMS (ESI) m/z: $[M+H]^+$ calculated for $[C_{15}H_{17}O_3S]^+$ 277.0893 found 277.0899.

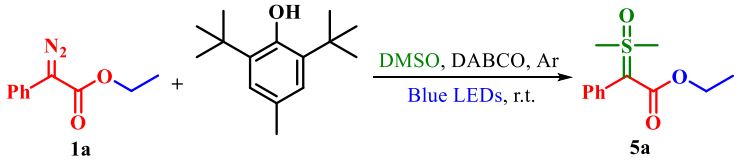
2.6.3 Gram scale synthesis of 5a



A 100 mL RB charged with a magnetic stir bar, **1a** (1g, 5.26 mmol), DABCO (2.95g 26.29 mmol) and DMSO (26.29 mL, 0.2 M) solvent under an argon atmosphere then this reaction mixture kept under the irradiation of oppositely arranged two 15 W blue LEDs bulbs. After complete consumption of starting material **1a (**monitored by TLC) reaction mixture was quenched with ice-cold water and the aqueous layer was next extracted into the chloroform solvent. The organic layer was dried over sodium sulphate salt and the solvent evaporated under reduced pressure. The impure compound was further purified by column chromatography by using ethyl acetate and hexane (70:30) mixture to afford pure **5a** (1.05 g 83% yield).

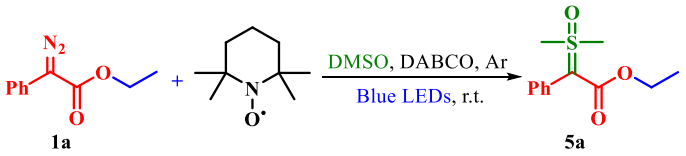
2.6.4 Control experiments

a. Reaction of 1a with BHT



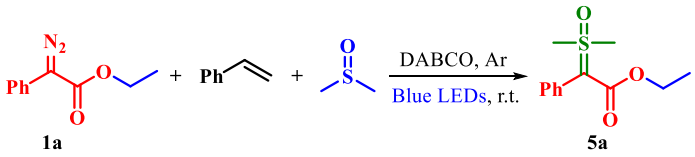
A 10 mL screw cap vial charged with a magnetic stir bar, **1a** (38.04 mg, 0.2 mmol), BHT (110.18 mg 0.5 mmol), DABCO (112.1 mg, 1 mmol) and DMSO (1 mL, 0.2M) solvent under argon atmosphere then reaction mixture kept under the irradiation of 15W Blue LED bulb with constant stirring. After complete consumption of **1a** (monitored by TLC) reaction mixture was quenched with ice-cold water and an aqueous layer was extracted into the chloroform solvent. The organic layer was dried over the sodium sulfate salt and the solvent was further evaporated under reduced pressure. The impure compound was purified by column chromatography by using ethyl acetate and hexane (70:30) as the eluant to obtain pure **5a** (36.6 mg 76% yield) and BHT was recovered as it is.

b. Reaction of 1a with TEMPO



A 10 mL screw cap vial charged with a magnetic stir bar, **1a** (38.04 mg, 0.2 mmol), TEMPO (78.12 mg 0.5 mmol), DABCO (112.1 mg, 1 mmol) and DMSO (1 mL, 0.2 M) solvent under argon atmosphere and whole reaction mixture kept under the irradiation of 15 W Blue LED. After complete consumption of **1a** (monitored by TLC) reaction mixture was quenched with ice-cold water and the aqueous layer was extracted into the chloroform solvent. The organic layer was further dried over the sodium sulfate salt and the solvent was evaporated under reduced pressure. The impure compound was purified by column chromatography to obtain pure **5a** (36 mg 75% yield) and TEMPO was recovered as it is.

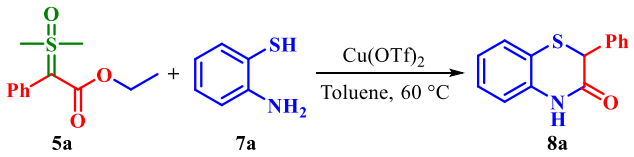
c. Reaction of 1a with an equimolar amount of DMSO and styrene



The **1a** (0.2 mmol, 38.04 mg) and DABCO (1 mmol, 112.17 mg) were added into a 10 mL screw cap vial containing equimolar amount of styrene (4.8 mmol, 549.97 mmL) and DMSO (4.8 mmol, 340.92 mmL) under argon atmosphere. Then the reaction mixture was kept under the irradiation of 15 W Blue LEDs and the reaction was monitored by TLC. After complete consumption of **1a**, the reaction mixture was quenched with ice-cold water, and the aqueous layer was extracted into the chloroform. The organic layer was dried over sodium sulfate and the solvent was removed under reduced pressure. The impure compound was further purified by column chromatography to afford pure **5a** with a 73% yield.

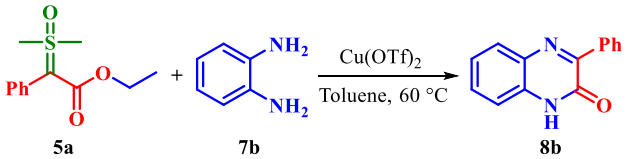
2.6.5 Further application of 5a

a. Synthesis of 2-phenyl-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one (8a):



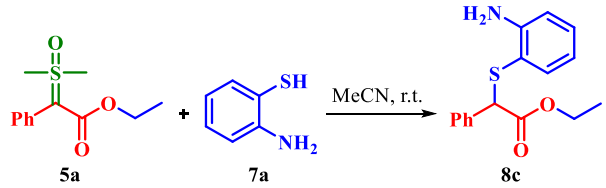
The **5a** (0.1 mmol, 24.03 mg) was treated with **7a** (0.1 mmol, 12.52 mg) in presence of $Cu(OTf)_2$ (0.01 mmol, 3.62 mg) in 1 mL toluene at 60 ℃ under an inert condition. After complete consumption of **5a** crude reaction mixture was purified by column chromatography to afford **8a** as 14.7 mg white solid in 61% yield. *Rf* = 0.51 (petroleum ether/EtOAc 80:20). MP: (206.5-207.5 °C). ^{1}H NMR (400 MHz, DMSO-D_6) δ 10.87 (s, 1H), 7.35 – 7.23 (m, 6H), 7.22 – 7.15 (m, 1H), 7.02 (d, *J* = 7.3 Hz, 1H), 6.97 (dd, *J* = 10.9, 4.2 Hz, 1H), 4.96 (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-D_6) δ 165.5, 137.0, 136.2, 128.5, 127.9, 127.8, 127.5, 127.2, 123.2, 118.1, 116.9, 44.6. HRMS (ESI) m/z: $[M+H]^+$ calculated for $[C_{14}H_{12}NOS]^+$ 242.0634 found 242.0633.

b. Synthesis of 3-phenylquinoxalin-2(1*H*)-one (8b):



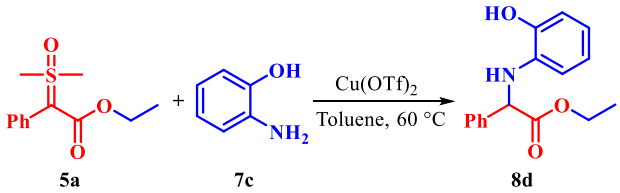
The mixture of **5a** (0.1 mmol, 24.03 mg) and **7b** (0.1 mmol, 10.81mg) was stirred in 1 mL toluene at 60 ℃ under inert condition in presence of $Cu(OTf)_2$ (0.01 mmol, 3.62 mg). After complete consumption of **5a** the crude reaction mixture was purified by column chromatography to afford **8b** as 10.3 mg yellow solid in 46% yield. *Rf* = 0.18 (petroleum ether/EtOAc 60:40). MP: (247.2-249.1 ℃). ^{1}H NMR (400 MHz, DMSO-D_6) δ 12.59 (s, 1H), 8.34 – 8.27 (m, 2H), 7.88 – 7.81 (m, 1H), 7.58 – 7.47 (m, 4H), 7.36 – 7.30 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-D_6) δ 154.6, 154.2, 135.6, 132.1, 132.0, 130.4, 130.2, 129.2, 128.8, 127.9, 123.4, 115.1. HRMS (ESI) m/z: $[M+H]^+$ calculated for $[C_{14}H_{11}N_2O]^+$ 223.0866 found 223.0862.

c. Synthesis of ethyl 2-((2-aminophenyl)thio)-2-phenylacetate (8c):



In the acetonitrile (0.1mL) both **5a** (0.1 mmol, 24.03 mg) and **7a** (0.1 mmol, 12.52 mg) were stirred in 5 mL round bottom flask at room temperature. After complete consumption of **5a** the solvent acetonitrile was removed under reduced pressure and the crude reaction mixture was further purified by using column chromatography to afford **8c** as a white solid in 20.1 mg (71% yield). *Rf* = 0.51 (petroleum ether/EtOAc 60:40). MP: (204.5-206.2 ℃). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.39 (m, 2H), 7.33 – 7.24 (m, 4H), 7.15 – 7.09 (m, 1H), 6.69 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.60 (td, *J* = 7.5, 1.3 Hz, 1H), 4.76 (s, 1H), 4.39 (s, 2H), 4.16 – 4.03 (m, 2H), 1.14 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 170.9, 149.3, 137.6, 136.1, 131.1, 128.7, 128.6, 128.3, 118.5, 115.6, 115.1, 61.8, 55.2, 14.1. HRMS (ESI) m/z: $[M+H]^+$ calculated for $[C_{16}H_{18}NO_2S]^+$ 288.1053 found 288.1064.

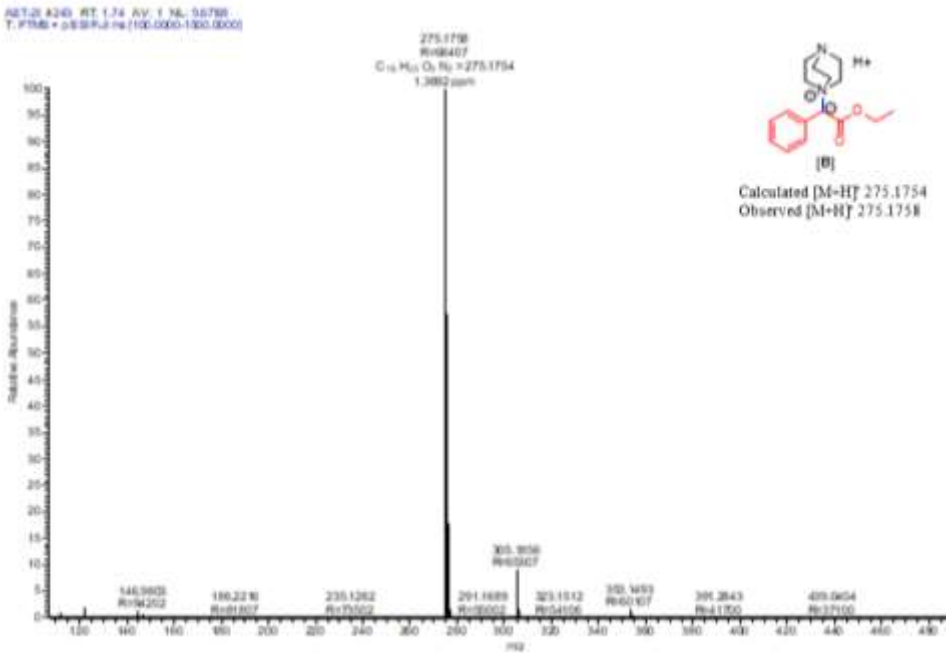
d. Synthesis of ethyl 2-((2-hydroxyphenyl)amino)-2-phenylacetate (8d):



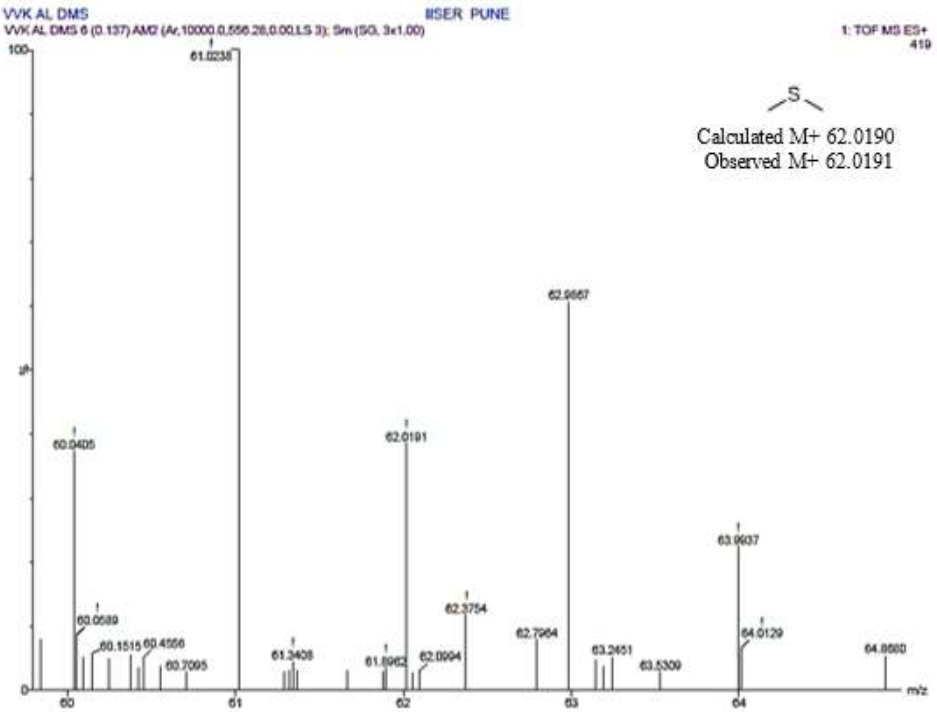
Both compound **5a (**0.1 mmol, 24.03 mg**)** and **7c** (0.1 mmol, 10.91 mg) were treated in 5 mL round bottom flask in presence of $Cu(OTf)_2$ (0.01 mmol) at 60 ℃ in 1 mL toluene. After complete consumption of **5a** the solvent were evaporated under reduced pressure and crude reaction mixture was further purified by column chromatography to afford **8d** as 12 mg white solid (44% yield). *Rf* = 0.6 (petroleum ether/EtOAc 60:40). MP: (103.4-105.6 ℃). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (dt, *J* = 3.7, 2.1 Hz, 2H), 7.38 – 7.28 (m, 3H), 6.76 – 6.71 (m, 2H), 6.62 (dd, *J* = 10.8, 4.2 Hz, 1H), 6.51 – 6.46 (m, 1H), 5.63 (s, 1H), 5.13 (s, *J* = 25.9 Hz, 1H), 5.06 (s, 1H), 4.30 – 4.11 (m, 2H), 1.25 – 1.20 (m, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 172.6, 144.4, 137.7, 135.0, 129.0, 128.4, 127.4, 121.4, 118.9, 114.8, 113.6, 62.0, 61.6, 14.2. HRMS (ESI) m/z: $[M+H]^+$ calculated for $[C_{16}H_{18}NO_3]^+$ 272.1281 found 272.1286.

2.7 Appendix I

a. HRMS of Intermediate [B]



b. HRMS of DMS



2.8 Appendix II

Table 2.2: ^{1}H, $^{13}C\{^{1}H\}$ spectral data of representative compounds

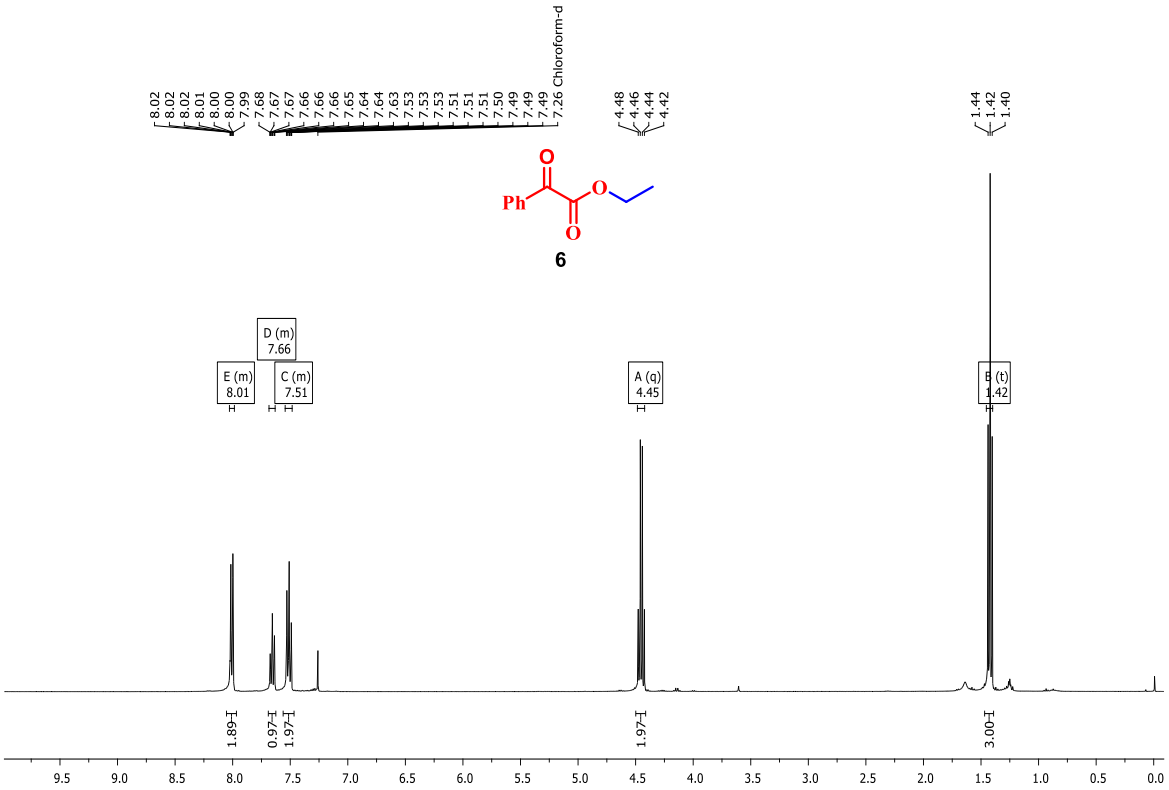


Figure 2.2 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **6**

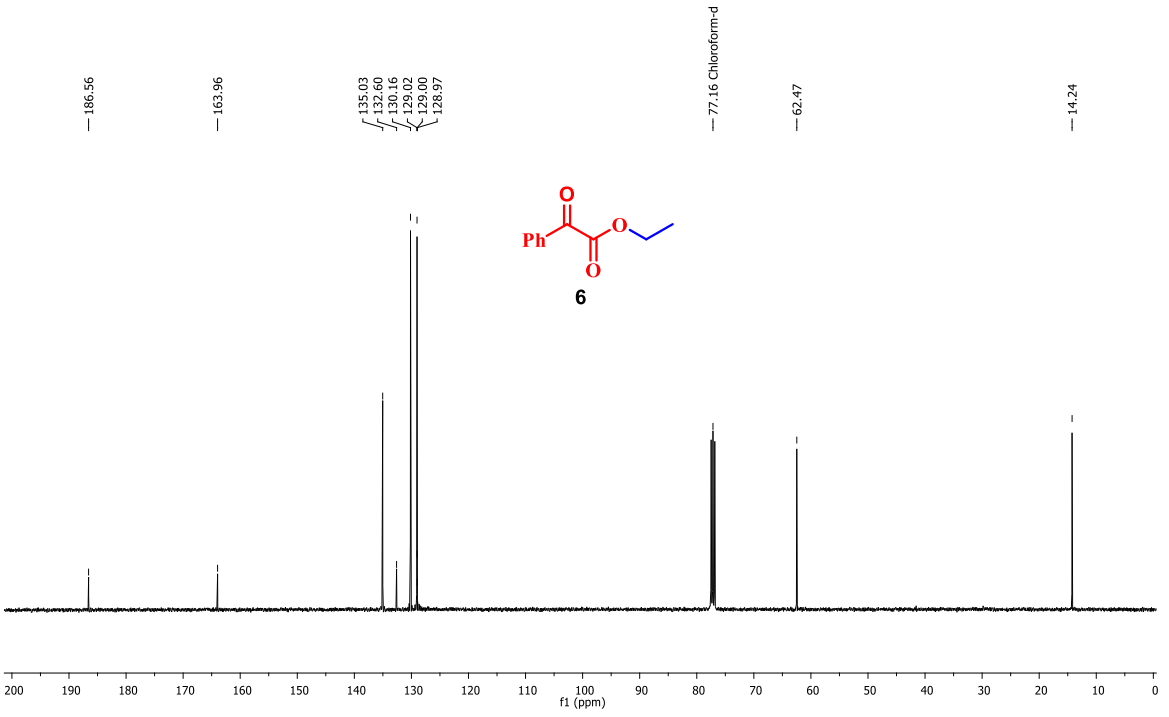


Figure 2.3 $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of compound **6**

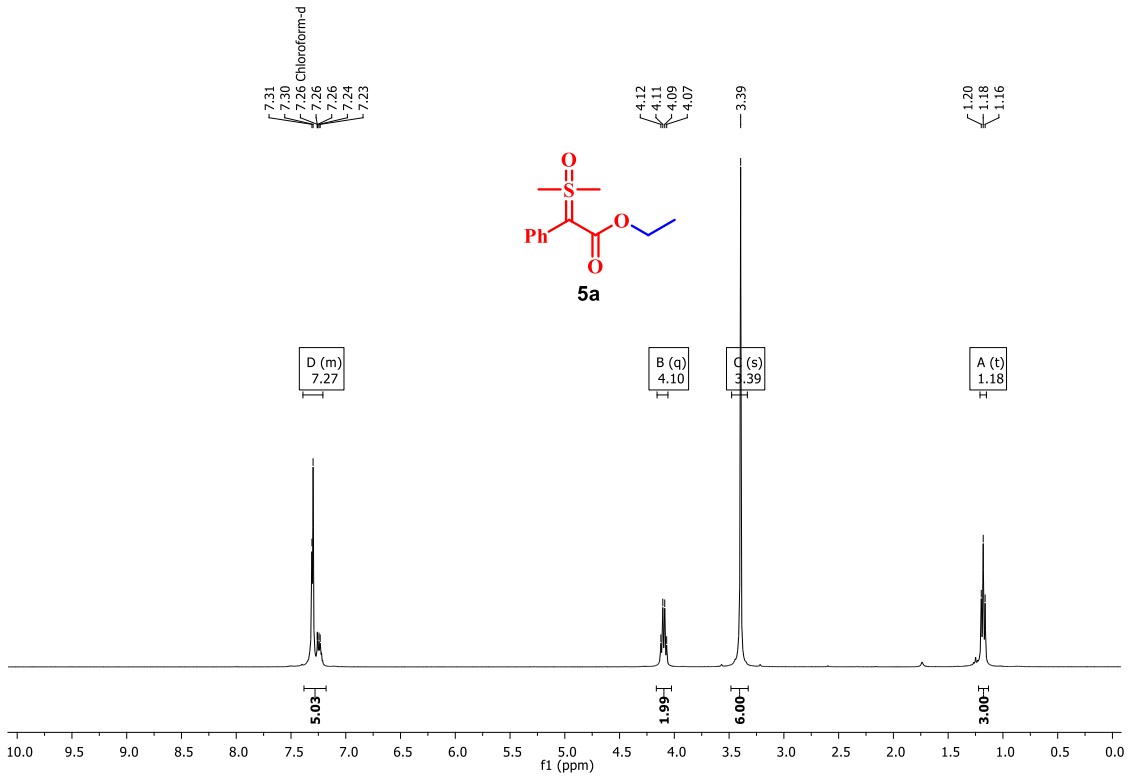


Figure 2.4 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **5a**

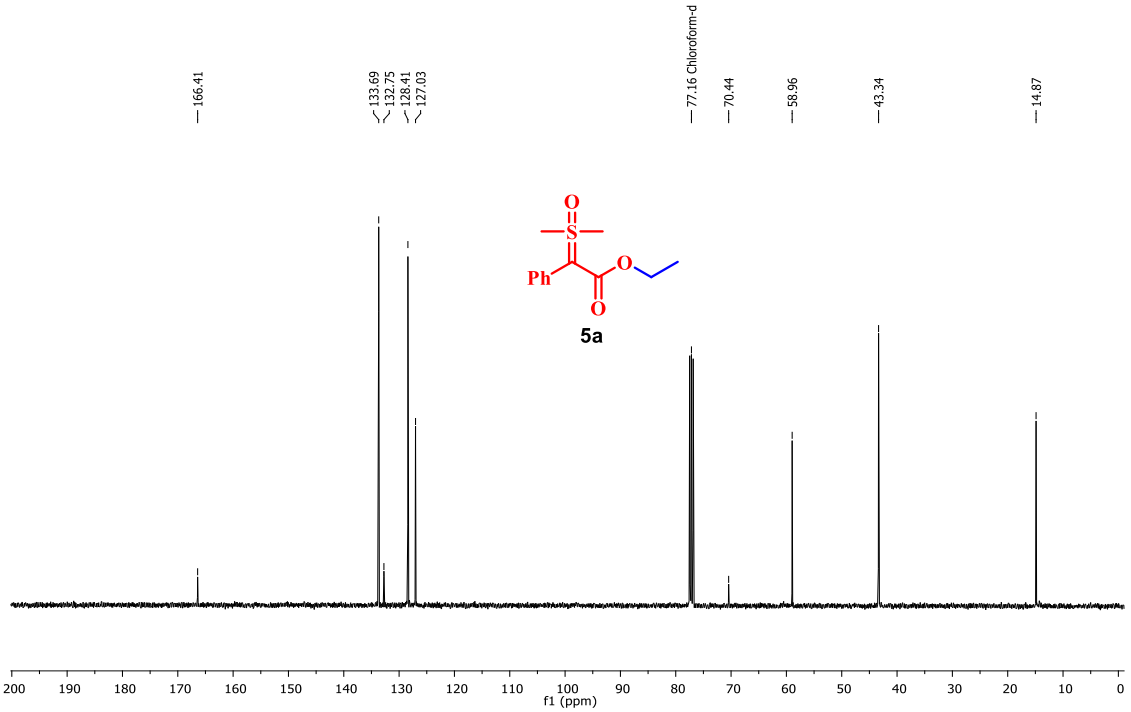


Figure 2.5 $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) Spectrum of compound **5a**

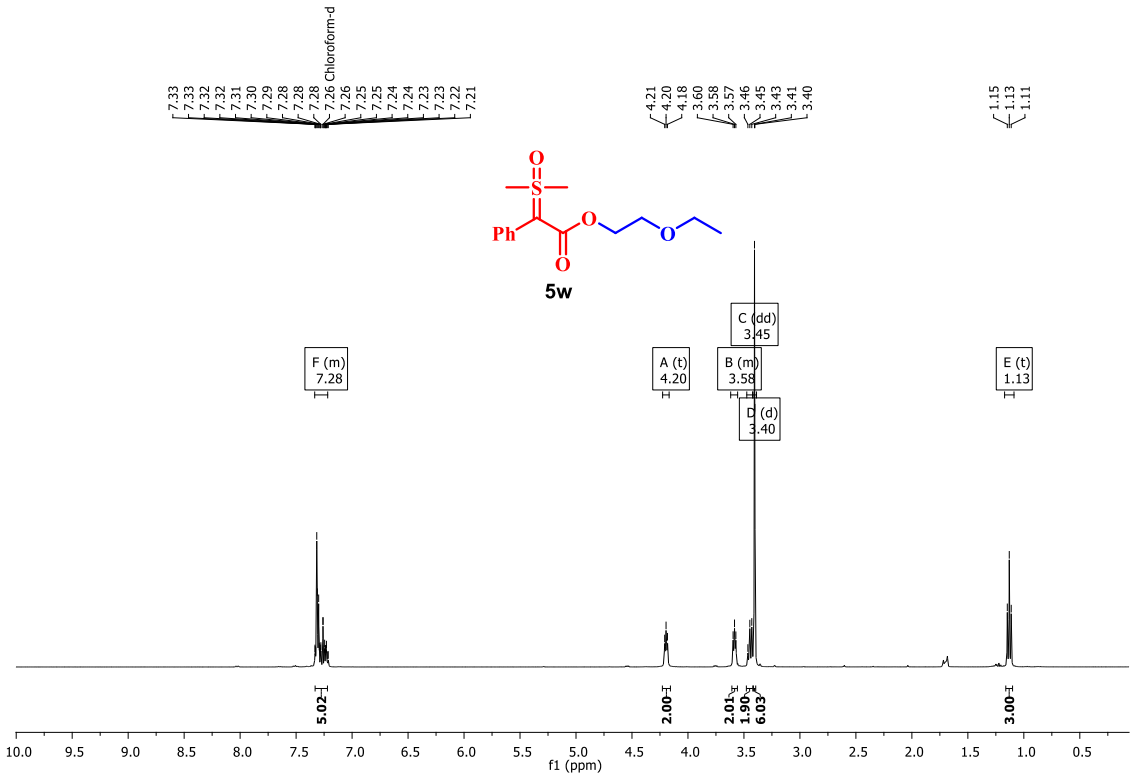


Figure 2.6 ^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of compound **5w**

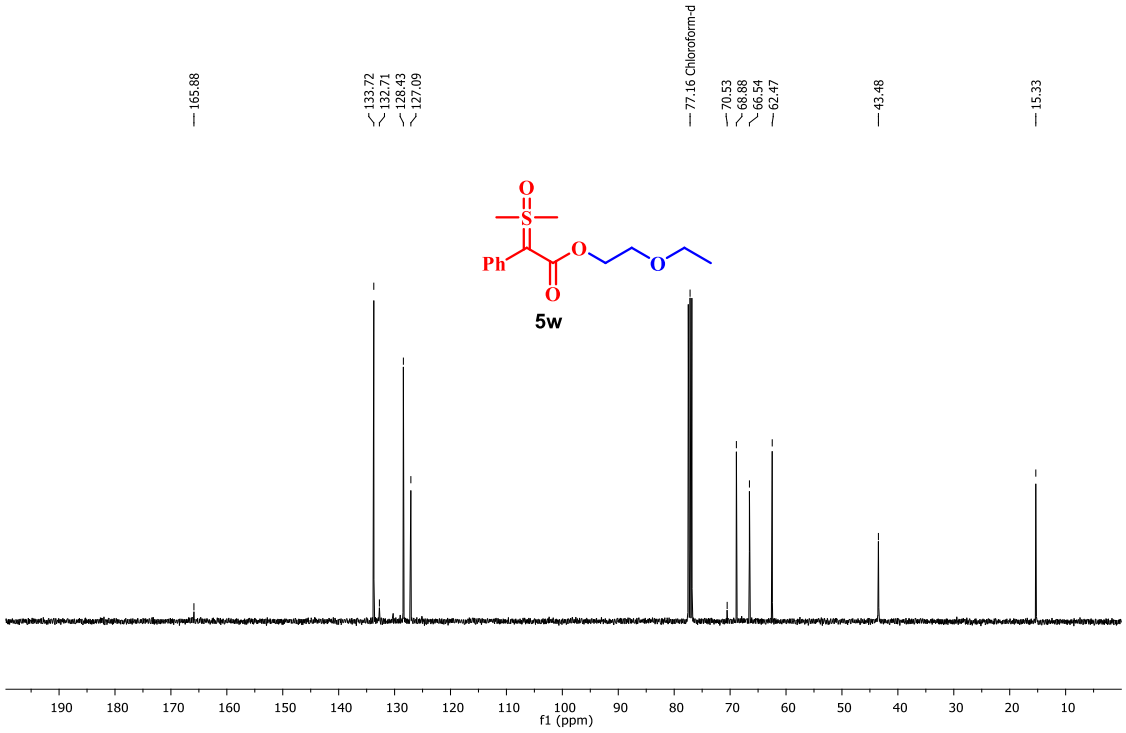


Figure 2.7 $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of compound **5w**

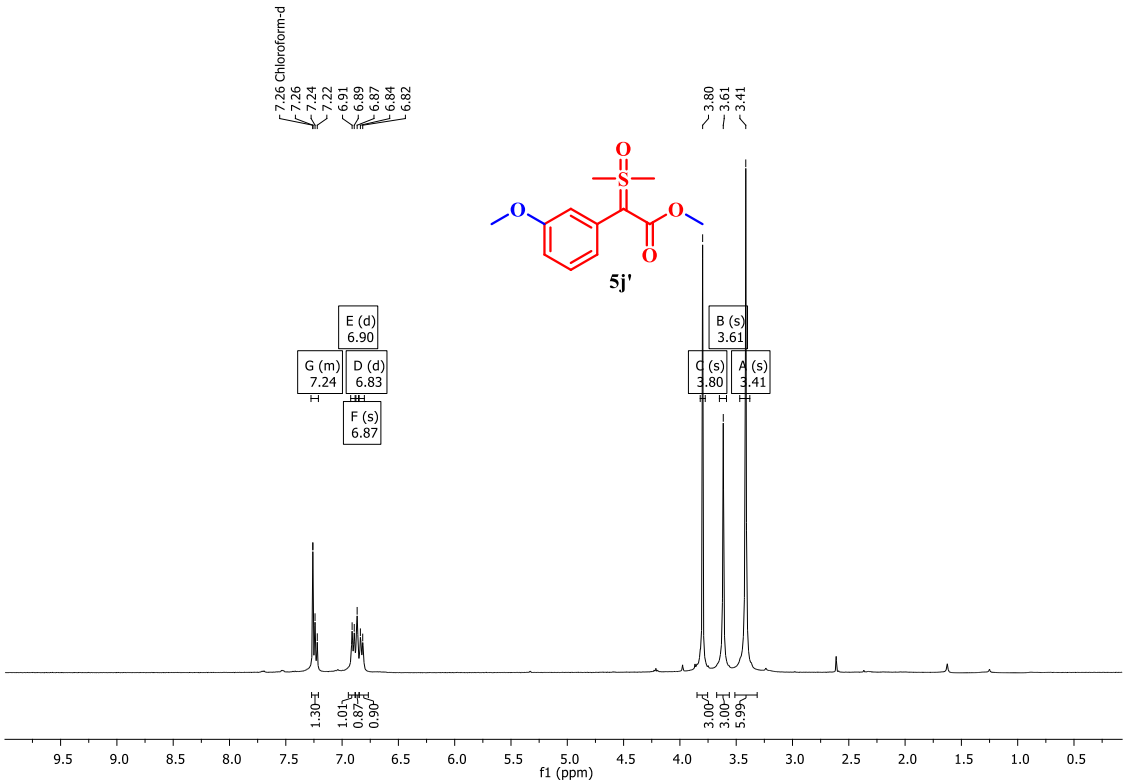


Figure 2.8 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **5j'**

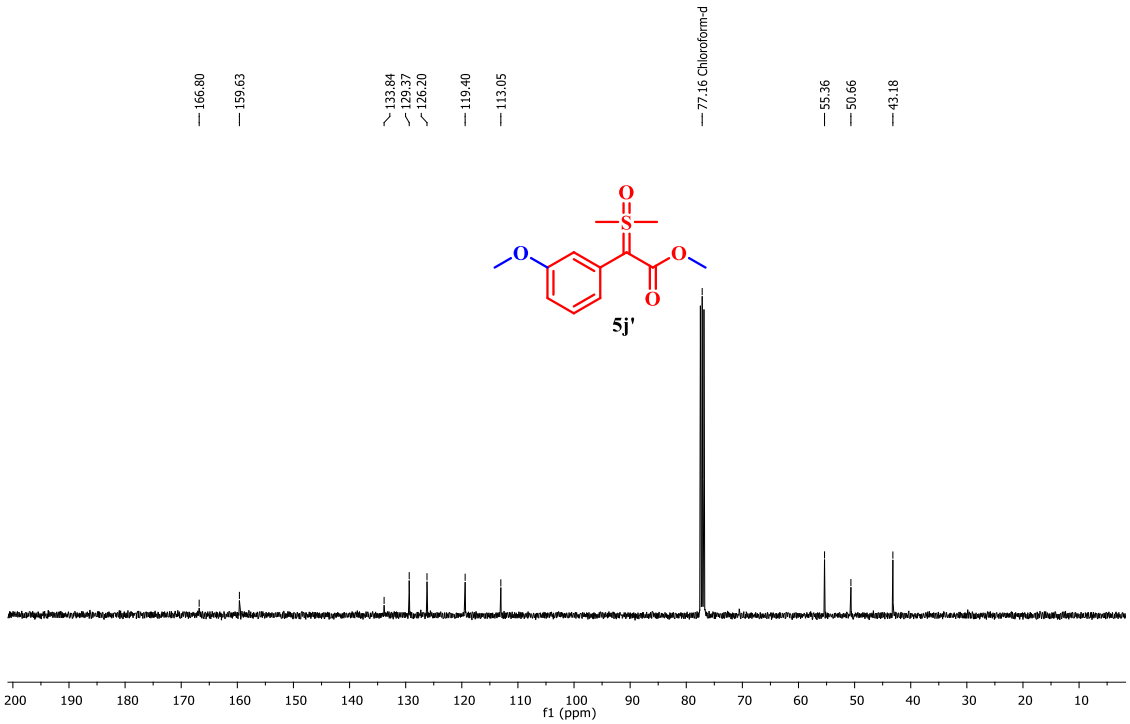


Figure 2.9 $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of compound **5j'**

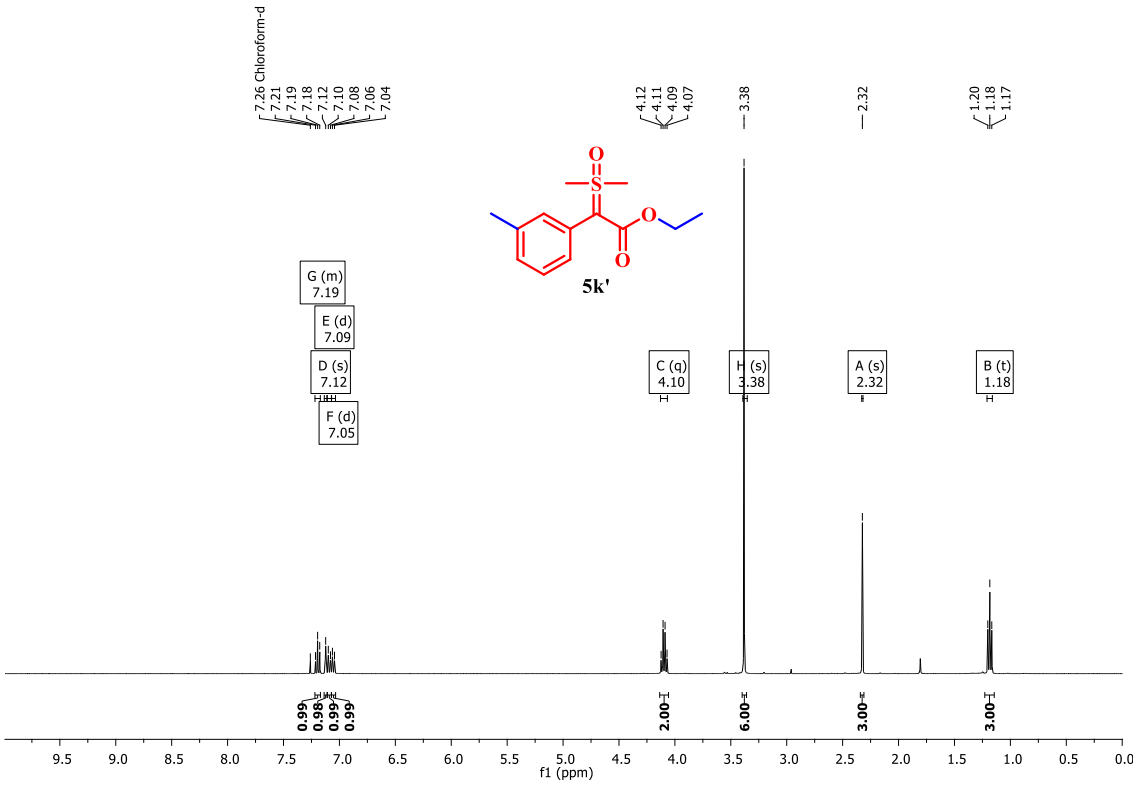


Figure 2.10 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **5k'**

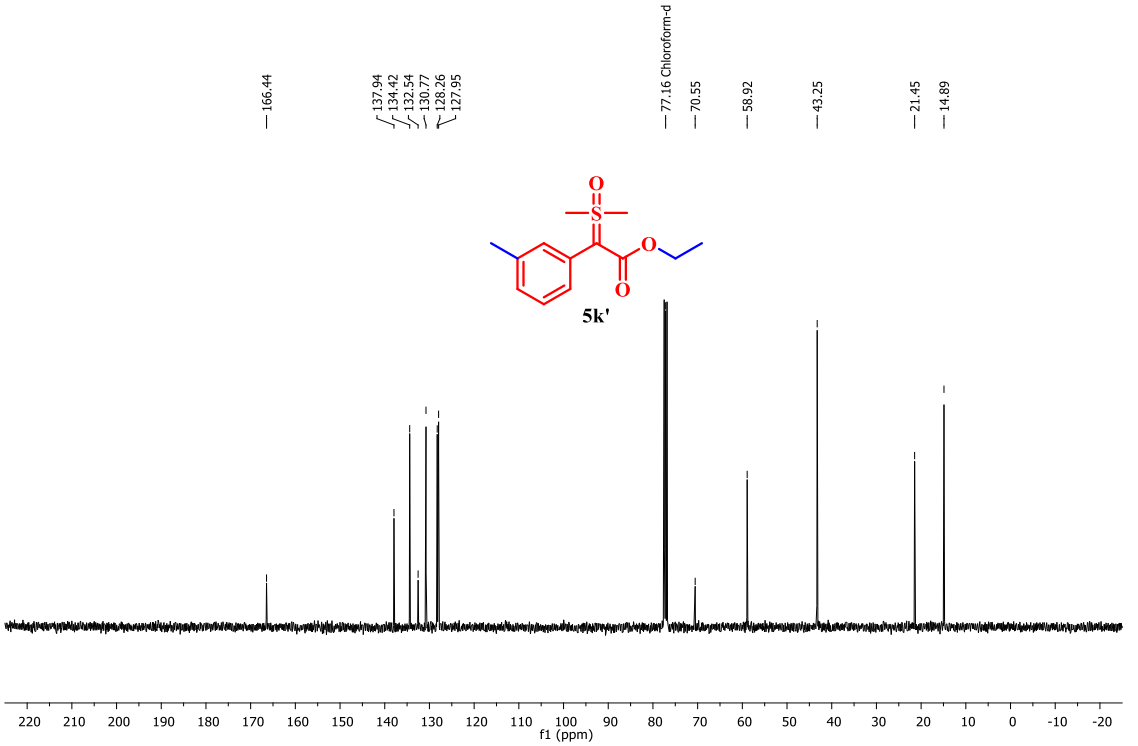


Figure 2.11 $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of compound **5k'**

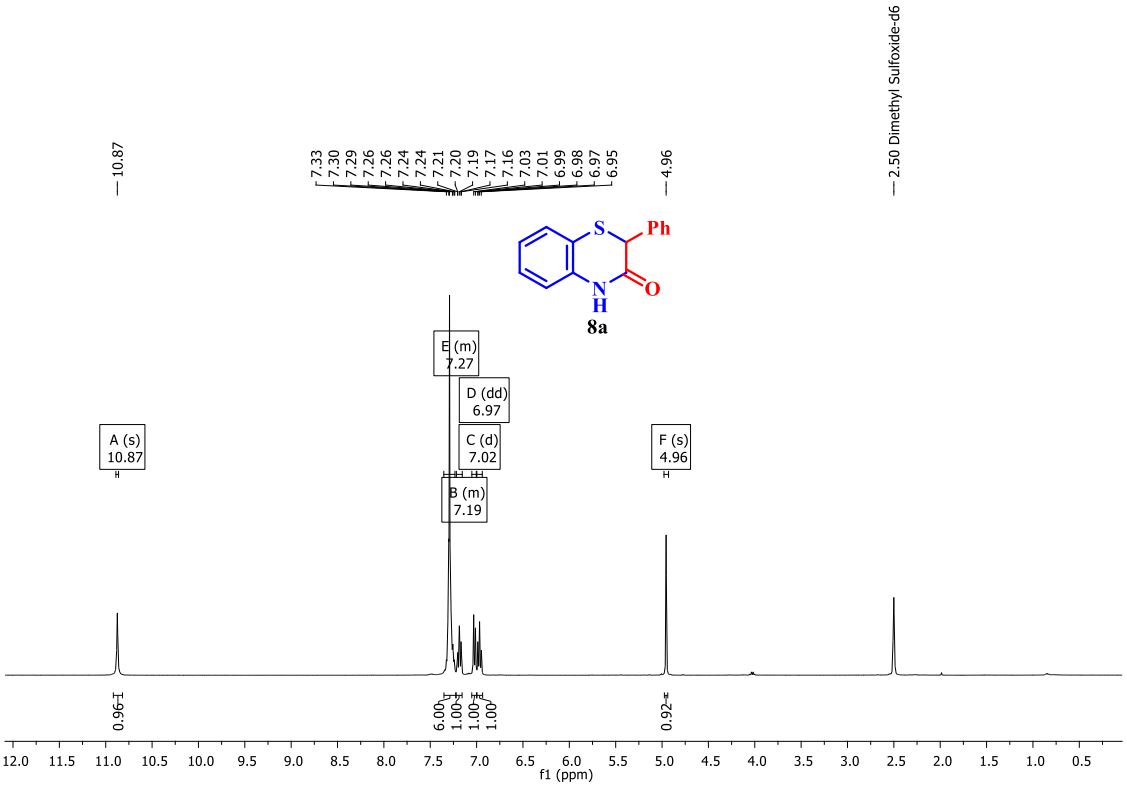


Figure 2.12 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **8a**

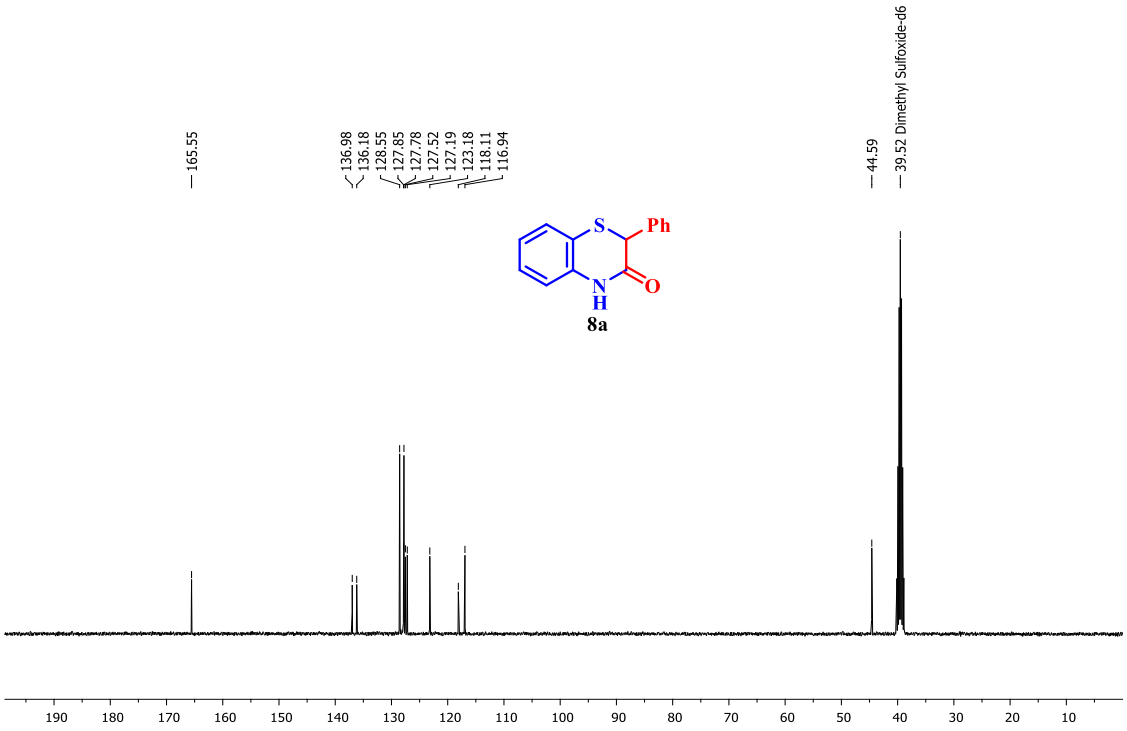


Figure 2.13 $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of compound **8a**

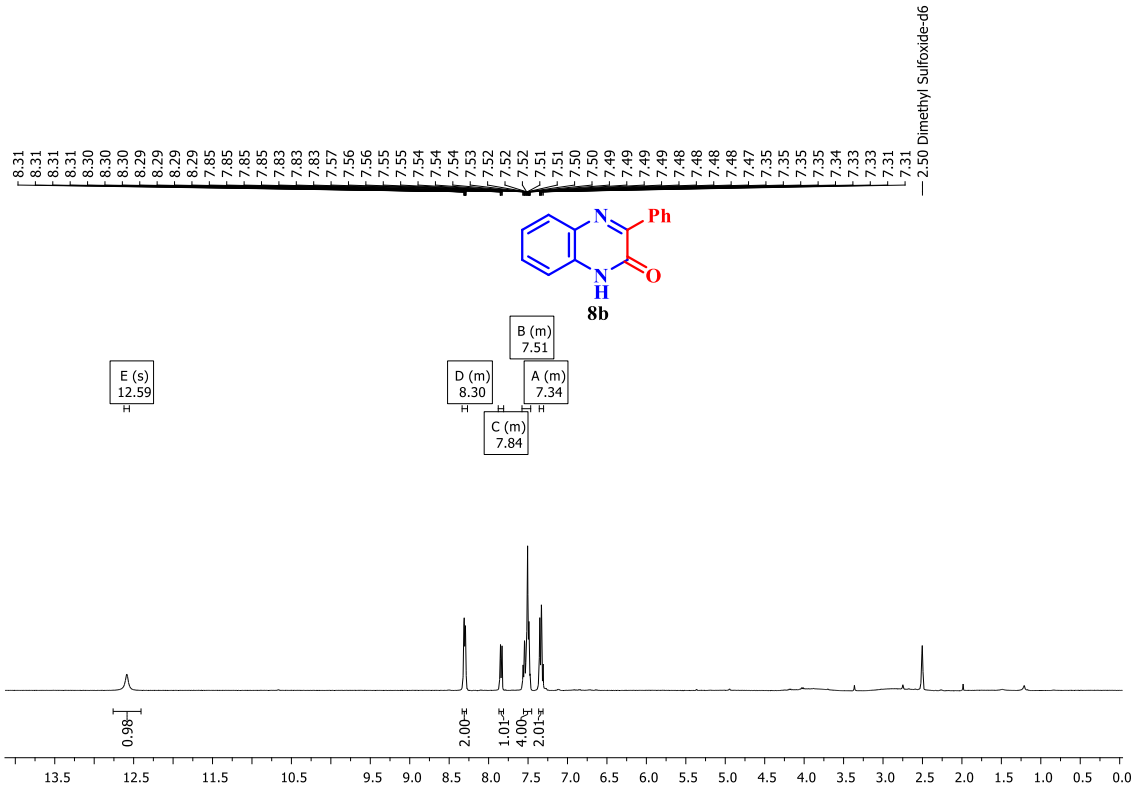


Figure 2.14 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **8b**

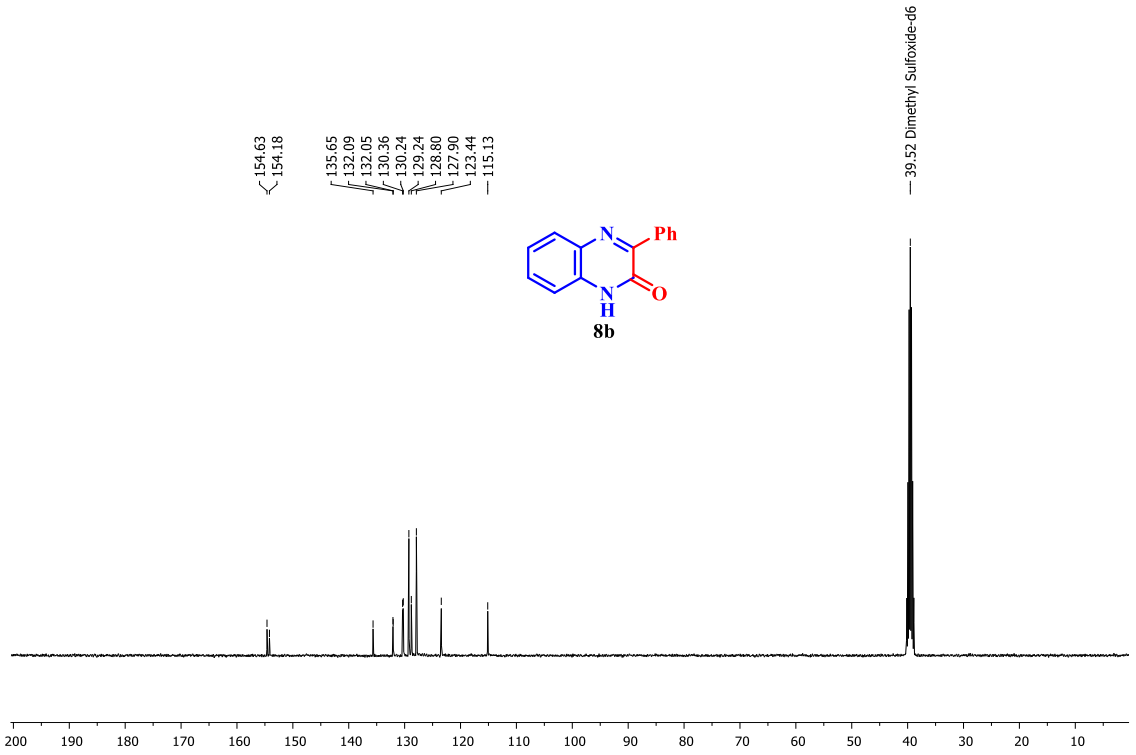


Figure 2.15 $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of compound **8b**

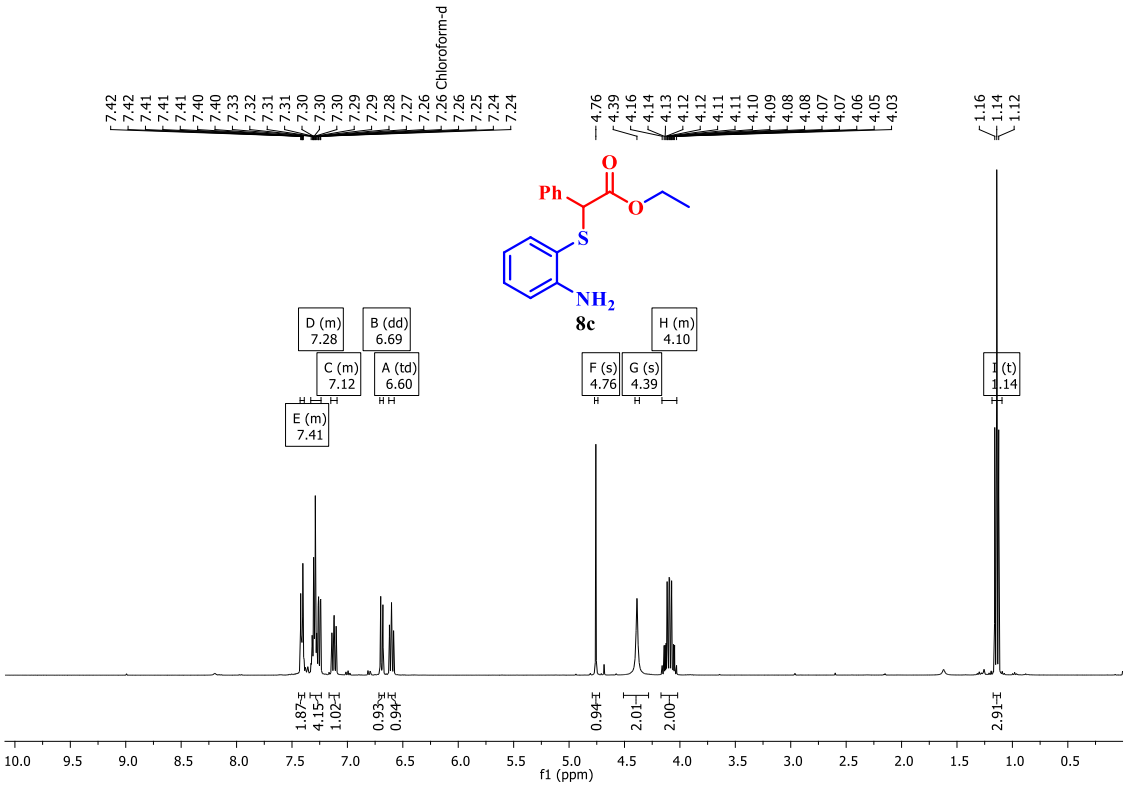


Figure 2.16 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **8c**

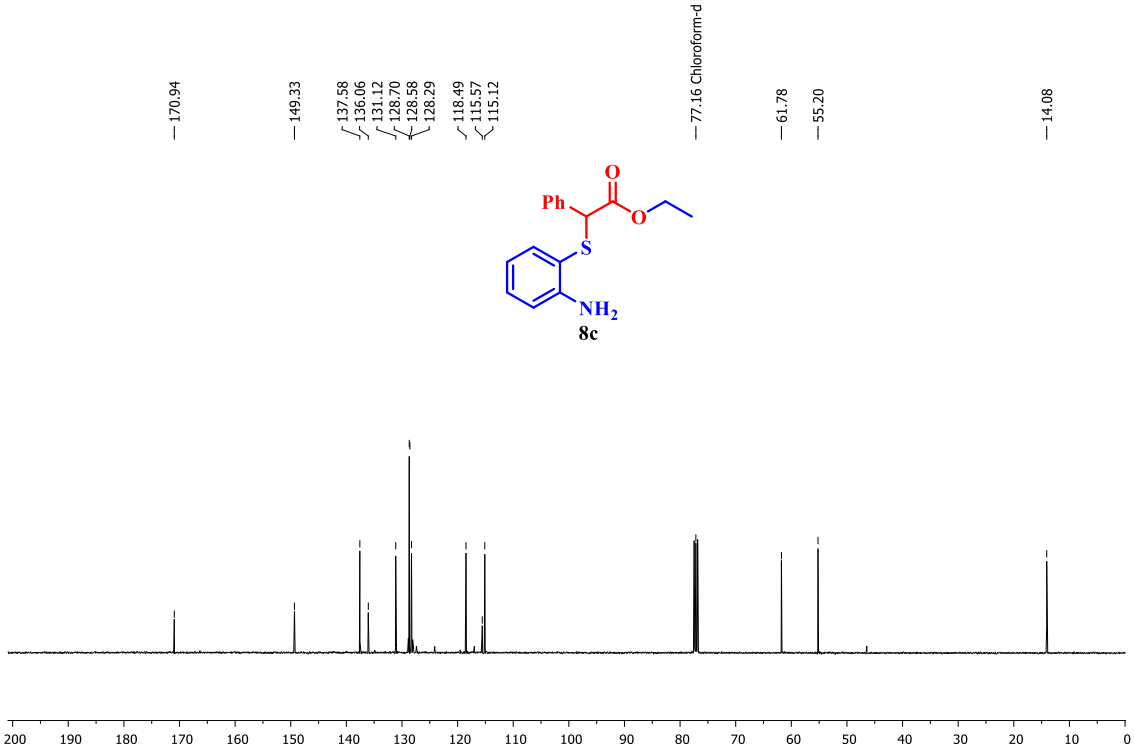


Figure 2.17 ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of compound **8c**

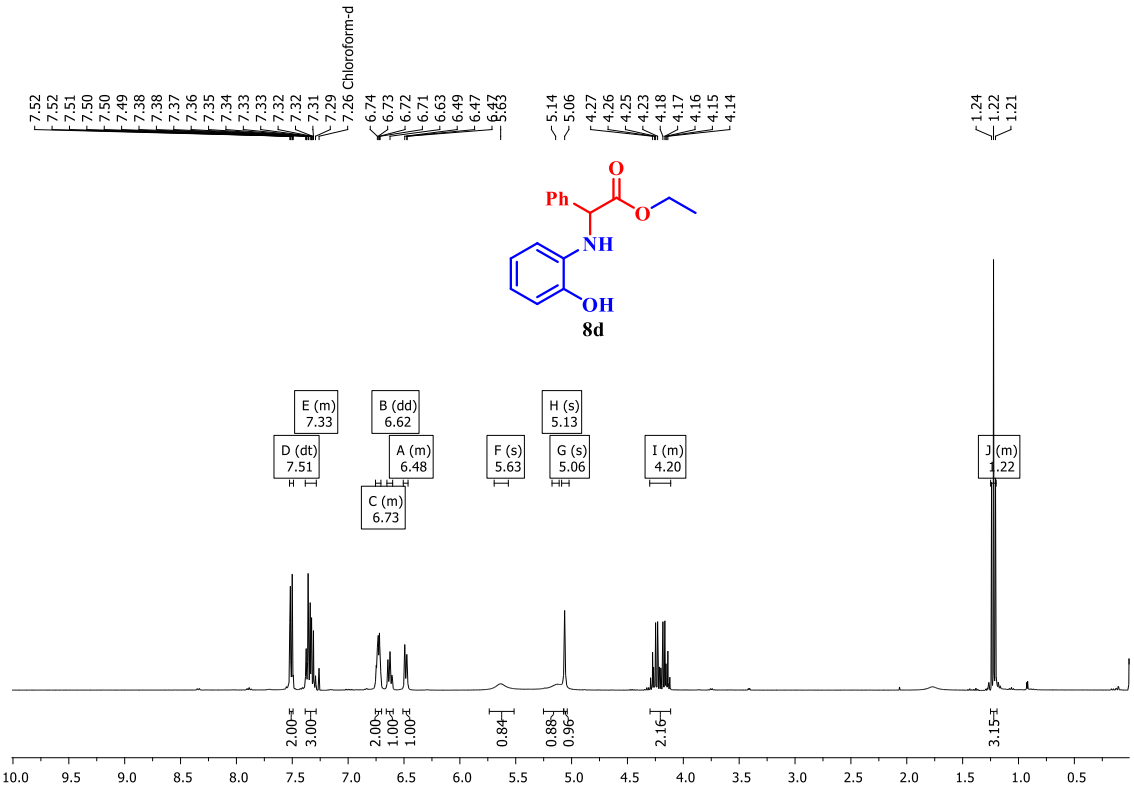


Figure 2.18 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **8d**

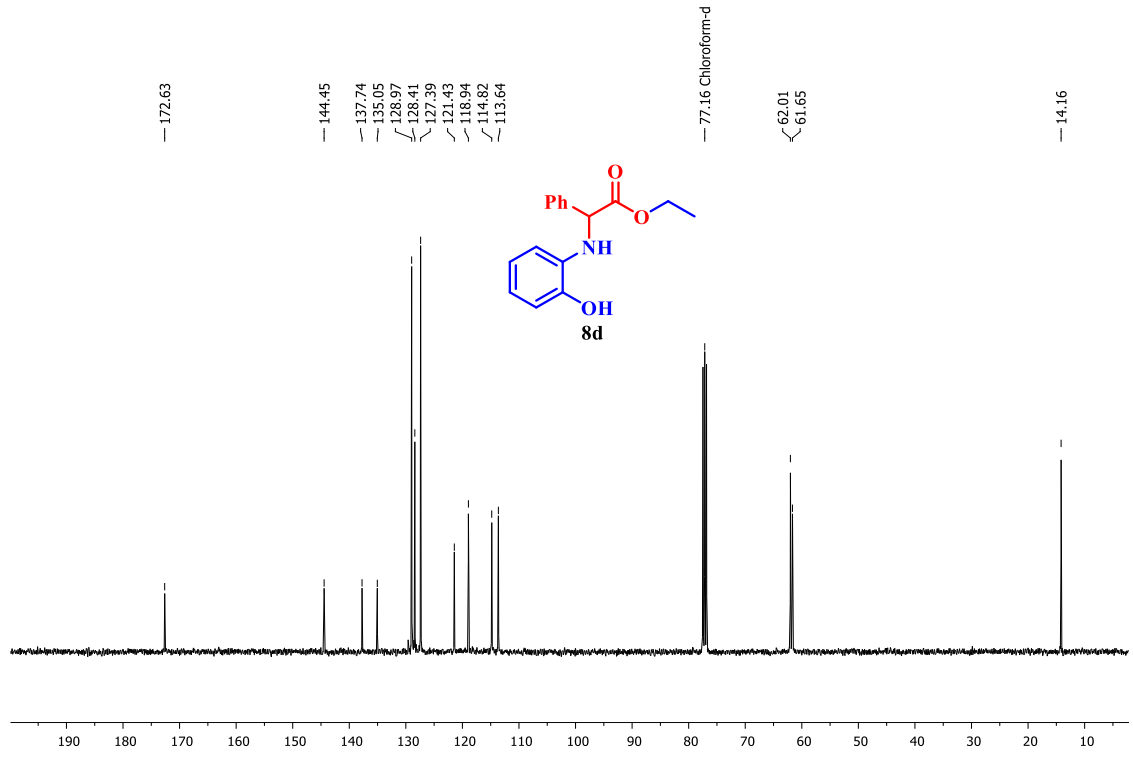


Figure 2.19 $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of compound **8d**

2.9 References

1. (a) L.-Q. Lu, T.-R. Li, Q. Wang, W.-J. Xiao. *Chem. Soc. Rev.*, **2017**, *46*, 4135-4149; (b) E. M. McGarrigle, E. L. Myers, O. Illa, M. A. Shaw, S. L. Riches, V. K. Aggarwal. *Chem. Rev.*, **2007**, *107*, 5841-5883; (c) X.-L. Sun, Y. Tang, *Acc. Chem. Res.*, **2008**, *41*, 937-948; (*d*) V. K. Aggarwal, C. L. Winn. *Acc. Chem. Res.*, **2004**, *37*, 611-620; (e) P. A. Byrne, D. G. Gilheany. *Chem. Soc. Rev.*, **2013**, *42*, 6670; (f) Z. Wang, X. Xu, O. Kwon, *Chem. Soc. Rev.*, **2014**, *43*, 2927-2940.
2. (a) G. D. Bisag, S. Ruggieri, M. Fochi, L. Bernardi. *Org. Biomol. Chem.*, **2020**, *18*, 8793-8809; (b) F. Wang, B.-X. Liu, W. Rao, S.-Y. Wang. *Org. Lett.*, **2020**, *22*, 6600-6604.
3. I. K. Mangion, R. T. Ruck, N. Rivera, M. A. Huffman, M. Shevlin. *Org. Lett*., **2011**, *13*, 5480-5483.
4. (a) C. Molinaro, P. G. Bulger, E. E. Lee, B. Kosjek, S. Lau, D. Gauvreau, M. E. Howard, D. J. Wallace, P. D. OShea. *J. Org. Chem.*, **2012**, *77*, 2299-2309; (b) C. A. D. Caiuby, L. G. Furniel and A. C. B. Burtoloso. *Chem. Sci.*, **2022**, *13*, 1192-1209.
5. (a) I. K. Mangion, I. K. Nwamba, M. Shevlin, M. A. Huffman. *Org. Lett.*, **2009**, *11*, 3566-3569; (b) I. K. Mangion, M. Weise. *Tetrahedron Lett.*, **2010**, *51*, 5490-5492; (c) R. M. P. Dias, A. C. B. Burtoloso. *Org. Lett.*, **2016**, *18*, 3034-3037; (d) K. Ramakrishna, A. Jayarani, F. Febin, K. C. Sivasankar. *Appl. Organomet. Chem*., **2020**, *34*, 5748; (e) X. Zhang, Y. Zhang, C. Liang, J. Jiang. *Org. Biomol. Chem.*, **2021**, *19*, 5767-5771; (f) L.G. Furniel, A. C. B. Burtoloso. *Tetrahedron*, **2020**, *76*, 131313.
6. (a) P. B. Momo, A. N. Leveille, E. H. E. Farrar, M. N. Grayson, A. E. Mattson, A. C. B. Burtoloso. *Angew. Chem. Int. Ed.*, **2020**, *59*, 15554-15559; (b) L. G. Furniel, R. Echemendía, A. C. B. Burtoloso. *Chem. Sci.*, **2021**, *12*, 7453-7459.
7. (a) K. Yan, M. He, J. Li, H. He, R. Lai, Y. Luo, L. Guo, Y. Wu. *Chem. Commun.*, **2020**, *56*, 14287-14290; (b) A. N. Leveille, R. Echemendía, A. E. Mattson, A. C. B. Burtoloso. *Org. Lett.*, **2021**, *23*, 9446-9450.
8. F. Dost, J. Gosselck. *Tetrahedron Lett.*, **1970**, *11*, 5091-5093.
9. A. G. Talero, B. S. Martins, A. C. B. Burtoloso. *Org. Lett.*, **2018**, *20*, 7206-7211.
10. C. Janot, P. Palamini, B. C. Dobson, J. Muir, C. Aïssa. *Org. Lett.*, **2019**, *21*, 296-299.
11. I. D. Jurberg, H. M. L. Davies. *Chem. Sci.*, **2018**, *9*, 5112-5118.

12. R. Hommelsheim, Y. Guo, Z. Yang, C. Empel, R. M. Koenigs. *Angew. Chem. Int. Ed.*, **2019**, *58*, 1203-1207.
13. Y. Guo, T. V. Nguyen, R. M. Koenigs. *Org. Lett.*, **2019**, *21*, 8814-8818.
14. Y. Guo, C. Empel, C. Pei, I. Atodiresei, T. Fallon, R. M. Koenigs. *Org. Lett.*, **2020**, *22*, 5126-5130.
15. X. Zhang, C. Du, H. Zhang, X-C. Li, Y-L. Wang, J-L. Niu, M-P. Song. *Synthesis*, **2019**, *51*, 889-898.
16. (a) J. Yang, J. Wang, H. Huang, G. Qin, Y. Jiang, T. Xiao. *Org. Lett.*, **2019**, *21*, 2654-2657; (b) K. Orłowska, K R.-Jasińska, P. Krajewski, D. Gryko. *Org. Lett.*, **2020**, *22*, 1018-1021; (c) Z. Yang, Y. Guo, R. M. Koenigs. *Chem. Eur. J.*, **2019**, *25*, 6703-6706; (d) F. Li, F. He, R. M. Koenigs. *Synthesis*, **2019**, *51*, 4348-4358; (e) S. Jana, Z. Yang, C. Pei, X. Xu, R. M. Koenigs. *Chem. Sci.*, **2019**, *10*, 10129-10134.
17. S. Jana, F. Li, C. Empel, D. Verspeek, P. Aseeva, R. M. Koenigs. *Chem. Eur. J.*, **2020**, *26*, 2586-2591.
18. C. Empel, F. W. Patureau, R. M. Koenigs. *J. Org. Chem.*, **2019**, *84*, 11316-11322.
19. J. Yang, G. Wang, S. Chen, B. Ma, H. Zhou, M. Song, C. Liu, C. Huo. *Org. Biomol. Chem.*, **2020**, *18*, 9494-9498.
20. L-Z. Qin, X. Yuan, Y-S. Cui, Q. Sun, X. Duan, K-Q. Zhuang, L. Chen, J-K. Qiu, K. Guo. *Adv. Synth. Catal.*, **2020**, *362*, 5093-5104.
21. S. Jana, Z. Yang, F. Li, C. Empel, J. Ho, R. M. Koenigs. *Angew. Chem. Int. Ed.*, **2020**, *59*, 5562-5566.
22. Z. Yang, M. L. Stivanin, I. D. Jurberg, R. M. Koenigs. *Chem. Soc. Rev.*, **2020**, *49*, 6833-6847.
23. R. Liu, Q. Liu, H. Meng, H. Ding, J. Hao, Z. Ji, H. Yue, W. Wei. *Org. Chem. Front.*, **2021**, *8*, 1970-1975.
24. N. R. O'Connor, P. Bolgar, B. M. Stoltz. *Tetrahedron Lett.*, **2016**, *57*, 849-851.
25. C. Y. Okada, C. Y. dos Santos, I. D. Jurberg. *Tetrahedron*, **2020**, *76*, 131316-131325.
26. (a) S. A. M. El-Hawash, N. S. Habib, M. A. Kassem, *Arch. Pharm. Chem. Life Sci.*, **2006**, *339*, 564-571; (b) N. Abad, H. H. Sallam, F. H. A-Ostoot, H. A. Khamees, S. A. A-horaibi, S. M. A., S. A. Khanum, M. Madegowda, M. E. Hafi, J. T. Mague, E. M. Essassi, Y. Ramli. *J. Mol. Struct.*, **2021**, *1232*, 130004; (c) H. E. A. Ahmed, S. K. Ihmaid, A. M.

Omar, A. M. Shehata, H. S. Rateb, M. F. Zayed, S. Ahmed, M. M. Elaasser. *Bioorg. Chem.*, **2018**, *76*, 332.

27. (a) W-W. Chan, S-H. Yeung, Z. Zhou, A. S. C. Chan, W-Y. Yu. *Org. Lett.*, **2010**, *12*, 604; (b) H. Keipour, T. Ollevier. *Org. Lett.*, **2017**, *19*, 5736.
28. (a) J. Lu, L. Li, X.-K. He, G.-Y. Xu, J. Xuan. *Chin. J. Chem.*, **2021**, *39*, 1646-1650; (b) L. S. Munaretto, C. Y. dos Santos, R. D. C. Gallo, C. Y. Okada Jr., V. M. Deflon, I. D. Jurberg. *Org. Lett.*, **2021**, *23*, 9292–9296 (Both authors reported the procedure that relied upon the use of flame-dried Schlenk-tube, DMSO in dry DCM after degassing the reaction mixture via 'freeze-pump-thaw' procedure [3-time cycles] under 24 W blue LED. Interestingly, they did not report the formation of α-phenyl-α-ketoester if any under the reaction conditions)

Blue Light Promoted Direct Synthesis of 1,3-Dithiolanes from Terminal Aromatic Alkynes

3

3.1 Abstract:

A regioselective dihydrothionation of terminal aromatic as well as heteroaromatic alkynes has been developed by using Eosin Y as organo-photocatalyst at room temperature under visible light conditions. This methodology gave direct access to different 1,3-dithioacetals starting from terminal aromatic as well as heteroaromatic alkynes at room temperature via C–S bond constructing strategy. Alkynes substituted with electron-deactivating, electron-withdrawing and electron-donating moieties are well-tolerated reaction conditions to afford the corresponding 1,3-dithioacetals. The practicality of the protocol has been also demonstrated on the gram-scale synthesis and as an extension of this methodology, phenylacetaldehyde has been synthesized. In order to have insights into the reaction mechanism, a series of control experiments, cyclic voltammetry and Stern-Volmer experiments have been carried out. This method uses clean energy sources such as visible light under metal-free conditions.

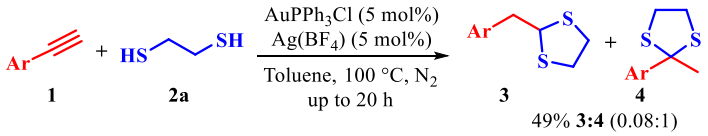
3.2 Introduction

Dithioacetals are very useful intermediates and they have been utilized in many useful transformations for the synthesis of various biologically active compounds, naturally occurring products, and many pharmaceuticals. Dithioacetals have been explored for their umpolung reactivity and is known to act as an acyl anion equivalent along with masking the carbonyl functionality. In view of this, a considerable amount of efforts have been made for the synthesis of thioacetals via various strategies.[1] The traditional method for synthesis of thioacetals is very simple by the condensation between dithiol and aldehyde in the presence of strong Brønsted acids, Lewis acids, high energy microwave irradiation and UV light /visible light irradiation conditions, etc.[2-6] However, synthesis of cyclic thioacetals via dihydrothionation of alkyne by

dithiols is relatively a challenging task as it is associated with few problems such as competitive reactions namely Markovnikov, anti-Markovnikov addition and control of stereoselectivity. The *Z* or *E* isomer of vinyl sulfide obtained via Markovnikov as well as anti-Markovnikov addition of thiols onto the alkynes have been utilized as key intermediates or precursors in the total synthesis of many natural products and for synthesis of useful compounds.[7] There are limited reports in the literature to access dithioacetals from alkynes and also systematic mechanistic study has not been carried out to the best of our knowledge.[8-11] Some of the selected protocols to synthesize cyclic thioacetals from terminal alkynes have been highlighted.

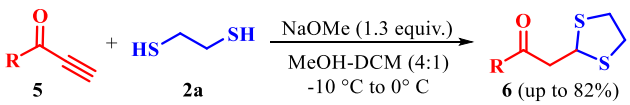
3.3 Previous approaches for the synthesis of thioacetals

Santos *et al.,* have reported the synthesis of regioisomers of dithioacetal starting from terminal alkynes **1** and ethane dithiol **2a** by the combined use of gold (I) and silver (I) complexes (5 mol% each one of) under an inert atmosphere at an elevated temperature to afford the corresponding mixture of cyclic thioacetals **3** and **4** in moderate yields (49%). It has been shown that the additional use of *p*-TsOH as a catalyst and additives enhanced the rate of reaction. (Scheme 3.1).[8] This protocol relied on expensive gold and silver catalysts at higher temperatures and did not afford single thioacetal exclusively.



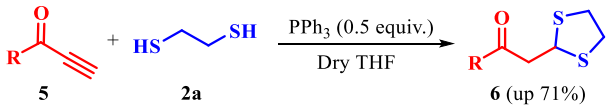
Scheme 3.1 Gold and Silver catalyzed synthesis of dithiolane

Ley and coworkers have reported the synthesis of 1,3-dithiolanes **6** by employing the activated terminal alkynes such as ynones **5** and ethane dithiol **2a** under the strongly basic conditions in methanol and DCM (4:1) via a double conjugate addition on ynones (Scheme 3.2).[9] The protocol gave access to 1,3-dithiolanes in good yields (82%) and the method requires ynones.



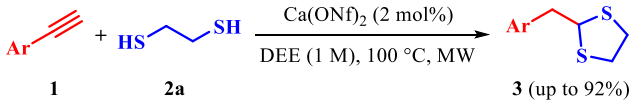
Scheme 3.2 Synthesis of 1,3-dithiolanes from ynones

Endo and co-workers have reported a protocol for the dihydrothionation of ynones **5** using easily accessible triphenylphosphine (0.5 equiv.) in dry THF at room temperature to afford the corresponding 1,3-dithiolanes **6** in good yield (Scheme 3.3).[10] The method is believed to take place via the activation of ynones by triphenylphosphine.



Scheme 3.3 Phosphine-based synthesis of 1,3-dithiolane

Kobayashi and coworkers have successfully developed a Lewis acid-catalyzed synthesis of 1,3-dithiolanes **3** starting from terminal alkynes **1** and ethane dithiol **2a** under microwave conditions. The strong Lewis acid $Ca(ONf)_2$ (2 mol%) proved to be efficient for the desired transformation under elevated temperature (100 °C) using microwave conditions. This protocol has shown the synthesis of a wide range of 1,3-dithiolanes **3** via Markovnikov-type dithioacetalization of terminal alkynes in good to excellent yields (92%, Scheme 3.4).[11]

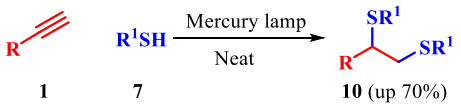


Scheme 3.4 Lewis acid-catalyzed synthesis of 1,3-dithiolane

There are few more reports on the synthesis of regioisomers of dihydrothionation products by different research groups. The dihydrothionation of terminal acetylenes have been achieved using thiols **7** in presence of palladium[12a]/indium[12b] complexes starting from alkynes *via* Markovnikov as well as anti-Markovnikov addition to affording the corresponding thioacetals **8** and **9** (Scheme 3.5).[12a-12b] Later, Taniguchi *et al.*, have carried out the anti-Markovnikov-type dihydrothionation of terminal alkynes **1** with thiols **7** using a hazardous zinc iodide complex at an elevated temperature (100 °C, Scheme 3.5).[12c]

Scheme 3.5 Transitional metal-based synthesis of dithioacetal

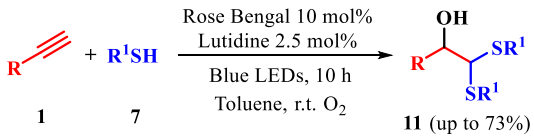
Bowman and co-workers have reported a protocol for the vicinal dihydrothionation of terminal alkynes by thiols **7** under the metal-free conditions while they have utilized mercury lamp to afford the corresponding **10** in 70% (Scheme 3.6).[13] This strategy has also been applied for photopolymerization.



Scheme 3.6 Vicinal dihydrothionation of alkyne

Almost all available procedures, rely on heating conditions or require the use of strong Lewis acid/Brønsted acid or strong bases, metal catalysts/reagents and more importantly, in some cases activated alkynes were essential for the successful transformations. Also, the practicality and wider applicability of some of these protocols were limited due to the formation of regioisomers with lesser substrate scope.

Over the years, the visible light-mediated organic synthetic transformations have been gaining more importance over some of the traditional methods that rely on harsh reaction conditions and expensive transition metal reagents. The visible light-mediated reactions generally use clean energy sources and usually, they are carried out under sustainable, ecofriendly and ambient reaction conditions.[14] Along with metal photocatalysts, various organic dyes have been also explored as effective organo-photocatalysts under visible light irradiation to initiate the single electron transfer (SET) process between the excited state photocatalyst with the donor or acceptor substrate effectively.[15]



Scheme 3.7 Synthesis of β-hydroxy acyclic dithioacetals.

Recently, Shah and coworkers have reported the synthesis of β-hydroxy acyclic dithioacetals **11** starting from the terminal alkynes **1** and aromatic thiols **7** using Rose Bengal as organo-photocatalysts (10 mol%) and lutidine (2.5 mol%) as a base under blue LEDs and aerobic conditions in good to very good yields (up to 73%, Scheme 3.7).[16]

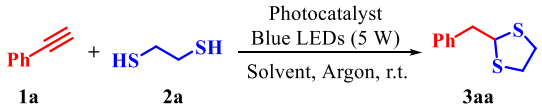
Based on our continuous interest in constructing novel carbon-heteroatom bonds and visible light mediated reactions, we hypothesized that under suitable visible light, photocatalytic, conditions, organic solvent could directly access a one-pot synthesis of cyclic thioacetals as a single regioisomer starting from terminal aromatic alkynes under neutral and mild reaction conditions.

3.4 Results and Discussion

In order to validate our hypothesis of direct dihydrothionation under visible light conditions, we commenced with a model reaction of phenylacetylene **1a** and ethane-1,2-dithiol **2a** using Eosin Y (10 mol%) as an organo-photocatalyst in acetonitrile solvent under the irradiation of visible light (Blue LEDs, 5 W) at room temperature for 24 h. Gratifyingly, we observed the complete consumption of phenylacetylene **1a** to afford the corresponding dihydrothionation product **3aa** in modest yield (31%, Table 1, Entry 1). Encouraged by this initial result, we planned to optimize the reaction systematically to enhance the yield of **3aa**. In this regard, we screened different photocatalysts such as riboflavin, viologens, methylene blue, $Ru(bpy)_3Cl_2$, iodine (I_2), 2,4,6-triphenylpyrelium-tetraborate (TPP), 9-mesityl-10-methylacridinium perchlorate (Mes-Acr-$MeClO_4$), rhodamine B in catalytic amount (10 mol%) in acetonitrile under visible light irradiation (Blue LEDs) (Table 1, Entries 2-9). Among all the photocatalysts screened, Eosin Y proved to be most efficient catalyst for smooth transformation to afford the desired product **3aa** (31% yield, Table 1, Entry 1). In order to enhance the yield of the **3aa** further, we screened different solvents (Table 1, Entries 10-16). Among all the solvents screened, DCM found to be advantageous to afford the corresponding dihydrothionation product **3aa** in relatively higher yield compared to other solvents (Table 1, Entry 10). Later in order to verify the effect the catalyst loading on the overall transformation, we screened the reaction by varying catalyst loading of Eosin Y. Interestingly, we observed that lower catalyst loading (5 mol%) of the Eosin Y efficiently catalyzed the reaction of **1a** to afford the desired product **3aa** in relatively higher yield (Table 1, entry 18). However, the yield was modest and needed further optimization. In order to enhance the yield, we turned our attention to screen the reaction with different light sources with varying intensities (power in W) (5-60 W, Table 1, Entries 20-24). Among all, 30 W blue LEDs worked smoothly to afford the desired product **3aa** in good yield 73% (Table 1,

Entry 21). However, the reaction under the irradiation of high-intensity blue LED (60 W) significantly reduced the yield of dihydrothionation product **3aa** (Table 1, Entry 22).

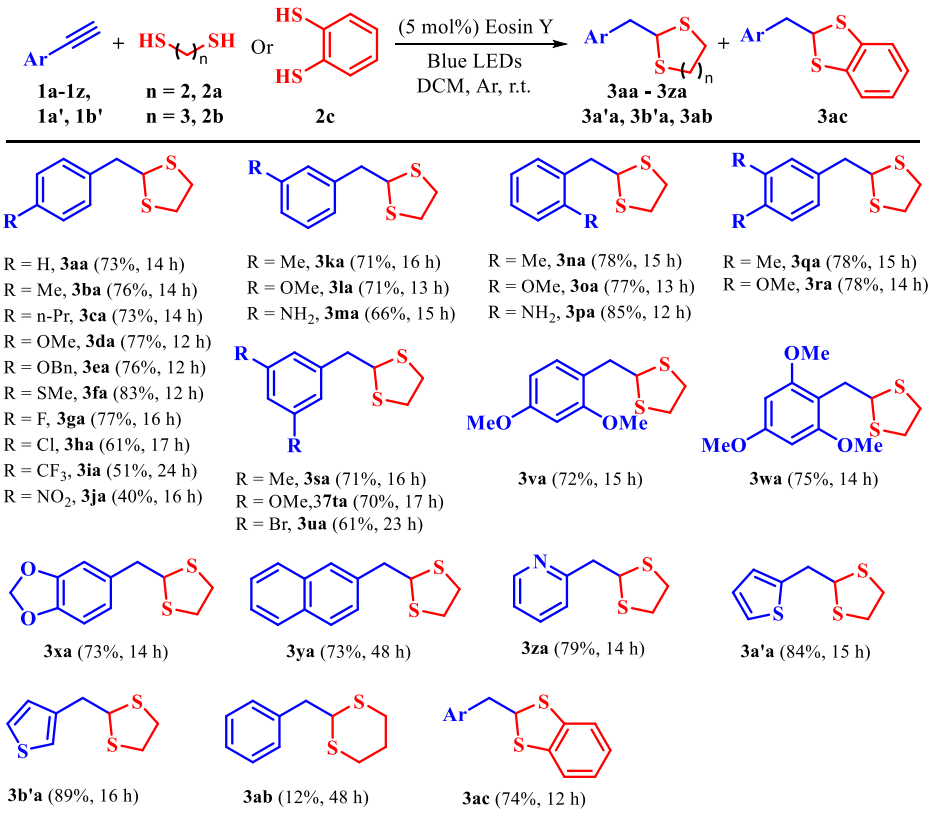
Table 3.1 Optimization of reaction conditions[l]



Entry	Photocatalyst	Solvent	Yield (%)
1	Eosin Y	MeCN	31
2	Riboflavin	MeCN	13
3	Methylene Blue	MeCN	NR
4	Viologen	MeCN	NR
5	$Ru(bpy)_3Cl_2.6H_2O$	MeCN	NR
6	I_2	MeCN	NR
7	TPP	MeCN	15
8	Mes-Acr-$MeClO_4$	MeCN	NR
9	Rhodamine B	MeCN	11
10	Eosin Y	DCM	36
11	Eosin Y	DMSO	27
12	Eosin Y	Toluene	Trace
13	Eosin Y	EtOAc	10
14	Eosin Y	THF	Trace
15	Eosin Y	Ethanol	5
16	Eosin Y	Acetone	23
17[a]	Eosin Y	DCM	28
18[b]	Eosin Y	DCM	47
19[c]	Eosin Y	DCM	29
20[d]	Eosin Y	DCM	62
21[e]	**Eosin Y**	**DCM**	**73**
22[f]	Eosin Y	DCM	54
23[g]	Eosin Y	DCM	NR
24[h]	Eosin Y	DCM	NR
25[i]	Eosin Y	DCM	NR
26[j]	Eosin Y	DCM	NR
27[k]	Eosin Y	DCM	NR
28	-	DCM	NR

Reaction condition: **1a** (0.2 mmol), **2a** (0.2 mmol equiv.), Photocatalyst 10 mol%, 2 mL solvent, 5 W blue LEDs, r.t., Ar. [a]2 mol% of Eosin Y, [b] 5 mol% of Eosin Y, [c]15 mol% of Eosin Y, [d]15 W Blue LEDs, [e]30 W Blue LEDs, [f]60 W Blue LEDs [g]30 W Green LEDs [h]15 W CFL [i]in presence of oxygen, [j]in presence of 20% H_2O, [k]under dark, [l]Dry and degassed reaction condition.

We observed that reaction of **1a** under the exposure of lower energy green LEDs was very sluggish and it was completed in longer reaction time (Table 1, Entry 23). While, the reaction led to decomposition when irradiated with visible light using CFL bulb within just 1 hour (Table 1, Entry 24). Later, we also observed that reaction of **1a** did not work in presence of oxygen atmosphere as well as in presence of water (Table 1, Entries 25, 26). Based on our systematic experimental results, it was evident that both the photocatalyst (Eosin Y) as well as visible light (Blue LEDs) are crucial for the dihydrothionation of terminal aromatic alkynes to synthesize **3aa** as the reaction did not work in the absence of any of these (Table 1, Entries 27, 28). Based on our detailed and systematic screening, terminal alkyne **1a** (1 equiv.), ethane 1,2-dithiol **2a** (1 equiv.), Eosin Y (5 mol%) as a photocatalyst in DCM solvent under the irradiation of blue light (30 W, Blue LEDs) while maintaining the inert atmosphere at room temperature proved to be optimum reaction conditions to furnish the corresponding desired product **3aa** in very good yield (Table 1, Entry 21).



Reaction condition: **1a** (1 equiv.), **2a** (1 equiv.), Eosin Y (5 mol%), DCM (2 mL), blue LEDs (30 W), r.t., under Ar.

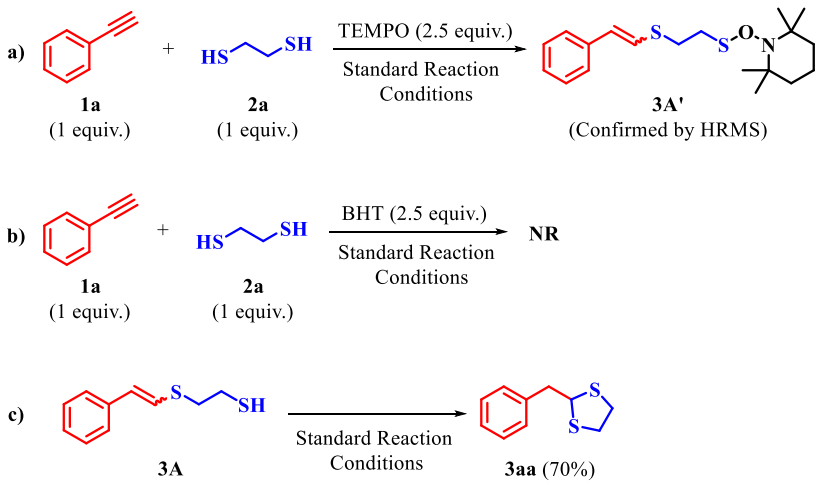
Scheme 3.8 Substrate scope of 1,3-dithiacetals

Having obtained the optimized reaction conditions, we have further explored the substrate scope of this transformation to generalise the synthetic protocol. In this regard, we have prepared different terminal alkynes following the reported procedures.[17] Under the optimized reaction conditions, different phenylacetylene derivatives having electron-donating groups such as alkyl, alkoxy, and thiomethyl at the *para* position of phenyl moiety afforded the corresponding dihydrothionation products (**3aa-3fa,** up to 83% yield, Scheme 3.8). Likewise, phenylacetylene derivatives having electron deactivating groups such as halogen and trifluoromethyl at the *para* position of phenyl moiety reacted smoothly with 1,2-ethanedithiol **2a** to furnish the corresponding 1,3-dithiolanes (**3ga-3ia**, up to 77% yield). The phenyl acetylene having nitro substituent (electron-withdrawing) at the para position also furnished the corresponding product **3ja** in modest yield under optimized reaction conditions. The phenylacetylene derivatives having substituents such as alkyl, alkoxy and amino groups at *meta* as well as *ortho* positions also afforded the corresponding dithiolanes (**3ka-3pa,** up to 78%). The phenylacetylene derivatives having disubstituted groups (alkyl and alkoxy groups) on phenyl ring underwent smooth dihydrothionation to offer the corresponding 1,3-dithiolanes (**3qa-3va,** up to 78%). Even the phenylacetylene having trisubstituted phenyl ring also reacted with the ethane dithiol under the reaction conditions to afford the corresponding 1,3-dithiolane **3wa** in very good yield (75%). We observed that steric hindrance did not affect the outcome of the reaction significantly. Later, we explored the reaction of 1,3-benzodioxole substituted phenylacetylene under the reaction conditions to access the corresponding cyclic 1,3-dithioacetal (**3xa**) in good yield. Then, we explored reaction of 2-naphthyl substituted acetylene under (rich aromatic system) optimum reaction conditions to afford the corresponding dithiolane **3ya** in very good yield (73%) but the reaction took relatively longer reaction time.

Interestingly, heterocyclic aromatic alkynes such as 2-ethynyl pyridine, 1-ethynyl thiophene and 2-ethynyl thiophene under the optimum reaction condition gave the corresponding 1,3-dithiolane products (**3za**, **3a'a** and **3b'a**) in very good yields. Surprisingly, the reaction between phenylacetylene **1a** and propane-1,3-dithiol **2b** was very sluggish. After a prolong reaction time (48 h), we obtained the corresponding dithiane **3ab** in poor yield (12%). While the benzene-1,2-dithiole **2c** reacted smoothly with phenylacetylene **1a** under the optimized reaction conditions to afford dithiolane **3ac** in very good yield (79%). Unfortunately, all our efforts towards the

dihydrothionation of aliphatic alkynes under the optimum reaction conditions were not successful.

In order to have an insight into the reaction mechanism, we performed few control experiments systematically. To begin with we carried out the reaction of **1a** with radical scavengers such as TEMPO and BHT separately while maintaining the standard optimum reaction conditions (Scheme 3.9a, b). We observed that both the reactions did not furnish the desired dihydrothionation product **3aa** in presence of radical scavengers. However, surprisingly we isolated a TEMPO trapped product **3A'** (detected by HRMS) in case the reaction of **1a** in presence of TEMPO (Scheme 3.9a). Based on these results and preceding literature reports,[18] we surmised that the reaction might be following through **3A'** type intermediate. In order to validate the assumption, we further prepared the anticipated intermediate **3A** following the literature procedure.[18] Gratifyingly, the treatment of **3A** under standard optimum reaction conditions afforded the corresponding desired dihydrothionation product **3aa** in 70% yield (Scheme 3.9c).



Scheme 3.9 Control experiments

In order to have further understanding about the reaction pathway, we carried out cyclic voltammetry (CV) and Stern-Volmer experiment (see Fig. 3.1). We have proposed a most plausible reaction mechanism based on the control experiments, CV studies, Stern-Volmer plots, and previous literature reports (see Scheme 3.10).[6b,19,20] Initial reaction of **1a** and **2a** furnishes an anti-Markovnikov-type of product **3A** ($E_{ox1/2}$= +0.94 V vs SCE). Simultaneously, photocatalyst Eosin Y (**EY**) gets excited under blue light irradiation to form an excited state photocatalyst **EY*** (Scheme 3.10). This excited photocatalyst **EY*** ($E_{red1/2}$= +0.83 V vs SCE) easily interacts with

the in situ formed intermediate **3A** to furnish the corresponding intermediate **I** and reduced species of Eosin Y (**$EY^{\bullet-}$**) via SET process. The electron transfer is viable between **3A** and **EY*** even though the reduction potential of **EY*** is relatively less than the $E_{P/2}$ oxidation potential of **3A**. This is probably due to a wider range of oxidation potential of **3A** ranging from the +0.77 V to +1.18 V (see Fig. 3.1F) observed from the cyclic voltammogram. Further, the SET process between excited state photocatalyst **EY*** and **3A** was also confirmed by the Stern-Volmer experiment. We observed that with the increase in the concentration of **3A**, emission intensity of **EY** quenched (See fig. 3.1A). The intermediate **3A** would interact with the **EY*** to form the radical cation intermediate **I** along with generation of **EY***. The oxidized radical cationic intermediate **I** would further undergo deprotonation to generate the radical intermediate **II**. This reactive and unstable radical would immediately cyclize (intramolecular) to form relatively more stable benzylic radical intermediate **III** Further, this intermediate **III** would react with radical anion of photocatalyst **$EY^{\bullet-}$** to form the benzylic carbonian **IV** via the reduction to regenerate the photocatalyst ground state **EY** thus completing the catalytic cycle. Finally, the carbonian intermediate **IV** would abstract the proton to furnish the desired dithiolane product **3aa** (Scheme 3.10).

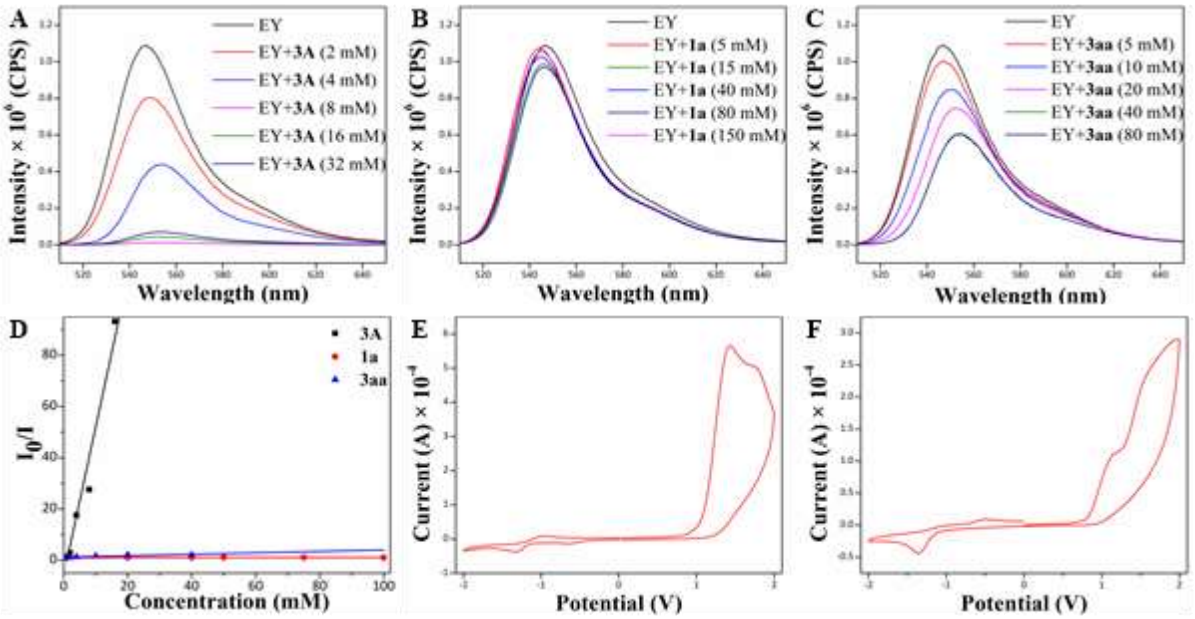
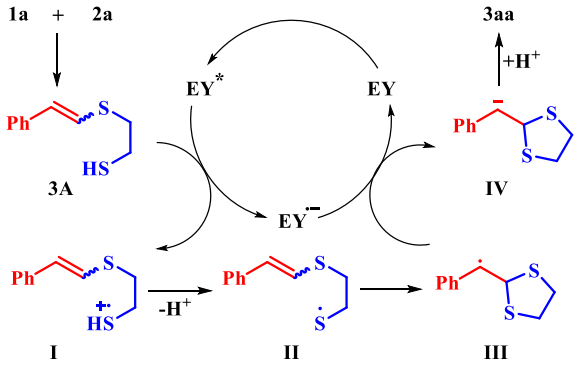


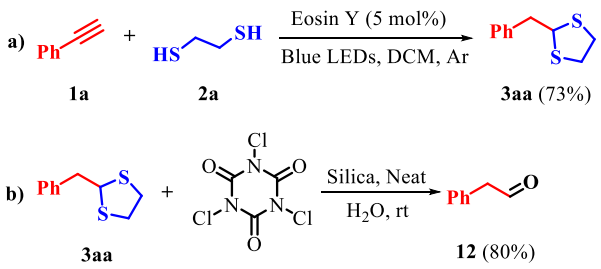
Figure 3.1 A) Emission spectra of Eosin Y with increasing concentration of **3A;** B) Emission spectra of Eosin Y with increasing concentration of **1a;** C) Emission spectra of Eosin Y with increasing concentration of **3aa;** D)

Emission quenching Stern-Volmer plot of Eosin Y with increasing concentration of **3A**, **1a** and **3aa;** E) Cyclic voltammogram of **3a;** F) Cyclic voltammogram of **3A**



Scheme 3.10 Plausible reaction mechanism.

To demonstrate the practicality and wider applicability of this protocol, we synthesized compound **3aa** on a gram quantity (73%, see scheme 3.11a) and this reaction proved to be scalable. Later, we subjected the compound 2-benzyl-1,3-dithiolane **3aa** for the complete deprotection using trichloroisocyanuric acid to obtain the corresponding phenyl acetaldehyde **9** in very good yield (80%, Scheme 3.11b).



Scheme 3.11 Gram scale synthesis and deprotection of 1,3-dithiolane.

3.5 Conclusions

In summary, we developed a visible light promoted regioselective dihydrothionation of terminal aromatic as well as heteroaromatic alkynes using Eosin Y as an organo-photoredox catalyst under an inert atmosphere at room temperature. The protocol relied on blue LEDs as a clean energy source for the successful construction of two C–S bonds to access cyclic thioacetals. This transformation utilized commercially viable organophotocatalyst under mild, neutral and sustainable reaction conditions. We have carried out a few control experiments, cyclic

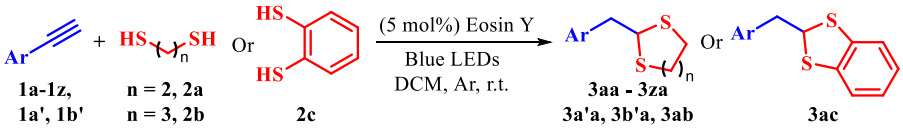
voltammetry (CV) and Stern-Volmer experimental to have an insight into the mechanism. The protocol is proved to be scalable on gram quantity and the facile deprotection of 1,3-dithiolane has been demonstrated.

3.6 Experimental Section

3.6.1 General

Cyclic voltammetry was performed using a glassy carbon as a working electrode, a platinum-plated counter electrode, and Ag/AgCl as a reference electrode. Samples were prepared with a concentration of 3 mM substrate and 100 mM of tetra-*n*-butylammonium hexafluorophosphate in a dry, degassed acetonitrile electrolyte solution. The data was recorded with a scan rate of 50 mV/S. Reductions were measured by scanning potentials in the negative direction and oxidations in the positive direction and the glassy carbon electrode was polished before each scan. The cyclic voltammetry of phenylacetylene was previously reported.[20] Emission spectra were collected on Fluoromax-4 spectrophotometer from Horiba Jobin-Yvon, with xenon light source with excitation and emission slit widths of 1 and 2 nm respectively. Experiments were carried out using a 1 µM solution of **EY** in acetonitrile and variable concentrations of quencher (**3A/1a/3a**) in a 3 mL, Hellma fluorescence cuvette (path length 1.0 cm). Samples were excited at 490 nm and the intensity of emission was monitored at 547 nm and expressed as the I_0/I as a function of the quencher concentration was measured. I_0 is the emission intensity of **EY** at 547 nm in the absence of a quencher and I is the observed intensity in presence of a quencher. The terminal aromatic alkynes were prepared according to the literature procedure.[17] (**Note**: Please see section 2.6.1 of chapter 2 for general experimental, page no 29)

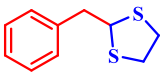
3.5.2 General Procedure A for the Synthesis of 1,3-dithiolanes (3aa-3za 3a'a-3b'a, 3ab-3ac):



An oven-dried round bottom flask containing a stir bar charged with **1** (0.2 mmol), Eosin Y (5 mol%,), **2** (0.2 mmol), DCM (2 mL) under inert atmosphere. Then the reaction mixture was degassed by purging argon gas for 5 min to remove any dissolved air and oxygen. Then the reaction mixture was stirred under the irradiation of Blue LEDs (30 W) at room temperature for

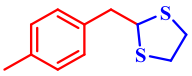
12-24 h. (Monitored by TLC). After the completion of the reaction, the solvent was removed under reduced pressure and the crude residue was further purified by preparative thin-layer chromatography using a mixture of petroleum ether/EtOAc as an eluent to afford the 1,3-dithiolane **3** as oil or solid.

2-benzyl-1,3-dithiolane (3aa):



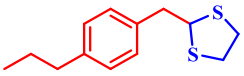
3aa was synthesized by following the general procedure **A**. Colourless liquid (73% yield, 35 mg). *Rf* = 0.88 (petroleum ether/EtOAc 99:1) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 1H), 7.29 (m, 1H), 7.26 (m, 2H), 7.25 – 7.23 (m, 1H), 4.73 (t, *J* = 7.1 Hz, 1H), 3.30 – 3.15 (m, 4H), 3.12 (d, *J* = 7.1 Hz, 2H). ^{13}C{^{1}H} NMR (400 MHz, $CDCl_3$) δ 139.2, 129.2, 128.5, 126.9, 55.0, 45.4, 38.7. HRMS (ESI TOF) m/z $[M+H]^+$ calculated for $[C_{10}H_{13}S_2]^+$ 197.0453 found 197.0459.

2-(4-methylbenzyl)-1,3-dithiolane (3ba):



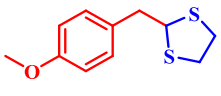
3ba was synthesized by following the general procedure **A**. Colourless liquid (76% yield, 32 mg). *Rf* = 0.85 (petroleum ether/EtOAc 99:1) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 – 7.13 (m, 2H), 7.11 (d, *J* = 8.1 Hz, 2H), 4.71 (t, *J* = 7.2 Hz, 1H), 3.22 (tdt, *J* = 14.2, 9.3, 7.0 Hz, 4H), 3.08 (d, *J* = 7.2 Hz, 2H), 2.33 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 136.5, 136.3, 129.2, 129.1, 55.3, 45.0, 38.7, 21.2. HRMS (ESI TOF) *m/z* $[M+H]^+$ calculated for $[C_{11}H_{15}S_2]^+$ 211.0610 found 211.0640.

2-(4-propylbenzyl)-1,3-dithiolane (3ca):



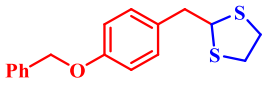
3ca was synthesized by following the general procedure **A**. Colourless liquid (73% yield, 35 mg). *Rf* = 0.86 (petroleum ether/EtOAc 99:1) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, *J* = 8.1 Hz, 2H), 7.12 (d, *J* = 8.1 Hz, 2H), 4.72 (t, *J* = 7.1 Hz, 1H), 3.23 (tdt, *J* = 14.2, 9.4, 7.0 Hz, 4H), 3.09 (d, *J* = 7.1 Hz, 2H), 2.60 – 2.54 (m, 2H), 1.64 (dq, *J* = 14.8, 7.4 Hz, 2H), 0.94 (t, *J* = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 141.3, 136.5, S7 129.1, 128.6, 55.2, 45.0, 38.7, 37.8, 24.6, 14.0. HRMS (ESI TOF) m/z $[M]^+$ calculated for $[C_{13}H_{18}S_2]^+$ 238.0850 found 238.0868.

2-(4-methoxybenzyl)-1,3-dithiolane (3da):



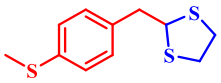
3da was synthesized by following the general procedure **A**. Colourless liquid (77% yield, 35 mg). *Rf* = 0.70 (petroleum ether/EtOAc 99:1) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 – 7.15 (m, 2H), 6.88 – 6.82 (m, 2H), 4.69 (t, *J* = 7.1 Hz, 1H), 3.79 (s, 3H), 3.28 – 3.14 (m, 4H), 3.27 – 3.05 (d, *J* =7.1, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.5, 131.3, 130.2, 113.8, 55.3, 55.2, 44.4, 38.5. HRMS (ESI TOF) m/z $[M+H]^+$ calculated for $[C_{11}H_{15}OS_2]^+$ 227.0559 found: 227.0564.

2-(4-(benzyloxy)benzyl)-1,3-dithiolane (3ea):



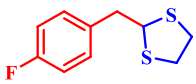
3ea was synthesized by following the general procedure **A**. White solid (76% yield, 46 mg). MP. 70.5-73.2 ℃. *Rf* = 0.70 (petroleum ether/EtOAc 99:1) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.41 (m, 1H), 7.41 – 7.36 (m, 1H), 7.34 – 7.30 (m, 1H), 7.20 – 7.15 (m, 2H), 6.94 – 6.90 (m, 2H), 5.05 (s, 2H), 4.69 (t, *J* = 7.1 Hz, 1H), 3.27 – 3.15 (m, 4H), 3.05 (d, *J* = 7.1 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.9, 137.2, 131.7, 130.3, 128.7, 128.1, 127.6, 114.8, 70.1, 55.4, 44.5, 38.7. HRMS (ESI TOF) *m/z* $[M+H]^+$ calculated for $[C_{17}H_{19}OS_2]^+$ 303.0872 found 303.0888.

2-(4-(methylthio)benzyl)-1,3-dithiolane (3fa):



3fa was synthesized by following the general procedure **A**. Colourless liquid (83% yield, 40 mg). *Rf* = 0.90 (petroleum ether/EtOAc 99:1) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.12 (m, 4H), 4.69 (t, *J* = 7.1 Hz, 1H), 3.29 – 3.14 (m, 4H), 3.07 (d, *J* = 7.1 Hz, 2H), 2.47 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 129.8, 128.5, 126.8, 126.6, 55.0, 44.9, 38.7, 16.1. HRMS (ESI TOF) *m/z* $[M]^+$ calculated for $[C_{11}H_{14}S_3]^+$ 242.0258 found 242.0233.

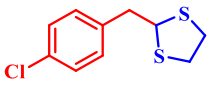
2-(4-fluorobenzyl)-1,3-dithiolane (3ga):



3ga was synthesized by following the general procedure **A**. Colourless liquid (77% yield, 33 mg). *Rf* = 0.80 (petroleum ether/EtOAc 99:1) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.19 (m, 2H), 7.02 – 6.95 (m, 2H), 4.69 (t, *J* = 7.0 Hz, 1H), 3.26 – 3.15 (m, 4H), 3.08 (d, *J* = 7.0 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.97 (d, *J* = 244.9 Hz),

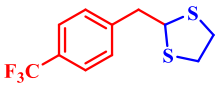
134.83 (d, *J* = 3.2 Hz), 130.83 (d, *J* = 7.9 Hz), 115.27 (d, *J* = 21.2 Hz), 54.98 (d, *J* = 1.4 Hz), 44.54, 38.71. ^{19}F NMR (377 MHz, $CDCl_3$) δ -116.1. HRMS (ESI TOF) *m/z* $[M]^+$ calculated for $[C_{10}H_{11}S_2F]^+$ 214.0258 found 214.0213.

2-(4-chlorobenzyl)-1,3-dithiolane (3ha):



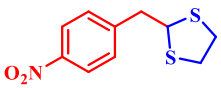
3ha was synthesized by following the general procedure **A**. Colourless liquid (61% yield, 28 mg). *Rf* = 0.78 (petroleum ether/EtOAc 99:1) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 4.68 (t, *J* = 7.0 Hz, 1H), 3.26 – 3.15 (m, 4H), 3.07 (d, *J* = 7.0 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 137.5, 132.8, 130.7, 128.6, 54.7, 44.7, 38.8. HRMS (ESI TOF) *m/z* $[M+H]^+$ calculated for $[C_{10}H_{12}ClS_2]^+$ 231.0063 found 231.0080.

2-(4-(trifluoromethyl)benzyl)-1,3-dithiolane (3ia):



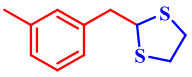
3ia was synthesized by following the general procedure **A**. Colourless liquid (51% yield, 27 mg). *Rf* = 0.70 (petroleum ether/EtOAc 99:1) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.1 Hz, 2H), 7.38 (d, *J* = 8.1 Hz, 2H), 4.72 (t, *J* = 7.0 Hz, 1H), 3.29 – 3.19 (m, 4H), 3.16 (d, *J* = 7.0 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 143.01 (d, *J* = 1.5 Hz), 129.75 (s), 128.47 (s), 125.44 (q, *J* = 4.0 Hz), 54.34 (s), 45.23 (s), 38.82 (s). ^{19}F NMR (472 MHz, $CDCl_3$) δ -62.6. HRMS (ESI TOF) *m/z* $[M+H]^+$ calculated for $[C_{11}H_{12}F_3S_2]^+$ 265.0327 found 265.0355.

2-(4-nitrobenzyl)-1,3-dithiolane (3ja):



3ja was synthesized by following the general procedure **A**. Yellow solid. (40% yield, 36 mg). *Rf* = 0.8 (petroleum ether/EtOAc 95:5) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 – 8.14 (m, 2H), 7.46 – 7.40 (m, 2H), 4.72 (t, *J* = 6.9 Hz, 1H), 3.23 – 3.18 (m, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 147.1, 146.4, 130.4, 123.7, 53.9, 45.2, 38.9. HRMS (ESI TOF) *m/z* $[M+H]^+$ calculated for $[C_{10}H_{12}NO_2S_2]^+$ 242.0304 found: 242.0310.

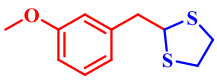
2-(3-methylbenzyl)-1,3-dithiolane (3ka):



3ka was synthesized by following the general procedure **A**. Colourless liquid

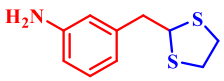
(71% yield, 30 mg). *Rf* = 0.81 (petroleum ether/EtOAc 99:1) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 – 7.18 (m, 1H), 7.07 (m, 3H), 4.74 (t, *J* = 7.2 Hz, 1H), 3.31 – 3.17 (m, 4H), 3.09 (d, *J* = 7.2 Hz, 2H), 2.35 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 139.2, 138.1, 130.0, 128.4, 127.7, 126.2, 55.1, 45.3, 38.7, 21.5. HRMS (ESI TOF) *m/z* $[M+H]^+$ calculated for $[C_{11}H_{15}S_2]^+$ 211.0610 found 211.0641.

2-(3-methoxybenzyl)-1,3-dithiolane (3la):



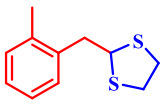
3la was synthesized by following the general procedure **A**. Colourless liquid (71% yield, 32 mg). *Rf* = 0.68 (petroleum ether/EtOAc 99:1) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.23 (m, 1H), 6.88 (d, *J* = 7.6 Hz, 1H), 6.86 – 6.81 (m, 2H), 4.76 (t, *J* = 7.2 Hz, 1H), 3.84 (s, 3H), 3.35 – 3.18 (m, 4H), 3.13 (d, *J* = 7.1 Hz, 2H) $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 160.0, 141.1, 129.8, 121.9, 115.2, 112.6, 55.6, 55.2, 45.8, 39.0. HRMS (ESI TOF) *m/z* $[M+1]^+$ calculated for $[C_{11}H_{15}OS_2]^+$ 227.0559 found: 227.0555.

3-((1,3-dithiolan-2-yl)methyl)aniline (3ma):



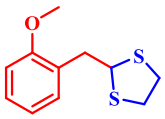
3ma was synthesized by following the general procedure **A**. Pale yellow coloured liquid (66% yield, 28 mg). *Rf* = 0.40 (petroleum ether/EtOAc 80:20) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (m, 1H), 6.65 (m, 1H), 6.57 (m, 2H), 4.71 (t, *J* = 7.2 Hz, 1H), 3.64 (s, 2H), 3.31 – 3.16 (m, 4H), 3.03 (d, *J* = 7.2 Hz, 2H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 146.5, 140.5, 129.4, 119.4, 115.9, 113.8, 55.0, 45.4, 38.7. HRMS (ESI TOF) *m/z* $[M+H]^+$ calculated for $[C_{10}H_{14}NS_2]^+$ 212.0562 found 212.0567.

2-(2-methylbenzyl)-1,3-dithiolane (3na):



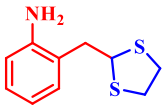
3na was synthesized by following the general procedure **A**. Colourless liquid (78% yield, 33 mg). *Rf* = 0.80 (petroleum ether/EtOAc 99:1) ^{1}H NMR (400 MHz, $CDCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (ddd, *J* = 6.6, 4.3, 2.4 Hz, 1H), 7.16 (dd, *J* = 5.4, 4.0 Hz, 3H), 4.76 (t, *J* = 7.3 Hz, 1H), 3.36 – 3.18 (m, 4H), 3.15 (d, *J* = 7.3 Hz, 2H), 2.36 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 137.6, 136.3, 130.5, 129.9, 127.0, 126.0, 54.0, 42.5, 38.7, 19.8. HRMS (ESI TOF) *m/z* $[M+H]^+$ calculated for $[C_{11}H_{15}S_2]^+$ 211.0610 found 211.0633.

2-(2-methoxybenzyl)-1,3-dithiolane (3oa):



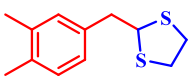
3oa was synthesized by following the general procedure **A**. Colourless liquid (77% yield, 35 mg). *Rf* = 0.65 (petroleum ether/EtOAc 99:1) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (dd, *J* = 7.3, 3.9 Hz, 1H), 7.20 (d, *J* = 7.5 Hz, 1H), 6.90 (t, *J* = 7.4 Hz, 1H), 6.84 (d, *J* = 8.2 Hz, 1H), 4.88 (t, *J* = 7.3 Hz, 1H), 3.83 (s, 3H), 3.25 (ddq, *J* = 10.3, 8.4, 6.7 Hz, 4H), 3.11 (d, *J* = 7.3 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.6, 131.1, 128.3, 127.7, 120.4, 110.3, 55.3, 53.2, 40.8, 38.6. HRMS (ESI TOF) *m/z* $[M+H]^+$ calculated for $[C_{11}H_{13}OS_2]^+$ 227.0559 found: 227.0564.

2-((1,3-dithiolan-2-yl)methyl)aniline (3pa):



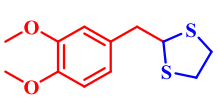
3pa was synthesized by following the general procedure **A**. Pale yellow coloured liquid (85% yield, 36 mg). *Rf* = 0.45 (petroleum ether/EtOAc 80:20) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (m, 1H), 7.07 (m, 1H), 6.77 (m, 1H), 6.69 (m, 1H), 4.83 (t, *J* = 7.0 Hz, 1H), 3.81 (br, 2H), 3.32 – 3.19 (m, 4H), 3.06 (d, *J* = 7.0 Hz, 2H). ^{13}C{^{1}H} NMR (400 MHz, $CDCl_3$) δ 144.6, 131.0, 128.1, 124.3, 119.1, 116.5, 53.5, 41.3, 38.8. HRMS (ESI TOF) *m/z* $[M+H]^+$ calculated for $[C_{10}H_{14}NS_2]^+$ 212.0562 found 212.0563.

2-(3,4-dimethylbenzyl)-1,3-dithiolane (3qa):



3qa was synthesized by following the general procedure **A**. Colourless liquid (78% yield, 35 mg). *Rf* = 0.74 (petroleum ether/EtOAc 99:1) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (d, *J* = 7.6 Hz, 1H), 7.03 (s, 1H), 7.01 – 6.97 (m, 1H), 4.72 (t, *J* = 7.2 Hz, 1H), 3.24 (tdt, *J* = 13.7, 9.2, 6.7 Hz, 4H), 3.06 (d, *J* = 7.2 Hz, 2H), 2.26 (s, 3H), 2.24 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 136.8, 136.6, 135.1, 130.4, 129.8, 126.5, 55.3, 44.9, 38.6, 19.9, 19.5. HRMS (ESI TOF) *m/z* $[M+H]^+$ calculated for $[C_{12}H_{17}S_2]^+$ 225.0772 found 225.0750.

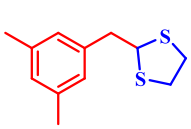
2-(3,4-dimethoxybenzyl)-1,3-dithiolane (3ra):



3ra was synthesized by following the general procedure **A**. Colourless liquid (78% yield, 40 mg). *Rf* = 0.55 (petroleum ether/EtOAc 99:1) ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (s, 3H), 4.70 (t, *J* = 7.1 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.21 (ddq, *J* = 14.3, 9.4, 7.1 Hz, 4H), 3.05 (d, *J* = 7.1 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.0,

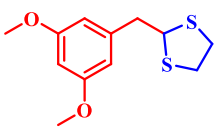
158.4, 131.3, 120.2, 103.6, 98.4, 55.4, 55.3, 53.5, 40.0, 38.1. HRMS (ESI TOF) *m/z* $[M]^+$ calculated for $[C_{12}H_{16}S_2O_2]^+$ 256.0592 found 256.0596.

2-(3,5-dimethylbenzyl)-1,3-dithiolane (3sa):



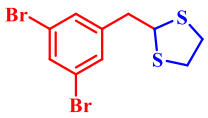
3sa was synthesized by following the general procedure **A**. Colourless liquid (71% yield, 32 mg). *Rf* = 0.80 (petroleum ether/EtOAc 99:1) ^{1}H NMR (400 MHz, CDCl3) δ 6.89 (s, 1H), 6.87 (s, 2H), 4.73 (t, *J* = 7.2 Hz, 1H), 3.33 – 3.15 (m, 4H), 3.06 (d, *J* = 7.2 Hz, 2H), 2.31 (s, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 139.2, 138.2, 128.6, 126.9, 55.1, 45.3, 38.7, 21.4. HRMS (ESI TOF) *m/z* $[M+H]^+$ calculated for $[C_{12}H_{17}S_2]^+$ 225.0772 found 225.0750.

2-(3,5-dimethoxybenzyl)-1,3-dithiolane (3ta):



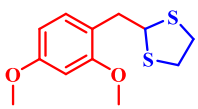
3ta was synthesized by following the general procedure **A**. Colourless liquid (70% yield, 36 mg). *Rf* = 0.60 (petroleum ether/EtOAc 99:1) ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.41 (d, *J* = 2.2 Hz, 2H), 6.35 (t, *J* = 2.2 Hz, 1H), 4.71 (t, *J* = 7.2 Hz, 1H), 3.78 (s, 6H), 3.32 – 3.14 (m, 4H), 3.05 (d, *J* = 7.2 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.8, 141.5, 107.1, 98.9, 55.4, 54.8, 45.7, 38.7. HRMS (ESI TOF) *m/z* $[M]^+$ calculated for $[C_{12}H_{16}O_2S_2]^+$ 256.0592 found 256.0596.

2-(3,5-dibromobenzyl)-1,3-dithiolane (3ua):



3ua was synthesized by following the general procedure **A**. Colourless liquid (61% yield, 43 mg). *Rf* = 0.66 (petroleum ether/EtOAc 99:1) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (m, 1H), 7.35 (s, 2H), 4.65 (t, *J* = 7.0 Hz, 1H), 3.33 – 3.15 (m, 4H), 3.03 (d, *J* = 7.0 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 142.5, 132.4, 131.0, 122.6, 53.8, 44.5, 38.5. HRMS (ESI TOF) *m/z* $[M]^+$ calculated for $[C_{10}H_{10}S_2Br_2]^+$ 351.8591 found 351.8595.

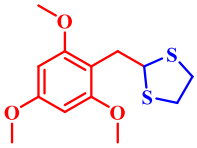
2-(2,4-dimethoxybenzyl)-1,3-dithiolane (3va):



3va was synthesized by following the general procedure **A**. Colourless liquid (72% yield, 37 mg). *Rf* = 0.54 (petroleum ether/EtOAc 99:1) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 – 7.05 (m, 1H), 6.43 (m, 1H), 6.43 – 6.41 (m, 1H), 4.83 (t, *J* = 7.3 Hz, 1H),

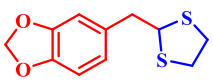
3.79 (s, 3H), 3.79 (s, 3H), 3.33 – 3.15 (m, 4H), 3.02 (d, *J* = 7.3 Hz, 2H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 160.0, 158.4, 131.3, 120.3, 103.7, 98.5, 55.4, 55.3, 53.5, 40.0, 38.5. HRMS (ESI TOF) *m/z* $[M]^+$ calculated for $[C_{12}H_{16}O_2S_2]^+$ 256.0592 found 256.0596.

2-(2,4,6-trimethoxybenzyl)-1,3-dithiolane (3wa):



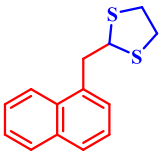
3wa was synthesized by following the general procedure **A**. Colourless liquid (75% yield, 43 mg). *Rf* = 0.45 (petroleum ether/EtOAc 99:1) ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.12 (s, 2H), 4.86 (t, *J* = 7.6 Hz, 1H), 3.80 (s, 3H), 3.80 (s, 6H), 3.35 – 3.14 (m, 4H), 3.09 (d, *J* = 7.6 Hz, 2H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 160.1, 159.3, 109.0, 90.7, 55.8, 55.4, 53.7, 38.2, 31.8. HRMS (ESI TOF) *m/z* $[M+H]^+$ calculated for $[C_{13}H_{19}O_3S_2]^+$ 287.0776 found 287.0775.

5-((1,3-dithiolan-2-yl)methyl)benzo[d][1,3]dioxole (3xa):



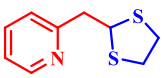
3xa was synthesized by following the general procedure **A**. Colourless liquid (73% yield, 35 mg). *Rf* = 0.55 (petroleum ether/EtOAc 99:1) ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75 (dd, *J* = 4.7, 3.1 Hz, 2H), 6.70 (dd, *J* = 7.9, 1.6 Hz, 1H), 5.93 (s, 2H), 4.66 (t, *J* = 7.1 Hz, 1H), 3.28 – 3.15 (m, 4H), 3.02 (d, *J* = 7.1 Hz, 2H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 147.6, 146.5, 133.1, 122.3, 109.6, 108.3, 101.0, 55.3, 45.1, 38.7. HRMS (ESI TOF) *m/z* $[M+H]^+$ calculated for $[C_{11}H_{13}O_2S_2]^+$ 241.0351 found 241.0360.

2-(naphthalen-1-ylmethyl)-1,3-dithiolane (3ya):



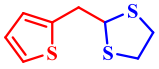
3ya was synthesized by following the general procedure **A**. Pal yellow coloured liquid (73% yield, 36 mg). *Rf* = 0.80 (petroleum ether/EtOAc 99:1) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (m, 1H), 7.87 (m, 1H), 7.78 (m, 1H), 7.57 – 7.43 (m, 4H), 4.94 (t, *J* = 7.2 Hz, 1H), 3.59 (d, *J* = 7.2 Hz, 2H), 3.35 (ddd, *J* = 12.4, 8.8, 7.1 Hz, 2H), 3.23 (ddd, *J* = 12.4, 8.8, 7.1 Hz, 2H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 135.3, 134.0, 131.7, 129.1, 127.9, 127.4, 126.2, 125.8, 125.5, 123.5, 54.2, 42.6, 38.8. HRMS (ESI TOF) *m/z* $[M+Na]^+$ calculated for $C_{14}H_{14}S_2$ 269.0434 found 269.0424.

2-((1,3-dithiolan-2-yl)methyl)pyridine (3za)



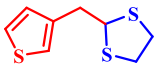
3za was synthesized by following the general procedure **A**. Colourless liquid (79% yield, 31 mg). *Rf* = 0.80 (petroleum ether/EtOAc 70:30) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 – 8.46 (m, 1H), 7.54 (td, *J* = 7.7, 1.8 Hz, 1H), 7.13 (d, *J* = 7.8 Hz, 1H), 7.08 (ddd, *J* = 7.5, 4.9, 1.0 Hz, 1H), 4.94 (t, *J* = 7.3 Hz, 1H), 3.25 – 3.11 (m, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.6, 149.3, 136.3, 123.5, 121.7, 52.7, 47.6, 38.5. HRMS (ESI TOF) *m/z* $[M+H]^+$ calculated for $[C_9H_{12}NS_2]^+$ 198.0406 found: 198.0411.

2-(thiophen-2-ylmethyl)-1,3-dithiolane (3a'a):



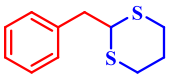
3a'a was synthesized by following the general procedure **A**. Colourless liquid (84% yield, 35 mg). *Rf* = 0.70 (petroleum ether/EtOAc 80:20) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 2.4 Hz, 1H), 7.59 (dd, *J* = 8.2, 2.5 Hz, 1H), 7.27 (d, *J* = 8.7 Hz, 2H), 4.67 (t, *J* = 6.7 Hz, 1H), 3.23 – 3.12 (m, 4H), 3.07 (d, *J* = 6.7 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 150.7, 140.0, 133.0, 123.9, 53.9, 41.7, 38.9. HRMS (ESI TOF) *m/z* $[M+H]^+$ calculated for $[C_8H_{11}S_3]^+$ 203.0023 found: 203.0023

2-(thiophen-3-ylmethyl)-1,3-dithiolane (3b'a):



3b'a was synthesized by following the general procedure **A**. Colourless liquid (89% yield, 36 mg). *Rf* = 0.75 (petroleum ether/EtOAc 80:20) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (dd, *J* = 4.7, 3.1 Hz, 1H), 7.02 (d, *J* = 2.1 Hz, 1H), 6.95 (d, *J* = 4.9 Hz, 1H), 4.65 (t, *J* = 6.9 Hz, 1H), 3.17 – 3.09 (m, 4H), 3.07 (d, *J* = 6.9 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 139.5, 128.5, 125.5, 122.4, 54.2, 40.0, 38.7. HRMS (ESI TOF) *m/z* $[M+H]^+$ calculated for $[C_8H_{11}S_3]^+$ 203.0017 found: 203.0023.

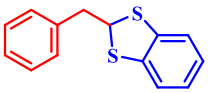
2-benzyl-1,3-dithiane (3ab):



3ab was synthesized by following the general procedure **A** where instead of **2a**, 1,3-propanedithiol **2b** was used. Colourless liquid. (20% yield, 36 mg). *Rf* = 0.4 (petroleum ether/EtOAc 98:2) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.34 (m, 1H), 7.34 – 7.31 (m, 1H), 7.31 – 7.26 (m, 3H), 4.28 (t, *J* = 7.4 Hz, 1H), 3.06 (d, *J* = 7.4 Hz, 2H), 2.89 – 2.84 (m, 4H), 2.18 – 2.09 (m, 1H), 1.95 – 1.83 (m, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 137.4, 129.3,

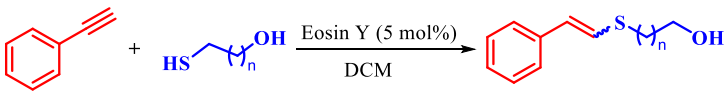
128.4, 127.1, 48.7, 41.8, 30.6, 25.8. HRMS (ESI TOF) *m/z* $[M+H]^+$ calculated for $[C_{11}H_{15}S_2]^+$ 211.0610 found: 211.0612.

2-benzylbenzo[d][1,3]dithiole (3ac):



3ac was synthesized by following the general procedure **A** where instead of **2a**, benzene1,2-dithiol **2c** was used. Red coloured liquid. (74% yield, 36 mg). *Rf* = 0.8 (petroleum ether/EtOAc 95:5) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (tt, *J* = 7.9, 1.9 Hz, 2H), 7.31 (dt, *J* = 5.6, 2.3 Hz, 1H), 7.29 – 7.25 (m, 4H), 7.08 (dd, *J* = 5.8, 3.2 Hz, 2H), 5.05 (t, *J* = 7.5 Hz, 1H), 3.26 (d, *J* = 7.5 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 137.6, 137.2, 129.6, 128.6, 127.2, 125.6, 122.7, 55.7, 45.2. HRMS (ESI TOF) *m/z* $[M+H]^+$ calculated for $[C_{14}H_{13}S_2]^+$ 245.0453 found: 245.0472.

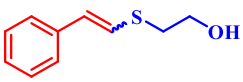
3.6.3 General procedure B for Thiol-yne reaction of 2d-2e on phenylacetylene/ Synthesis of 3ad-3ae:



1a | **2d - 2e** (**2d** n = 0, **2e** n = 1) | **3ad - 3ae** (**3ad** n = 0, **3ae** n = 1)

An oven-dried round bottom flask containing a stir bar charged with **1a** (0.2 mmol), **3d-3e** (0.2 mmol), Eosin Y (5 mol%,), DCM (2 mL) under inert atmosphere. Then the reaction mixture was degassed by purging argon gas for 5 min to remove any dissolved air and oxygen. Then the reaction mixture was stirred under the irradiation of Blue LEDs (30 W) at room temperature for 12-24 h. (Monitored by TLC). After the completion of the reaction, the solvent was removed under reduced pressure and the crude residue was further purified by preparative thin-layer chromatography using a mixture of petroleum ether/EtOAc as an eluent to afford respective compounds (**7ad-7ae**) as oil.

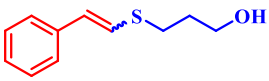
Mixture of (*E*)-2-(styrylthio)ethan-1-ol and (*Z*)-2-(styrylthio)ethan-1-ol (3ad):



3ad was synthesized by following the general procedure **B** where **2d** was used as reaction partner. Colourless liquid (35 mg, 79%) *Rf* = 0.80 (petroleum ether/EtOAc 95:5) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.5 - 7.2 (5H), 6.7 - 6.2 (2H), 3.8

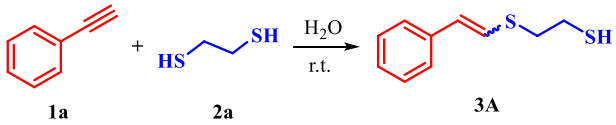
(2H), 3.0 - 2.9 (2H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 136.7, 136.7, 129.1, 128.8, 128.8, 128.4, 127.3, 127.1, 126.9, 126.3, 125.8, 123.8, 61.6, 61.1, 38.8, 36.1. HRMS (ESI TOF) *m/z* $[M+H]^+$ calculated for $[C_{10}H_{13}OS]^+$ 181.0682 found: 181.0678.

Mixture of (*E*)-2-(styrylthio)propa-1-ol and (*Z*)-2-(styrylthio)propa-1-ol (3ae):



3ae was synthesized by following the general procedure **B** where **2e** was used as reaction partner. Colourless liquid (36 mg, 76%) *Rf* = 0.81 (petroleum ether/EtOAc 95:5) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.5 - 7.2 (5H), 6.7 - 6.2 (2H), 3.8 - 3.7 (2H), 2.9 (2H), 2.0 - 1.9 (2H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 137.1, 137.0, 128.8, 128.7, 128.4, 127.5, 127.2, 127.1, 126.8, 126.0, 125.6, 124.8, 61.4, 61.1, 32.8, 32.4, 32.1, 29.2. HRMS (ESI TOF) *m/z* $[M+H]^+$ calculated for $[C_{11}H_{15}OS]^+$ 195.0838 found: 195.0848.

3.6.4 Procedure for the synthesis of 3A[18]

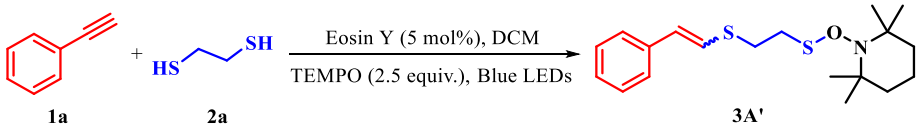


1a 2a 3A

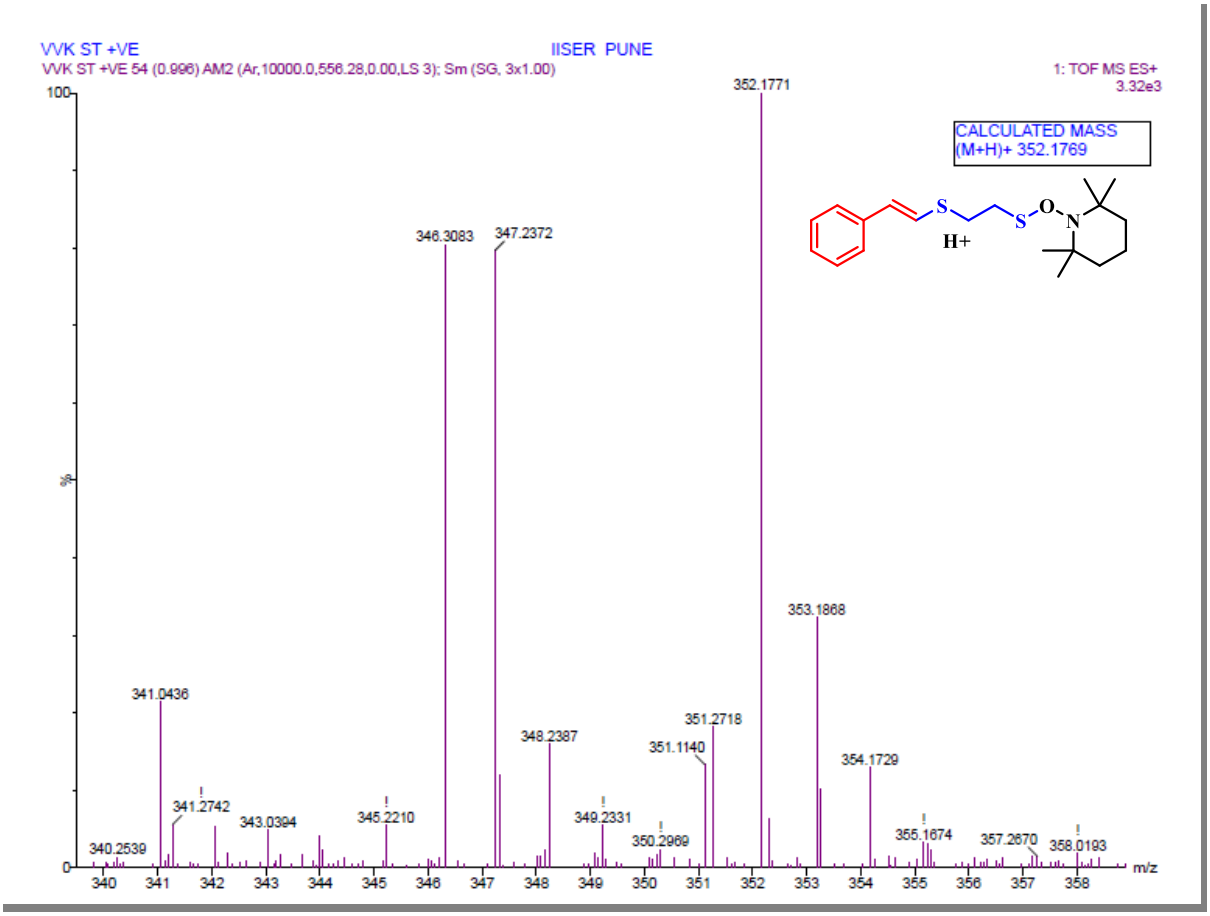
An oven-dried round bottom flask containing a stir bar charged with **1a** (2 mmol), **2a** (2 mmol), H_2O (5 mL). Then the reaction mixture was stirred for 3 h. After completion of reaction the reaction mixture was extracted in diethyl ether two times (20 mL x 2). The combined organic layer was filtered through anhydrous sodium sulphate then diethyl ether was evaporated under reduced pressure. The crude product was further purified by column chromatography over silica gel using mixture of petroleum ether/EtOAc as an eluent to obtain **3A** with 70% yield as a colourless oil.[18] *Rf* = 0.79 (petroleum ether/EtOAc 99:1) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.14 (m, 6H), 6.65 (d, *J* = 15.6 Hz, 1H), 6.56 (d, *J* = 15.6 Hz, 1H), 6.47 (d, *J* = 10.8 Hz, 1H), 6.19 (d, *J* = 10.8 Hz, 1H), 3.80 (td, *J* = 5.9, 4.6 Hz, 2H), 2.95 (dt, *J* = 7.6, 6.0 Hz, 2H), 2.03 (s, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 136.7, 136.7, 129.1, 128.8, 128.8, 128.4, 127.3, 127.1, 126.9, 126.3, 125.8, 123.8, 77.2, 61.6, 61.1, 38.8, 36.1. HRMS (ESI TOF) *m/z* $[M+H]^+$ calculated for $[C_{10}H_{13}S_2]^+$ 197.0453 found: 197.0460.

3.6.5 Control experiments:

a. Reaction with TEMPO

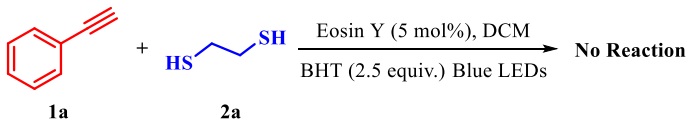


The 10 mL round bottom flask containing a magnetic stir bar charged with **1a** (0.2 mmol,), **2a** (0.2 mmol), Eosin Y (5 mol%), TEMPO (0.5 mmol, 78.13 mg) in 2 mL DCM under an inert atmosphere. The reaction mixture was initially degassed for 5 minutes then it was subjected to the irradiation of blue light. After 24 hours we have taken the TLC of the reaction mixture and we came to know that our dihydrothionation type of product was not formed but starting material was completely consumed then we have given the HRMS of the reaction mixture. We notified that TEMPO trapped **3A'** product was formed and the HRMS of **3A'** is shown below.



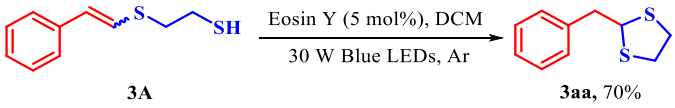
HRMS Spectrum of 3A'

b. Reaction with BHT



A 10 mL round bottom flask containing a magnetic stir bar was charged with **1a** (0.2 mmol), **2a** (0.2 mmol), Eosin Y (5 mol%,), BHT (0.5 mmol) in 2 mL DCM under an inert atmosphere. The reaction mixture was initially degassed for 5 minutes then it was subjected to the irradiation of blue light. After 24 hours we have taken TLC of the reaction mixture and we came to know that our dihydrothionation type of product was not formed.

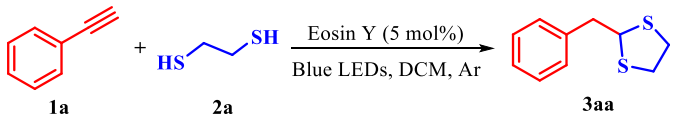
c. The reaction of 3A under optimized reaction conditions:



A 10 mL round bottom flask containing a magnetic stir bar was charged with **3A** (0.2 mmol), and Eosin Y (5 mol%) in 2 mL DCM solvent under an inert atmosphere. The reaction mixture was initially degassed for 5 minutes then it was kept under the irradiation of blue LED (30 W). The reaction was monitored by TLC, after completion of the reaction solvent was evaporated and **3aa** was purified by preparative thin-layer chromatography (70% yield).

3.6.6 Applications of 2-benzyl-1,3-dithiol

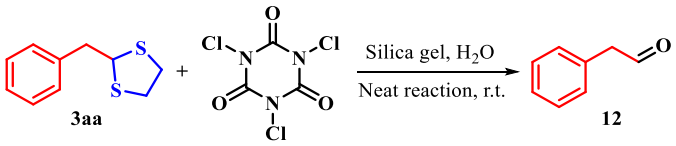
a. Gram scale synthesis of (3aa):



An oven-dried round bottom flask (100 mL) containing a stir bar was charged with **1a** (9.79 mmol, 1 equiv., 1 g), **2a** (9.79 mmol, 0.922 g, 1 equiv.), Eosin Y (5 mol%, 0.308 g), DCM (80 mL). The reaction mixture was initially purged with argon for 5 min to remove any dissolved air and the argon atmosphere was maintained throughout the reaction (using a balloon). After complete consumption of starting material, the solvent was evaporated under the reduced

pressure and the crude product was further purified by column chromatography over silica gel using a mixture of petroleum ether/EtOAc as an eluent to afford **3aa** as colourless oil (73% yield, 1.4 g).

b. Deprotection of 3aa[21]:



A mixture of **3aa** (2 mmol, 39.26 mg), trichloroisocyanuric acid (3 mmol, 69.72 mg) and silica gel (2 g) was grinding in a mortar with the help of a piston. Water (10-15 drops) was added with constant stirring and the resultant mixture was extracted in 5ml of hexane/ethyl acetate (5:1). The organic layer was filtered through sodium sulfate and evaporated under reduced pressure to afford phenyl acetaldehyde **12** as a colourless liquid. (80%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (t, *J* = 2.4 Hz, 1H), 7.41 – 7.36 (m, 2H), 7.32 (dt, *J* = 9.7, 4.4 Hz, 1H), 7.25 – 7.21 (m, 2H), 3.70 (d, *J* = 2.4 Hz, 2H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 199.6, 132.0, 129.7, 129.1, 127.5, 50.7. HRMS (ESI TOF) *m/z* $[M+H]^+$ calculated for $[C_8H_9O]^+$ 121.0648 found: 121.0644.

Appendix III:

Table 3.2: ^{1}H and $^{13}C\{^{1}H\}$ NMR Spectral data of representative compounds

Compound No.	Figure 3.N	Data	Page No.
3aa	Figure 3.2 and figure 3.3	^{1}H and $^{13}C\{^{1}H\}$ NMR	87
3a'a	Figure 3.4 and figure 3.5	^{1}H and $^{13}C\{^{1}H\}$ NMR	88
3A	Figure 3.6 and figure 3.7	^{1}H and $^{13}C\{^{1}H\}$ NMR	89
9	Figure 3.8 and figure 3.9	^{1}H and $^{13}C\{^{1}H\}$ NMR	90

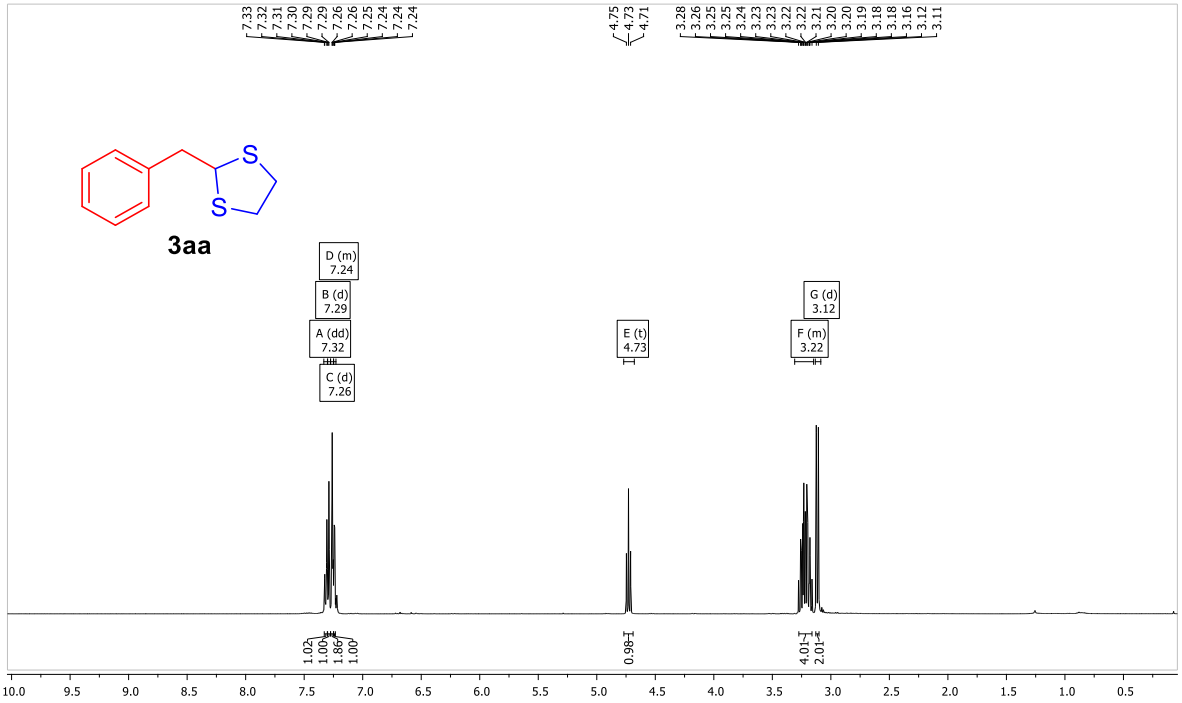


Figure 3.2 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3aa**

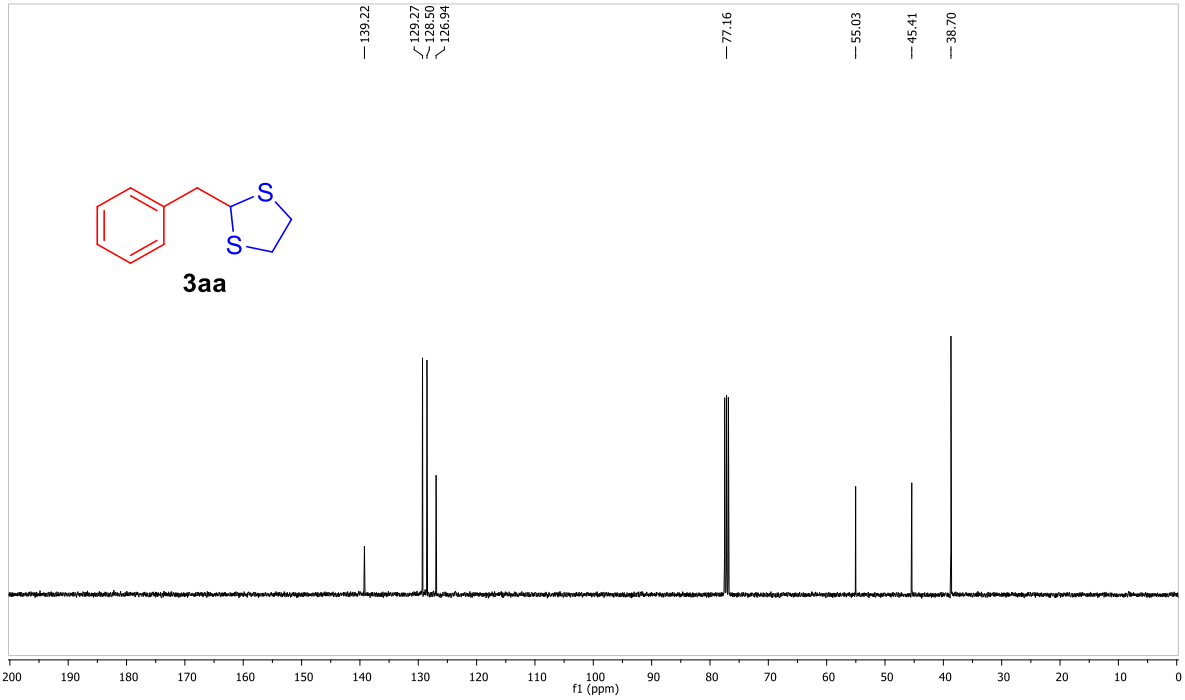


Figure 3.3 $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of compound **3aa**

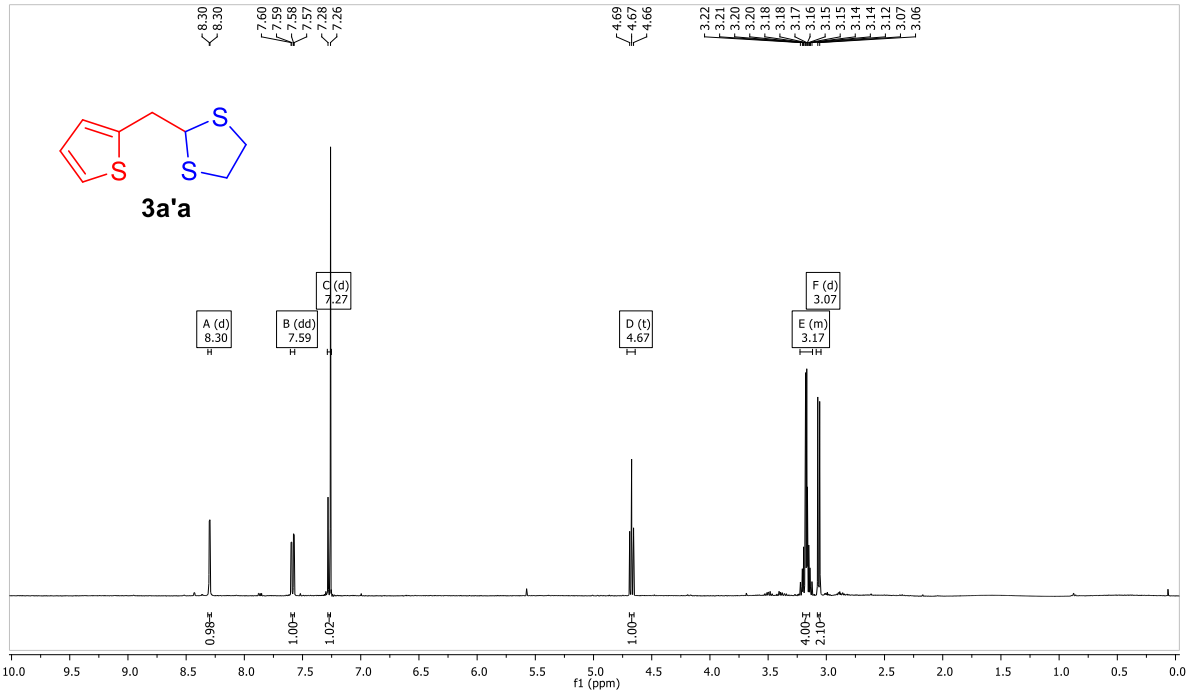


Figure 3.4 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3a'a**

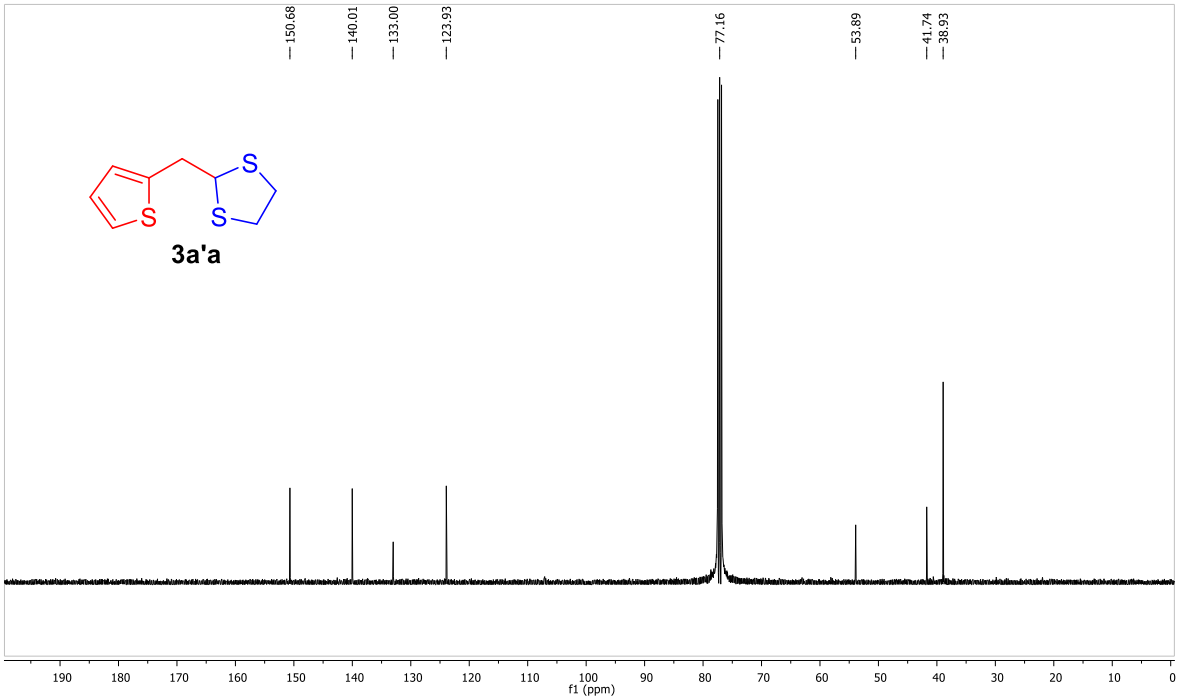


Figure 3.5 $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of compound **3a'a**

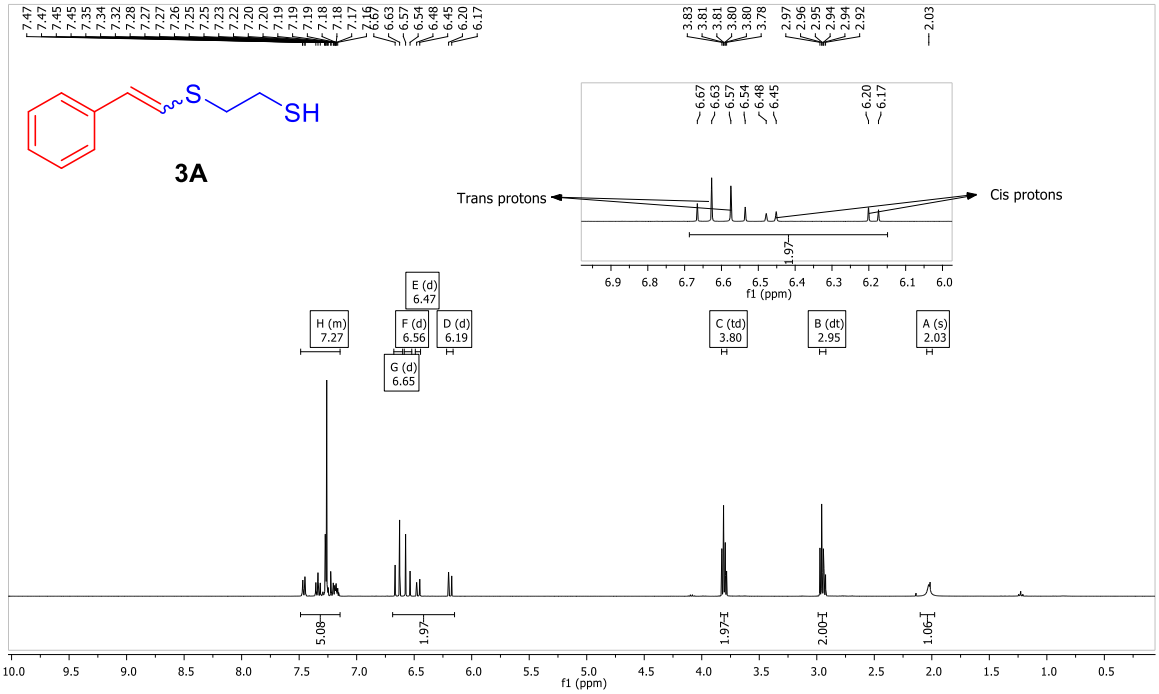


Figure 3.6 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3A**

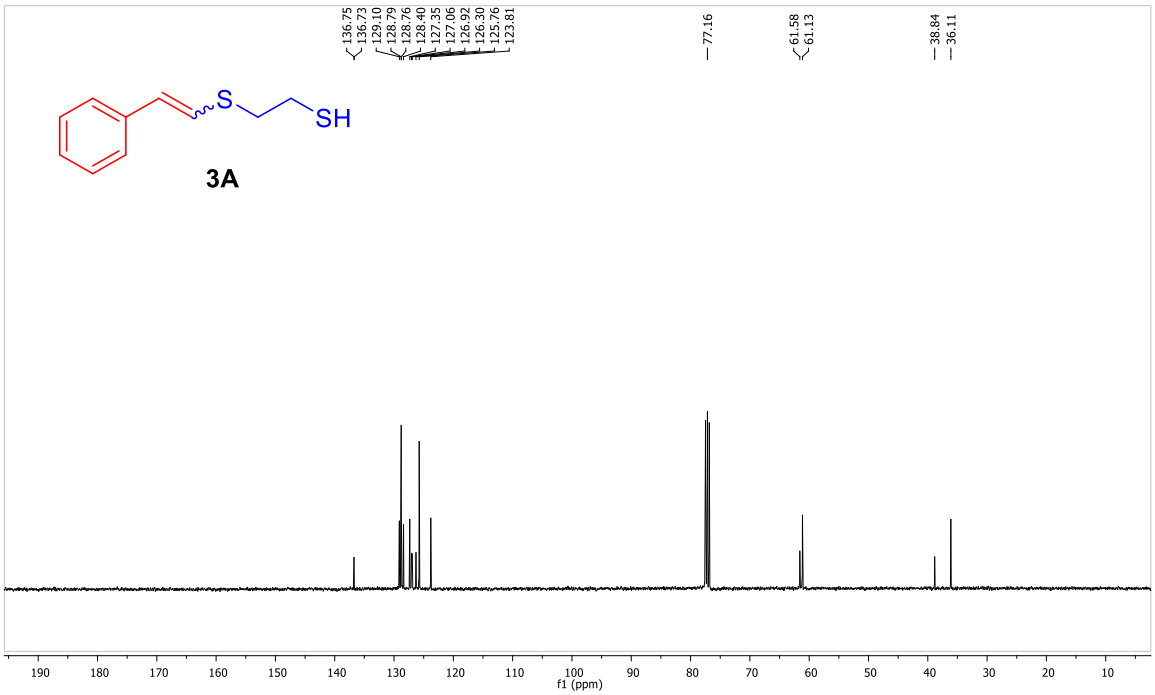


Figure 3.7 $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of compound **3A**

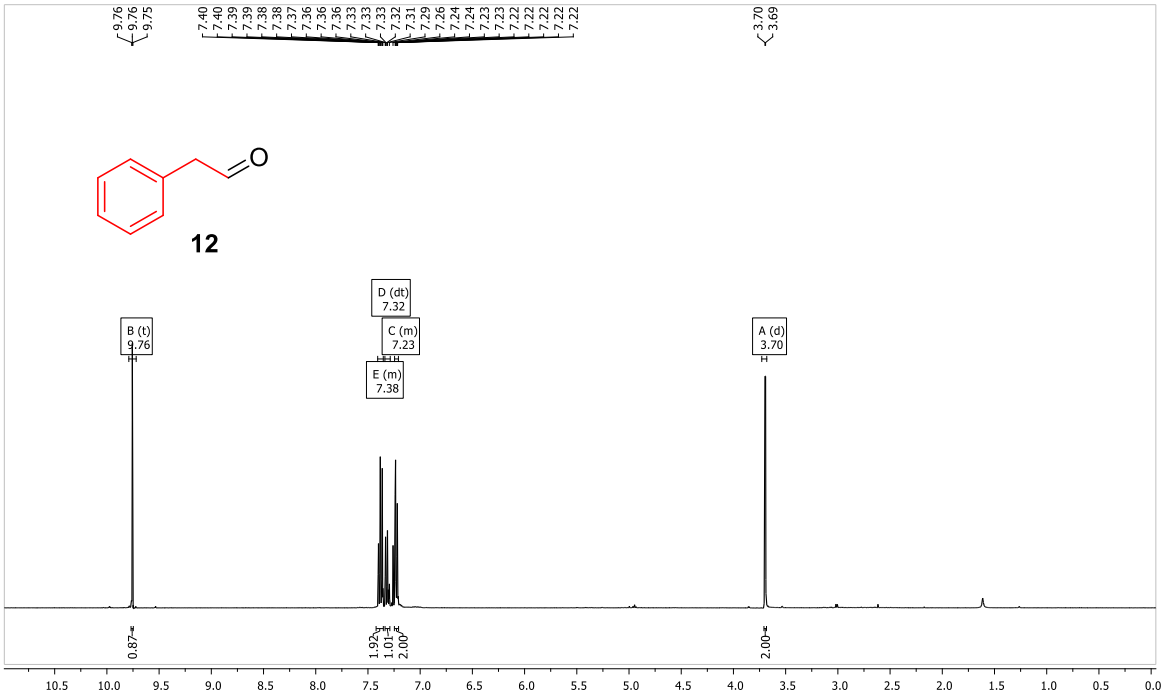


Figure 3.7 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **9**

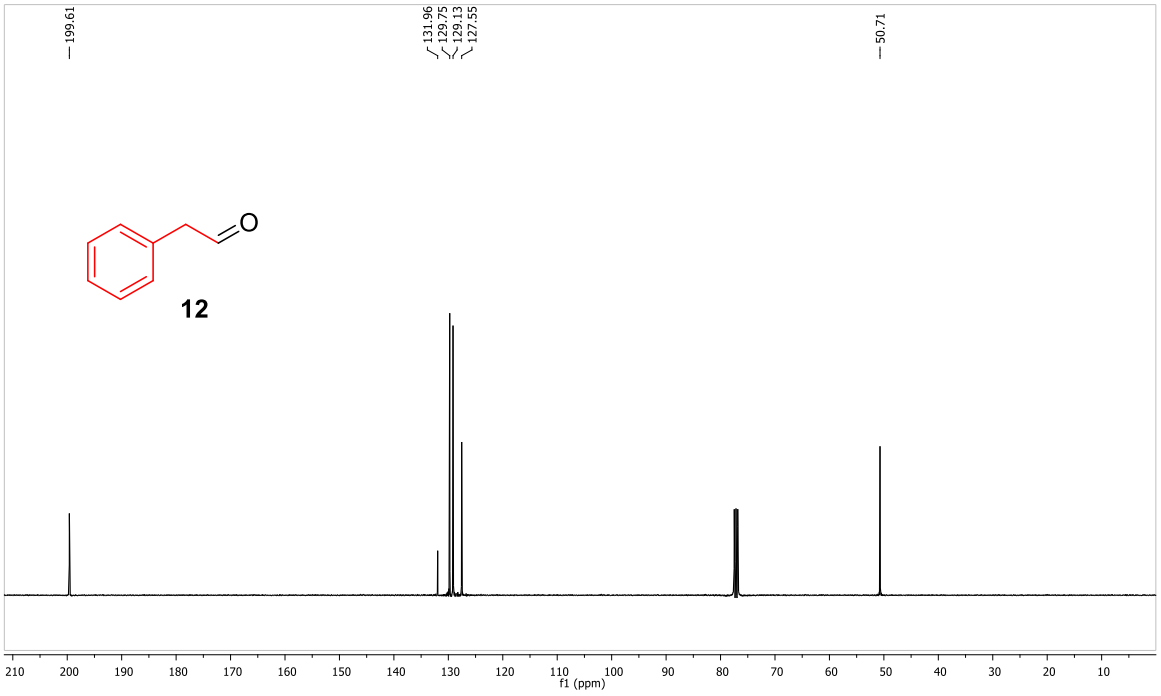


Figure 3.9 ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **9**

3.7 References

1. (a) Y. Mori, Y. Kohchi, M. Suzuk. *J. Org. Chem.*, **1991**, *56*, 631-637; (b) S. D. Rychnovsky, *Chem. Rev.*, **1995**, *95*, 2021-2040; (c) A. B. Smith, S. M. Condon, J. A. McCauley. *Acc. Chem. Res.*, **1998**, *31*, 35-46; (d) V. Aucagne, C. Lorin, A. Tatibouët, P. Rollin. *Tetrahedron Lett.*, **2005**, *46*, 4349-4352; (e) W. H. Pearson, I. Y. Lee, Y. Mi, P. Stoy. *J. Org. Chem.*, **2004**, *69*, 9109-9122; (f) C. A. Woodland, G. C. Crawley, R. C. Hartley. *Tetrahedron Lett.*, **2004**, *45*, 1227-1231; (g) H. Mizuno, K. Domon, K. Masuya, K. Tanino, I. Kuwajima. *J. Org. Chem.*, **1999**, *64*, 2648-2656.
2. (a) M. H. Ali, M. G. Gomes. *Synthesis*, **2005**, 1326-1332; (b) B. Das, R. Ramu, M. R. Reddy, G. Mahender. *Synthesis*, **2005**, 250-254; (c) S. Rudrawar, R. C. Besra, A. K. Chakraborti. *Synthesis*, **2006**, 2767-2771; (d) M. Hideyoshi, N. Yuichi, S. Mitsuru. *Chem. Lett.*, **2007**, *36*, 104-105; (e) B. Karimi, M. Khalkhali. *J. Mol. Catal. A: Chem.*, **2007**, *271*, 75-79.
3. (a) S.-S. Weng, S.-C. Chang, T.-H. Chang, J.-P. Chyn, S.-W. Lee, C.-A. Lin, F.-K. Chen. *Synthesis*, **2010**, 1493-1499; (b) S. K. De. *Tetrahedron Lett.*, **2004**, *45*, 2339-3241; (c) F. Bracher, T. Litz. *Arch. Pharm.*, **1995**, *328*, 235-238.
4. G. Bez, D. Gogoi. *Tetrahedron Lett.*, **2006**, *47*, 5155-5157.
5. K. Chaiseeda, W. Chavasiri. *Phosphorus, Sulfur Silicon Relat. Elem.*, **2017**, *192*, 1034-1039.
6. (a) Z. Xing, M. Yang, H. Sun, Z. Wang, P. Chen, L. Liu, X. Wang, X. Xie, X. She. *Green Chem.*, **2018**, *20*, 5117-5122; (b) K. Du, S.-C. Wang, R. S. Basha, C.-F. Leea. *Adv. Synth. Catal.*, **2019**, *361*, 1597-1605.
7. N. Muraoka, M. Mineno, K. Itami, J.-I. Yoshida. *J. Org. Chem.*, **2005**, *70*, 6933-6936.
8. L. L. Santos, V. R. Ruiz, M. J. Sabater, A. Corma. *Tetrahedron*, **2008**, *64*, 7902-7909.
9. M. J. Gaunt, H. F. Sneddon, P. R. Hewitt, P. Orsini, D. F. Hook, S. V. Ley. *Org. Biomol. Chem.*, **2003**, *1*, 15-16.
10. H. Kuroda, I. Tomita, T. Endo. *Synth. Commun.*, **1996**, *26*, 1539-1543.
11. M. Hut'ka, T. Tsubogo, S. Kobayashi. *Organometallics*, **2014**, *33*, 5626-5629.
12. (a) M. Takenori, D. Masayuki, N. Akihiro, O. Akiya. *Bull. Chem. Soc. Jpn.*, **2011**, *84*, 413-415; (b) J. S. Yadav, B. V. S. Reddy, A. Raju, K. Ravindar, G. Baishya. *Chem. Lett.*, **2007**, *36*, 1474-1475; (c) N. Taniguchi, K. Kitayama. *Synlett.*, **2018**, 2712-2716.

13. B. D. Fairbanks, T. F. Scott, C. J. Kloxin, K. S. Anseth, C. N. Bowman. *Macromolecules,* **2009**, *42*, 211-217.
14. V. Balzani, A. Credi, M. Venturi. *ChemSusChem*., **2008**, *1*, 26-58.
15. (a) N. A. Romero, D. A. Nicewicz. *Chem. Rev.,* **2016**, *116*, 10075-10166; (b) M. H. Shaw, J. Twilton, D. W. C. MacMillan. *J. Org. Chem.,* **2016**, *81*, 6898-6926; (c) D. Ravelli, M. Fagnoni. *ChemCatChem.*, **2012**, *4*, 169-171.
16. F. M. Manhas, J. Kumar, S. Raheem, P. Thakur, M. A. Rizvi, B. A. Shah. *ChemPhotoChem*, **2021**, *5*, 235.
17. (a) Y. Thummala, G. V. Karunakar, V. R. Doddi. *Adv. Synth. Catal.*, **2019**, *361*, 611-616; (b) U. Dutta, S. Maity, R. Kancherla, D. Maiti. *Org. Lett.,* **2014**, *16*, 6302–6305.
18. (a) S. Bhadra, B. C. Ranu. *Can. J. Chem.,* **2009**, *87*, 1605-1609; (b) Z. Jin, B. Xu, G. B. Hammond. *Eur. J. Org. Chem.*, **2010**, 168-173.
19. (a) S. S. Zalesskiy, N. S. Shlapakov, V. P. Ananikov. *Chem. Sci*., **2016**, *7*, 6740-6745; (b) D. A. Nicewicz, T. M. Nguyen. *ACS Catal*., **2014**, *4*, 355; (c) D. P. Hari, B. König. *Chem. Commun*., **2014**, *50*, 6688; (d) D. Ravelli, M. Fagnoni. *ChemCatChem*, **2012**, *4*, 169; (e) D. P. Hari, B. König. *Org. Lett*., **2011**, *13*, 3852.
20. H. G. Roth, N. A. Romero, D. A. Nicewicz. *Synlett* **2016**, 714-723.
21. H. Firouzabadi, N. Iranpoor, H. Hazarkhani. *Phosphorus, Sulfur and Silicon*, **2002**, *177*, 2571-2577.

An Access to Strenuous Fused Dihalo-Aziridino Quinoxalinone via C3-H Functionalization followed by Tandem Cyclization of Quinoxalinone.

4

4.1 Abstract:

Quinoxalinones are a privileged class of organic compounds and they play an important role in the synthesis of many bioactive compounds, natural products and pharmaceuticals. Quinoxalinone is a promising framework for different functionalization and the slight modification of the quinoxalinone skeleton offers a wide range of compounds for drug discovery. Owing to the importance of quinoxalinone scaffold, we have developed a base-mediated protocol for the C3-H functionalization of quinoxalinone followed by tandem cyclization to access a novel type of strenuous and fused dihalo-aziridino-quinoxalinone heterocycles via C–C and C–N bond construction. The protocol proved to be simple and practical to access the desired products in excellent yields (Up to 98% yield). The highly functionalized fused dihalo-aziridino-quinoxalinone molecule has been utilized for further application under photoredox conditions as well as reduction purposes. Moreover, the protocol has been demonstrated on the gram scale and these fused dihalo-aziridino-quinoxalinones may be of potential use.

4.2 Importance of Quinoxalin-2(1*H*)-one

Quinoxalin-2(1*H*)-one is one of the important class of bioactive frameworks that is commonly found in many pharmaceutical compounds. Quinoxalin-2(1*H*)-one derived compounds known for their anticonvulsant,[1] antidepression,[2] antibacterial,[3] antiviral,[4] anti-inflammatory,[5] anti-allergy,[6] antithrombosis,[7] anti-diabetes,[8] anti-oxidation,[9] properties (Figure 4.1). Looking at their exceptional biological importance and in the drug discovery process, even the little modification of quinoxalin-2(1*H*)-one backbone has been considered as useful as a wide variety of new chemical entities (NCE) with potential bioactivities. Owing to this, in recent years, the direct C3-H functionalization of quinoxalinone has gained great attention to access novel compounds and to explore potential biological activity for newer targets.[10]

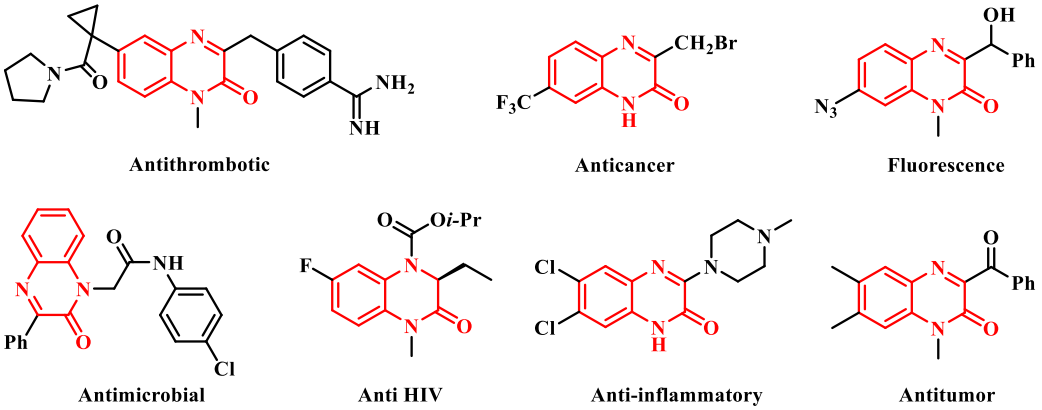
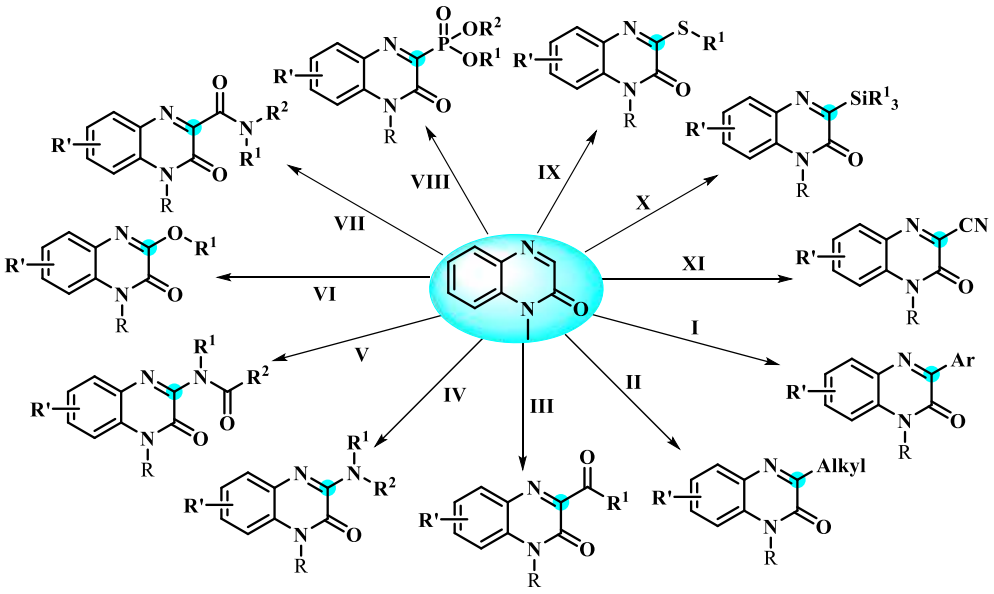


Figure 4.1 Representative quinoxalin-2(1*H*)-ones derivative with varied biological properties

Similarly, three-membered *N*-heterocyclic compounds such as aziridines are also known for their intrinsic reactivity due to their steric strain. They are also widely present in many natural products, and biomolecules. They have been utilized in various organic transformations due to their inherent reactivity and to access many interesting compounds.[11]

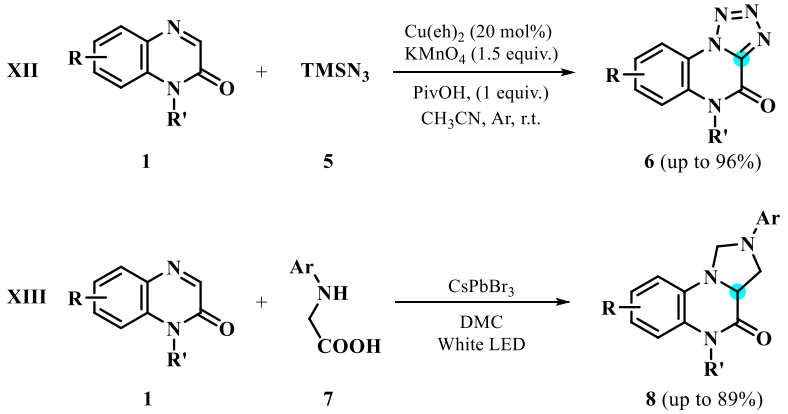
4.3 Previous approaches for C-3 functionalization of quinoxalin-2(1*H*)-one

Considering the importance of quinoxalin-2(1*H*)-one skeleton, many researchers have dedicated their efforts to the direct functionalization of quinoxalin-2(1*H*)-one moiety to access different quinoxalinone derivatives. Many novel, mild, efficient, and sustainable synthetic strategies have been reported for the C3-arylation of quinoxalinones by using different reagents such as aryl boronic acids,[12a] arylhydrazines,[12b] diaryliodonium salts,[12c] arylamines,[12d,e] aryl diazonium salts,[12f] and simple arenes as well.[12g] The metal-mediated and metal-free approaches have been explored for the simple C3-alkylation of quinoxalinone either under thermal or photochemical conditions.[13] Recently, the C3-acylation of quinoxalinone has been achieved by utilizing α-oxo acids[14] and aldehydes.[15] Other strategies such as C3-amination,[16] amidation,[17] alkoxylation,[18] carboamylation,[19] phosphonation,[20] thiolation,[21] silylation,[22] and cynation[23] have been also successfully demonstrated relying on photocatalysis, electrocatalysis, metal catalysis, and radical oxidative coupling reactions (Scheme 4.1).



Scheme 4.1 C-3 functionalization of quinoxalin-2(1*H*)-one (**I**: arylation, **II**: alkylation, **III**: acylation, **IV**: amination, **V**: amidation, **VI**: alkoxylation, **VII**: carboamylation, **VIII**: phosphonation, **IX**: thiolation, **X**: silylation, **XI**: cynation)

All these functionalization strategies rely on the formation of C–C, C–O, C–N, C–S, C–P, and C–Si bonds. Likewise, the C–N and (N–N or C–C) bond formation strategies have been explored in one-pot to access the fused quinoxalinones.



Scheme 4.2 C-3 functionalization of quinoxalin-2(1*H*)-one followed by tandem cyclization

Qiming Yang *et. al.*, have described the copper-catalyzed C-3 functionalization of quinoxalin-2(1*H*)-ones followed by the tandem cyclization to access different fused **6** tetrazolo[1,5-*a*]quinoxalin-4(5*H*)-ones using commercially viable and relatively safer trimethylsilyl azide

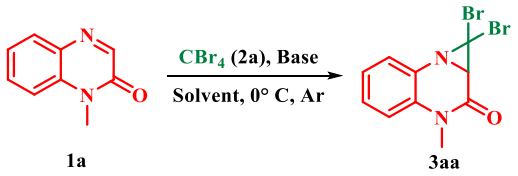
($TMSN_3$) as an azide source (up to 96%, Scheme 4.2**XI**).[24a] This protocol has successively constructed C–N and N–N bonds in one pot under mild and simple reaction conditions. Cheng and coworkers have reported the C-3 functionalization of quinoxalin-2(1*H*)-one followed by tandem cyclization starting from α-amino acid derivatives using $CsPbBr_3$ perovskite under visible light irradiations to from corresponding fused compound tetrahydroimidazo[1,5-*a*]quinoxalin-4(*5H*)-ones **7** in good to very good yields (up to 89%, Scheme 4.2**XII**).[24b] The strategy relied on the subsequent C–C and C–N forming reactions to access tetrahydroimidazo[1,5-*a*]quinoxalin-4(5*H*)-ones. Owing to the importance of quinoxalinone core and aziridine framework and also looking at the importance of *N*-heterocyclic fused quinoxalinone we planned to explore the synthesis of fused aziridino quinoxalinones via a simple and practical strategy. We hypothesized that the construction of C–C and C–N bonds will be the key to the effective C3-functionalization of quinoxalinones and for the further synthesis of fused quinoxalinone scaffold.

In this chapter, we present the development of a protocol for the direct synthesis of novel class of fused dihalo-aziridino-quinoxalinone derivatives starting from *N*-alkyl/aryl-quinoxalinones and sodium *tert*-butoxide as a base, CBr_4 as a one-carbon source reagent in acetonitrile solvent under an inert atmosphere via C3-alkylation followed by a tandem cyclization (annulation).

4.4 Results and Discussion

To explore the proposed plan, we commenced with a model reaction of 1-methyl quinoxalin-2(1*H*)-one **1a** and carbon tetrabromide **2a** using potassium *tert*-butoxide (KO*t*-Bu) in acetonitrile at 0 °C under inert atmosphere (0.5 h). Interestingly, we observed the complete consumption of **1a**, to afford the corresponding desired fused dibromo-aziridine-quinoxalinone **3aa** albeit in poor yield (25%, see Table 4.1, Entry 1). Further to enhance the yield of **3aa**, we screened different bases. Among all, potassium *tert*-butoxide, potassium hydroxide, sodium *tert*-butoxide and sodium *tert*-pentoxide proved to be effective for the desired transformation and sodium *tert*-butoxide proved to be the most efficient base affording the **3aa** in 57% yield (Table 4.1, Entries 1, 4, 7, 8). While the other bases such as potassium carbonate, potassium phosphate, potassium acetate, potassium bisulfate, and sodium ethoxide did not work (Table 4.1 Entries 2-4, 5-6, 9). We further screened the reaction by varying the stoichiometric amount of CBr_4 and sodium *tert*-butoxide to examine the effect on the outcome of the reaction (Table 4.1, Entries 10, 11).

Table No. 4.1 Optimization of reaction condition[s]



Entry	Base	Solvent	Time (h)	Yield (%)
1	KO^{t}Bu	MeCN	0.5	25
2	K_2CO_3	MeCN	48	ND
3	K_3PO_4	MeCN	48	ND
4	KOH	MeCN	48	15
5	KOAc	MeCN	48	ND
6	$KHSO_4$	MeCN	48	ND
7	NaO^{t}Bu	MeCN	1	53
8	NaO^{t}Am	MeCN	3	17
9	NaOEt	MeCN	48	ND
10[b]	NaO^{t}Bu	MeCN	1	80
11[c]	NaO^{t}Bu	MeCN	1	90
12	NaO^{t}Bu	DCM	4	36
13	NaO^{t}Bu	Hexane	48	ND
14	NaO^{t}Bu	THF	3	50
15	NaO^{t}Bu	DMF	24	25
16	NaO^{t}Bu	DMSO	2	82
17	NaO^{t}Bu	Ethanol	24	ND
18	NaO^{t}Bu	EtOAc	48	ND
19	NaO^{t}Bu	Benzene	24	Trace
21[d]	NaO^{t}Bu	MeCN	1.25	93
22[e]	**NaO^{t}Bu**	**MeCN**	**1**	**97**
23[f]	NaO^{t}Bu	MeCN	2	97

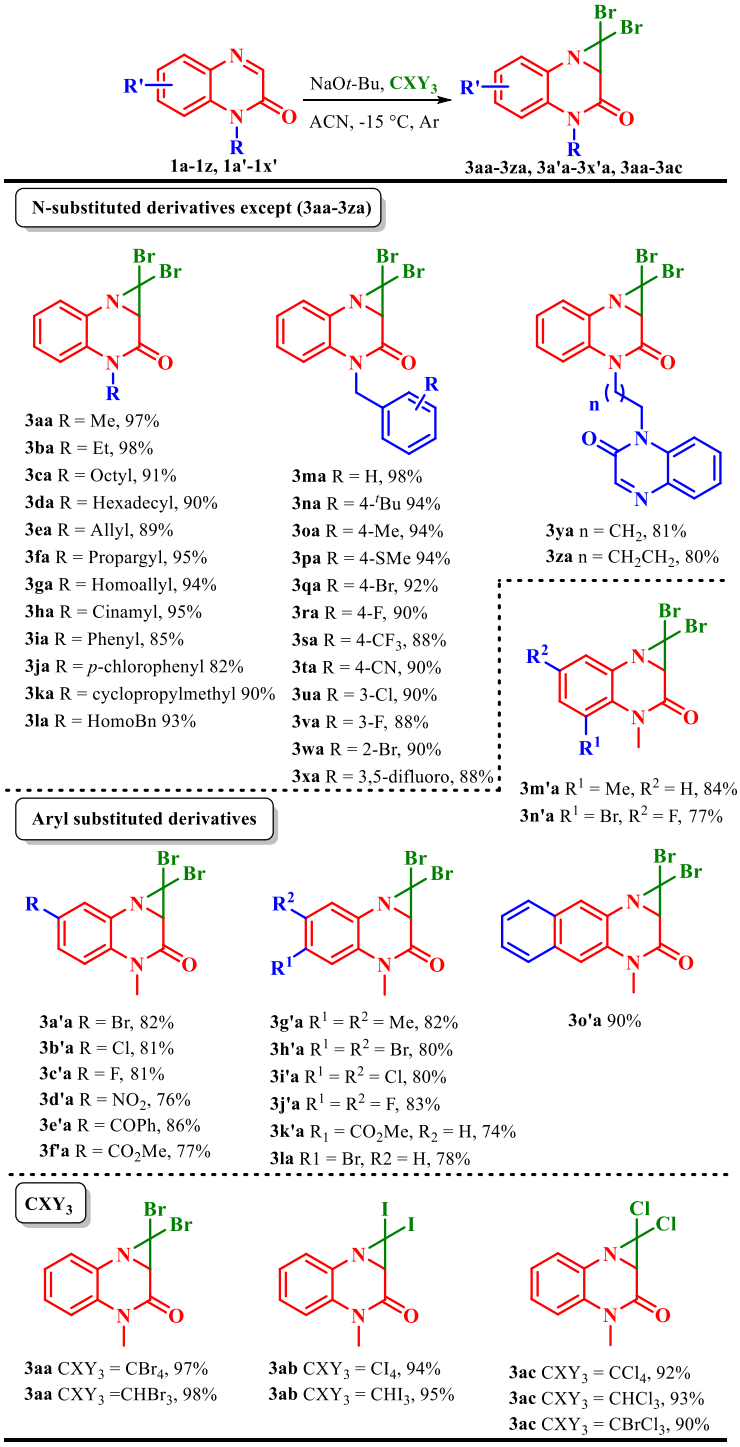
[a]**Reaction conditions: 1a** (0.2 mmol), **2a** (0.2 mmol), Base (0.3 mmol), MeCN (2 mL) under Ar at 0 °C. [b]**2a** (0.3 mmol), Base (0.3 mmol), [c]**2a** (0.4 mmol), Base (0.4 mmol) [d]**2a** (0.4 mmol), Base (0.4 mmol) at -10 °C, [e]**2a** (0.4 mmol), Base (0.4 mmol) at -15 °C, [f]**2a** (0.4 mmol), Base (0.4 mmol) at -20 °C.

Interestingly, we observed two-fold access of CBr_4 **2a** (2 equiv.) and sodium *tert*-butoxide **(**2 equiv.) afforded the corresponding the desired product **3aa** in excellent yield (90%, Table 4.1, Entry 11). We also screened different solvents such as DCM, Hexane, THF, DMSO, ethanol, ethyl acetate, benzene. None of these solvents were found to be as advantageous as acetonitrile (Table 4.1 Entries 12-19). Later, we carried out the reaction at different temperatures. Interestingly, we observed that reaction of **1a**, **2a** in presence of sodium *tert*-butoxide in acetonitrile afforded the corresponding desired product **3aa** in excellent yield at (-20 to -10 °C)

(Table 4.1, Entries 20-22). Reaction worked smoothly and fastest at -15 °C (1 h) to afford the desired product **3aa** in excellent yield (97%, Table 4.1, Entry 22). Based on the exhaustive and systematic screening, 1-methyl quinoxalin-2(1*H*)-one **1a** (1 equiv.), CBr_4, **2a** (2 equiv.), sodium *t*-butoxide (2 equiv.), in MeCN under an inert atmosphere at -15 °C proved to be the optimum reaction conditions to afford the desired fused dibromo-aziridino 1-methyl quinoxalinone **3aa** in excellent yield.

Having obtained the optimized reaction condition, we further planned to generalize this protocol by screening different *N*-alkyl quinoxalin-2(1*H*)-one derivatives (Scheme 4.3). The *N*-protected quinoxalin-2(1*H*)-one derivatives such as *N*-methyl as well as *N*-ethyl quinoxalin-2(1*H*)-ones afforded the corresponding fused dibromo-aziridino quinoxalinones (**3aa**, **3ba**) in excellent yields (up to 98%, Scheme 4.3). The long-chain alkyl-protected substrates such as *N*-octyl- and *N*-hexadecyl quinoxalin-2(1*H*)-ones also reacted smoothly under the optimum reaction condition to afford the corresponding desired products (**3ca** and **3da)** in excellent yields (up to 91%, Scheme 4.3). *N*-allyl/-propargyl/-homoallyl/-cinnamyl quinoxalin-2(1*H*)-ones (**1e-1h**) also reacted well under the optimum reaction conditions to afford the corresponding fused dibromo-aziridino quinoxalinones (**3ea**-**3ha)** in excellent yields (95%, Scheme 4.3). Interestingly, the olefin moieties (unsaturation) as protecting groups tolerated the reaction condition and we did not observe any cyclopropanation or cyclopropenation-derived products that are known to form under the conditions.[25] *N*-Phenyl and *N*-*p*-chlorophenyl quinoxalin-2(1*H*)-ones (**1i**, **1j**) also reacted smoothly under the optimum reaction conditions to afford the corresponding dibromo-aziridino quinoxalinones **3ia** and **3ja** respectively (up to 85%, Scheme 4.3). *N*-cyclopropyl and *N*-homobenzylic quinoxalin-2(1*H*)-ones (**1k** and **1l**) reacted smoothly under optimum reaction conditions to afford corresponding desired products (**3ka** and **3la)** respectively in excellent yield (93%, Scheme 4.3). The *N*-benzyl quinoxalin-2(1*H*)-one (**1m**) as well as *N*-*para*-substituted benzyl moieties such as *N*-4-*tert*-butyl benzyl (**1n**), *N*-4-methyl benzyl **1o**, *N*-4-thiomethoxy benzyl (**1p**), *N*-4-bromobenzyl (**1q**), *N*-4-fluorobenzyl (**1r**), *N*-4-trifluoromethyl benzyl (**1s**), and *N*-4-cynobenzyl (**1t**)-quinoxalin-2(1*H*)-one derivatives (having electron-donating and electron-deactivating, electron-withdrawing groups) reacted smoothly under the reaction conditions to furnish the corresponding fused dibromo-aziridino quinoxalinones (**3ma**-**3ta)** in excellent yields (up to 98%, Scheme 4.3). While *N*-3-chlorolobenzyl- and *N*-3-fluorobenzyl-quinoxalin-2(1*H*)-

ones (deactivating groups) afforded the corresponding **3ua-3va** in excellent yields (up to 90%, Scheme 4.3).



(Reaction Conditions: 1a (0.2 mmol), **2a** (0.4 mmol), Base (0.4 mmol), MeCN (2 mL) under Ar at -15 °C)

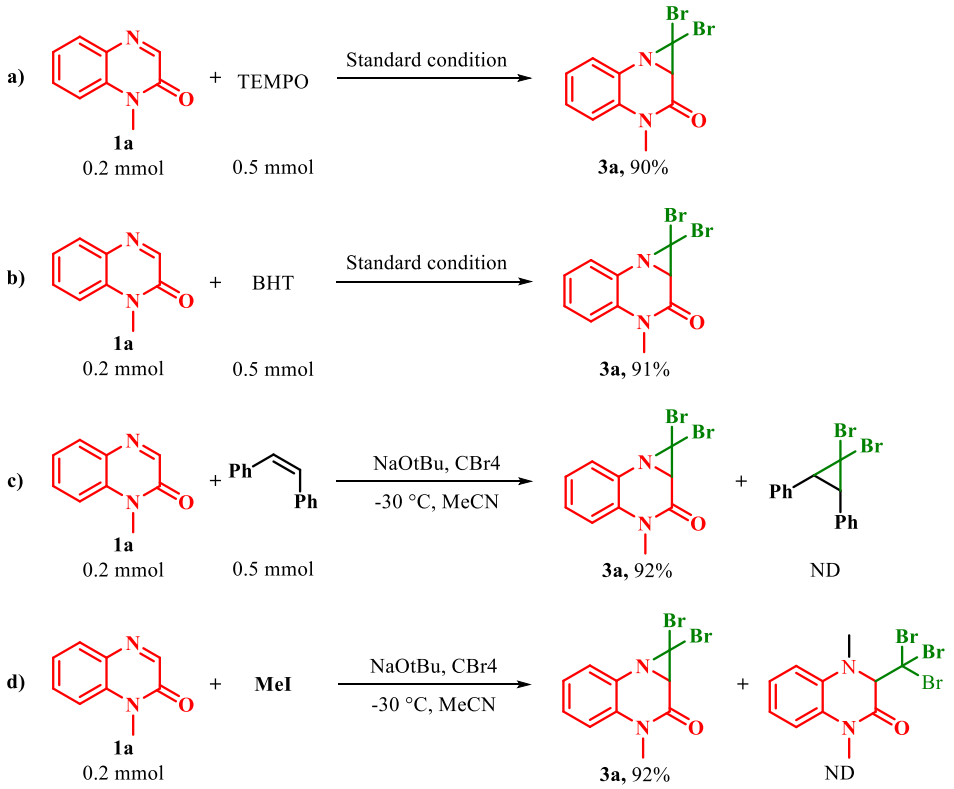
Scheme 4.3 Substrate scope for fused dihalo-aziridine-quinoxalinones

Even the *N*-2-bromo benzyl-quinoxalin-2(1*H*)-one (**1w**) afforded the corresponding fused dibromo-aziridino quinoxalinone **3wa** in excellent yield (up to 90%, Scheme 4.3). Interestingly, the *N*-disubstituted benzyl such as *N*-3,5-difluoro dibenzyl quinoxalin-2(*1H*)-one (**1x**) afforded the corresponding desired product **3xa** in excellent yield (88%, Scheme 4.3). We observed that different protecting groups, steric as well as the electronic effect of protecting group did not have any impact on the outcome of the yield; probably due to the distal presence from the reactive site. However, more importantly, the reactive olefinic protecting group did not react under these reaction conditions. Later, we explored the reaction of quinoxalinone dimers connected through ethyl (**1y**), and as well as propyl (**1z**) linkage also underwent reaction smoothly at one side of the dimer to afford the fused dibromo-aziridino quinoxalinones (**3ya** and **3za)** respectively in excellent yields (up to 81%, Scheme 4.4). We also observed that unprotected quinoxalin-2(*1H*)-one and *N*-substituted methyl acyl as well as *N*-ethyl methyl ester did not afford the corresponding fused dibromo aziridino quinoxalinones under the reaction condition due to the presence of free acidic proton under the basic condition.

Later, we explored the reactivity of different *N*-methyl quinoxalin-2(1*H*)-ones having substituents on the aryl part. We observed that under optimum reaction conditions all the derivatives reacted smoothly to afford the corresponding products with good to very good yields (up to 86%, Scheme 4.3). The *N*-methylquinoxalin-2(1*H*)-ones having electron deactivating groups at 6-position (Bromo **1a'**, Chloro **1b'**, Fluoro **1c'**) furnished the corresponding products **3a'a**, **3b'a**, **3c'a** respectively in good yields (up to 82%, Scheme 4.3). *N*-methylquinoxalin-2(1*H*)-ones having electron-withdrawing groups such as -NO_2 (**1d'**), -C(O)Ph (**1e'**), -CO_2Me (**1f'**) at 6-position also smoothly reacted under the optimum reaction conditions to afford the corresponding products (**3d'a-3f'a)** in moderate to good yields (up to 86%, Scheme 4.4). Di-substituted *N*-methylquinoxalin-2(1*H*)-ones (at 6 and 7-positions) having electron-donating (**1g'**) and electron-deactivating groups (**1h'-1j'**) furnished the corresponding desired products (**3g'a**, **3h'a-3j'a**) in good to excellent yields (up to 83%, Scheme 4.3). *N*-Methylquinoxalin-2(1*H*)-one having bromo group (**1k'**), methyl ester group at 7 positions (**1l'**) gave the corresponding products (**3k'a-3l'a**) in good yields (up to 78%, Scheme 4.3). The *N*-methyl, 1,8-dimethyl quinoxalinone **1m'** afforded the corresponding product **3m'a** in very good yield (84%, Scheme 4.3). The reaction of 8-bromo-6-fluoro-1-methylquinoxalin-2(1*H*)-one **1n'** under standard reaction conditions afforded the corresponding **3n'a** in good yield. Highly aromatic 1-

methylbenzo[*g*]quinoxalin-2(1*H*)-one **1o'** afforded the corresponding product **3o'a** in excellent yield (90%, Scheme 4.3).

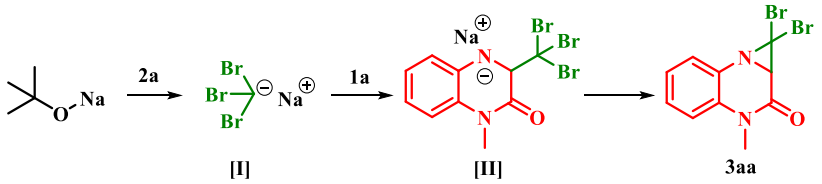
To evaluate the reactivity of carbon tetrahalides and to synthesize different fused dihalo-aziridino quinoxalinones we treated the *N*-methyl quinoxalin-2(1*H*)-one with different carbon tetrahalides as a carbon source for aziridination under the standard reaction conditions. $CHBr_3$ (**2b**) also reacted smoothly under the reaction conditions to afford **3aa** in excellent yield (98%). Also, CI_4 (**2c**) and CHI_3 (**2d**) reacted well under the reaction conditions to afford the corresponding desired products **3ab** in excellent yields. Likewise, CCl_4 (**2e**) and $CHCl_3$ (**2f**) reacted with *N*-methylquinoxalin-2(1*H*)-one under optimized reaction conditions to afford the corresponding fused dichloro-aziridine 1-methyl quinoxalinone **3ac** in excellent yields. $CBrCl_3$ (**2g**) also reacted with **1a** under optimum reaction conditions to afford the fused dichloro-aziridine **3ac** in excellent yield. Though there was no significant variation in the yield of the desired products, CBr_4, and $CHBr_3$ afforded the corresponding fused dibromo-aziridine *N*-methyl quinoxalinone relatively slightly higher yield.



Scheme 4.4 Control experiments

To probe the reaction mechanism, we performed a series of control experiments. The reactions of **1a** with carbon tetrabromide **2a** in presence of radical scavengers such as BHT (2.5 equiv.) as well as TEMPO (2.5 equiv.) in presence of sodium *tert*-butoxide under optimized reaction conditions afforded the desired product **3aa** in good yields (Scheme 4.4a, 4.4b). These experimental observations indicated that reaction does not involve a radical pathway. Later, we performed the reaction of **1a** with **2a** in presence of *cis*-stilbene under optimum reaction conditions to afford the corresponding desired product **3aa** exclusively (Scheme 4.4c). This result indicated that the reaction does not involve the carbene pathway during the course of the reaction. The reaction of **1a** and **2a** in presence of methyl iodide at -30 °C also afforded **3aa** with excellent yield (92%, Scheme 4.4d). These results concluded that intramolecular reactions are faster than intermolecular reactions.

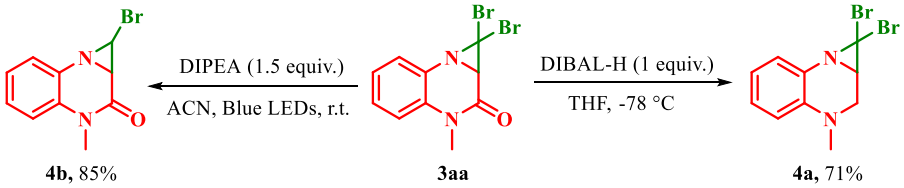
Based on our experimental observations and a series of control experiments a plausible reaction mechanism has been depicted (Scheme 4.5). The carbon tetrabromide reacts with sodium *tert*-butoxide to form an unstable carbanion [**I**]. This reactive intermediate [**I**] subsequently reacts with *N*-methyl quinoxalin-2(1*H*)-one **1a** to form unstable salt species [**II**]. This unstable salt intermediate further reacts intramolecularly with electrophilic carbon β to nitrogen via the elimination of bromine (instead of reacting with methyl iodide) to form the desired **3aa**.



Scheme 4.5 Plausible reaction mechanism

In order to explore the further utility of this product, we planned to explore the reactivity of **3aa** under visible light reaction conditions. Our lab has been working in the area of photoredox catalysis[26] and we explored the chemoselective and regioselective reduction of **3aa** in presence of DIPEA (1.5 equiv.) in acetonitrile to afford the corresponding product **4b** in very good yield (85%) under visible light conditions.[27] Alongside, we have also carried out the reduction of the amide group of **3aa** using DIBAL-H in THF at -78 °C to afford corresponding fused dibromo-aziridino piperazine derivative **4a** in good yield (71%). Later, to explore the practicality of the

transformation, we carried out the gram-scale synthesis of **3aa** (91% yield experimental section 4.6.4, page no. 120).



Scheme 6. Application of **3aa**

4.5 Conclusions

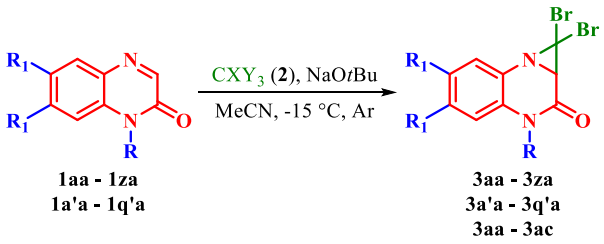
In summary, we have synthesized novel fused dihalo-aziridino quinoxalinone scaffold starting from *N*-substituted/aryl-substituted quinoxalin-2(1*H*)-one and haloforms/tetrahalo methanes under basic conditions via C–C as well as C–N bond construction. The protocol is very simple and practical and it has been demonstrated on a gram scale. A series of control experiments have been carried out to have insights into the mechanism. From an application view, **3aa** has been employed for the amide reduction and also under visible light reaction conditions for the selective reduction of halogen of aziridine ring.

4.6 Experimental Section

4.6.1 General

Note: (Please see section 2.6.1 for the general experiment, page no. 29)

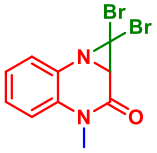
4.6.2 General procedure A for the synthesis of (3a-3w) and (3a'-3n'):



An oven-dried 25 mL round bottom flask equipped with a stir bar and rubber septum was charged with **1** (0.2 mmol) and sodium *tert*-butoxide (0.4 mmol) in acetonitrile (2 mL) solvent under inert conditions. The whole mixture was cooled up to -15 °C. The solution of **2** (0.4 mmol) in acetonitrile (1 mL) was added dropwise into the cooled solution of the reaction mixture under

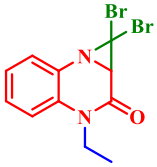
inert conditions. The reaction was monitored by thin-layer chromatography. After completion of the reaction, the solvent was evaporated under reduced pressure and the crude residue was purified by column chromatography using a mixture of petroleum ether/EtOAc as an eluent to afford the **3** as solid.

1,1-dibromo-3-methyl-1,1a-dihydroazirino[1,2-*a*]quinoxalin-2(3*H*)-one (3aa):



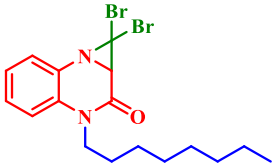
3aa was synthesized by following general procedure **A** where **2a** was utilized for the reaction. White solid (98% yield, 65 mg). M.P. (82.6-84.4 ℃) *Rf* = 0.70 (petroleum ether/EtOAc 90:10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (dt, *J* = 7.8, 2.0 Hz, 1H), 7.30 (ddd, *J* = 8.2, 7.5, 1.6 Hz, 1H), 7.14 (td, *J* = 7.6, 1.3 Hz, 1H), 6.98 – 6.94 (m, 1H), 3.75 (s, 1H), 3.34 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.7, 134.1, 128.5, 128.2, 128.0, 124.1, 114.9, 48.0, 35.5, 28.3. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{10}H_9Br_2N_2O]^+$ 330.9076, found 330.9089.

1,1-dibromo-3-ethyl-1,1a-dihydroazirino[1,2-*a*]quinoxalin-2(3*H*)-one (3ba):



3ba was synthesized by following general procedure **A** where **2a** was utilized for the reaction. White solid (98% yield, 68 mg). M.P. (100.1-102.1 ℃). *Rf* = 0.71 (petroleum ether/EtOAc 90:10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (dt, *J* = 4.5, 2.9 Hz, 1H), 7.29 (ddd, *J* = 8.3, 7.5, 1.6 Hz, 1H), 7.12 (td, *J* = 7.6, 1.2 Hz, 1H), 6.96 (dd, *J* = 8.3, 1.0 Hz, 1H), 4.10 (dq, *J* = 14.4, 7.2 Hz, 1H), 3.88 (dq, *J* = 14.3, 7.1 Hz, 1H), 3.71 (s, 1H), 1.22 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.3, 132.8, 128.7, 128.6, 128.0, 123.9, 114.8, 47.7, 36.2, 35.5, 12.1. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{11}H_{11}Br_2N_2O]^+$ 344.9233, found 344.9240.

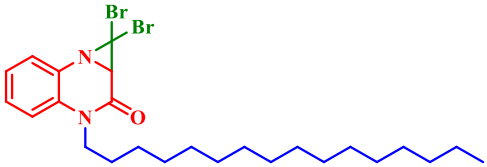
1,1-dibromo-3-octyl-1,1a-dihydroazirino[1,2-*a*]quinoxalin-2(3*H*)-one (3ca):



3ca was synthesized by following general procedure **A** where **2a** was utilized for the reaction. White solid (91% Yield, 78 mg), M.P. (88.4-90.2 ℃). *Rf* = 0.72 (petroleum ether/EtOAc 90:10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.31 – 7.25 (m, 1H), 7.11 (td, *J* = 7.6, 1.1 Hz, 1H), 6.92 (dd, *J* = 8.3, 1.0 Hz, 1H), 3.99 (dt, *J* = 14.3, 8.1 Hz, 1H), 3.81 – 3.72 (m, 1H), 3.71 (s, 1H), 1.64 – 1.52 (m, 2H), 1.44 – 1.19 (m, 10H), 0.87 (t, *J* = 6.9 Hz, 3H). ^{13}C{^{1}H}

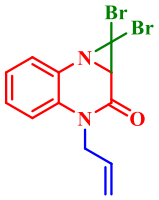
NMR (100 MHz, $CDCl_3$) δ 158.4, 133.1, 128.7, 128.5, 127.9, 123.8, 114.9, 64.6, 55.8, 47.8, 41.4, 35.6, 31.9, 27.1, 22.7, 18.2, 14.2. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{17}H_{23}Br_2N_2O]^+$ 429.0172, found 429.0168.

1,1-dibromo-3-hexadecyl-1,1a-dihydroazirino[1,2-*a*]quinoxalin-2(3*H*)-one (3da):



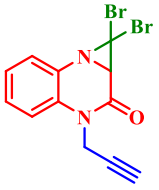
3da was synthesized by following general procedure **A** where **2a** was utilized for the reaction. White solid (90% yield, 98 mg), M.P. (67.8-70.5 °C) *Rf* = 0.75 (petroleum ether/EtOAc 90:10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.31 – 7.26 (m, 1H), 7.12 (td, *J* = 7.7, 1.2 Hz, 1H), 6.93 (dd, *J* = 8.2, 0.8 Hz, 1H), 4.00 (dt, *J* = 14.4, 8.0 Hz, 1H), 3.82 – 3.73 (m, 1H), 3.72 (s, 1H), 1.58 (dd, *J* = 15.5, 7.7 Hz, 2H), 1.42 – 1.35 (m, 2H), 1.32 (d, *J* = 6.7 Hz, 2H), 1.25 (s, 22aH), 0.87 (t, *J* = 6.8 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.4, 133.1, 128.7, 128.5, 128.0, 123.8, 114.9, 47.8, 41.5, 35.6, 32.1, 29.8, 29.8, 29.8, 29.7, 29.7, 29.5, 29.4, 27.1, 26.8, 22.8, 14.3. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{25}H_{39}Br_2N_2O]^+$ 541.1424, found 541.1428.

3-allyl-1,1-dibromo-1,1a-dihydroazirino[1,2-*a*]quinoxalin-2(3*H*)-one (3ea):



3ea was synthesized by following general procedure **A** where **2a** was utilized for the reaction. White solid (89% yield, 64 mg), M.P. (83.2-86.2 °C) *Rf* = 0.65 (petroleum ether/EtOAc 90:10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (dt, *J* = 7.8, 2.5 Hz, 1H), 7.29 – 7.22 (m, 1H), 7.15 – 7.09 (m, 1H), 6.93 (dd, *J* = 8.3, 1.2 Hz, 1H), 5.80 (ddt, *J* = 17.3, 10.3, 5.0 Hz, 1H), 5.28 – 5.19 (m, 2H), 4.63 (ddt, *J* = 16.7, 4.8, 1.8 Hz, 1H), 4.50 (ddt, *J* = 16.7, 5.1, 1.5 Hz, 1H), 3.76 (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.6, 133.1, 131.1, 128.6, 128.3, 127.9, 124.1, 118.0, 115.7, 47.9, 43.9, 35.5. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{12}H_{11}Br_2N_2O]^+$ 356.9233, found 356.9245.

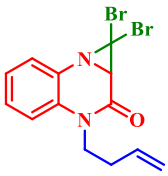
1,1-dibromo-3-(prop-2-yn-1-yl)-1,1a-dihydroazirino[1,2-*a*]quinoxalin-2(3*H*)-one (3fa):



3fa was synthesized by following general procedure **A** where **2a** was utilized for the reaction. White solid (95% yield, 68 mg), M.P. (134.2-137.1 °C) *Rf* = 0.67 (petroleum ether/EtOAc 90:10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.47 (m, 1H), 7.37 – 7.32 (m, 1H), 7.18 (td, *J* = 7.6, 1.2 Hz, 1H), 7.09 (dd, *J* = 8.2, 1.1 Hz,

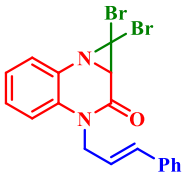
1H), 4.80 (d, *J* = 17.7 Hz, 1H), 4.66 (d, *J* = 17.7 Hz, 1H), 3.76 (s, 1H), 1.57 (s, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 158.4, 132.4, 128.7, 128.4, 128.1, 124.5, 115.5, 73.3, 47.7, 44.7, 35.2, 31.7. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{12}H_8Br_2N_2O]^+$ 353.9003, found 353.9011.

1,1-dibromo-3-(but-3-en-1-yl)-1,1a-dihydroazirino[1,2-*a*]quinoxalin-2(3*H*)-one (3ga):



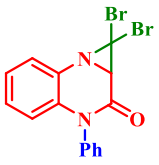
3ga was synthesized by following general procedure **A** where **2a** was utilized for the reaction. White solid (91% yield, 68 mg). M.P. (109.5-11.1 ℃). *Rf* = 0.67 (petroleum ether/EtOAc 90:10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.32 – 7.27 (m, 1H), 7.13 (td, *J* = 7.7, 1.1 Hz, 1H), 6.95 (d, *J* = 8.3 Hz, 1H), 5.83 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H), 5.16 – 5.07 (m, 2H), 4.12 – 4.03 (m, 1H), 3.94 – 3.84 (m, 1H), 3.73 (s, 1H), 2.36 (dd, *J* = 15.0, 7.5 Hz, 2H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 158.5, 134.2, 132.9, 128.7, 128.6, 128.0, 124.0, 117.6, 114.8, 47.8, 40.7, 35.5, 31.1. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{13}H_{13}Br_2N_2O]^+$ 370.9389, found 370.9397.

(E)-1,1-dibromo-3-(4-phenylbut-3-en-1-yl)-1,1a-dihydroazirino[1,2-*a*]quinoxalin-2(3*H*)-one (3ha):



3ha was synthesized by following general procedure **A** where **2a** was utilized for the reaction. White solid (96% yield, 83 mg). M.P. (82.5-84.8 ℃). *Rf* = 0.65 (petroleum ether/EtOAc 90:10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.42 (m, 1H), 7.27 – 7.19 (m, 6H), 7.11 (d, *J* = 1.2 Hz, 1H), 6.99 (dd, *J* = 8.3, 1.1 Hz, 1H), 6.61 – 6.56 (m, 1H), 6.11 (dt, *J* = 16.0, 5.7 Hz, 1H), 4.75 (ddd, *J* = 16.5, 5.5, 1.6 Hz, 1H), 4.64 (ddd, *J* = 16.6, 5.8, 1.2 Hz, 1H), 3.76 (s, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 158.7, 136.2, 133.3, 133.2, 128.7, 128.7, 128.4, 128.1, 128.0, 126.5, 124.1, 122.4, 115.6, 47.9, 43.5, 35.5. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{18}H_{15}Br_2N_2O]^+$ 432.9546, found 432.9551.

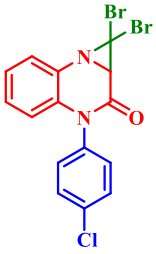
1,1-dibromo-3-phenyl-1,1a-dihydroazirino[1,2-*a*]quinoxalin-2(3*H*)-one (3ia):



3ia was synthesized by following general procedure **A** where **2a** was utilized for the reaction. White solid (85% yield, 67 mg) M.P. (183.0-185.8 ℃). *Rf* = 0.7 (petroleum ether/EtOAc 90:10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.53 (m, 2H), 7.51 (ddd, *J* = 3.9, 2.8, 1.7 Hz, 2H), 7.24 (d, *J* = 7.8 Hz, 1H), 7.16 (dd, *J* = 5.5, 3.5 Hz, 1H), 7.14 – 7.05 (m, 2H), 6.26 – 6.23 (m, 1H), 3.87 (s, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ

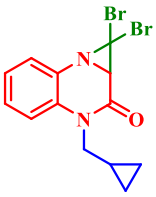
158.7, 135.6, 135.5, 130.6, 130.4, 129.5, 129.0, 128.8, 128.1, 128.0, 127.6, 124.2, 116.9, 48.1, 35.9. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{15}H_{11}Br_2N_2O]^+$ 392.9233, found 392.9238.

1,1-dibromo-3-(4-chlorophenyl)-1,1a-dihydroazirino[1,2-*a*]quinoxalin-2(3*H*)-one (3ja):



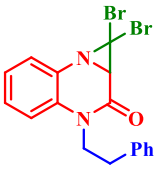
3ja was synthesized by following general procedure **A** where **2a** was utilized for the reaction. White solid (82% yield, 70 mg). M.P. (193.8-196.2 ℃) *Rf* = 0.67 (petroleum ether/EtOAc 90:10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.48 (m, 3H), 7.19 (dd, *J* = 8.4, 2.5 Hz, 1H), 7.16 – 7.06 (m, 3H), 6.29 – 6.23 (m, 1H), 3.85 (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.8, 135.5, 135.2, 134.1, 130.9, 130.7, 130.4, 130.3, 128.3, 128.0, 127.8, 124.5, 116.7, 48.0, 35.7. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{15}H_{10}Br_2ClN_2O]^+$ 426.8843, found 426.8850.

1,1-dibromo-3-(cyclopropylmethyl)-1,1a-dihydroazirino[1,2-*a*]quinoxalin-2(3*H*)-one (3ka):



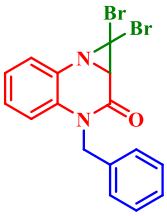
3ka was synthesized by following general procedure **A** where **2a** was utilized for the reaction. White solid (90% yield, 67 mg). M.P. (68.3-69.0 ℃) *Rf* = 0.75 (petroleum ether/EtOAc 90:10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.30 (td, *J* = 8.2, 1.5 Hz, 1H), 7.14 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.10 (d, *J* = 7.3 Hz, 1H), 3.91 (dd, *J* = 14.7, 7.4 Hz, 1H), 3.82 (dd, *J* = 14.7, 6.4 Hz, 1H), 3.73 (s, 1H), 1.17 – 1.05 (m, 1H), 0.55 – 0.42 (m, 4H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.9, 133.4, 128.6, 128.5, 127.9, 123.9, 115.3, 47.9, 45.1, 35.5, 9.2, 4.4, 4.2. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{13}H_{13}Br_2N_2O]^+$ 370.9389, found 370.9390.

1,1-dibromo-3-phenethyl-1,1a-dihydroazirino[1,2-*a*]quinoxalin-2(3*H*)-one (3la):



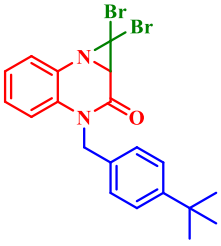
3la was synthesized by following general procedure **A** where **2a** was utilized for the reaction. White solid (93% yield, 79 mg). M.P. (93.8-96.1 ℃) *Rf* = 0.76 (petroleum ether/EtOAc 90:10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.37 – 7.23 (m, 6H), 7.15 (td, *J* = 7.6, 1.1 Hz, 1H), 7.02 (d, *J* = 7.8 Hz, 1H), 4.25 (ddd, *J* = 14.1, 10.2, 6.6 Hz, 1H), 4.02 (ddd, *J* = 14.2, 10.0, 6.6 Hz, 1H), 3.74 (s, 1H), 2.96 – 2.82 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.5, 137.9, 132.9, 128.9, 128.9, 128.8, 128.7, 128.1, 127.0, 124.0, 114.7, 47.8, 42.7, 35.5, 33.0. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{17}H_{15}Br_2N_2O]^+$ 420.9546, found 420.9554.

3-benzyl-1,1-dibromo-1,1a-dihydroazirino[1,2-*a*]quinoxalin-2(3*H*)-one (3ma):



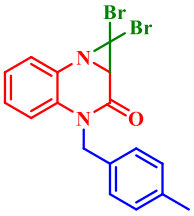
3ma was synthesized by following general procedure **A** where **2a** was utilized for the reaction. White solid (98% yield, 80 mg) M.P. (105.8-108.1 ℃) *Rf* = 0.70 (petroleum ether/EtOAc 90:10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.34 – 7.24 (m, 5H), 7.17 – 7.13 (m, 1H), 7.09 (td, *J* = 7.6, 1.4 Hz, 1H), 6.88 (dd, *J* = 8.1, 1.4 Hz, 1H), 5.19 (d, *J* = 16.1 Hz, 1H), 5.11 (d, *J* = 16.2 Hz, 1H), 3.86 (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.3, 135.5, 133.3, 129.0, 128.7, 128.2, 127.9, 127.7, 126.8, 124.2, 116.0, 48.0, 45.7, 35.6. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{16}H_{13}Br_2N_2O]^+$ 406.9389, found 406.9392.

1,1-dibromo-3-(4-(tert-butyl)benzyl)-1,1a-dihydroazirino[1,2-*a*]quinoxalin-2(3*H*)-one (3na):



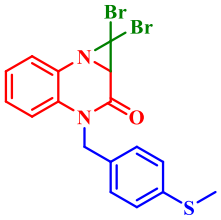
3na was synthesized by following general procedure **A** where **2a** was utilized for the reaction. White solid (85% yield, 79 mg) M.P. (163.0-164.4 ℃). *Rf* = 0.69 (petroleum ether/EtOAc 90:10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.34 – 7.30 (m, 2H), 7.20 (d, *J* = 8.2 Hz, 2H), 7.16 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.09 (td, *J* = 7.6, 1.3 Hz, 1H), 6.91 (dd, *J* = 8.1, 1.2 Hz, 1H), 5.17 (d, *J* = 16.1 Hz, 1H), 5.07 (d, *J* = 16.0 Hz, 1H), 3.85 (s, 1H), 1.28 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.2, 150.7, 133.4, 132.3, 128.7, 128.1, 127.9, 126.5, 125.9, 124.1, 116.1, 48.0, 45.4, 35.6, 34.6, 31.4. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{20}H_{21}Br_2N_2O]^+$ 463.0015, found 463.0020.

1,1-dibromo-3-(4-methylbenzyl)-1,1a-dihydroazirino[1,2-*a*]quinoxalin-2(3*H*)-one (3oa):



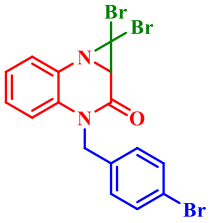
3oa was synthesized by following general procedure **A** where **2a** was utilized for the reaction. White solid (94% yield, 79 mg). M.P. (161.8-163.3 ℃). *Rf* = 0.72 (petroleum ether/EtOAc 90:10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.20 – 7.05 (m, 6H), 6.90 (dd, *J* = 8.1, 1.3 Hz, 1H), 5.16 (d, *J* = 16.0 Hz, 1H), 5.06 (d, *J* = 16.1 Hz, 1H), 3.85 (s, 1H), 2.30 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 159.2, 137.4, 133.4, 132.4, 129.6, 128.7, 128.2, 127.9, 126.9, 124.1, 116.0, 48.0, 45.4, 35.6, 21.2. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{17}H_{15}Br_2N_2O]^+$ 420.9546, found 420.9551.

1,1-dibromo-3-(4-(methylthio)benzyl)-1,1a-dihydroazirino[1,2-*a*]quinoxalin-2(3*H*)-one (3pa):



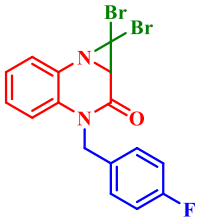
3pa was synthesized by following general procedure **A** where **2a** was utilized for the reaction. White solid (94% yield, 85 mg) M.P. (107.8-108.9 °C). *Rf* = 0.7 (petroleum ether/EtOAc 90:10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.22 – 7.16 (m, 4H), 7.16 – 7.13 (m, 1H), 7.09 (td, *J* = 7.5, 0.8 Hz, 1H), 6.87 (d, *J* = 8.1 Hz, 1H), 5.18 (d, *J* = 16.1 Hz, 1H), 5.02 (d, *J* = 16.0 Hz, 1H), 3.84 (s, 1H), 2.44 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 159.2, 138.0, 133.2, 132.2, 128.7, 128.2, 127.9, 127.5, 127.0, 124.2, 115.9, 48.0, 45.2, 35.6, 15.9. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{17}H_{15}Br_2N_2OS]^+$ 452.9266 found 452.9250.

1,1-dibromo-3-(4-bromobenzyl)-1,1a-dihydroazirino[1,2-*a*]quinoxalin-2(3*H*)-one (3qa):



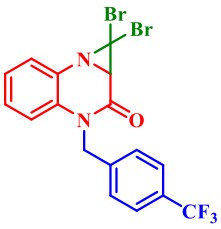
3qa was synthesized by following general procedure **A** where **2a** was utilized for the reaction. White solid (92% yield, 90 mg) M.P. (163.0-164.4 °C). *Rf* = 0.69 (petroleum ether/EtOAc 90:10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.45 – 7.41 (m, 2H), 7.19 – 7.13 (m, 3H), 7.11 (td, *J* = 7.5, 1.5 Hz, 1H), 6.81 (dd, *J* = 8.1, 1.4 Hz, 1H), 5.15 (d, *J* = 16.2 Hz, 1H), 5.01 (d, *J* = 16.2 Hz, 1H), 3.84 (s, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 159.3, 134.5, 133.1, 132.1, 128.7, 128.5, 128.3, 127.9, 124.3, 121.7, 115.7, 47.9, 45.1, 35.5. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{16}H_{12}Br_3N_2O]^+$ 484.8494, found 484.8500.

1,1-dibromo-3-(4-fluorobenzyl)-1,1a-dihydroazirino[1,2-*a*]quinoxalin-2(3*H*)-one (3ra):



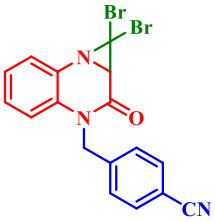
3ra was synthesized by following general procedure **A** where **2a** was utilized for the reaction. White solid (90% yield, 77 mg) M.P. (71.4-73.9 °C) *Rf* = 0.75 (petroleum ether/EtOAc 90:10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.26 – 7.22 (m, 2H), 7.18 – 7.13 (m, 1H), 7.11 – 7.06 (m, 1H), 7.00 – 6.95 (m, 2H), 6.84 (dd, *J* = 8.1, 1.3 Hz, 1H), 5.09 (dd, *J* = 55.4, 16.1 Hz, 1H), 3.82 (s, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 163.5, 161.0, 159.3, 133.1, 131.2, 131.2, 128.9, 128.7, 128.7, 128.6, 128.3, 127.9, 124.3, 116.0, 115.8, 115.7, 77.2, 47.9, 44.9, 35.5. ^{19}F NMR (377 MHz, $CDCl_3$) δ -111.6. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{16}H_{12}Br_2FN_2O]^+$ 424.9295, found 424.9300.

1,1-dibromo-3-(4-(trifluoromethyl)benzyl)-1,1a-dihydroazirino[1,2-*a*]quinoxalin-2(3*H*)-one (3sa):



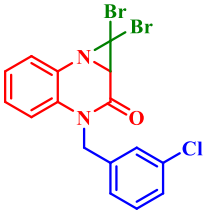
3sa was synthesized by following general procedure **A** where **2a** was utilized for the reaction. White solid (88% yield, 84 mg) M.P. (122.8-124.1 ℃) *Rf* = 0.6 (petroleum ether/EtOAc 90:10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.2 Hz, 2H), 7.50 – 7.46 (m, 1H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.19 – 7.14 (m, 1H), 7.12 (td, *J* = 7.5, 1.6 Hz, 1H), 6.77 (dd, *J* = 8.0, 1.5 Hz, 1H), 5.27 (d, *J* = 16.5 Hz, 1H), 5.13 (d, *J* = 16.5 Hz, 1H), 3.86 (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.3, 139.6, 133.1, 130.3, 130.0, 128.7, 128.4, 128.0, 127.2, 126.1, 126.1, 126.0, 126.0, 125.4, 124.5, 115.6, 48.0, 45.3, 35.4. ^{19}F NMR (377 MHz, $CDCl_3$) δ -62.6. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{17}H_{12}Br_2F_3N_2O]^+$ 474.9263, found 474.9258.

4-((1,1-dibromo-2-oxo-1a,2-dihydroazirino[1,2-*a*]quinoxalin-3(1*H*)-yl)methyl)benzonitrile (3ta):



3ta was synthesized by following general procedure **A** where **2a** was utilized for the reaction. White solid (90% yield, 78 mg) M.P. (152.6-154.8 ℃) *Rf* = 0.6 (petroleum ether/EtOAc 90:10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.60 (m, 2H), 7.50 – 7.47 (m, 1H), 7.39 (d, *J* = 8.5 Hz, 2H), 7.14 (dqd, *J* = 14.7, 7.5, 1.7 Hz, 2H), 6.72 (dd, *J* = 7.9, 1.5 Hz, 1H), 5.25 (d, *J* = 16.7 Hz, 1H), 5.12 (d, *J* = 16.7 Hz, 1H), 3.85 (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.3, 141.0, 132.8, 128.7, 128.5, 128.0, 127.5, 124.6, 118.5, 115.4, 111.9, 47.9, 45.4, 35.3. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{17}H_{12}Br_2N_3O]^+$ 431.9342, found 431.9358.

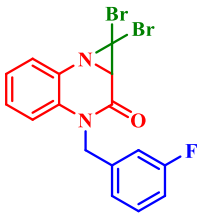
1,1-dibromo-3-(3-chlorobenzyl)-1,1a-dihydroazirino[1,2-*a*]quinoxalin-2(3*H*)-one (3ua):



3ua was synthesized by following general procedure **A** where **2a** was utilized for the reaction. White solid (90% yield, 80 mg) M.P. (180.2-182.4 ℃) *Rf* = 0.72 (petroleum ether/EtOAc 90:10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.31 – 7.28 (m, 1H), 7.26 (td, *J* = 5.8, 2.4 Hz, 2H), 7.20 (ddd, *J* = 6.2, 5.7, 1.7 Hz, 2H), 7.14 (td, *J* = 7.6, 1.4 Hz, 1H), 6.83 (dd, *J* = 8.1, 1.3 Hz, 1H), 5.21 (d, *J* = 16.4 Hz, 1H),

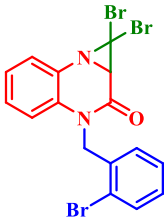
5.08 (d, *J* = 16.3 Hz, 1H), 3.88 (s, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 159.3, 137.5, 134.9, 133.1, 130.3, 128.7, 128.3, 128.0, 128.0, 126.9, 125.0, 124.4, 115.7, 48.0, 45.1, 35.4. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{16}H_{12}Br_2ClN_2O]^+$ 440.8999, found 440.9005.

1,1-dibromo-3-(3-fluorobenzyl)-1,1a-dihydroazirino[1,2-*a*]quinoxalin-2(3*H*)-one (3va):



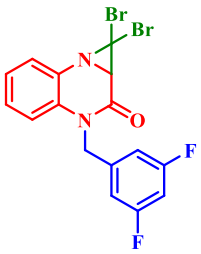
3va was synthesized by following general procedure **A** where **2a** was utilized for the reaction. White solid (88% yield, 75 mg) M.P. (160.1-162.0 °C) *Rf* = 0.72 (petroleum ether/EtOAc 90:10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.45 (m, 1H), 7.32 – 7.27 (m, 1H), 7.19 – 7.15 (m, 1H), 7.11 (ddd, *J* = 7.5, 6.0, 1.5 Hz, 1H), 7.08 – 7.05 (m, 1H), 6.96 (ddd, *J* = 9.6, 6.4, 2.8 Hz, 2H), 6.82 (dd, *J* = 8.1, 1.4 Hz, 1H), 5.19 (d, *J* = 16.4 Hz, 1H), 5.09 (d, *J* = 16.4 Hz, 1H), 3.85 (s, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 159.3, 138.1, 133.1, 130.7, 130.6, 128.7, 128.3, 128.0, 124.4, 122.4, 115.7, 114.9, 114.7, 114.0, 113.8, 48.0, 45.2, 35.5. ^{19}F NMR (377 MHz, $CDCl_3$) δ -112.1. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{16}H_{12}Br_2FN_2O]^+$ 424.9295, found 424.9300.

1,1-dibromo-3-(2-bromobenzyl)-1,1a-dihydroazirino[1,2-*a*]quinoxalin-2(3*H*)-one (3wa):



3wa was synthesized by following general procedure **A** where **2a** was utilized for the reaction. White solid (90% yield, 77 mg) M.P. (142.3-146.3 °C) *Rf* = 0.67 (petroleum ether/EtOAc 90:10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.48 (dd, *J* = 7.5, 1.9 Hz, 1H), 7.21 – 7.15 (m, 2H), 7.12 (ddd, *J* = 9.0, 5.2, 1.8 Hz, 2H), 7.05 (dd, *J* = 7.5, 1.6 Hz, 1H), 6.63 (dd, *J* = 7.9, 1.5 Hz, 1H), 5.23 (d, *J* = 17.2 Hz, 1H), 5.14 (d, *J* = 17.2 Hz, 1H), 3.88 (s, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 159.3, 133.9, 133.2, 133.0, 129.2, 128.7, 128.2, 128.1, 128.0, 127.2, 124.4, 122.4, 116.0, 48.1, 46.3, 35.5. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{16}H_{12}Br_3N_2O]^+$ 484.8494, found 484.9500.

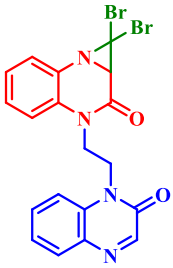
1,1-dibromo-3-(3,5-difluorobenzyl)-1,1a-dihydroazirino[1,2-*a*]quinoxalin-2(3*H*)-one (3xa):



3xa was synthesized by following general procedure **A** where **2a** was utilized for the reaction. White solid (84% yield, 75 mg) M.P. (125.8-127.4 °C) *Rf* = 0.65 (petroleum ether/EtOAc 90:10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (dd, *J*

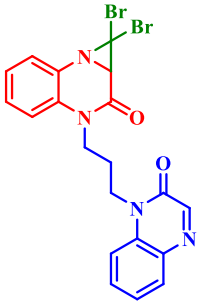
= 7.6, 1.7 Hz, 1H), 7.19 (td, *J* = 7.8, 1.8 Hz, 1H), 7.13 (td, *J* = 7.6, 1.4 Hz, 1H), 6.81 (d, *J* = 5.8 Hz, 2H), 6.76 (dd, *J* = 8.1, 1.3 Hz, 1H), 6.71 (ddd, *J* = 8.8, 5.6, 2.3 Hz, 1H), 5.17 (d, *J* = 16.7 Hz, 1H), 5.05 (d, *J* = 16.6 Hz, 1H), 3.85 (s, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 159.3, 139.6, 133.0, 128.7, 128.5, 128.1, 124.6, 115.5, 109.9, 109.8, 109.7, 109.6, 103.7, 103.4, 103.2, 48.0, 45.1, 35.3. ^{19}F NMR (377 MHz, $CDCl_3$) δ -108.5. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{16}H_{11}Br_2F_2N_2O]^+$ 442.9201, found 442.9210.

1,1-dibromo-3-(2-(2-oxoquinoxalin-1(2H)-yl)ethyl)-1,1a-dihydroazirino[1,2-*a*]quinoxalin-2(3*H*)-one (3ya):



3ya was synthesized by following general procedure **A** where **2a** was utilized for the reaction. White solid (81% yield, 79 mg) M.P. (150.0-152.5 °C) *Rf* = 0.60 (petroleum ether/EtOAc 90:10) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 8.02 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.82 (dd, *J* = 8.3, 1.0 Hz, 1H), 7.73 – 7.67 (m, 1H), 7.59 (ddd, *J* = 8.3, 7.0, 1.4 Hz, 1H), 7.48 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.42 (dd, *J* = 8.3, 1.1 Hz, 1H), 7.39 – 7.33 (m, 1H), 7.17 (td, *J* = 7.6, 1.3 Hz, 1H), 4.76 – 4.63 (m, 2H), 4.52 (dt, *J* = 13.1, 6.4 Hz, 1H), 4.42 – 4.32 (m, 1H), 3.76 (s, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 159.1, 156.7, 140.1, 139.4, 139.2, 133.3, 130.5, 129.2, 128.7, 128.6, 128.0, 127.2, 127.1, 124.3, 115.4, 62.3, 47.8, 39.8, 29.8. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{29}H_{15}Br_2N_2O]^+$ 488.9556, found 488.9561.

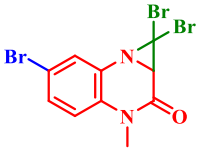
1,1-dibromo-3-(2-(2-oxoquinoxalin-1(2H)-yl)propyl)-1,1a-dihydroazirino[1,2-*a*]quinoxalin-2(3*H*)-one (3za):



3za was synthesized by following general procedure **A** where **2a** was utilized for the reaction. White solid (80% yield, 81 mg) M.P. (162.4-164.5 °C) *Rf* = 0.60 (petroleum ether/EtOAc 90:10) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 8.02 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.80 (dd, *J* = 8.3, 1.0 Hz, 1H), 7.67 (ddd, *J* = 8.4, 7.0, 1.4 Hz, 1H), 7.57 (ddd, *J* = 8.3, 7.0, 1.4 Hz, 1H), 7.47 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.30 – 7.24 (m, 2H), 7.13 (td, *J* = 7.6, 1.2 Hz, 1H), 7.06 (dd, *J* = 8.3, 0.9 Hz, 1H), 4.59 (t, *J* = 6.2 Hz, 2H), 4.29 (dt, *J* = 14.8, 7.3 Hz, 1H), 4.08 (dt, *J* = 21.7, 7.1 Hz, 1H), 3.74 (s, 1H), 2.23 – 2.15 (m, 2H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 158.7, 157.1, 140.4, 139.5, 139.1, 133.0, 130.4, 129.1, 128.8, 128.7, 128.1, 127.4, 126.9, 124.1, 114.7, 64.1,

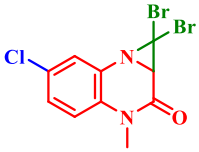
47.8, 38.6, 35.4, 26.4. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{30}H_{14}Br_2N_2O]^+$ 502.9715, found 502.9718.

1,1,6-tribromo-3-methyl-1,1a-dihydroazirino[1,2-*a*]quinoxalin-2(3*H*)-one (3a'a):



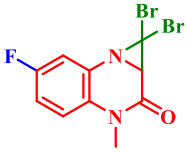
3a'a was synthesized by following general procedure **A** where **2a** was utilized for the reaction. White solid (82%, 67 mg) M.P. (114.5-117.3 ℃) *Rf* = 0.7 (petroleum ether/EtOAc 90:10) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.30 (m, 1H), 7.26 – 7.23 (m, 1H), 7.08 (d, *J* = 2.0 Hz, 1H), 3.74 (s, 1H), 3.30 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.6, 135.4, 129.5, 127.6, 126.9, 121.3, 118.2, 48.0, 34.9, 28.5. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{10}H_8Br_3N_2O]^+$ 408.8181, found 408.8205.

1,1-dibromo-6-chloro-3-methyl-1,1a-dihydroazirino[1,2-*a*]quinoxalin-2(3*H*)-one (3b'a):



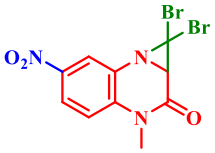
3b'a was synthesized by following general procedure **A** where **2a** was utilized for the reaction. White solid (81% yield, mg) M.P. (126.8-128.8 ℃) *Rf* = 0.7 (petroleum ether/EtOAc 90:10) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.31 (m, 1H), 7.27 – 7.24 (m, 1H), 7.09 (d, *J* = 2.0 Hz, 1H), 3.74 (s, 1H), 3.31 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.9, 134.7, 128.8, 127.0, 126.2, 120.6, 117.5, 76.2, 47.3, 34.2, 27.8. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{10}H_8Br_2ClN_2O]^+$ 364.8686, found 364.8694.

1,1-dibromo-6-fluoro-3-methyl-1,1a-dihydroazirino[1,2-*a*]quinoxalin-2(3*H*)-one (3c'a):



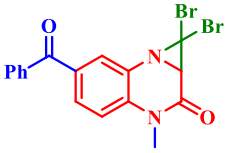
3c'a was synthesized by following general procedure **A** where **2a** was utilized for the reaction. White solid (81% yield, 57 mg) M.P. (115.9-119.7 ℃) *Rf* = 0.7 (petroleum ether/EtOAc 90:10) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 8.7, 5.7 Hz, 1H), 6.83 (ddd, *J* = 8.6, 7.7, 2.6 Hz, 1H), 6.67 (dd, *J* = 10.2, 2.6 Hz, 1H), 3.73 (s, 1H), 3.30 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 163.0, 160.5, 158.7, 135.7, 135.6, 129.5, 129.4, 124.5, 124.5, 110.4, 110.2, 103.1, 102.8, 47.8, 35.5, 35.5, 28.5. ^{19}F NMR (377 MHz, $CDCl_3$) δ -111.6. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{10}H_8Br_2FN_2O]^+$ 348.8982, found 348.8985.

1,1-dibromo-3-methyl-6-nitro-1,1a-dihydroazirino[1,2-*a*]quinoxalin-2(3*H*)-one (3d'a):



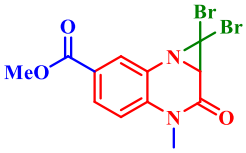
3d'a was synthesized by following general procedure **A** where **2a** was utilized for the reaction. White solid (76% yield, 57 mg) M.P. (164.1-166.2 ℃) *Rf* = 0.7 (petroleum ether/EtOAc 90:10) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (t, *J* = 3.3 Hz, 1H), 8.19 (dd, *J* = 9.1, 2.6 Hz, 1H), 7.06 (d, *J* = 9.1 Hz, 1H), 3.82 (s, 1H), 3.40 (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.6, 143.5, 139.7, 128.9, 123.8, 123.7, 115.1, 48.0, 33.8, 28.9. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{11}H_8Br_2N_3O_3]^+$ 374.8854, found 374.88.

6-benzoyl-1,1-dibromo-3-methyl-1,1a-dihydroazirino[1,2-*a*]quinoxalin-2(3*H*)-one (3e'a):



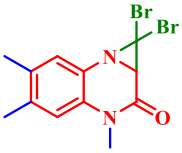
3e'a was synthesized by following general procedure **A** where **2a** was utilized for the reaction. White solid (86% yield, 75 mg) M.P. (147.8- 148.9 ℃) *Rf* = 0.7 (petroleum ether/EtOAc 90:10) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 – 7.77 (m, 1H), 7.65 – 7.60 (m, 1H), 7.56 – 7.48 (m, 5H), 3.81 (s, 1H), 3.38 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 195.3, 158.4, 137.1, 137.0, 134.7, 133.0, 132.3, 130.1, 128.6, 127.8, 126.3, 116.3, 48.2, 34.7, 28.6. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{17}H_{12}Br_2N_2O_2]^+$ 434.9338, found 434.93.

methyl 1,1-dibromo-3-methyl-2-oxo-1,1a,2,3-tetrahydroazirino[1,2-*a*]quinoxaline-6-carboxylate (3f'a):



3f'a was synthesized by following general procedure **A** where **2a** was utilized for the reaction. White solid (77% yield, 60 mg) M.P. (133.0-134.9 ℃) *Rf* = 0.7 (petroleum ether/EtOAc 90:10) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 2.0 Hz, 1H), 7.99 – 7.96 (m, 1H), 7.00 (d, *J* = 8.6 Hz, 1H), 3.94 (s, 3H), 3.78 (s, 1H), 3.37 (s, 3H) ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.9, 158.9, 137.9, 129.6, 129.4, 128.4, 125.9, 114.8, 52.5, 47.9, 34.8, 28.6. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{12}H_{11}Br_2N_2O_3]^+$ 388.9131, found 398.9153.

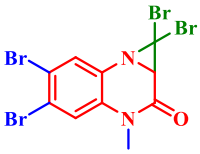
1,1-dibromo-3,5,6-trimethyl-1,1a-dihydroazirino[1,2-*a*]quinoxalin-2(3*H*)-one (3g'a):



3g'a was synthesized by following general procedure **A** where **2a** was utilized for the reaction. White solid (82% yield, 59 mg) M.P. (166.5-167.9 ℃) *Rf* = 0.7

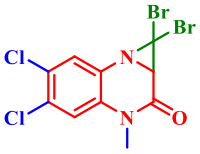
(petroleum ether/EtOAc 90:10) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (s, 1H), 6.71 (s, 1H), 3.70 (s, 1H), 3.31 (s, 3H), 2.26 (s, 6H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 158.8, 136.5, 132.5, 131.6, 129.0, 125.9, 116.2, 47.9, 36.4, 28.2, 20.1, 19.0. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{12}H_{13}Br_2N_2O]^+$ 358.9389, found 358.9395.

1,1,5,6-tetrabromo-3-methyl-1,1a-dihydroazirino[1,2-*a*]quinoxalin-2(3*H*)-one (3h'a):



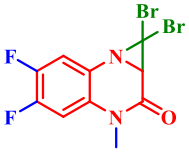
3h'a was synthesized by following general procedure **A** where **2a** was utilized for the reaction. White solid (80% yield, 78 mg) M.P. (178.5-180.2 °C) *Rf* = 0.7 (petroleum ether/EtOAc 90:10) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.18 (s, 1H), 3.75 (s, 1H), 3.30 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 158.3, 134.5, 132.5, 128.7, 123.8, 119.6, 118.8, 48.0, 34.4, 28.5. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{10}H_7Br_2N_2O]^+$ 486.7286, found 486.72.

1,1-dibromo-5,6-dichloro-3-methyl-1,1a-dihydroazirino[1,2-*a*]quinoxalin-2(3*H*)-one (3i'a):



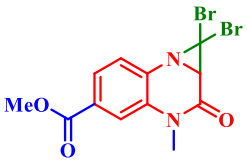
3n'a was synthesized by following general procedure **A** where **2a** was utilized for the reaction. White solid (80% yield, 64 mg) M.P. (178.1-180.0 °C) *Rf* = 0.7 (petroleum ether/EtOAc 90:10) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (s, 1H), 7.02 (s, 1H), 3.75 (s, 1H), 3.30 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 158.2, 133.9, 131.8, 129.5, 128.0, 127.3, 116.5, 47.9, 34.6, 28.5. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{10}H_7Br_2Cl_2N_2O]^+$ 398.8297, found 398.8340.

1,1-dibromo-5,6-difluoro-3-methyl-1,1a-dihydroazirino[1,2-*a*]quinoxalin-2(3*H*)-one (3j'a)



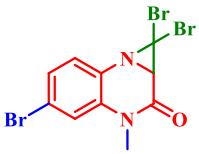
3j'a was synthesized by following general procedure **A** where **2a** was utilized for the reaction. White solid (83% yield, 61 mg) M.P. (139.1-141.0 °C) *Rf* = 0.7 (petroleum ether/EtOAc 90:10) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (dd, *J* = 9.8, 7.8 Hz, 1H), 6.78 (dd, *J* = 11.6, 7.1 Hz, 1H), 3.73 (s, 1H), 3.29 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 158.2, 150.4, 150.3, 148.0, 147.8, 147.2, 147.1, 144.7, 144.6, 131.2, 131.2, 131.2, 131.1, 124.5, 124.5, 124.4, 124.4, 117.5, 117.5, 117.3, 117.3, 104.7, 104.4, 47.9, 34.8, 28.7. ^{19}F NMR (377 MHz, $CDCl_3$) δ -135.8, -135.8, -142.3, -142.4. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{10}H_7Br_2F_2N_2O]^+$ 366.8888, found 366.8892.

methyl 1,1-dibromo-3-methyl-2-oxo-1,1a,2,3-tetrahydroazirino[1,2-*a*]quinoxaline-5-carboxylate (3k'a)



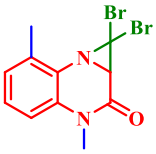
3k'a was synthesized by following general procedure **A** where **2a** was utilized for the reaction. White solid (74% yield, 58 mg) M.P. (128.5-130.6 °C) *Rf* = 0.7 (petroleum ether/EtOAc 90:10) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.64 (d, *J* = 1.7 Hz, 1H), 7.52 (d, *J* = 8.1 Hz, 1H), 3.94 (s, 3H), 3.79 (s, 1H), 3.39 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.1, 158.4, 134.4, 132.7, 129.8, 128.2, 125.4, 116.2, 52.7, 48.2, 34.6, 28.6. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{12}H_{11}Br_2N_2O_3]^+$ 388.9131, found 398.9153.

1,1,5-tribromo-3-methyl-1,1a-dihydroazirino[1,2-*a*]quinoxalin-2(3*H*)-one (3l'a):



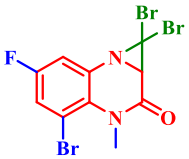
3l'a was synthesized by following general procedure **A** where **2a** was utilized for the reaction. White solid (78% yield, 64 mg) M.P. (128.5-130.6 °C) *Rf* = 0.75 (petroleum ether/EtOAc 90:10) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.3 Hz, 1H), 7.25 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.08 (d, *J* = 1.9 Hz, 1H), 3.74 (s, 1H), 3.31 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.5, 135.4, 129.5, 127.6, 126.9, 121.3, 118.1, 47.9, 34.9, 28.5. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{10}H_8Br_3N_2O]^+$ 408.8181, found 408.8205.

1,1-dibromo-3,7-dimethyl-1,1a-dihydroazirino[1,2-*a*]quinoxalin-2(3*H*)-one (3m'a):



3m'a was synthesized by following general procedure **A** where **2a** was utilized for the reaction. White solid (84% yield, 58 mg) M.P. (168.1-169.9 °C) *Rf* = 0.7 (petroleum ether/EtOAc 90:10) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (t, *J* = 7.9 Hz, 1H), 7.03 – 7.01 (m, 1H), 6.79 (d, *J* = 8.2 Hz, 1H), 3.75 (s, 1H), 3.32 (s, 3H), 2.48 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.5, 137.1, 133.9, 127.5, 127.2, 125.7, 112.6, 47.7, 34.8, 28.5, 18.1. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{11}H_{11}Br_2N_2O]^+$ 344.9233, found 344.9238.

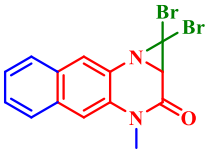
1,1,5-tribromo-7-fluoro-3-methyl-1,1a-dihydroazirino[1,2-*a*]quinoxalin-2(3H)-one (3n'a):



3n'a was synthesized by following general procedure **A** where **2a** was utilized for the reaction. White solid (77% yield, 66 mg) M.P. (108.9-111.0 °C) *Rf* = 0.7 (petroleum ether/EtOAc 90:10) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 2.3 Hz, 1H), 7.47 (d, *J* = 2.3 Hz, 1H), 3.73 (s, 1H), 3.52 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ

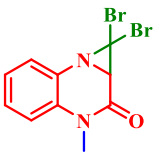
161.5, 133.8, 133.0, 132.5, 130.2, 123.1, 121.8, 121.6, 116.7, 115.6, 115.4, 77.2, 47.5, 37.7, 36.6. ^{19}F NMR (377 MHz, $CDCl_3$) δ -116.9. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{10}H_7Br_3N_2O]^+$ 426.8087, found 426.8092.

1,1-dibromo-3-methyl-1,1a-dihydroazirino[1,2-a]benzo[g]quinoxalin-2(3H)-one (3o'a):



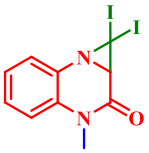
3o'a was synthesized by following general procedure **A** where **2a** was utilized for the reaction. White solid (yield, mg) M.P. (99.5-101.1 °C) *Rf* = 0.7 (petroleum ether/EtOAc 90:10) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.84 – 7.81 (m, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.53 – 7.44 (m, 2H), 7.27 (s, 1H), 3.82 (s, 1H), 3.46 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 132.7, 132.5, 129.9, 128.0, 127.5, 127.4, 127.3, 126.9, 126.1, 112.0, 47.7, 36.6, 28.6. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{14}H_{11}Br_2N_2O]^+$ 380.9233, found 380.92.

1,1-dibromo-3-methyl-1,1a-dihydroazirino[1,2-a]quinoxalin-2(3H)-one (3aa):



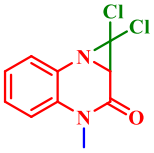
3aa was synthesized by following general procedure A where bromoform **2b** was utilized for the reaction. White solid (98% yield, 65 mg). **Note:** The purification and spectroscopic data same as to **3aa** mentioned on page no. 104

1,1-diiodo-3-methyl-1,1a-dihydroazirino[1,2-a]quinoxalin-2(3H)-one (3ab):



3ab was synthesized by following general procedure **A** where carbon tetraiodide **2c** was utilized for the reaction. White solid (94% yield, 80 mg) M.P. (67.2-68.3 °C) *Rf* = 0.7 (petroleum ether/EtOAc 90:10) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.30 (ddd, *J* = 8.2, 7.5, 1.6 Hz, 1H), 7.14 (td, *J* = 7.6, 1.3 Hz, 1H), 6.96 (dd, *J* = 8.2, 1.2 Hz, 1H), 3.75 (s, 1H), 3.34 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.1, 134.3, 128.4, 128.0, 127.1, 124.1, 114.9, 69.5, 48.1, 28.4. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{10}H_9I_2N_2O]^+$ 426.8799, found 426.8806. **3ab** was also synthesized by following general procedure A where iodoform **2d** was utilized for the reaction. White solid (95% yield, 82 mg) **Note:** The M.P. and spectroscopic data same as to above mentioned.

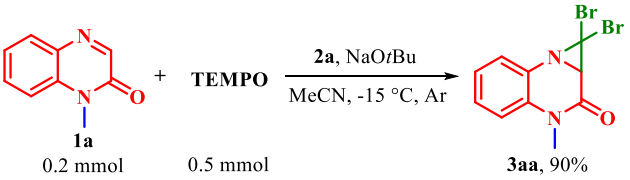
1,1-dichloro-3-methyl-1,1a-dihydroazirino[1,2-a]quinoxalin-2(3H)-one (3ac):



3ac was synthesized by following general procedure **A** where carbon tetrachloride **2e** was utilized for the reaction. White solid (93% yield, 45 mg) M.P. (98.7-100.2 ℃) *Rf* = 0.7 (petroleum ether/EtOAc 90:10) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.32 – 7.27 (m, 1H), 7.14 (td, *J* = 7.6, 1.2 Hz, 1H), 6.97 (dd, *J* = 8.2, 1.1 Hz, 1H), 3.71 (s, 1H), 3.36 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 15.1, 134.3, 128.4, 128.0, 127.1, 124.1, 114.9, 69.5, 48.1, 28.4. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{10}H_9Cl_2N_2O]^+$ 243.0086, found 243.0092. **3ac** was also synthesized by following general procedure A where chloroform **2f** was used as a reaction partner. White solid (94% yield, 46 mg). Further, **3ab** was also synthesized by following general procedure A where bromo trichloromethane **2g** was utilized the reaction. White solid (90% yield, 44 mg). (**Note:** The purification and spectroscopic data same as to above mentioned).

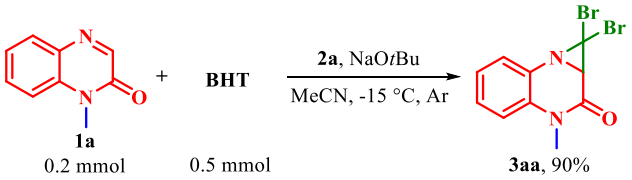
4.6.3 Control experiments:

a) Reaction of 1a with TEMPO:



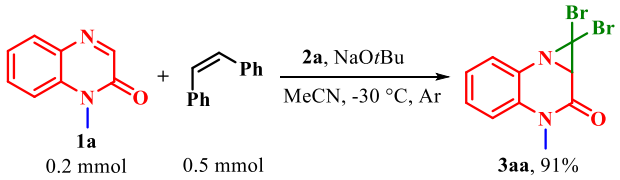
An oven-dried 25 mL round bottom flask equipped with a stir bar and rubber septum was charged with the mixture of **1aa**, (0.2 mmol, 32.03 mg) sodium *tert*-butoxide (0.4 mmol 38.44 mg) and TEMPO (0.4 mmol, 78.13 mg) in acetonitrile (2 mL) solvent under inert condition. The reaction mixture was cooled up to -15 ℃. The solution of **2a** (0.4 mmol, 132.65 mg) in acetonitrile (1 mL) was added dropwise into the cooled solution of the reaction mixture under inert conditions. The reaction was monitored by thin-layer chromatography. After completion of the reaction, the solvent was evaporated under reduced pressure and the crude residue was purified by column chromatography using a mixture of petroleum ether/EtOAc as an eluent to afford the **3aa** as a white solid (90% yield, 60 mg) and TEMPO was recovered.

b) Reaction of 1a with BHT:



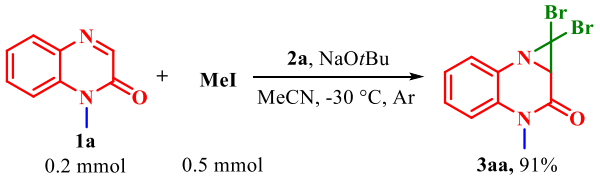
An oven-dried 25 mL round bottom flask equipped with a stir bar and rubber septum was charged with the mixture of **1a** (0.2 mmol, 32.03 mg), sodium *tert*-butoxide (0.4 mmol 38.44 mg) and BHT (0.5 mmol, 109.68 mg) in acetonitrile (2 mL) solvent under inert condition. The whole mixture was cooled up to -15 ℃. The solution of **2a** (0.4 mmol, 132.65 mg) in acetonitrile (1 mL) was added dropwise into the cooled solution of the reaction mixture under inert conditions. The reaction was monitored by thin-layer chromatography. After completion of the reaction, the solvent was evaporated under reduced pressure and the crude residue was purified by column chromatography using a mixture of petroleum ether/EtOAc as an eluent to afford the **3aa** as a white solid (92% yield, 61 mg) and BHT was recovered as it is.

c) Reaction 1a with *cis*-stilbene:



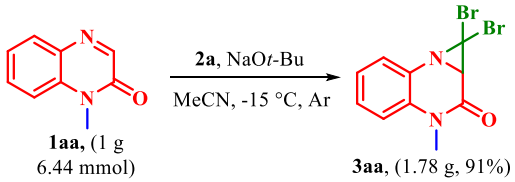
An oven-dried 25 mL round bottom flask equipped with a stir bar and rubber septum was charged with the mixture of **1a**, (0.2 mmol, 32.03 mg) NaO*t*-Bu (0.4 mmol 38.44 mg) and *cis*-stilbene (0.5 mmol, 90.13 mg) in acetonitrile (2 mL) solvent under inert condition. The whole mixture was cooled up to the -30 ℃ temperature. The solution of **2a** (0.4 mmol, 132.65 mg) in acetonitrile (1 mL) was added dropwise into the cooled solution of the reaction mixture under inert conditions. The reaction was monitored by thin-layer chromatography. After completion of the reaction, the solvent was evaporated under reduced pressure and the crude residue was purified by column chromatography using a mixture of petroleum ether/EtOAc as an eluent to afford the **3aa** as a white solid (92% yield, 61 mg) and cis stilbene was recovered as it is.

d) Reaction of 1a with methyl iodide:



An oven-dried 25 mL round bottom flask equipped with a stir bar and rubber septum was charged with the mixture of **1a**, (0.2 mmol, 32.03 mg) sodium *tert*-butoxide (0.4 mmol 38.44 mg) and methyl iodide (0.5 mmol, 70.97 mg) in acetonitrile (2 mL) solvent under inert condition. The whole mixture was cooled up to -30 ℃ with the help of a cooling bath. The solution of **2a** (0.4 mmol, 132.65 mg) in acetonitrile (1 mL) was added dropwise into the cooled solution of the reaction mixture under inert conditions. The reaction was monitored by thin-layer chromatography. After completion of the reaction, the solvent was evaporated under reduced pressure and the crude residue was purified by column chromatography using a mixture of petroleum ether/EtOAc as an eluent to afford the **3aa** as a white solid. (90% yield, 60 mg)

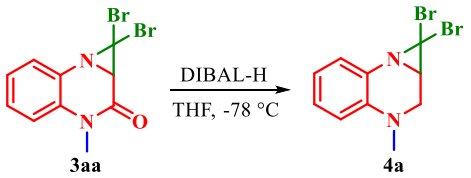
4.6.4 Gram scale synthesis of 3a:



An oven-dried 25 mL round bottom flask equipped with a stir bar and rubber septum was charged with the mixture of **1a**, (6.44 mmol, 1 g) and sodium *tert*-butoxide (12.49 mmol 1.2 g) in acetonitrile (65 mL) solvent under inert condition. The whole reaction mixture was cooled up to -15 ℃ with the help of a cooling bath. The solution of **2a** (12.49 mmol, 4.14 g) in acetonitrile (30 mL) was added dropwise into the cooled solution of the reaction mixture under inert conditions. The reaction was monitored by thin-layer chromatography. After completion of the reaction, the solvent was evaporated under reduced pressure and the crude residue was purified by column chromatography using a mixture of petroleum ether/EtOAc as an eluent to afford the **3aa** as a white solid. (86% yield, 1.78 g)

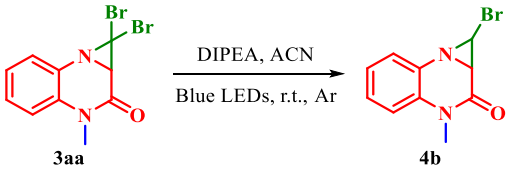
4.6.5 Applications of 3aa:

a) Selective reduction of amide group of 3aa or synthesis of 1,1-dibromo-3-methyl-1,1a-dihydroazirino[1,2-*a*]quinoxalin-2(3*H*)-one (4a):



An oven-dried 25 mL round bottom flask equipped with a stir bar and rubber septum was charged with the **3aa** (0.1 mmol) in THF (2 mL) solvent. The whole reaction mixture was cooled up to -78 °C with the help of a cooling bath. The dropwise addition of DIBAL-H (0.1 mmol) was done in the cooled reaction mixture. The reaction was monitored by TLC. After complete consumption of **3aa**, reaction was quenched with ice-cold water and an aqueous layer was extracted in diethyl ether two times (15 mL). The organic layer was passed through the sodium sulfate and evaporated under the reduced pressure and the crude residue was purified by column chromatography using a mixture of petroleum ether/EtOAc as an eluent to afford the **4a** as colorless liquid. (71% yield, 27 mg) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.10 (ddd, *J* = 8.1, 7.5, 1.6 Hz, 1H), 6.82 (td, *J* = 7.6, 1.3 Hz, 1H), 6.69 (dd, *J* = 8.2, 1.2 Hz, 1H), 3.64 – 3.58 (m, 1H), 3.32 – 3.28 (m, 1H), 2.83 (s, 3H), 2.84 – 2.79 (m, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 139.6, 130.2, 126.1, 125.3, 118.5, 112.4, 49.7, 46.1, 43.3, 38.6. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{10}H_{11}Br_2N_2]^+$ 316.9283, found 316.9286.

b) Selective reduction of dihaloaziridine of 3aa or 1,1-dibromo-3-methyl-1,1a-dihydroazirino[1,2-*a*]quinoxalin-2(3*H*)-one (4b):



An oven dried 25 mL round bottom flask charged with stir bar, **3aa** (0.1 mmol, 1 equiv.) and DIPEA (0.15 mmol, 1.5 equiv.) in 2 ml acetonitrile solvent under inert atmosphere. The whole

reaction mixture kept under the irradiation of Blue LEDs. The reaction was monitored by TLC. After complete consumption of **3aa** solvent were evaporated under reduced pressure and the crude reaction mixture were purified by column chromatography using mixture of petroleum ether/EtOAc as an eluent to afford the **4b** as white solid. (85% yield, 21.5 mg) M.P. (69.9-71.8 °C) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.26 (s, 1H), 7.10 (td, *J* = 7.6, 1.3 Hz, 1H), 6.96 (dd, *J* = 8.2, 1.0 Hz, 1H), 4.67 (d, *J* = 4.9 Hz, 1H), 3.41 (d, *J* = 4.8 Hz, 1H), 3.38 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 161.0, 135.1, 129.3, 128.1, 127.2, 123.7, 114.4, 38.6, 37.3, 28.1. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{10}H_{10}BrN_2O]^+$ 252.9971, found 252.9988.

4.7 Appendix IV:

Table No. 4.2: ^{1}H and $^{13}C\{^{1}H\}$ spectral data of representative compounds

Compound No.	Figure 4.N	Data	Page No.
3aa	Figure 4.2 and figure 4.3	^{1}H and $^{13}C\{^{1}H\}$ NMR	123
3m'a	Figure 4.4 and figure 4.5	^{1}H and $^{13}C\{^{1}H\}$ NMR	124
4a	Figure 4.6 and figure 4.7	^{1}H and $^{13}C\{^{1}H\}$ NMR	125
4b	Figure 4.8 and figure 4.9	^{1}H and $^{13}C\{^{1}H\}$ NMR	126

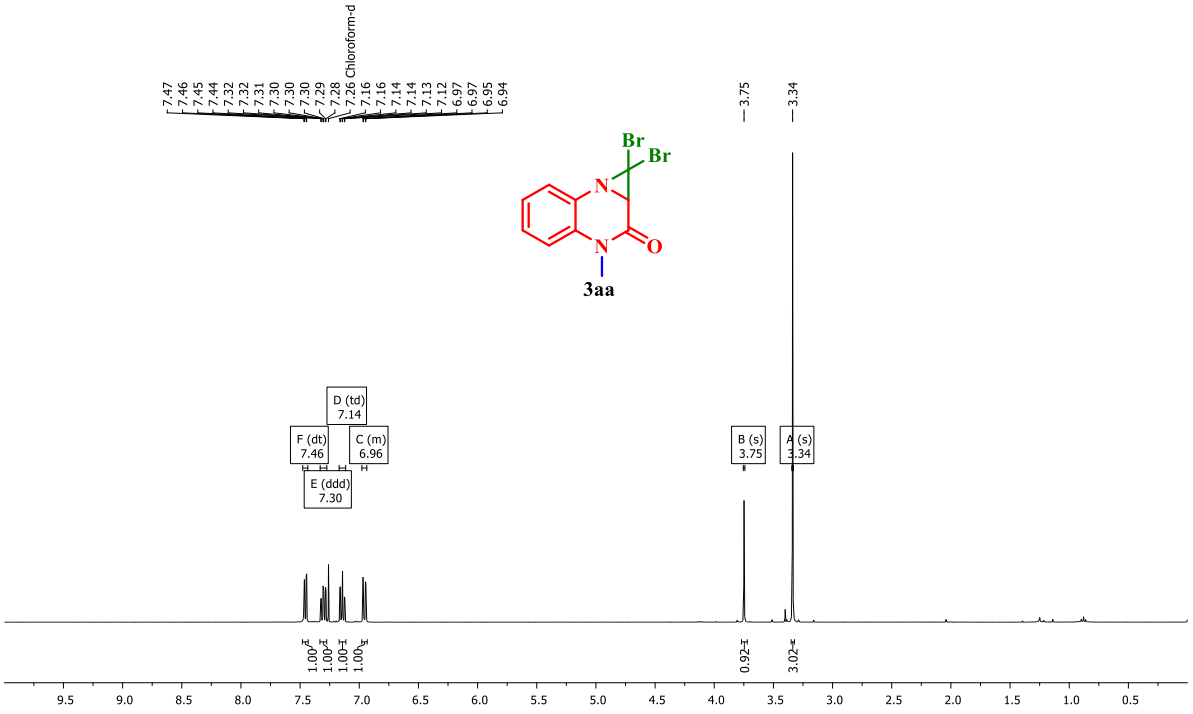


Figure 4.2 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3aa**

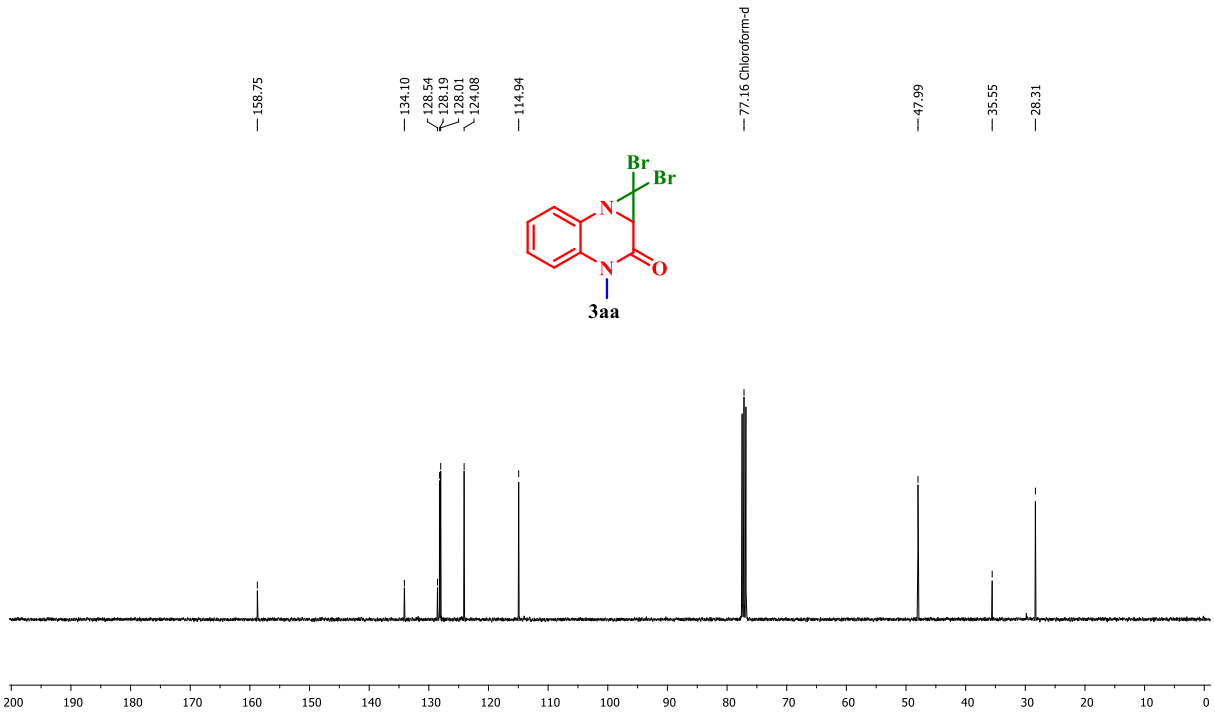


Figure 4.3 ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of compound **3aa**

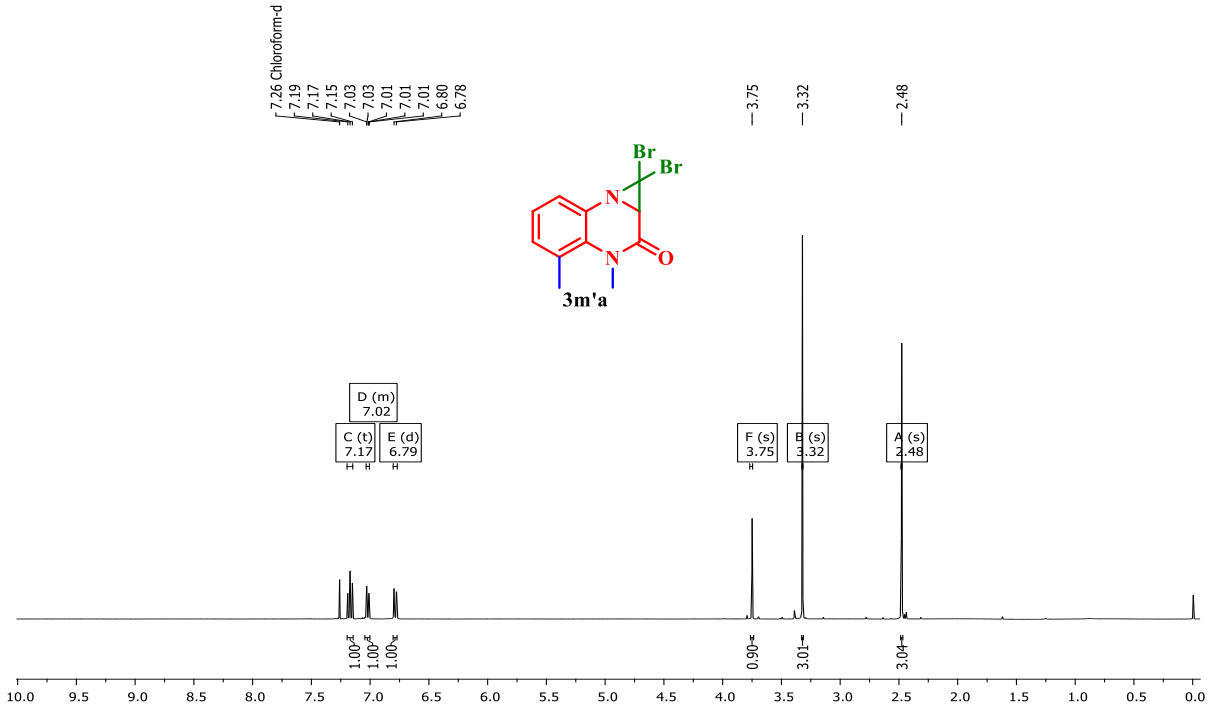


Figure 4.4 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3m'a**

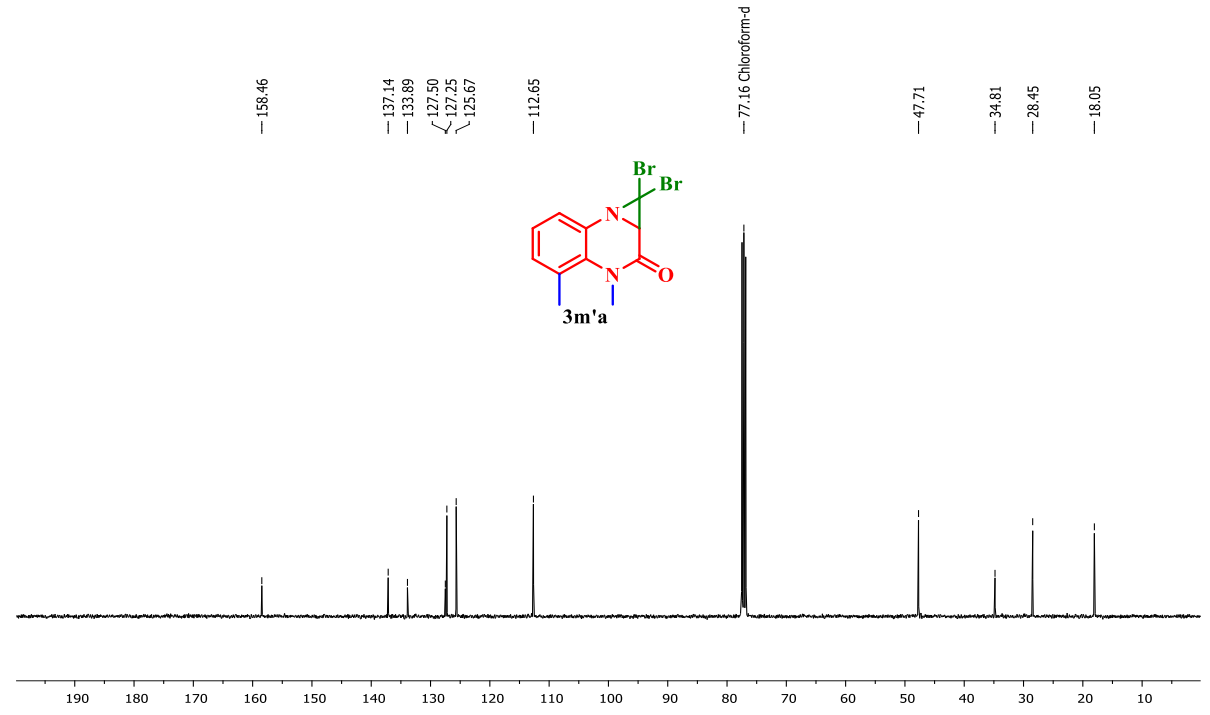


Figure 4.5 $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of compound **3m'a**

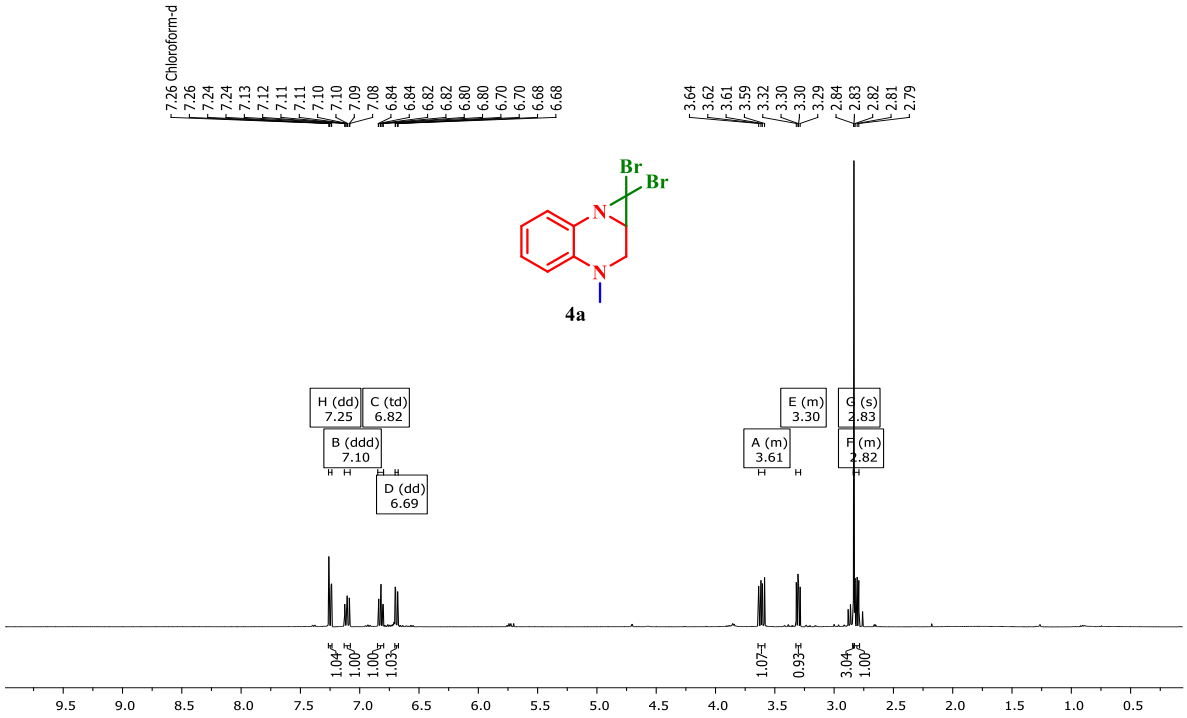


Figure 4.6 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **4a**

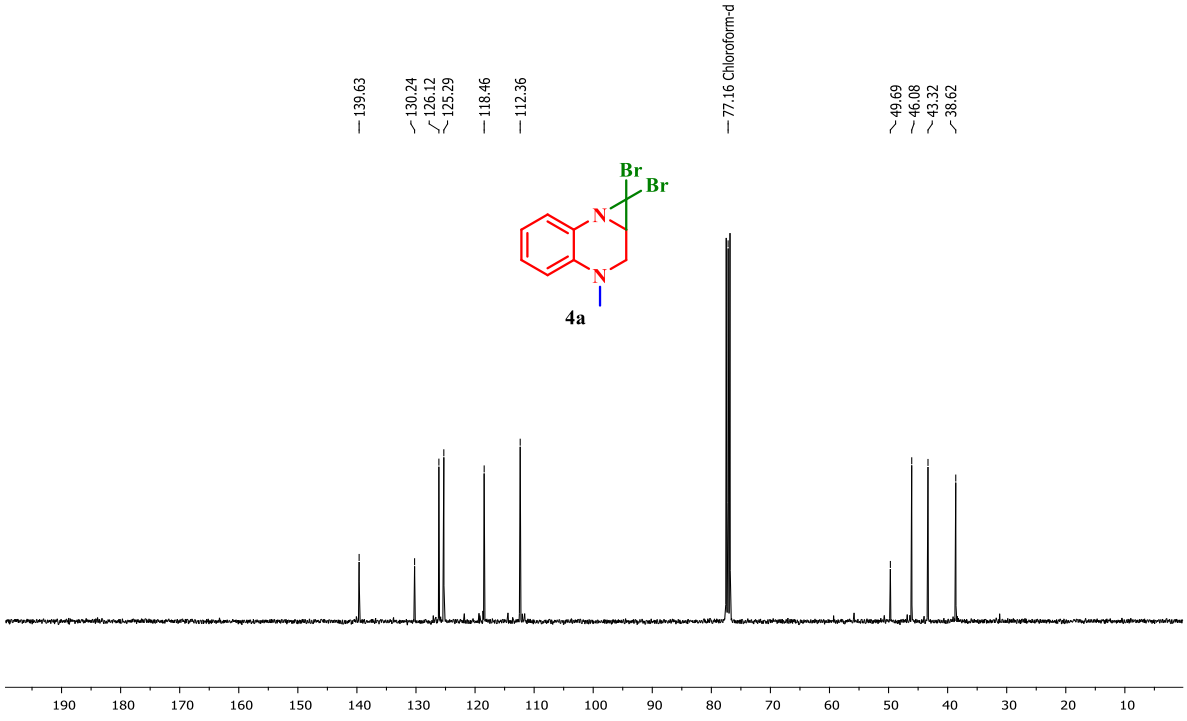


Figure 4.7 ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of compound **4a**

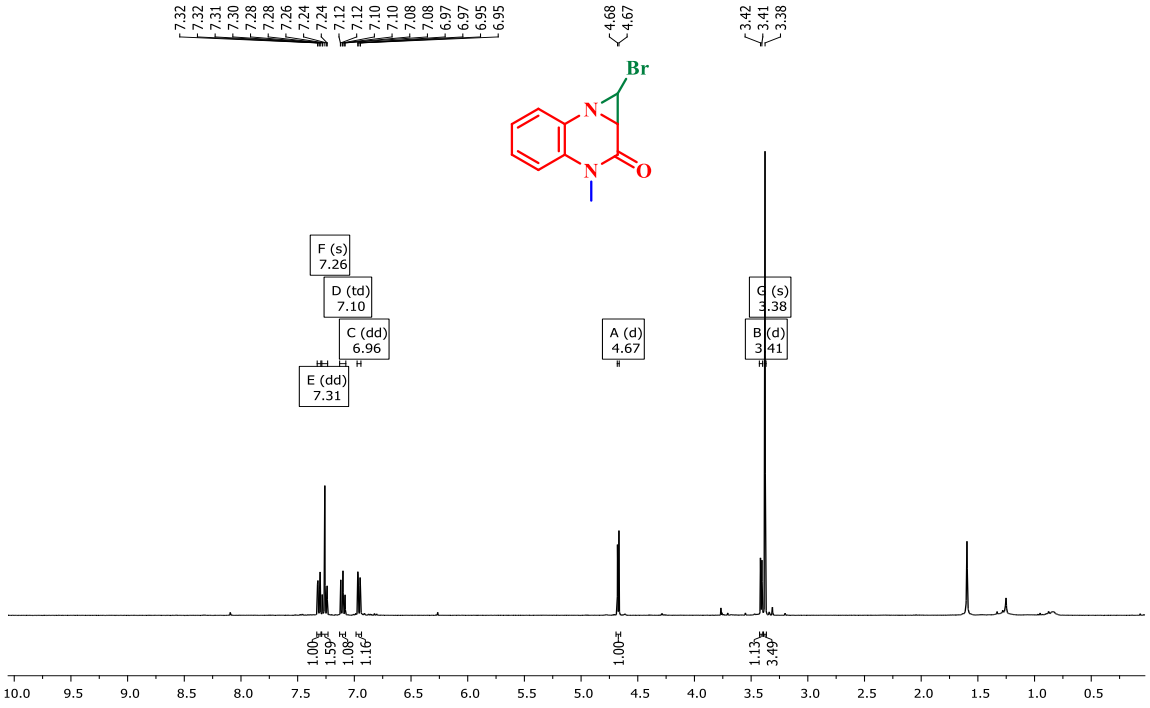


Figure 4.8 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **4b**

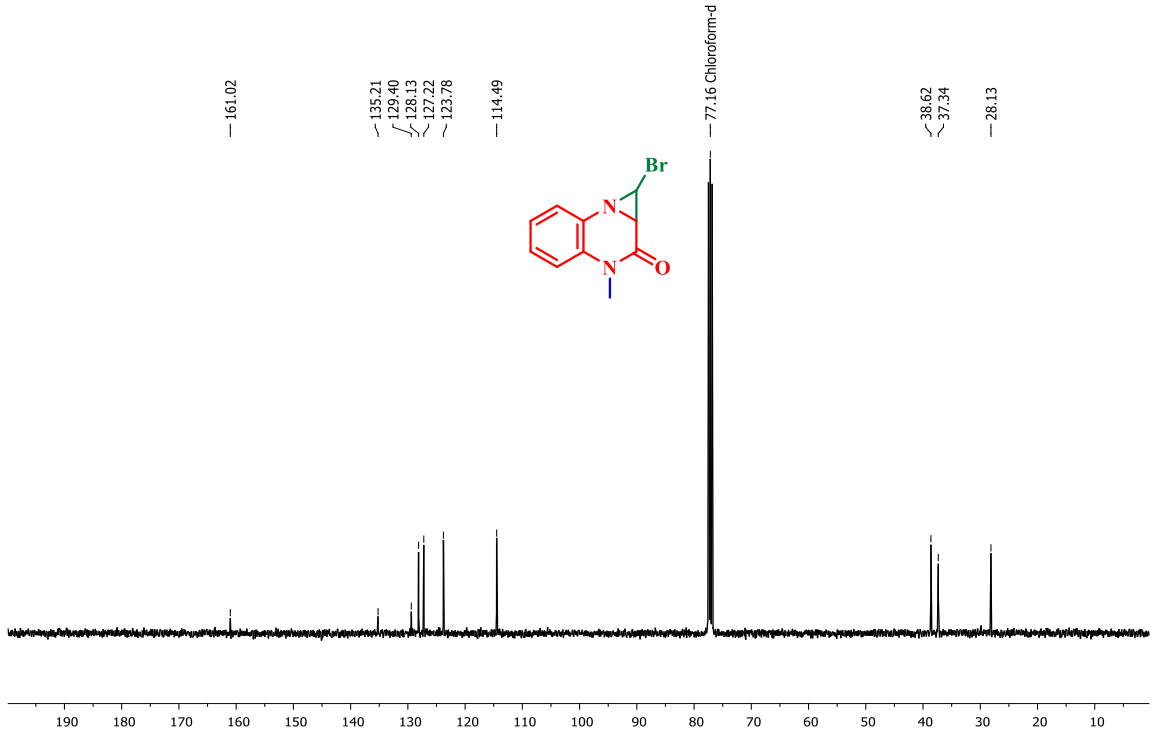


Figure 4.9 $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of compound **4b**

4.7 References

1. A. A. Elhelby, R. R. Ayyad, M. F. Zayed. *Arzneimittelforschung*. **2011,** *61*, 379-381.
2. S. N. Khattab, S. A. H. A. Moneim, A. A. Bekhit, A. M. El Massry, S. Y. Hassan, A. El-Faham, H. E. A. Ahmed, A. Amer. *Eur. J. Med. Chem.*, **2015**, *93*, 308-220.
3. L. S. Li, A. A. Okumu, S. Nolan, A. English, S. Vibhute, Y. Lu, K. H.-Thomas, J. T. Seffernick, L. Azap, S. L. Cole, D. Shinabarger, L. M. Koeth, S. Lindert, J. C. Yalowich, D. J. Wozniak, M. J. Mitton-Fry. *ACS Infect. Dis*., **2019**, *5*, 1115-1128.
4. L. Fabian, M. T. Porro, N. Gomez, M. Salvatori, G. Turk, D. Estrin, A. Moglioni. *Eur. J. Med. Chem.*, **2020**, *188*, 111987.
5. Q. K. Shen, G. H. Gong, G. Li M. Jin, L. H. Cao, Z. S. Quan. *J. Enzym. Inhib. Med. Chem.*, **2020**, *35*, 85-95.
6. B. Love, J. H. Musser, R. E. Brown, H. Jones, R. Kahen, F. C. Huang, A. Khandwala, P. S.-Goldman, M. J. Leibowitz. *J. Med. Chem.*, **1985**, *28*, 363-366.
7. J. A. Willardsen, D. A. Dudley, W. L. Cody, L. Chi, T. B. McClanahan, T. E. Mertz, R. E. Potoczak, L. S. Narasimhan, D. R. Holland, S. T. Rapundalo, J. J. Edmunds. *J. Med. Chem.*, **2004**, *47*, 4089-4099.
8. Y. P. Ji, X. Chen, H. Chen, X. Zhang, Z. Y. Fan, L. N. Xie, B. Ma, C. J. Zhu. *Bioorg. Med. Chem.*, **2019**, *27*, 1658-1669.
9. T. Settypalli, V. R. Chunduri, A. K. Maddineni, N. Begari, R. Allagadda, P. Kotha, A. R. Chippada. *New J. Chem.*, **2019**, *43*, 15435-15452.
10. (a) Q. Ke, G. Yan, J. Yu, X. Wua. *Org. Biomol. Chem.*, **2019**, *17*, 5863-5881. (b) Y. Tan, J. Wang, H.-Y. Zhang, Y. Zhang, J. Zhao. *Front. Chem.*, **2020,** *8*, 582.
11. (a) J. B. Sweeney. *Chem. Soc. Rev.*, **2002**, *31*, 247-258; (b) I. D. G. Watson, L. Yu, A. K. Yudin. *Acc. Chem. Res.* **2006**, *39*, 194-206. (c) S. Stanković, M. D'hooghe, S. Catak, H. Eum, M. Waroquier, V. V. Speybroeck, D. K. Norbert, H.-J. Ha. *Chem. Soc. Rev.*, **2012**, *41*, 643-665.
12. (a) A. Carrër, J.-D. Brion, S. Messaoudi, M. Alami. *Org. Lett.*, **2013**, *15*, 5606-5609; (b) S. Paul, J. H. Ha, G. E. Park, Y. R. Lee. *Adv. Synth. & Catal.*, **2017**, *359*, 1515-1521; (c) K. Yin, R. Zhang. *Org. Lett.*, **2017**, *19*, 1530-1533; (d) J. Yuan, S. Liu, L. Qu. *Adv. Synth. Catal.*, **2017**, *359*, 4197-4207; (e) S. J. Kwon, H. I. Jung, D. Y. Kim. *ChemistrySelect*,

2018, *3*, 5824-5827; (f) S. Paul, H. D. Khanal, C. D. Clinton, S. H. Kim. Y. R. Lee. *Org. Chem. Front.*, **2019**, *6*, 231-235.

13. (a) J. Yuan, J. Fu, J. Yin, Z. Dong, Y. Xiao, P. Mao, L. Qu. *Org. Chem. Front.*, **2018**, *5*, 2820-2828; (b) W. Wei, L. Wang, H. Yue, P. Bao, W. Liu, C. Hu, D. Yang, H. Wang. *ACS Sustain. Chem. Eng.*, **2018**, *6*, 17252-17257; (c) L.-Y. Xie, L.-L. Jiang, J.-X. Tan, Y. Wang, X.-Q. Xu, B. Zhang, Z. Cao, W.-M. He. *ACS Sustain. Chem. Eng.*, **2019**, *7*, 14153-14160; (d) L. Hu, J. Yuan, J. Fu, T. Zhang, L. Gao, Y. Xiao, P. Mao L. Qu. *Eur. J. Org. Chem.*, **2018**, 4113-4120; (e) J. Fu, J. Yuan, Y. Zhang, Y. Xiao, P. Mao, X. Diaoa, L. Qu. *Org. Chem. Front.*, **2018**, *5*, 3382-3390.
14. (a) L.-Y. Xie, Y.-S. Bai, X.-Q. Xu, X. Peng, H.-S. Tang, Y. Huang, Y.-W. Lin, Z. Cao, W.-M. He. *Green Chem.*, **2020**, *22*, 1720-1725; (b) P. Bao, F. Liu, Y. Lv, H. Yue, J.-S. Li, W. Wei. *Org. Chem. Front.*, **2020**, *7*, 492-498; (c) K. C. C. Aganda, B. Hong, A. Lee. *Adv. Synth. Catal.*, **2021**, *363*, 1443-1448.
15. (a) J.-W. Yuan, J.-H. Fu, S.-N. Liu, Y.-M. Xiao, P. Mao, L.-B. Qu. *Org. Biomol. Chem.*, **2018**, *16*, 3203-3212; (b) H. Ni, Y. Li, J. Deng, X. Shia, Q. Pan. *New J. Chem.*, **2021**, *45*, 22432-22436.
16. (a) A. Gupta, M. S. Deshmukh, N. Jain. *J. Org. Chem.*, **2017**, *82*, 4784-4792; (b) W. Wei, L. Wang, P. Bao, Y. Shao, H. Yue, D. Yang, X. Yang, X. Zhao, H. Wang. *Org. Lett.*, **2018**, *20*, 7125-7130; (c) L. Zheng, Y.-E. Qian, Y.-Z. Hu, J.-A. Xiao, Z.-P. Ye, K. Chen, H.-Y. Xiang, X.-Q. Chen, H. Yang. *Org. Lett.*, **2021**, *23*, 1643-1647.
17. (a) G. Li, C. Jia, K. Sun. *Org. Lett.*, **2013**, *15*, 5198-5201; (b) J. Yuan, J. Zhu, J. Fu, L. Yang, Y. Xiao, P. Mao, X. Dua, L. Qu. *Org. Chem. Front.*, **2019**, *6*, 925-935; (c) L.-Y. Xie, J.-L. Hu, Y.-X. Song, G.-K. Jia, Y.-W. Lin, J.-Y. He, Z. Cao, W.-M. He. *ACS Sustain. Chem. Eng.*, **2019**, *7*, 19993-19999.
18. (a) J. Xu, H. Yang, H. Cai, H. Bao, W. Li, P. Zhang. *Org. Lett.*, **2019**, *21*, 4698-4702; (b) X. Jiang, L. Yang, Z. Ye, X. Du, L. Fang, Y. Zhu, K. Chen, J. Li, C. Yu. *Eur. J. Org. Chem.*, **2020**, 1687-1694; (c) X. Jiang, L. Yang, Z. Ye, X. Du, L. Fang, Y. Zhu, C. Keda, J. Li, C. Yu. *Eur. J. Org. Chem.*, **2020**, 1687-1694.
19. (a) X. Chu, Y. Wu, H. Lu, B. Yang, C. Ma. *Eur. J. Org. Chem.*, **2020**, 1141-1144; (b) J.-W. Yuan, J.-L. Zhu, H.-L. Zhu, F. Peng, L.-Y. Yang, P. Mao, S.-R. Zhang, Y.-C. Li, L.-

B. Qu. *Org. Chem. Front.*, **2020**, *7*, 273-285; (c) J. Li, J. Hu, Y. Xiao, K. Yin, W. Dan, S. Fan, F. Jin, H. Wu, R. Zhang, J. Li. *Tetrahedron Lett.*, **2021**, *88*, 153511.

20. (a) M. Gao, Y. Li, L. Xie, R. Chauvin, X. Cui. *Chem. Commun.*, **2016**, *52*, 2846-2849; (b) Y. Kim, D. Y. Kim. *Tetrahedron Lett.*, **2018**, *59*, 2443-2446; (c) D. Rawat, R. Kumara, A. Subbarayappa. *Green Chem.*, **2020**, *22*, 6170-6175.
21. (a) L.-Y. Xie, Y.-L. Chen, L. Qin, Y. Wen, J.-W. Xie, J.-X. Tan, Y. Huang, Z. Cao, W.-M. He. *Org. Chem. Front.*, **2019**, *6*, 3950-3955; (b) J. Zhou, P. Zhou, T. Zhao, Q. Ren, J. Li. *Adv. Synth. Catal.*, **2019**, *361*, 5371-5382; (c) J. Zhou, Z. Li, Z. Sun, Q. Ren, Q. Zhang, H. Li, J. Li. *J. Org. Chem.*, **2020**, *85*, 4365-4372.
22. C. Dai, Y. Zhan, P. Liu P. Sun. *Green Chem.*, **2021**, *23*, 314-319.
23. (a) J. Wang, B. Sun, L. Zhang, T. Xu, Y. Xie, C. Jin. *Org. Chem. Front.*, **2020**, *7*, 113-118; (b) Y. Zhan, Y. Li, J. Tong, P. Liu, P. Sun. *Eur. J. Org. Chem.*, **2021**, 2193-2197.
24. (a) Q. Yang, Y. Zhang, Q. Sun, K. Shang, H.-Y. Zhang, J. Zhao. *Adv. Synth. Catal.*, **2018**, *360*, 4509-4514. (b) Y.-F. Si, K. Sun, X.-L. Chen, X.-Y. Fu, Y. Liu, F.-L. Zeng, T. Shi, L.-B. Qu, B. Yu. *Org. Lett.*, **2020**, *22*, 6960-6965.
25. A. P. Thankachan, K. S. Sindhu, K. K. Krishnana, G. Anilkumar. *Org. Biomol. Chem.*, **2015**, *13*, 8780-8802.
26. (a) P. D. Dharpure, A. Bhowmick, P. K. Warghude, R. G. Bhat. *Tetrahedron Lett.*, **2020**, *61*, 151407 (b) V. V. Khade, A. S. Thube, P. K. Warghude, R. G. Bhat. *Tetrahedron Lett.*, **2021**, *77*, 153258-153262; (c) A. Bhowmick, P. K. Warghude, P. D. Dharpure, R. G. Bhat. *Org. Chem. Front.*, **2021**, *8*, 4777; (d) V. V. Khade, A. S. Thube, P. D. Dharpure, R. G. Bhat. *Org. Biomol. Chem.*, **2022**, *20*, 1315-1319.
27. (a) M. D. Rathnayake, J. D. Weaver III. *Org. Lett.*, **2019**, *21*, 9681-9687; (b) J. M. R. Narayanam, J. W. Tucker, C. R. J. Stephenson. *J. Am. Chem. Soc.*, **2009**, *131*, 8756-8757; (c) J. J. Devery III, J. D. Nguyen, C. Dai, C. R. J. Stephenson. *ACS Catal.* **2016**, *6*, 5962-5967

An Access to Aziridino Fused Piperid-1-enes and Epoxy Fused Piperid-1-enes Starting from Amino Enones

5

5.1 Abstract

Fused bicyclic piperidines are known for their biological activities and have been explored as potential bioactive templates for various targets. Some of the fused heterocycles are also known to act as energy materials due to their steric and angle strain. It has been well documented that even the smallest manipulation of piperidine core usually results in interesting different properties. Owing to the importance, this chapter describes the development of a protocol to access aziridino fused piperid-1-enes (2-aryl-3,4-aziridino piperid-1-ene) and epoxy fused piperid-1-enes (2-aryl-3,4-epoxy-piperid-1-ene) starting from δ-amino-enones using DMDA and BocNHOTs or t-BuOOH respectively. This protocol proved to be very simple, mild and metal-free to access very useful fused bicyclic piperid-1-enes in moderate to good yields.

5.2 Introduction

It has been well documented that the various natural products have diverse functionalities, chemical diversity, biochemical specificity and potent bioactivity.[1] Undoubtedly, over the centuries, many natural products are known for their medicinal values and also their analogues have been employed for drug discovery processes and making libraries of new chemical entities (NCEs). Alkaloid is a class of natural products that contain nitrogen atom and they are utilized as diet ingredients, supplements, pharmaceuticals and in many other applications.[2] More importantly, the alkaloid containing 3,4-epoxy piperidine core is known to show different biological activities depending on the substituents present on the core scaffold (Fig. 5.1). Some of the fused bicyclic piperidine alkaloids such as (+)-kaousine[3] (isolated from the aerial parts of *Piper capense*) showed antiplasmodial activity and (+)-piplaroxide[4] (isolated from the leaves of *Piper tuberculatum*) showed repellent activity against leafcutter ant *Atta cephalotes*. Some of the

other compounds such as (–)-tendanalactam[5] showed antifungal activity (isolated from the sponge *Tedania ignis*) and (–)-3,4-epoxy-5-pipermethystine[6] (isolated from the aerial parts of kava, *Piper methysticum*) also contains the 3,4-epoxy piperidine skeleton. 3,4-epoxy-piperidine also acts as a precursor for the synthesis of isofagomine[7] (treat Gaucher's disease), mGluR5[8], paroxetine[9] (antidepressant), esamicol[10] (cholinergic physiological antagonist), femoxetine[11] (antidepressant) (Fig. 5.1A). Likewise, 3,4-aziridino piperidine scaffold is very important and useful for the synthesis of many bioactive compounds. mGluR5 is a therapeutic agent for the treatment of depression as well as it is used for the treatment of CNS disorders. Interestingly, 3,4-aziridino piperidine has been successfully employed for the synthesis of mGluR5.[8] Christoffers and coworkers have utilized 3,4-aziridino piperidine for the triazole containing 3-amino piperidines **18** successfully (see figure 5.1).[24d] Doyle and co-workers have synthesized β-Fluoroamines **19** as valuable building blocks in the medicinal chemistry starting from 3,4-aziridino piperidine (see figure 5.1).[24e] Diez and coworkers have successfully utilized 3,4-aziridino piperidine core for the ring opening reaction to access amino piperidines **20/21** (see figure 5.1).[24b]

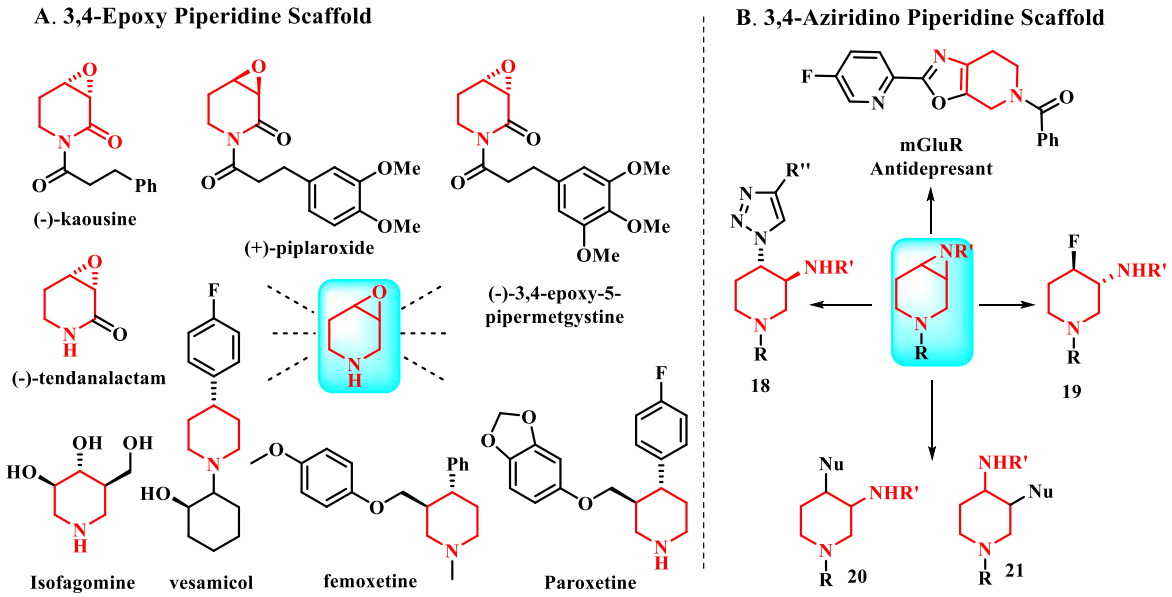
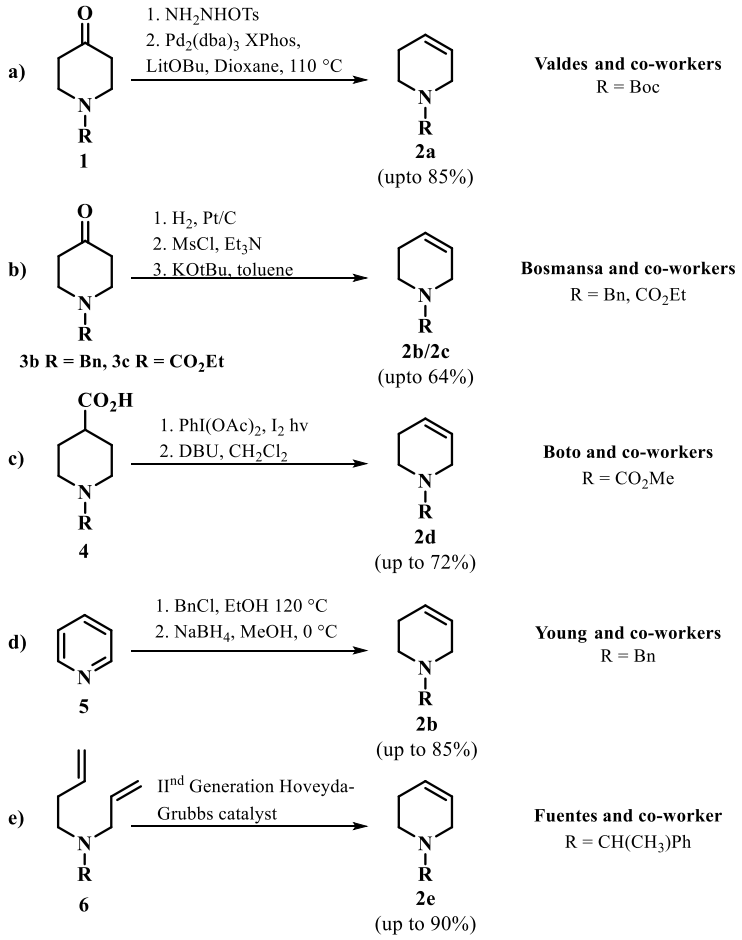


Figure 5.1 Utility of 3,4-epoxy piperidine and 3,4-aziridino piperidine to access useful compounds

5.3 Previous approaches for the synthesis of 3,4-epoxy and 3,4-aziridino fused piperidines

Owing to the importance of the fused bicyclic piperidines in general and the wider presence of 3,4-epoxy fused piperidine in particular, many research groups from across the globe have developed the synthesis for this framework and its analogues as well as for its precursors.[12-23] *N*-protected 2,3,6-tetrahydropyridine **2** derivatives have been synthesized using different approaches. Many have utilized this framework to synthesize the corresponding epoxy (oxirane) fused piperidine derivatives. Some protocols for the synthesis of *N*-protected 2,3,6-tetrahydropyridine **2** have been discussed followed by their epoxidation using different oxidizing agents (Scheme 5.1 and 5.2).

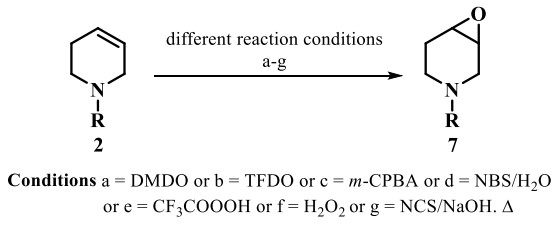


Scheme 5.1 Synthesis of *N*-substituted-2,3,6-tetrahydropyridine

In 2008, Valdes and co-workers have disclosed the synthesis of *N*-Boc-2,3,6-tetrahydropyridine **2a** via palladium-catalyzed thermal degradation of hydrazone derived from *N*-butyloxycarbonyl-

(*N*-Boc)-protected 4-piperidone **1** in very good yield (85%, Scheme 5.1a).[12] Bosmansa and coworkers have reported the synthesis of *N*-benzyl-3,4-dehydropiperidine **2b** and *N*-ethylacetate-3,4-dehydropiperidine **2c** starting from *N*-benzyl-3,4-piperidone **3b** and *N*-ethyacetate-3,4-dehydropiperidine **3c** respectively through the catalytic hydrogenation of the carbonyl group followed the protection of hydroxyl group (as OMs) and the subsequent elimination in 64%, (Scheme 5.1b).[13] Boto and coworkers have shown the decarboxylation of γ-amino acid such as *N*-protected piperidine-4-carboxylic acid **4** via iodination followed by the elimination to access *N* methyloxycarbonyl-3,4-dehydro piperidines **2d** as an antifungal agent (72%, Scheme 5.1c).[14] Young and coworkers have synthesized *N*-benzyl-3,4-dehydro piperidine **2b** by subjecting pyridine for the alkylation using benzyl chloride followed by subsequent reduction using sodium borohydride in methanol (85%, Scheme 5.1d).[15] Fuentes and co-workers have synthesized *N*-protected-3,4-dehydro piperidines **2e** via the metathesis of *N*-allyl *N*-homoallyl derivative of tertiary amine **6** using the IInd generation Hoveyda-Grubbs catalyst in excellent yield (90%, Scheme 5.1e).[16]

Likewise, many research groups have employed the *N*-protected 2,3,6-tetrahydropyridine or *N*-protected-3,4-dehydro piperidines **2** for the epoxidation to access the corresponding *N*-protected 3,4-epoxy piperidines. Different research groups have explored various oxidizing agents for the efficient epoxidation. Some of the oxidizing reagents such as dimethyl dioxirane,[17] methyl(trifluoromethyl)dioxirane,[17] *m*-chloroperoxybenzoic acid (*m*-CPBA),[18] *N*-bromosuccinimide (NBS)/H_2O,[19] trifluoroperacetic acid ($CF_3C(O)OOH$),[20] hydrogen peroxide H_2O_2,[21] *N*-chorosuccinimide (NCS)/NaOH,[22] etc. have been utilized for epoxidation (Scheme 5.2).

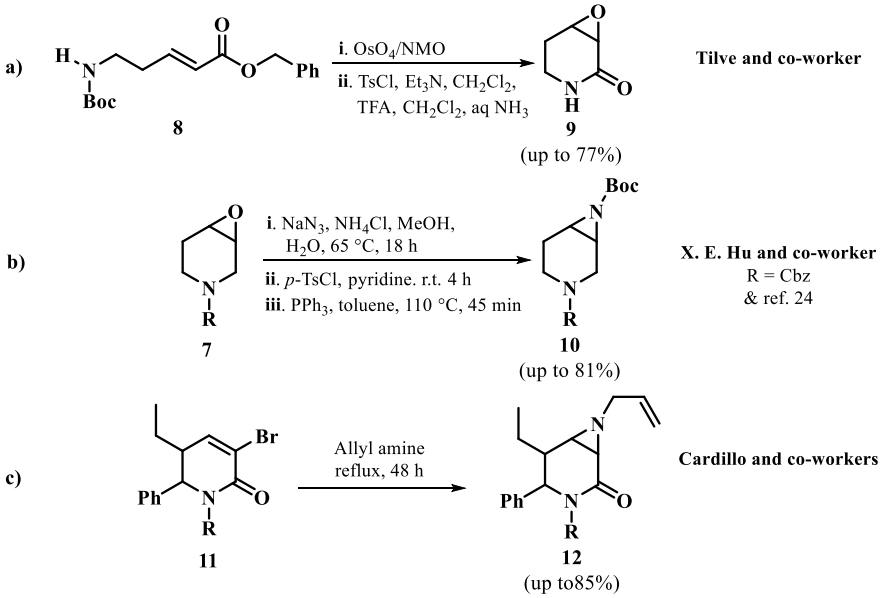


Scheme 5.2 Synthesis of 3,4-epoxy piperidines

However, these protocols to access *N*-protected-3,4-dehydro piperidines **2** relied on transition metal catalyst or on the alkylation of pyridine followed by the reduction/oxidation or on

metathesis reaction conditions. Also, many strategies subjected *N*-protected-3,4-dehydro piperidines **2** under strongly oxidizing agents to access 3,4-epoxy piperidines **7** in multiple steps.

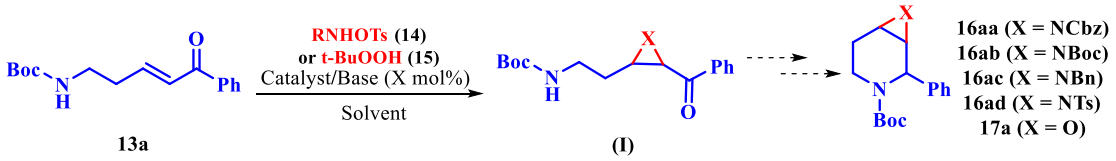
Tilve and co-workers have disclosed the synthesis of 3,4-epoxy-2-piperidones **9** in one-pot starting from the *δ*-amino-*α,β*-unsaturated esters **8**. While they have utilized strong oxidizing agent OsO_4 for the oxidation of the double bond of compound **8** followed by the regioselective protection of alcohol and subsequent elimination to obtain the desired product in good yield (77%, Scheme 5.3a).[23] In 2002, Hu[24a] and co-workers for the first time utilized 3,4-epoxy piperidines **7** followed by many other research groups[24b-24e] utilized **7** for the synthesis of 3,4-aziridino piperidine **10** using sodium azide in multiple steps (Scheme 5.3b).[24] This 3,4-aziridino piperidine **10** has been further utilized for the synthesis of mGluR antagonist as an antidepressant compound.[8] G. Cardillo and co-workers have synthesized the fused bicyclic *N*-allyl-aziridines **12** from 3-bromo-5-ethy-5,6-dihydropyridin-2-ones **11** under reflux conditions (up 85%, Scheme 5.3c).[25]



Scheme 5.3 Synthesis of fused bicyclic piperidine derivatives

However, these interesting methods relied on multiple steps with strong oxidizing reagent, multiple reagents to access fused bicyclic piperidine derivatives. Owing to the importance of the aziridino/epoxy fused bicyclic piperidine derivatives, the development of newer and milder protocols is highly desirable as well as challenging. Our lab has been working in the area of

organocatalysis and we became interested in exploring the organocatalytic pathway to access aziridino/epoxy fused bicyclic piperidine derivatives under suitable conditions. Based on our earlier experience in different organocatalytic transformations[26] and preceding literature[27] we hypothesized that aziridino/epoxy fused bicyclic piperidines possibly can be obtained starting from suitable *N*-protected δ-amino enones **13** and BocNHOTs/*t*-BuOOH respectively via the tandem aziridination/epoxidation-cyclization.



Scheme 5.4 Synthetic plans for aziridino fused piperidenes and epoxy fused piperidenes

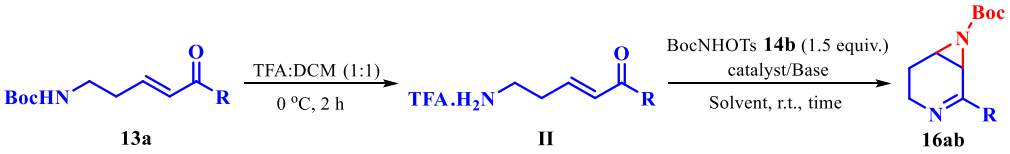
Here in this chapter, we describe the development of an organocatalytic protocol to access 3,4-epoxy/aziridino fused bicyclic piperid-1-enes starting from *N*-protected δ-amino enones **13** and *t*-BuOOH/BocNHOTs in presence of a base under milder reaction conditions (Scheme 5.4).

5.4 Results and Discussion

Initially, we commenced with the aziridination of δ-(*N*-Boc) enone **13a** using as CbzHN-OTs (**14a**), *N*,*N*′-dimethylethylenediamine (DMDA, 0.2 equiv.) as a simple organocatalyst as well as a mild base to access the corresponding aziridine derived amino ketone (**I**) and to facilitate the subsequent cyclization to access the desired product aziridine fused piperidine **16a** (see scheme 5.4 and for more details see Appendix-I, page no. 152 Entry 1). Unfortunately, this model reaction did not work under the conditions (see Appendix-I, Entry 1). Further, increasing in amount of DMDA (1 equiv.) also did not work (Appendix-I, Entry 2). In this regard, we further screened the reaction of **13a** with other different RNHOTs (R = Boc **14b**, Bn **14c**, Ts **14d**) using different simple bases that can also act like organocatalysts using different solvents (see Appendix-I, Entries 3-18,). However, unfortunately, the reaction did not work under any of these conditions to furnish the expected product (**I**) (See Scheme 5.4 and for more details see Appendix-I). Our initial unsuccessful attempts for the aziridination of *N*-protected enone led us to believe that the reactivity of enone **13a** towards aziridination may be attributed to either its weak electrophilicity or very weaker catalyst-substrate (enone-catalyst/base) interactions viz. the

imine/enamine catalytic activation of enone **13a** by catalyst DMDA. To overcome this problem, we planned to deprotect Boc group of δ-(*N*-Boc) enone **13a** so as to enhance the reactivity and optimize the reaction conditions further (See Table 5.1).

Table 5.1: Screening of catalyst, bases and solvents



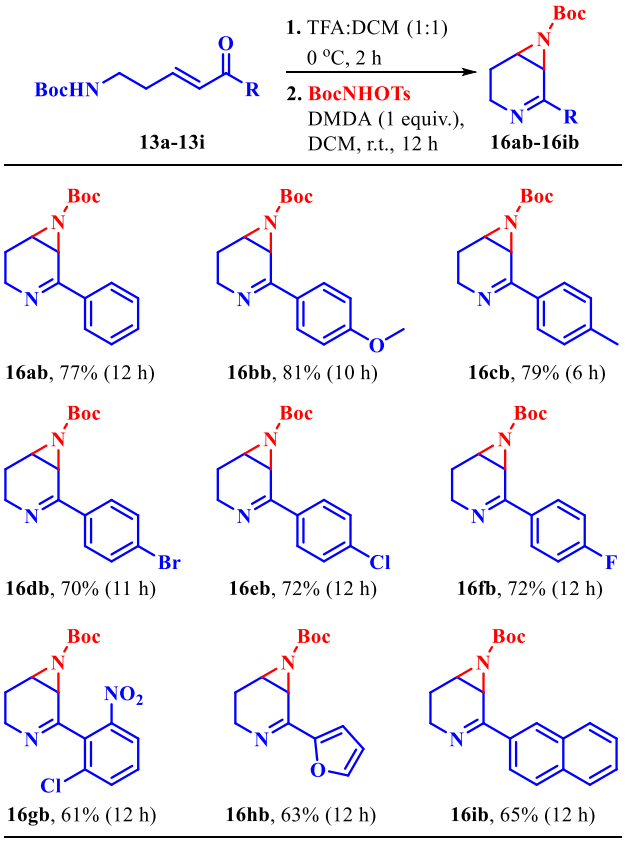
Entry[a]	Base	Solvent	Time (h)	Yield[b,c] (%)
1	DMDA (0.2 equiv.)	$CHCl_3$	12	32
2	DMDA (1 equiv.)	$CHCl_3$	12	65
3	DMDA (2 equiv.)	$CHCl_3$	12	66
4	Et_3N (1 equiv.)	$CHCl_3$	12	52
5	Pyridine (1 equiv.)	$CHCl_3$	12	45
6	DBU (1 equiv.)	$CHCl_3$	12	58
7	DABCO (1 equiv.)	$CHCl_3$	12	60
8	DIPEA (1 equiv.)	$CHCl_3$	12	55
9	DMAP (1 equiv.)	$CHCl_3$	12	57
10	Pyrrolidine (1 equiv.)	$CHCl_3$	12	50
11	**DMDA (1 equiv.)**	**CH_2Cl_2**	**12**	**77**
12	DMDA (1 equiv.)	EtOAc	24	50
12	DMDA (1 equiv.)	THF	24	38
13	DMDA (1 equiv.)	THF	24	38
14	DMDA (1 equiv.)	MeCN	24	42
15	DMDA (1 equiv.)	Toluene	24	55

Reaction condition: [a]δ-Amino-enone **13a** was deprotected by TFA:DCM (1:1) then the resulting TFA salt of δ-amino enone [**II]** was used directly without purification. BocNHOTs **14b** (1.5 equiv.), catalysts/base (0.2 to 2 equiv.), solvent, at room temperature. [b]isolated yield after column chromatography. [c]Yields based on the stoichiometry of enone **13a**. *N*,*N*′-dimethyl ethylene diamine (DMDA)

In this regard, to begin with, as a model reaction we treated **13a** with trifluoroacetic acid in DCM [TFA:DCM (v/v 1:1)] to deprotect the Boc group to afford the corresponding trifluoroacetic acid (TFA) salt of δ-amino-enone [**II].** We further utilized this amino-enone TFA salt [**II]** without any further purification for the next reaction to obtain the desired aziridine fused piperid-1-enes **16** and oxirane fused piperid-1-enes **17**. Initially, the TFA salt of δ-amino-enone [**II]** (impure) is utilized for the aziridination by using BocNHOTs as an aziridination agent in presence of DMDA as a catalyst (20 mol%) in chloroform at room temperature (Table 5.1, Entry 1). To our delight, TFA salt of δ-amino-enone [**II]** underwent facile tandem aziridination-cyclization reactions

sequence to furnish the corresponding aziridine fused 5,6-tetrahydropyridine derivative or 2-phenyl-3,4-aziridino piperid-1-ene **16ab** albeit in modest yield (Table 5.1, Entry 1). This product **16ab** exclusively formed as a *cis*-isomer and the stereochemistry of product was confirmed by proton NMR spectroscopy. Encouraged by this initial success, we planned to increase the catalyst (DMDA) loading to examine the outcome of the yield of product **16ab**. The stoichiometric addition of DMDA significantly increased the yield of product **16ab** (65%, Table 5.1, Entry 2). However, interestingly we observed that further increment in loading of DMAD did not increase the yield of product (66%, Table 5.1, Entry 3). Encouraged by this initial success in the tandem aziridination-cyclization reaction strategy, next, we screened different Lewis bases for optimization of the reaction (Table 5.1, Entries 4-10). Among all the Lewis bases screened DMDA proved to be more efficient (Table 5.1, Entries 2). Later, we screened the reaction of TFA salt of δ-amino-enone [**II]** in presence of DMDA (1 equiv.) in different solvents and among all we observed that DCM proved to be more advantageous at room temperature to afford the corresponding product **16ab** in good yield (77%, Table 5.1, Entry 11). Based on the systematic screening, TFA salt of δ-amino-enone [**II]** (1 equiv. based on the stoichiometry of **13a**), DMDA (1 equiv.), BocNHOTs (1.5 equiv.) in DCM as solvent at room temperature proved to be the optimum reaction conditions to access the corresponding aziridino fused piperid-1-enes **16.**

Having optimized reaction conditions, we explored the substrate scope of tandem aziridination-cyclization reaction by using various aromatic amino enones (**13a**-**13i**). All the required *N*-protected amino enones were synthesized following the known procedure.[28e] These *N*-protected amino enones were subjected to deprotection using TFA to obtain the corresponding TFA salt of δ-amino enones and were used for the next reaction without any further purification. TFA salt of δ-amino enones having aromatic as well as heteroaromatic moieties underwent smooth tandem aziridination-cyclization reaction to furnish the corresponding 2-aryl-3,4-aziridino piperid-1-enes (**16ab**-**16ib**) in moderate to excellent yields (Scheme 5.5). Various electron-donating, electron-withdrawing, and electron-deactivated groups on the aryl part of *δ*-amino enones smoothly reacted with BocNHOTs under standard reaction conditions to afford their 2-aryl-3,4-aziridino piperid-1-ene with good yields (**16ab-16ib**). The heteroaromatic and highly aromatic group-containing *δ*-amino enones also furnished their corresponding products (**16hb-16ib**) in good yields (Scheme 5.5). All these aziridino fused bicyclic piperid-1-enes have been synthesized starting from *N*-protected enones in one pot following two steps.

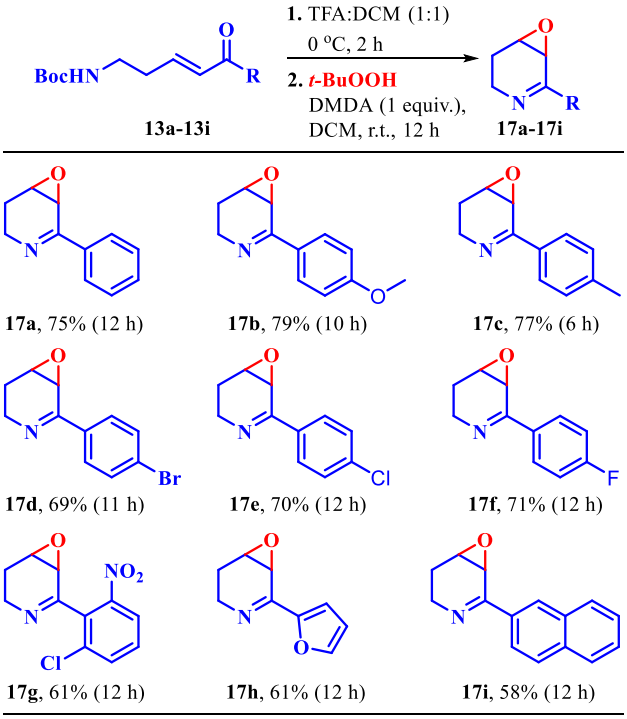


Reaction condition: [a]δ-Amino-enone **13a** was deprotected by TFA:DCM (1:1) then the resulting TFA salt of δ-amino enone **[II]** was used directly without purification. BocNHOTs **14b** (1.5 equiv.), catalysts/base (0.2 to 2 equiv.), solvent, at room temperature. [b]isolated yield after column chromatography. [c]Yields based on the stoichiometry of enone **13a**. *N*,*N*′-dimethyl ethylene diamine (DMDA)

Scheme 5.5 Tandem aziridination-cyclization reaction[a-c]

Having demonstrated the protocol to access 2-aryl-3,4-aziridino piperid-1-enes or aziridino fused bicyclic piperid-1-enes, we turned our attention towards constructing very important and useful bioactive scaffold such as epoxy fused bicyclic piperid-1-enes using this tandem strategy for the epoxidation-cyclization starting from δ-amino-enones. We believed that like aziridination reagent, epoxidation reagent such as *t*-BuOOH may serve as an effective reagent under the optimized reaction conditions to access corresponding 2-aryl-3,4-epoxy piperid-1-enes. Based on the earlier result, the reaction of TFA salt of δ-amino-enone **II** (1 equiv. based on the stoichiometry of **13a**), DMDA (1 equiv.), *t*-BuOOH (1.1 equiv.) in DCM as solvent at room temperature proved to be the optimum reaction conditions to access the corresponding epoxy fused piperid-1-ene **17a** in good yield (75%).

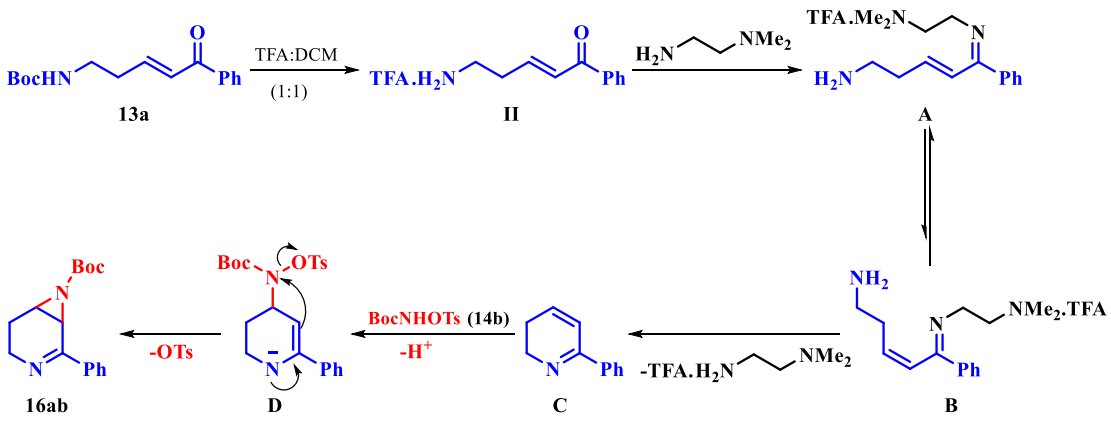
Encouraged by this result, we further planned to extend this protocol for the substrate scope of the tandem epoxidation-cyclization. In this regard, different aromatic amino enones (**13a-13i**) were subjected to deprotection of the Boc group using TFA then the resulting TFA salt of δ-amino enones were utilized for the tandem epoxidation-cyclization reaction without any further purification. Various δ-amino-enones (**13a-13c**) having electron-donating groups such as methoxy and methyl on the aryl part reacted smoothly under the optimized reaction conditions to afford the corresponding epoxy fused bicyclic piperid-1-enes (2-aryl-3,4-epoxy piperid-1-enes) (**17b-17c**) in moderate to good yields (Scheme 5.6). Also, δ-amino-enones (**13d-13f**) having aryl group containing electron deactivating groups such as bromo, chloro, and fluoro also reacted smoothly to furnish the corresponding desired products (**17d-17f**) in good yields (Scheme 5.6). Even the δ-amino enones **13g** having the phenyl group with nitro as well as chloro substituents reacted smoothly to give the corresponding 3,4-epoxy piperid-1-ene (**17g**) in moderate yield (Scheme 5.6). Interestingly, δ-amino-enones having heteroaromatic and highly aromatic moieties transformed to afford the corresponding desired products (**17h-17i**) in moderate yields.



Reaction condition: [a]δ-Amino-enone **13a** was deprotected by TFA:DCM (1:1) then the resulting TFA salt of δ-amino enone [**II]** was used directly without purification. *t*-BuOOH (1.5 equiv.), catalysts/base (0.2 to 2 equiv.), solvent, at room temperature. [b]isolated yield after column chromatography. [c]Yields based on the stoichiometry of enone **13a**. *N*,*N*′-dimethyl ethylene diamine (DMDA)

Scheme 5.6 Tandem epoxidation-cyclization

Based on the previous studies on aziridination reaction,[29] the plausible reaction mechanism for the tandem aziridination/epoxidation-cyclization sequence has been depicted in Scheme 5.7. δ-amino enone **13a** under acidic conditions (TFA: DCM v/v 1:1) forms the corresponding TFA salt of δ-amino enone **II**. This in situ generated salt **II** upon treatment with DMDA forms an imine **A** intermediate. This intermediate **A** undergoes isomerization to form kinetically stable *cis*-imine isomer intermediate **B** to facilitate the cyclization further. This imine intermediate **B** undergoes cyclization to form intermediate **C** along with the generation of DMDA·TFA salt. This intermediate **C** would eventually be attacked by relatively nucleophilic reagent BocNHOTs via Michael addition to form charged intermediate **D**. This charged intermediate **D** would further undergo intramolecular aziridination via the elimination of tosyl group to form the final desired aziridine fused bicyclic piperid-1-ene product **16ab**.



Scheme 5.7 Plausible reaction mechanism

5.5 Conclusions

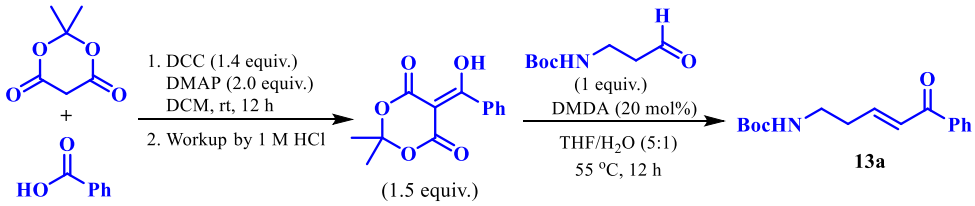
In summary, we have developed a novel, regioselective and mild organocatalytic protocol for the synthesis of fused bicyclic heterocyclic compounds in two steps in one pot starting from δ-*N*-protected amino enones. The wide verities of δ-*N*-protected amino enones worked well under the reaction condition to access aziridino/epoxy fused bicyclic piperid-1-ene derivatives in moderate to good yields via C–N and C–O bond construction. This protocol may find wider application in organic synthesis as piperidine is a very important scaffold in many natural products and pharmaceuticals.

5.6 Experimental section:

5.6.1 General

Note: (Please see section 2.6.1 of chapter 2 for general experimental, page no.29)

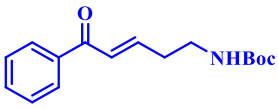
5.6.2 General procedure A for the synthesis of enone (13a-13i)



All the enones **13** were synthesized by the reported procedure.[26e] Freshly recrystallized Meldrum's acid (1.0 g, 6.9 mmol) and benzoic acid (0.85 g, 6.9 mmol) were dissolved in dry CH_2Cl_2 (10 mL) and stirred at room temperature for 5 minutes. DMAP (1.7 g, 13.9 mmol) followed by DCC (2.0 g, 9.7 mmol) were added to the reaction mixture and the mixture was stirred for 16 h under nitrogen. It was noted that colourless reaction mixture turned brown over some time. After the complete consumption of Meldrum's acid (monitored by TLC) solution was quenched with 1 M HCl (10 mL). The reaction was filtered through a sintered funnel over celite. The organic layer was collected and washed with 1 M HCl (10 mL X 3) followed by brine and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo*. A crude benzoyl Meldrum's acid (95% yield) was used immediately without any purification for condensation with an aldehyde.

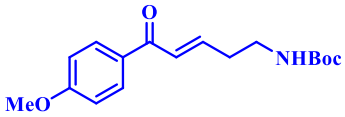
To a round-bottomed flask equipped with a magnetic bar, *N*-Boc-3-amino-propanal (173.22 mg, 0.1 mmol) and freshly prepared benzoyl Meldrum's acid (372.37 mg, 1.5 mmol) was added in 5 mL THF/H_2O (5:1). Then the catalyst DMDA (17.62 mL, 0.2 mmol) was added and the reaction mixture was allowed to stir for 12 h at 55 °C. After the complete consumption of *N*-Boc-3-amino-propanal (monitored by TLC), the reaction mixture was filtered through anhydrous Na_2SO_4 and the residue was purified by column chromatography over silica gel using ethyl acetate in petroleum ether as eluent. The product **13a** was obtained as pale-yellow viscous oil in 82% yield (225 mg).

***tert*-butyl *(E)*-(5-oxo-5-phenylpent-3-en-1-yl)carbamate (13a)**



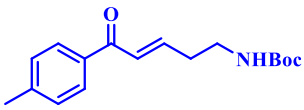
Compound **13a** prepared following the general procedure **A** and obtained as pale-yellow viscous oil. (225 mg, 82%) *Rf* = 0.67 (petroleum ether/EtOAc 70:30) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.91 (m, 2H), 7.59 – 7.53 (m, 1H), 7.46 (dd, *J* = 10.5, 4.7 Hz, 2H), 7.04 – 6.92 (m, 2H), 4.67 (s, 1H), 3.34 (dd, *J* = 12.5, 6.1 Hz, 2H), 2.52 (dd, *J* = 12.4, 6.5 Hz, 2H), 1.43 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 190.6, 156.0, 145.8, 137.8, 132.9, 128.7, 128.7, 127.8, 79.6, 39.3, 33.5, 28.5. HRMS (ESI TOF) *m/z* calcd. For $C_{16}H_{21}NO_3$+Na^+ $[M + Na]^+$ 298.1414, found 298.1428.

***tert*-butyl (*E*)-(5-(4-methoxyphenyl)-5-oxopent-3-en-1-yl)carbamate (13b)**



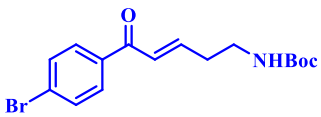
Compound **13b** prepared following the general procedure **A** and obtained as pale-yellow viscous oil. (239 mg, 78% yield). *Rf* = 0.51 (petroleum ether/EtOAc 70:30) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.9 Hz, 2H), 7.05 – 6.87 (m, 4H), 4.64 (s, 1H), 3.88 (s, 3H), 3.34 (d, *J* = 6.2 Hz, 2H), 2.51 (d, *J* = 3.9 Hz, 2H), 1.44 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 188.7, 163.5, 155.8, 144.5, 130.9, 130.6, 127.4, 113.8, 79.5, 55.5, 39.2, 33.2, 28.4. HRMS (ESI TOF) m/z calcd. For $C_{17}H_{23}NO_4$+Na^+ $[M + Na]^+$ 328.1519, found 328.1523.

***tert*-butyl (*E*)-(5-oxo-5-(p-tolyl)pent-3-en-1-yl)carbamate (13c)**



Compound **13c** prepared following the general procedure **A** and obtained as pale-yellow viscous oil. (230 mg, 79% yield). *Rf* = 0.66 (petroleum ether/EtOAc 70:30) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.2 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.01 – 6.87 (m, 2H), 4.72 (s, 1H), 3.32 (q, *J* = 6.3 Hz, 2H), 2.50 (q, *J* = 6.4 Hz, 2H), 2.40 (s, 3H), 1.42 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 190.0, 155.9, 145.3, 143.8, 135.1, 129.4, 128.8, 127.7, 79.5, 39.2, 33.3, 28.5, 21.7. HRMS (ESI TOF) m/z calcd. For $C_{17}H_{23}NO_3$+Na^+ $[M + Na]^+$ 312.1570, found 312.1577.

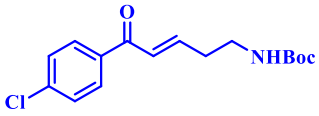
***tert*-butyl (*E*)-(5-(4-bromophenyl)-5-oxopent-3-en-1-yl)carbamate (13d)**



Compound **13d** prepared following the general procedure **A** and obtained as colorless viscous oil. (270 mg, 76% yield). *Rf* = 0.64

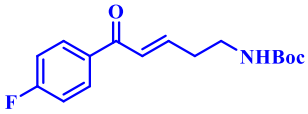
(petroleum ether/EtOAc 70:30) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.74 (m, 2H), 7.65 – 7.53 (m, 2H), 7.07 – 6.83 (m, 2H), 4.66 (s, 1H), 3.34 (q, *J* = 6.2 Hz, 2H), 2.51 (q, *J* = 6.5 Hz, 2H), 1.43 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 189.3, 155.8, 146.3, 136.4, 131.9, 130.1, 127.9, 127.2, 79.5, 39.1, 33.4, 28.4. HRMS (ESI TOF) m/z calcd. For $C_{16}H_{20}BrNO_3$+Na^+ $[M + Na]^+$ 376.0519, found 376.0537.

***tert*-butyl (*E*)-(5-(4-chlorophenyl)-5-oxopent-3-en-1-yl)carb amate (13e)**



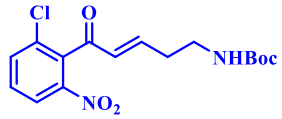
Compound **13e** prepared following the general procedure **A** and obtained as pale-yellow viscous oil. (260 mg, 84% yield). *Rf* = 0.60 (petroleum ether/EtOAc 70:30) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.7 Hz, 2H), 7.44 (d, *J* = 8.7 Hz, 2H), 7.05 – 6.84 (m, 2H), 4.66 (s, 1H), 3.34 (q, *J* = 6.2 Hz, 2H), 2.52 (q, *J* = 6.6 Hz, 2H), 1.43 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 189.1, 155.8, 146.2, 139.3, 136.0, 130.0, 128.9, 127.2, 79.6, 39.1, 33.4, 28.4. HRMS (ESI TOF) m/z calcd. For $C_{16}H_{20}ClNO_3$+Na^+ $[M + Na]^+$ 332.1024, found 332.1030.

***tert*-butyl (*E*)-(5-(4-fluorophenyl)-5-oxopent-3-en-1-yl)carbamate (13f)**



Compound **13f** prepared following the general procedure **A** and obtained as colourless viscous oil. (231 mg, 79% yield). *Rf* = 0.68 (petroleum ether/EtOAc 70:30) ^{1}H NMR (400 MHz, $CHCl_3$) δ 8.04 – 7.97 (m, 2H), 7.22 – 7.12 (m, 2H), 7.03 (dt, *J* = 15.4, 6.3 Hz, 1H), 6.96 (d, *J* = 15.6 Hz, 1H), 4.69 (s, 1H), 3.38 (dd, *J* = 12.5, 6.2 Hz, 2H), 2.55 (q, *J* = 6.5 Hz, 2H), 1.46 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 188.7, 165.6 (d, *J* = 254.5 Hz), 155.8, 145.9, 134.0 (d, *J* = 3.0 Hz), 131.2 (d, *J* = 9.3 Hz), 127.2, 115.7 (d, *J* = 21.8 Hz), 79.5, 39.1, 33.4, 28.4. HRMS (ESI TOF) m/z calcd. For $C_{16}H_{20}FNO_3$+Na^+ $[M + Na]^+$ 316.1319, found 316.1328.

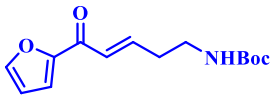
***tert*-butyl (*E*)-(5-(2-chloro-6-nitrophenyl)-5-oxopent-3-en-1-yl)carbamate (13g)**



Compound **13g** prepared following the general procedure **A** and obtained as colourless viscous oil. (265 mg, 75% yield). *Rf* = 0.47 (petroleum ether/EtOAc 70:30) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 2H), 8.22 (d, *J* = 2.7 Hz, 1H), 7.60 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.77 – 6.66 (m, 1H), 6.53 (d, *J* = 15.9 Hz, 1H), 4.61 (s, 1H), 3.29 (q, *J* = 6.4 Hz, 2H), 2.51 (q, *J* = 6.7 Hz, 2H), 1.40 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz,

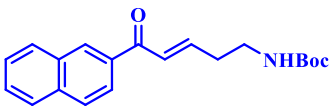
$CDCl_3$) δ 191.2, 155.8, 150.2, 146.5, 139.8, 138.1, 131.5, 131.1, 125.8, 124.4, 79.7, 38.9, 33.9, 28.4. HRMS (ESI TOF) m/z calcd. For $C_{16}H_{19}ClNO_5$+Na^+ $[M + Na]^+$ 377.0885, found 377.0884.

***tert*-butyl (*E*)-(5-(furan-2-yl)-5-oxopent-3-en-1-yl)carbamate (13h)**



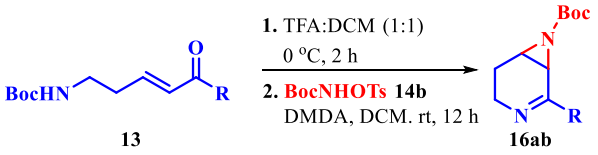
Compound **13h** prepared following the general procedure **A** and obtained as pale yellow viscous oil. (176 mg, 66% yield). *Rf* = 0.49 (petroleum ether/EtOAc 70:30) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 1.6, 0.6 Hz, 1H), 7.26 (d, *J* = 3.5 Hz, 1H), 7.07 (dt, *J* = 15.4, 7.0 Hz, 1H), 6.86 (d, *J* = 15.5 Hz, 1H), 6.56 (dd, *J* = 3.6, 1.7 Hz, 1H), 4.64 (s, 1H), 3.33 (q, *J* = 6.2 Hz, 2H), 2.51 (q, *J* = 6.5 Hz, 2H), 1.43 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 177.9, 155.9, 153.3, 146.8, 145.1, 126.9, 118.0, 112.6, 79.6, 39.2, 33.3, 28.5. HRMS (ESI TOF) m/z calcd. For $C_{14}H_{19}NO_4$+H^+ $[M + H]^+$ 266.1392, found 266.1384.

***tert*-butyl (*E*)-(5-(naphthalen-2-yl)-5-oxopent-3-en-1-yl)carbamate (13i)**



Compound **13i** prepared following the general procedure **A** and obtained as pale-yellow viscous oil. (200 mg, 61% yield). *Rf* = 0.71 (petroleum ether/EtOAc 70:30) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 – 8.15 (m, 1H), 8.07 – 8.06 (m, 1H), 7.87 – 7.83 (m, 2H), 7.56 – 7.53 (m, 1H), 7.49 – 7.45 (m, 2H), 7.16 – 7.11 (m, 1H), 6.94 – 6.91 (m, 1H), 4.02 (s, 1H), 3.17 – 3.12 (m, 2H), 2.52 – 2.49 (m, 2H), 1.45 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 190.4, 157.3, 147.3, 136.5, 134.5, 134.0, 131.3, 129.7, 128.8, 128.2, 127.7, 127.0, 126.5, 124.1, 80.7, 40.6, 31.8, 28.4. HRMS (ESI TOF) m/z calcd. For $C_{14}H_{19}NO_4$+H^+ $[M + H]^+$ 348.1570, found 348.1565.

5.6.3 General procedure B for the synthesis of 2-aryl-3,4-aziridino piperid-1-ene (16ab-16ib):

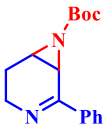


To a 10 mL round-bottomed flask equipped with a magnetic bar containing *δ*-amino-enone **13** (0.2 mmol) in DCM (1 mL) was added trifluoroacetic acid (TFA, 1 mL) at 0 °C. The reaction mixture was allowed to stir for 2 h at 0 °C. After the complete deprotection, the solution was concentrated under a vacuum. After which, DCM (5 mL) was added to the crude reaction

mixture and the solution was concentrated under a vacuum (the procedure was repeated 3 times) to obtain the δ-amino enone salt **II** and this was used without purification.

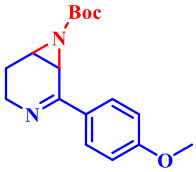
To a round bottom flask equipped with a magnetic bar containing TFA salt of δ-amino-enone **II** in DCM (2 mL) was added BocNHOTs (1.5 mmol), DMDA (1 mmol) at room temperature. After which (after 12 h) the solvent was removed under vacuum and the crude reaction mixture was further purified by column chromatography over silica gel using triethyl amine/ethyl acetate/petroleum ether mixture (1:15:84) as an eluent. Product **16** was obtained as a viscous liquid.

***tert*-butyl 2-phenyl-3,7-diazabicyclo[4.1.0]hept-2-ene-7-carboxylate (16ab)**



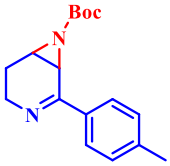
Compound **16ab** prepared following the general procedure **B** and obtained as pale-yellow viscous oil. (42 mg, 77% yield). *Rf* = 0.51 (petroleum ether/EtOAc 70:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.72 (m, 2H), 7.57 – 7.27 (m, 3H), 3.99 (ddt, *J* = 16.3, 5.6, 1.5 Hz, 1H), 3.65 (ddd, *J* = 16.3, 12.3, 6.3 Hz, 1H), 3.41 (d, *J* = 6.4 Hz, 1H), 3.21 – 3.07 (m, 1H), 2.22 (ddt, *J* = 14.1, 6.3, 1.6 Hz, 1H), 1.59 – 1.53 (m, 1H), 1.51 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 163.26, 161.53, 139.33, 129.95, 128.45, 126.65, 81.92, 44.91, 38.90, 32.12, 27.95, 19.32; HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{16}H_{21}N_2O_2]^+$ 273.1598, found 273.1606.

***tert*-butyl 2-(4-methoxyphenyl)-3,7-diazabicyclo[4.1.0]hept-2-ene-7-carboxylate (16bb)**



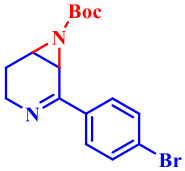
Compound **16bb** prepared following the general procedure **B** and obtained as colourless viscous oil. (81 mg, 81% yield). *Rf* = 0.41 (petroleum ether/EtOAc 70:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.9 Hz, 2H), 6.93 (d, *J* = 8.9 Hz, 2H), 3.94 (ddd, *J* = 16.2, 4.1, 1.5 Hz, 1H), 3.84 (s, 3H), 3.62 (ddd, *J* = 16.2, 12.3, 6.2 Hz, 1H), 3.40 (d, *J* = 6.4 Hz, 1H), 3.16 (dt, *J* = 6.4, 1.9 Hz, 1H), 2.20 (ddt, *J* = 14.0, 6.1, 1.5 Hz, 1H), 1.58 – 1.52 (m, 1H), 1.51 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 162.51, 161.71, 161.23, 132.11, 128.25, 113.86, 81.99, 55.43, 44.71, 39.03, 32.07, 28.03, 19.46; HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{17}H_{23}N_2O_3]^+$ 303.1703, found 303.1711.

***tert*-butyl 2-(p-tolyl)-3,7-diazabicyclo[4.1.0]hept-2-ene-7-carboxylate (16cb)**



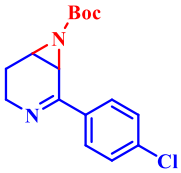
Compound **16cb** prepared following the general procedure **B** and obtained as pale-yellow viscous oil. (45 mg, 79% yield). *Rf* = 0.51 (petroleum ether/EtOAc 70:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.73 (m, 2H), 7.21 (dd, *J* = 8.5, 0.6 Hz, 2H), 3.95 (ddt, *J* = 16.2, 5.6, 1.4 Hz, 1H), 3.62 (ddd, *J* = 16.3, 12.4, 6.2 Hz, 1H), 3.39 (d, *J* = 6.4 Hz, 1H), 3.15 (dq, *J* = 6.1, 1.9 Hz, 1H), 2.37 (s, 3H), 2.23 – 2.16 (m, 1H), 1.57 – 1.51 (m, 1H), 1.49 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 163.2, 161.7, 140.2, 136.6, 129.3, 126.7, 82.0, 44.9, 39.0, 32.2, 28.0, 21.5, 19.4; HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{17}H_{23}N_2O_2]^+$ 287.1754, found 287.1764.

***tert*-butyl 2-(4-bromophenyl)-3,7-diazabicyclo[4.1.0]hept-2-ene-7-carboxylate (16db)**



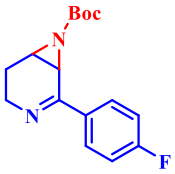
Compound **16db** prepared following the general procedure **B** and obtained as pale-yellow viscous oil. (49 mg, 70% yield). *Rf* = 0.55 (petroleum ether/EtOAc 70:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.70 (m, 2H), 7.56 – 7.51 (m, 2H), 3.96 (ddt, *J* = 16.4, 5.6, 1.5 Hz, 1H), 3.60 (dtd, *J* = 18.5, 12.4, 6.3 Hz, 1H), 3.33 (d, *J* = 6.4 Hz, 1H), 3.16 (dq, *J* = 6.1, 1.9 Hz, 1H), 2.20 (ddt, *J* = 14.2, 6.3, 1.6 Hz, 1H), 1.57 – 1.51 (m, 1H), 1.49 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 162.5, 161.5, 138.2, 131.7, 128.3, 124.7, 82.20, 45.1, 39.0, 31.8, 28.0, 19.3; HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{16}H_{20}BrN_2O_2]$+ 351.0703, found 351.0709.

***tert*-butyl 2-(4-chlorophenyl)-3,7-diazabicyclo[4.1.0]hept-2-ene-7-carboxylate (16eb)**



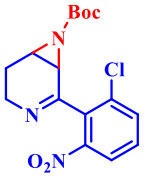
Compound **16eb** prepared following the general procedure **B** and obtained as white solid. (44 mg, 72% yield). *Rf* = 0.54 (petroleum ether/EtOAc 70:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.6 Hz, 2H), 7.39 (d, *J* = 8.7 Hz, 2H), 4.08 – 3.86 (m, 1H), 3.64 (ddd, *J* = 16.5, 12.3, 6.3 Hz, 1H), 3.35 (d, *J* = 6.4 Hz, 1H), 3.21 – 3.13 (m, 1H), 2.22 (ddt, *J* = 14.2, 6.3, 1.6 Hz, 1H), 1.60 – 1.52 (m, 1H), 1.51 (s, 9H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 162.36, 161.56, 137.87, 136.31, 128.84, 128.14, 82.23, 45.14, 39.09, 31.94, 28.10, 19.41; HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{16}H_{20}ClN_2O_2]^+$ 307.1208, found 307.1200.

***tert*-butyl 2-(4-fluorophenyl)-3,7-diazabicyclo[4.1.0]hept-2-ene-7-carboxylate (16fb)**



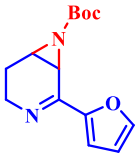
Compound **16fb** prepared following the general procedure **B** and obtained as pale-yellow viscous oil. (42 mg, 72% yield). *Rf* = 0.50 (petroleum ether/EtOAc 70:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.73 (m, 2H), 7.14 – 7.01 (m, 2H), 3.94 (ddd, *J* = 5.7, 5.0, 2.8 Hz, 1H), 3.64 – 3.53 (m, 1H), 3.34 (d, *J* = 6.4 Hz, 1H), 3.17 – 3.13 (m, 1H), 2.19 (ddt, *J* = 14.1, 6.1, 1.5 Hz, 1H), 1.56 – 1.50 (m, 1H), 1.48 (s, 9H), ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 164.01 (d, *J* = 249.9 Hz), 162.2, 161.5, 135.57 (d, *J* = 2.9 Hz), 128.73 (d, *J* = 8.5 Hz), 115.52 (d, *J* = 21.8 Hz), 82.14, 44.90, 39.05, 31.97, 28.00, 19.31. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{16}H_{20}FN_2O_2]^+$ 291.1503, found 291.1515.

***tert*-butyl 2-(2-chloro-6-nitrophenyl)-3,7-diazabicyclo[4.1.0]hept-2-ene-7-carboxylate (16gb)**



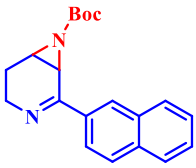
Compound **16gb** prepared following the general procedure **B** and obtained as colourless viscous oil. (43 mg, 61% yield). *Rf* = 0.49 (petroleum ether/EtOAc 70:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (dd, *J* = 3.6, 1.6 Hz, 1H), 8.21 – 8.16 (m, 1H), 7.58 (dd, *J* = 6.5, 3.8 Hz, 1H), 4.06 (td, *J* = 16.2, 6.3 Hz, 1H), 3.72 (ddd, *J* = 15.3, 12.3, 5.8 Hz, 1H), 3.32 – 3.14 (m, 2H), 2.28 (dd, *J* = 14.2, 6.3 Hz, 1H), 1.66 – 1.57 (m, 1H), 1.47 (s, 9H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 163.1, 161.1, 146.7, 140.4, 139.1, 131.0, 125.8, 124.9, 82.5, 45.8, 39.2, 34.8, 28.0, 19.4. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{16}H_{19}ClN_3O_4]^+$ 352.1059, found 352.1066.

***tert*-butyl 2-(furan-2-yl)-3,7-diazabicyclo[4.1.0]hept-2-ene-7-carboxylate (16hb)**



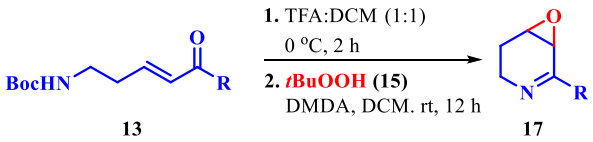
Compound **16hb** prepared following the general procedure **B** and obtained as pale-yellow viscous oil. (33 mg, 63% yield). *Rf* = 0.46 (petroleum ether/EtOAc 70:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.51 (m, 1H), 6.92 (d, *J* = 3.5 Hz, 1H), 6.49 (dd, *J* = 3.5, 1.8 Hz, 1H), 3.96 (ddt, *J* = 16.3, 5.5, 1.5 Hz, 1H), 3.63 (ddd, *J* = 16.3, 12.4, 6.1 Hz, 1H), 3.39 (d, *J* = 6.4 Hz, 1H), 3.15 (dq, *J* = 6.1, 1.9 Hz, 1H), 2.25 – 2.16 (m, 1H), 1.59 – 1.48 (m, 1H), 1.46 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.3, 154.0, 152.6, 144.6, 111.7, 111.6, 81.9, 44.5, 38.5, 31.4, 29.7, 27.9, 19.7. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{14}H_{19}N_2O_3]^+$ 263.1390, found 263.1402.

***tert*-butyl 2-(naphthalen-2-yl)-3,7-diazabicyclo[4.1.0]hept-2-ene-7-carboxylate (16ib)**



Compound **16ib** prepared following the general procedure **B** and obtained as pale-yellow viscous oil. (42 mg, 65% yield). *Rf* = 0.50 (petroleum ether/EtOAc 70:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (m, 1H), 8.01 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.92 – 7.85 (m, 3H), 7.53 – 7.50 (m, 2H), 4.08 – 4.03 (m, 1H), 3.71 (ddd, *J* = 16.4, 12.4, 6.3 Hz, 1H), 3.57 (d, *J* = 6.4 Hz, 1H), 3.23 (dt, *J* = 6.3, 1.8 Hz, 1H), 2.26 (ddd, *J* = 14.1, 4.8, 1.5 Hz, 1H), 1.64 – 1.58 (m, 1H), 1.56 (s, 7H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 163.24, 161.67, 136.76, 134.21, 133.08, 128.85, 128.39, 127.83, 127.06, 126.96, 126.49, 123.89, 82.12, 45.12, 39.05, 32.18, 28.10, 19.42; HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{20}H_{23}N_2O_2]^+$ 323.1754, found 323.1755.

5.6.4 General procedure C for the synthesis of 1-aryl-3,4-epoxy piperid-1-ene (17a-17i)



13 17

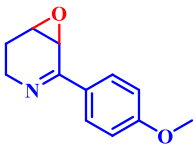
To a 10 mL round bottom flask equipped with a magnetic bar containing δ-amino enone **13** (0.2 mmol) in DCM (1 mL) was added trifluoroacetic acid (TFA, 1 mL) at 0 ℃. The reaction mixture was allowed to stir for 2 h at 0 ℃. After the complete deprotection, the solution was concentrated in a vacuum. DCM (5 mL) was added to the crude reaction mixture and the solution was concentrated in a vacuum (the procedure was repeated 3 times). The amino *δ*-enone salt **II** was used without purification.

To a round-bottomed flask equipped with a magnetic bar containing TFA salt of amino-enone in DCM (2 mL) was added *t*-BuOOH solution in decane (1.09 mmol) and DMDA (1 mmol) at room temperature. After which (12 h) the solvent was removed under vacuum and the crude reaction mixture was further purified by column chromatography over silica gel using triethyl amine/ethyl acetate/petroleum ether mixture (1:15:84) as an eluent. to furnish desired product **17** viscous liquid.

2-phenyl-7-oxa-3-azabicyclo[4.1.0]hept-2-ene (17a)

Compound **17a** prepared following the general procedure **C** and obtained as colourless viscous oil. (26 mg, 75% yield). *Rf* = 0.56 (petroleum ether/EtOAc 70:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.68 (m, 2H), 7.48 – 7.37 (m, 3H), 4.01 – 3.93 (m, 1H), 3.86 (d, *J* = 4.4 Hz, 1H), 3.74 – 3.70 (m, 1H), 3.69 – 3.63 (m, 1H), 2.24 (dddd, *J* = 14.6, 6.4, 2.4, 1.2 Hz, 1H), 1.69 (dddd, *J* = 14.6, 12.8, 5.8, 0.8 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 164.1, 139.0, 130.2, 128.7, 126.7, 53.9, 45.4, 44.7, 21.0. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{11}H_{12}NO]^+$ 174.0913, found 174.0927.

2-(4-methoxyphenyl)-7-oxa-3-azabicyclo[4.1.0]hept-2-ene (17b)

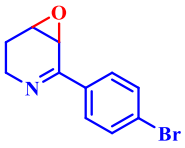


Compound **17b** prepared following the general procedure **C** and obtained as colourless viscous oil. (32 mg, 79% yield). *Rf* = 0.48 (petroleum ether/EtOAc 70:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.9 Hz, 2H), 6.94 (d, *J* = 8.9 Hz, 2H), 3.92 (ddt, *J* = 16.0, 5.9, 1.4 Hz, 1H), 3.86 (d, *J* = 4.4 Hz, 1H), 3.85 (s, 3H), 3.71 (dt, *J* = 3.9, 1.8 Hz, 1H), 3.65 (ddd, *J* = 16.0, 12.8, 6.3 Hz, 1H), 2.23 (dddd, *J* = 14.6, 6.3, 2.5, 1.2 Hz, 1H), 1.75 – 1.58 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 163.13, 161.33, 131.65, 128.17, 113.94, 55.45, 53.88, 45.31, 44.39, 20.97. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{12}H_{14}NO_2]^+$ 204.1019, found 204.1032.

2-(p-tolyl)-7-oxa-3-azabicyclo[4.1.0]hept-2-ene (17c)

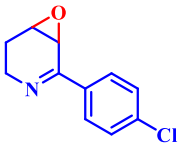
Compound **17c** prepared following the general procedure **C** and obtained as colourless viscous oil. (29 mg, 77% yield). *Rf* = 0.58 (petroleum ether/EtOAc 70:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.59 (m, 2H), 7.23 (d, *J* = 7.9 Hz, 2H), 3.95 (ddt, *J* = 16.0, 5.8, 1.4 Hz, 1H), 3.86 (d, *J* = 4.4 Hz, 1H), 3.71 (dt, *J* = 3.6, 1.9 Hz, 1H), 3.70 – 3.61 (m, 1H), 2.39 (s, 3H), 2.29 – 2.16 (m, 1H), 1.79 – 1.61 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 163.70, 140.30, 136.17, 129.24, 126.49, 53.74, 45.30, 44.45, 21.32, 20.89. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{12}H_{14}NO]^+$ 188.1070, found 188.1082.

2-(4-bromophenyl)-7-oxa-3-azabicyclo[4.1.0]hept-2-ene (17d)



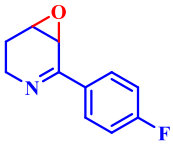
Compound **17d** prepared following the general procedure **C** and obtained as pale-yellow viscous oil. (35 mg, 69% yield). *Rf* = 0.51 (petroleum ether/EtOAc 70:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.64 (m, 2H), 7.56 – 7.52 (m, 2H), 3.99 – 3.90 (m, 1H), 3.78 (d, *J* = 4.3 Hz, 1H), 3.70 (dt, *J* = 4.5, 2.0 Hz, 1H), 3.68 – 3.57 (m, 1H), 2.23 (dddd, *J* = 14.6, 6.4, 2.5, 1.2 Hz, 1H), 1.72 – 1.62 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 163.2, 137.7, 131.8, 128.2, 124.9, 53.9, 45.1, 44.7, 20.8. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{11}H_{11}BrNO]^+$ 252.0019, found 252.0029.

2-(4-chlorophenyl)-7-oxa-3-azabicyclo[4.1.0]hept-2-ene (17e)



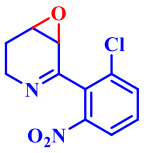
Compound **17e** prepared following the general procedure **C** and obtained as colourless viscous oil. (29 mg, 70% yield). *Rf* = 0.58 (petroleum ether/EtOAc 70:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.6 Hz, 2H), 7.40 (d, *J* = 8.6 Hz, 2H), 3.97 (ddt, *J* = 16.2, 5.8, 1.4 Hz, 1H), 3.81 (d, *J* = 4.4 Hz, 1H), 3.72 (dq, *J* = 3.7, 1.8 Hz, 1H), 3.66 (ddd, *J* = 16.2, 12.8, 6.4 Hz, 1H), 2.25 (dddd, *J* = 14.6, 6.4, 2.4, 1.2 Hz, 1H), 1.85 – 1.54 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 162.89, 137.23, 136.34, 128.77, 127.90, 53.77, 45.02, 44.64, 20.74. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{11}H_{11}ClNO]^+$ 208.0524, found 208.0540.

2-(4-fluorophenyl)-7-oxa-3-azabicyclo[4.1.0]hept-2-ene (17f)



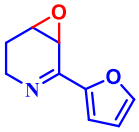
Compound **17f** prepared following the general procedure **C** and obtained as pale-yellow viscous oil. (27 mg, 71% yield). *Rf* = 0.57 (petroleum ether/EtOAc 70:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.80 (m, 2H), 7.17 – 7.10 (m, 2H), 4.02 – 3.95 (m, 1H), 3.85 (d, *J* = 4.4 Hz, 1H), 3.75 (dt, *J* = 4.3, 1.8 Hz, 1H), 3.69 (ddd, *J* = 16.1, 12.8, 6.4 Hz, 1H), 2.27 (dddd, *J* = 14.6, 6.4, 2.4, 1.2 Hz, 1H), 1.72 (dddd, *J* = 8.7, 8.1, 5.8, 1.7 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 164.1 (d, *J* = 249.1 Hz), 162.8, 135.1 (d, *J* = 3.2 Hz), 128.6 (d, *J* = 8.6 Hz), 115.6 (d, *J* = 21.8 Hz), 53.8, 45.2, 44.5, 20.8. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{11}H_{11}FNO]^+$ 192.0819, found 192.0829.

2-(2-chloro-6-nitrophenyl)-7-oxa-3-azabicyclo[4.1.0]hept-2-ene (17g)



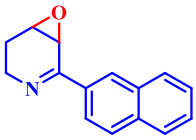
Compound **17g** prepared following the general procedure **C** and obtained as pale-yellow viscous oil. (31 mg, 61% yield). *Rf* = 0.44 (petroleum ether/EtOAc 70:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 2.7 Hz, 1H), 8.23 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.62 (d, *J* = 8.8 Hz, 1H), 4.11 – 4.02 (m, 1H), 3.80 (dd, *J* = 4.4, 2.0 Hz, 1H), 3.78 – 3.71 (m, 1H), 3.68 (d, *J* = 4.2 Hz, 1H), 2.34 (dddd, *J* = 14.8, 6.4, 2.4, 1.0 Hz, 1H), 1.84 – 1.75 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 164.4, 146.8, 139.9, 139.0, 130.9, 125.6, 125.1, 54.5, 47.3, 45.4, 20.9. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{11}H_{10}ClN_2O_3]^+$ 253.0374, found 253.0383.

2-(furan-2-yl)-7-oxa-3-azabicyclo[4.1.0]hept-2-ene (17h)



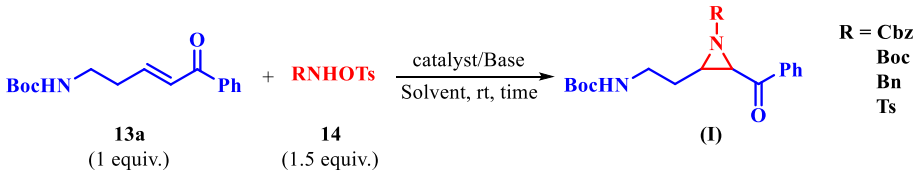
Compound **17h** prepared following the general procedure **C** and obtained as pale-yellow viscous oil. (20 mg, 61% yield). *Rf* = 0.48 (petroleum ether/EtOAc 70:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 1.7 Hz, 1H), 6.90 (d, *J* = 3.3 Hz, 1H), 6.49 (dd, *J* = 3.4, 1.8 Hz, 1H), 3.99 – 3.88 (m, 1H), 3.81 (d, *J* = 4.4 Hz, 1H), 3.72 – 3.68 (m, 1H), 3.67 – 3.59 (m, 1H), 2.23 (dddd, *J* = 14.6, 6.3, 2.6, 1.2 Hz, 1H), 1.76 – 1.71 (m, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 155.0, 152.6, 144.9, 111.9, 111.8, 53.5, 45.0, 44.4, 21.2. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_9H_{10}NO_2]^+$ 164.0706, found 164.0722.

2-(naphthalen-2-yl)-7-oxa-3-azabicyclo[4.1.0]hept-2-ene (17i)



Compound **17i** prepared following the general procedure **C** and obtained as pale-yellow viscous oil. (26 mg, 58% yield). *Rf* = 0.51 (petroleum ether/EtOAc 70:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 – 8.19 (m, 1H), 7.98 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.94 – 7.83 (m, 3H), 7.57 – 7.48 (m, 2H), 4.07 – 4.01 (m, 2H), 3.79 – 3.77 (m, 1H), 3.77 – 3.68 (m, 1H), 2.29 (dddd, *J* = 14.6, 6.4, 2.4, 1.1 Hz, 1H), 1.88 – 1.69 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 163.85, 136.25, 134.23, 133.02, 128.88, 128.52, 127.80, 127.21, 126.78, 126.59, 123.84, 53.95, 45.35, 44.79, 20.96. HRMS (EI) m/z $[M+H]^+$ calculated for $[C_{15}H_{14}NO]^+$ 224.1070, found 244.1078.

5.7 Appendix-V: Initial screening of δ-*N*-protected amino-enones **13a**



Entry[a]	Catalyst/Base	R^1	Solvent	Yield[b] (%) (I or 16ab)
1	DMDA (0.2 equiv.)	Cbz	$CHCl_3$	No reaction
2	DMDA (1 equiv.)	Cbz	$CHCl_3$	No reaction
3	DMDA (1 equiv.)	Boc	$CHCl_3$	No reaction
4	DMDA (1 equiv.)	Tosyl	$CHCl_3$	No reaction
5	DMDA (1 equiv.)	Benzyl	$CHCl_3$	No reaction
6	Et_3N (1 equiv.)	Boc	$CHCl_3$	No reaction
7	Pyridine (1 equiv.)	Boc	$CHCl_3$	No reaction
8	DBU (1 equiv.)	Boc	$CHCl_3$	No reaction
9	DABCO (1 equiv.)	Boc	$CHCl_3$	No reaction
10	DIPEA (1 equiv.)	Boc	$CHCl_3$	No reaction
11	DMAP (1 equiv.)	Boc	$CHCl_3$	No reaction
12	Pyrrolidine (1 equiv.)	Boc	$CHCl_3$	No reaction
13	DMDA (1equiv.)	Boc	CH_2Cl_2	No reaction
14	DMDA (1 equiv.)	Boc	EtOAc	No reaction
15	DMDA (1 equiv.)	Boc	THF	No reaction
16	DMDA (1 equiv.)	Boc	MeCN	No reaction
17	DMDA (1 equiv.)	Boc	Toluene	No reaction
18[c]	DMDA (0.2 equiv.)	Boc	$CHCl_3$	32[d]

Reaction Conditions: [a]Enone **1a** (1 equiv.), R^1NHOTs (1.5 equiv.), catalysts/base (0.2 to 1 equiv.), solvent, at room temperature. [b] isolated yield after column chromatography. [c]The δ-amino enone **13a** was deprotected by TFA:DCM (1:1) then the resulting amino enone **II** was used directly without purification. [d]Yield of product **16ab.**

5.8 Appendix VI:

Table No 4.2: ^{1}H and $^{13}C\{^{1}H\}$ NMR spectral data of representative compounds

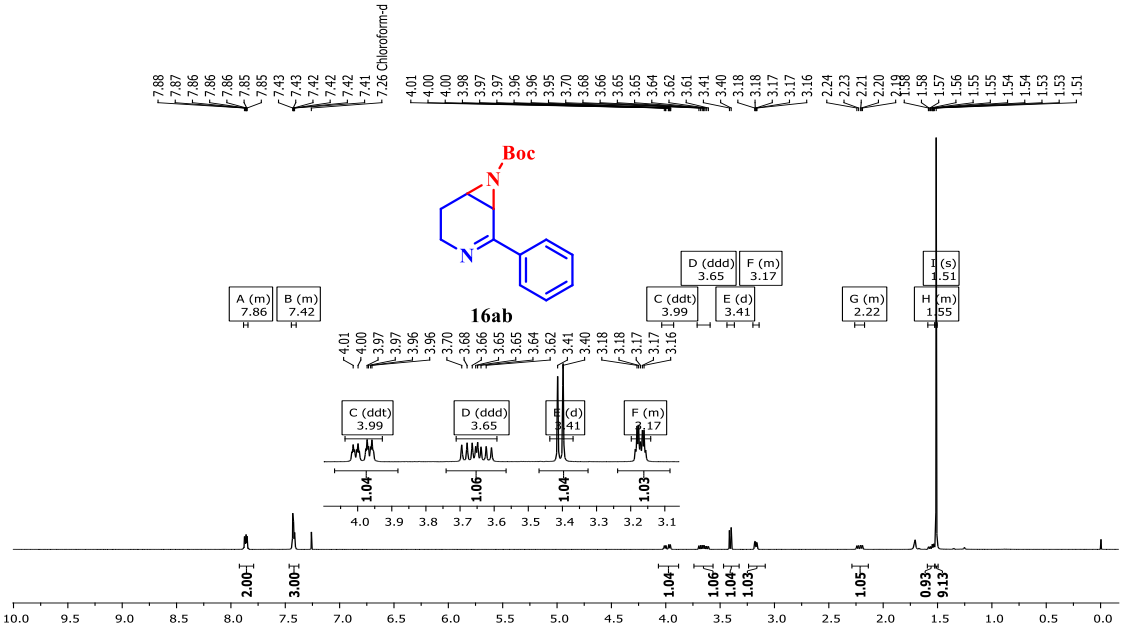


Figure 5.2 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **16ab**

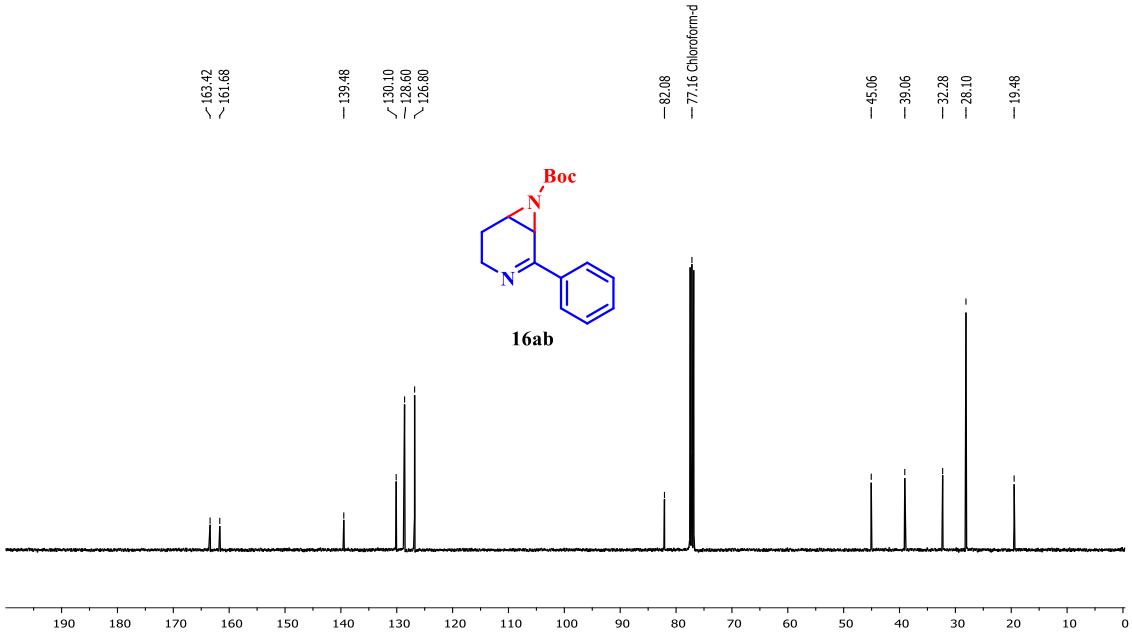


Figure 5.3 $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of compound **16ab**

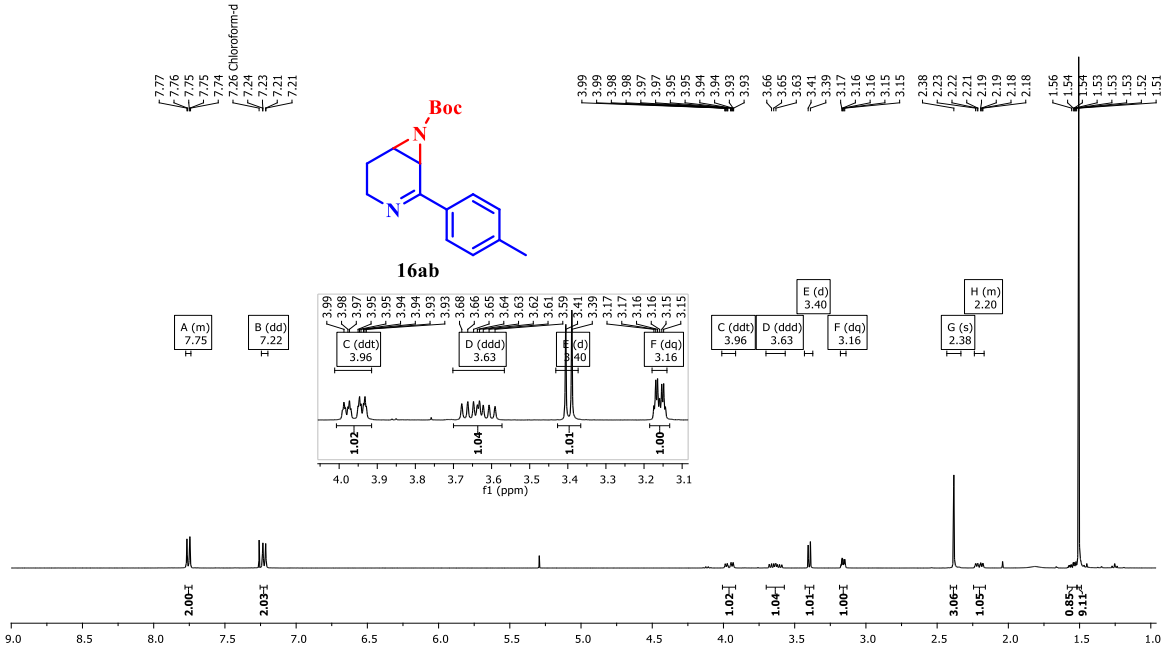


Figure 5.4 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **16cb**

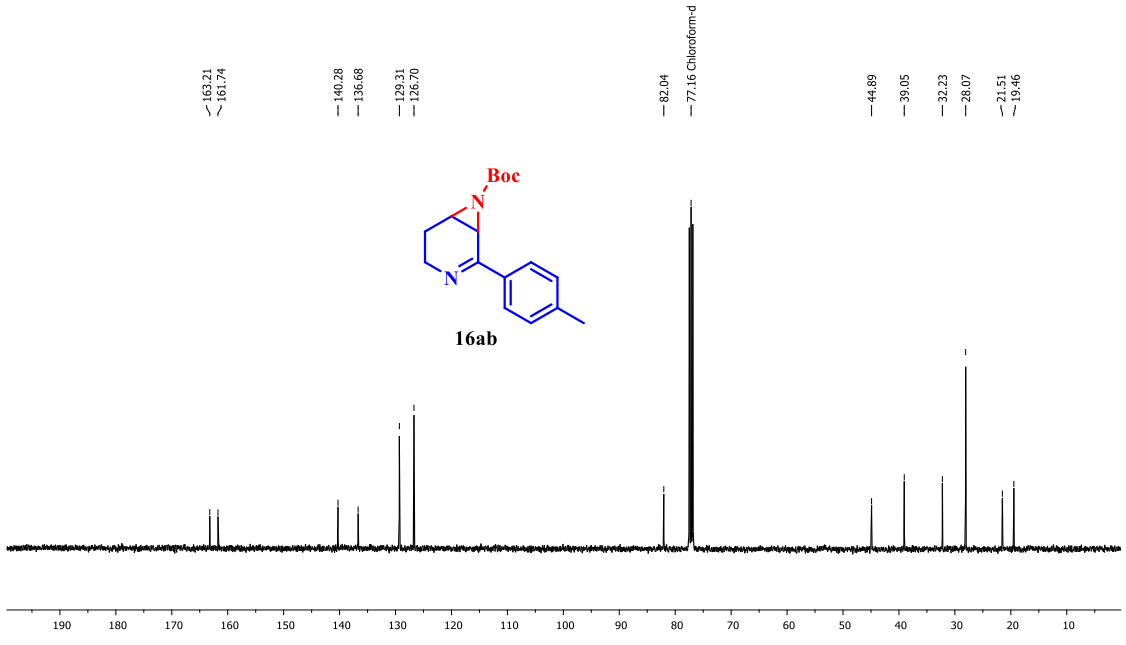


Figure 5.5 $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of compound **16cb**

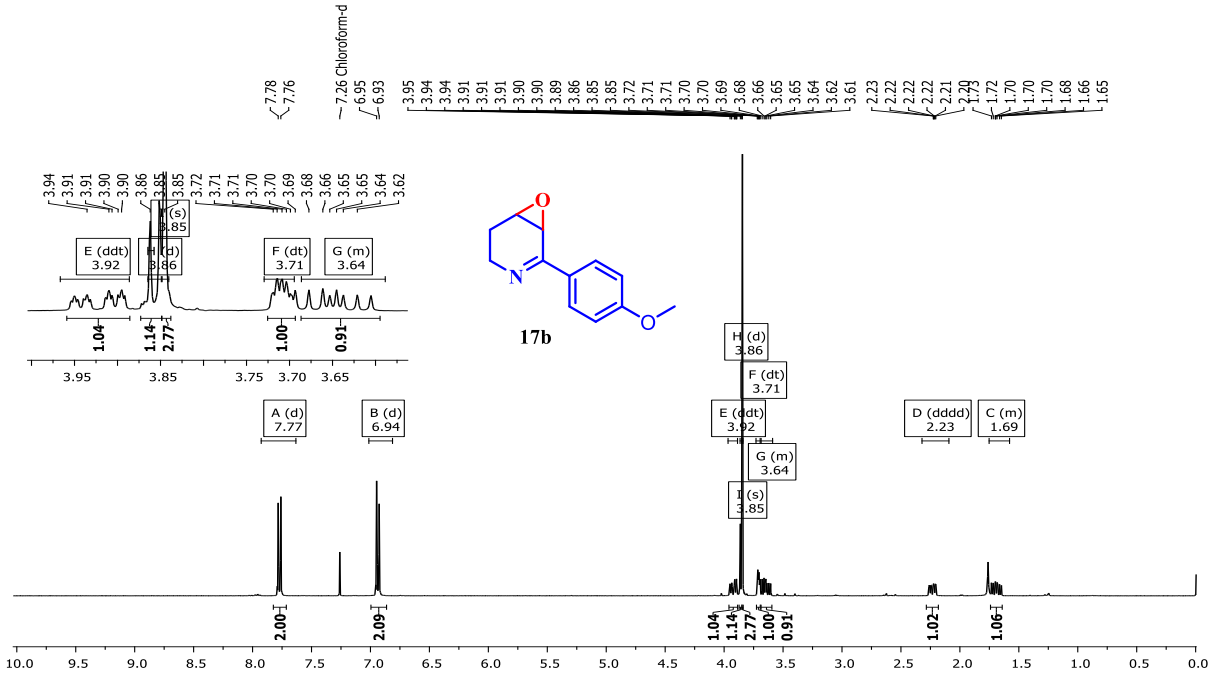


Figure 5.6 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **17b**

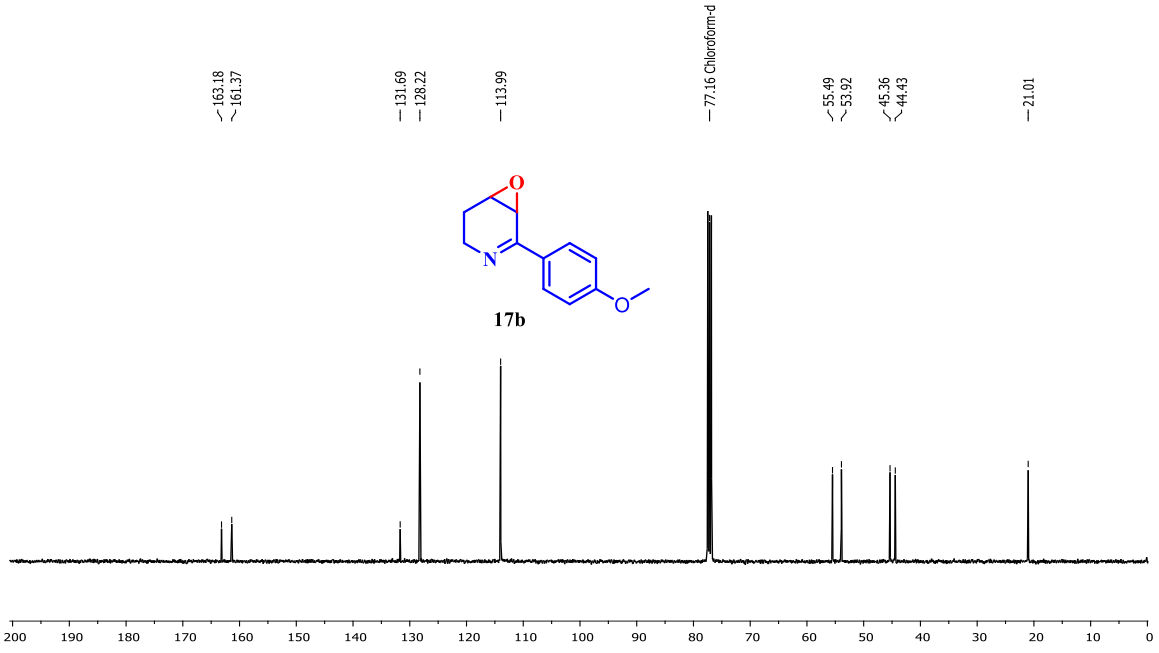


Figure 5.7 $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of compound **17b**

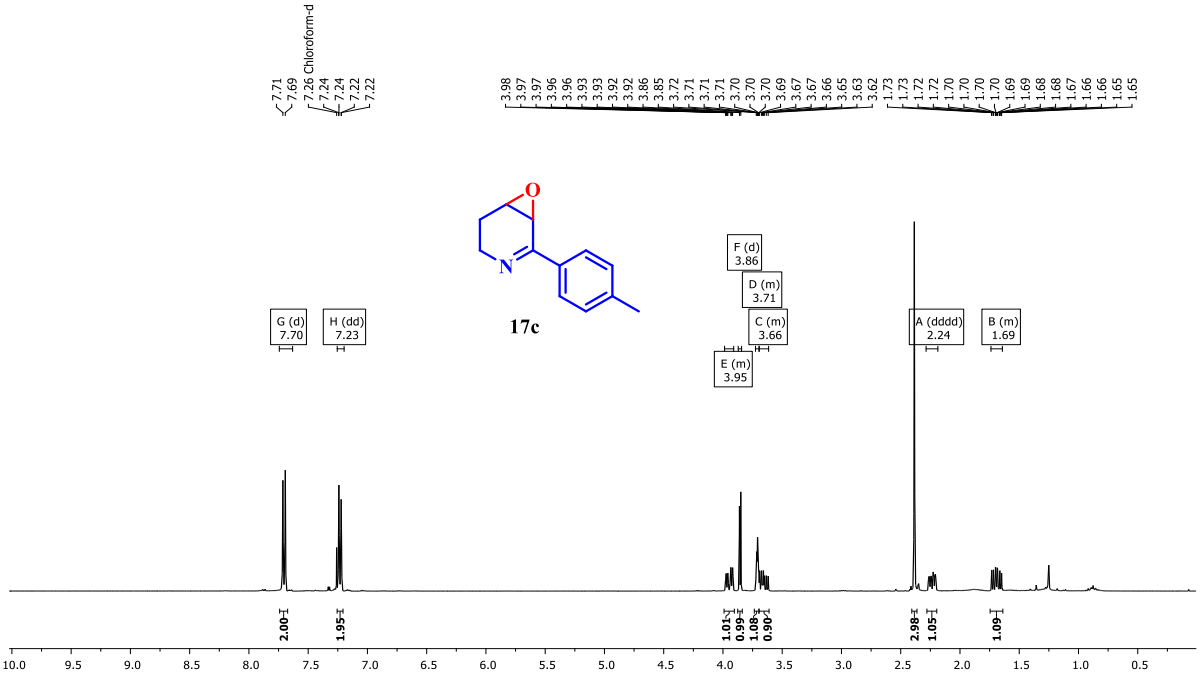


Figure 5.8 ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **17c**

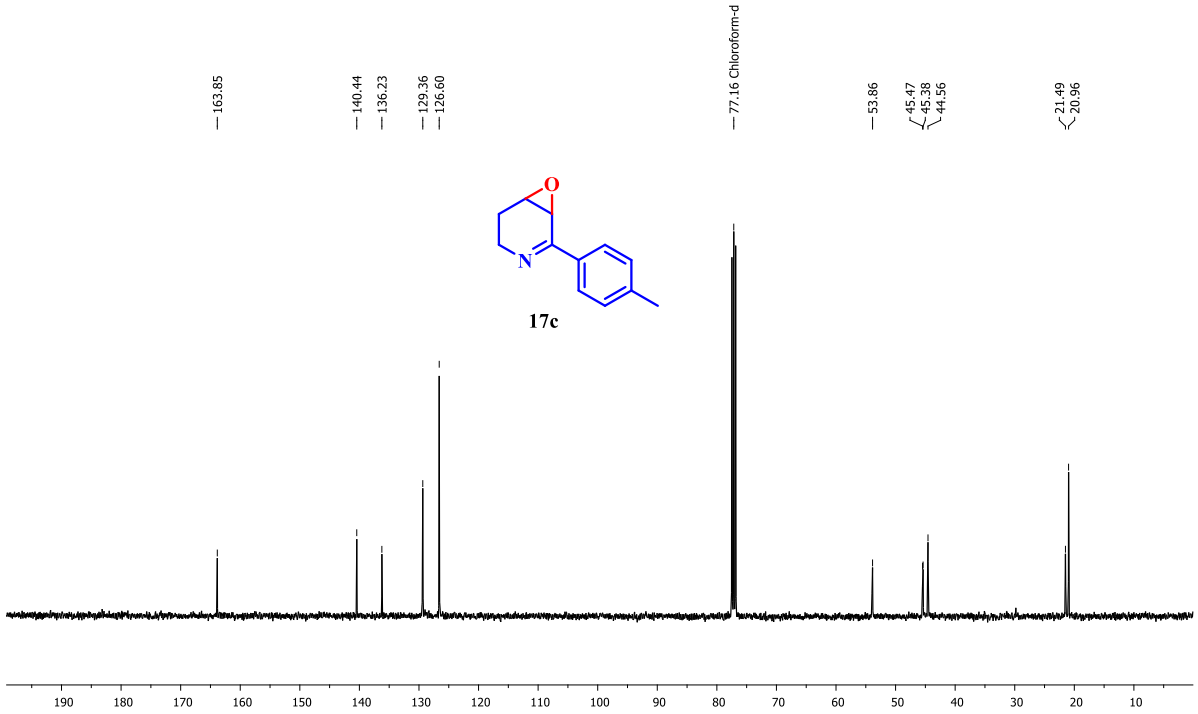


Figure 5.9 $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of compound **17c**

5.9 References

1 A. G. Atanasov, S. B. Zotchev, V. M. Dirsch. *Nat. Rev. Drug. Discov.*, **2021**, *20*, 200-216; (b) C. L. Wainwright, M. M. Teixeira, D. L. Adelson, F. C. Braga, E. J. Buenz, P. R. V. Campana, B. David, K. B. Glaser, Y. H.-Lee M.-J. R. Howes, A. A. Izzo, P. Maffia, A. M. S. Mayer, C. Mazars, D. J. Newman, E. N. Lughadha, R. M. Pádua, A. M. C. Pimenta, J. A. A. Parra, Z. Qu, H. Shen, M. Spedding, J.-L. Wolfenderp. *Pharmacol. Res.*, **2022**, *177*, 106076; (c) M. Lahlou, *Pharmacology & Pharmacy*, **2013**, *4(3A)*, 17-31.

2 Kurek, Joanna. "Introductory Chapter: Alkaloids - Their Importance in Nature and for Human Life" In Alkaloids: Their Importance in Nature and Human Life, edited by Joanna Kurek. London: IntechOpen, 2019. 10.5772/intechopen.85400J.

3 (a) K. Dragull, W. Y. Yoshida, C. Tang, *Phytochemistry*, **2003**, *64*, 555; (b) A. K. Mohamed, M. L. Valerie, C. Cecile, D. S. H. Laurent, A. E. O. Nadine, *Fitoterapia*, **2010**, *81*, 632-635.

4 (a) M. A. Capron, D. F. Wiemer, *J. Nat. Prod.*, **1996**, *59*, 794-795; (b) J. Romero-Ibañez, L. Xochicale-Santana, L. Quintero, L. Fuentes, F. Sartillo-Piscil, *J. Nat. Prod.*, **2016**, *79*, 1174-1178.

5 (a) J. M. Cronan Jr., Cardellina, J. H. II, *Nat. Prod. Lett.*, **1994**, *5*, 85-88; (b) J. H. J. Lago, M. J. Kato, *Nat. Prod. Res.*, **2007**, *21*, 910-914.

6 N. P. Seeram, P. A. Lewis, H. Jacobs, *J. Nat. Prod.*, **1996**, *59*, 436-437.

7 (a) T. M. Jespersen, W. Dong, M. R. Sierks, T. Skrydstrup, I. Lundt, M. Bols. *Angew. Chem., Int. Ed. Engl.*, **1994**, *33*, 1778-1779. (b) F. Clemente, C. Matassini, A. Goti, A. Morrone, P. Paoli, F. Cardona. *ACS Med. Chem. Lett.*, **2019**, *10*, 621-626.

8 W. Hirose, Y. Kato, I. Natsutani, M. Takata, M. Kitaichi, S. Imai, S. Hayashi, Y. Arai, K. Hoshino, K. Yoshida. *Bioorg. Med. Chem. Lett.*, **2017**, *27*, 4331-4335.

9 R. D. Slack, A. M. Abramyan, H. Tang, S. Meena, B. A. Davis, A. Bonifazi, J. B. Giancola, J. R. Deschamps, S. Naing, H. Yano, S. K. Singh, A. H. Newman, L. Shi. *ACS Chem. Neurosci.*, **2019**, *10*, 3946-3952.

10 Y.-W. Jung, K. A. Frey, G. K. Mulholland, R. del Rosario, P. S. Sherman, D. M. Raffel, M. E. V. Dort, D. E. Kuhl, D. L. Gildersleeve, D. M. Wieland. *J. Med. Chem.*, **1996**, *39*, 3331-3342.

11 N. S. Gunasekara, S. Noble, P. Benfield, *Drugs*, **1988**, *55*, 85.

12 J. Barluenga, M. T.-Gamasa, P. Moriel, F. Aznar, C. Valdés. *Chem. Eur. J.*, 2008, **14**, 4792-4795.

13 H. J. M. Gijsen, M. J. A. De Cleyn, C. J. Love, M. Surkyn, S. F. A. V. Brandt, M. G. C. Verdonck, L. Moens, J. Cuypers, J.-P. R. M. A. Bosmans. *Tetrahedron*, **2008**, *64*, 2456-2464.

14 A. Boto, R. Hernández, Y. de León, J. R. Murguía, A. Rodriguez-Afonso *Eur. J. Org. Chem.*, **2005**, 673-682.

15 I. S. Young, A. Ortiz, J. R. Sawyer, D. A. Conlon, F. G. Buono, S. W. Leung, J. L. Burt, E. W. Sortore. *Org. Process Res. Dev.*, **2012**, *16*, 1558-1565.

16 J. R.-Ibañez, L. X.-Santana, L. Quintero, L. Fuentes, F. S.-Piscil. *J. Nat. Prod.*, **2016**, *79*, 1174-1178.

17 G. Asensio, R. Mello, C. B.-Bernardini, M. E. G.-Nunez, G. Castellano. *J. Org. Chem.*, **1995**, *60*, 3692-3699.

18 S. G. Davies, A. L. A. Figuccia, A. M. F. Paul, M. Roberts, J. E. Thomson. *J. Org. Chem.*, **2016**, *81*, 6481-6495.

19 T. C. Coombs, G. H. Lushington, J. Douglas, J. Aub. *Angew. Chem.*, **2011**, *123*, 2786-2789.

20 D. M. Mazur, G. V. Grishina, A. T. Lebedev. *J. Pharm. Biomed. Anal.*, **2017**, *140*, 322-326.

21 A. V. Samoshin, I. S. Veselov, V. A. Chertkov, A. A. Yaroslavov, G. V. Grishina, N. M. Samoshina, V. V. Samoshin. *Tetrahedron Lett.*, **2013**, *54*, 5600-5604.

22 A. V.-Barro, V. Gotor, R. Brieva, *Tetrahedron*, **2015**, *71*, 6907-6912.

23 M. S. Majik, P. S. Parameswaran, S. G. Tilve. *J. Org. Chem.*, **2009**, *74*, 6378-6381.

24 (a) X. E. Hu, N. K. Kim, B. Ledoussal, A.-O. Colson. *Tetrahedron Lett.*, **2002**, 43, 4289-4293; (b) J. Piro, P. Forns, M. Bonin, J. Blanchet, M. Bonin, L. Micouin, A. Diez. *Tetrahedron: Asymmetry*, **2002**, *13*, 995-1004; (c) H. Schramma, M. Pavlovaa, C. Hoenkeb, J. Christoffers. *Synth.*, **2009**, *10*, 1659-1662; (d) H. Schramm, W. Saak, C. Hoenke, J. Christoffers. *Eur. J. Org. Chem.*, **2010**, 1745-1753; (e) J. A. Kalow, A. G. Doyle. *Tetrahedron*, **2013**, *69*, 5702-5709.

25 G. Cardillo, S. Fabbroni, L. Gentilucci, R. Perciaccante, F. Piccinelli, A. Tolomelli. *Tetrahedron*, **2004**, *60*, 5031-5040.

26 (a) T. M. Khopade, A. D. Sonawane, S. J. Arora, R. G. Bhat. *Adv. Synth. Catal.*, **2017**, *359*, 3905-3910; (b) T. M. Khopade, T. B. Mete, S. J. Arora, R. G. Bhat. *Chem. Eur. J.*, **2018**, *24*, 6036-6040; (c) P. K. Warghude, P. D. Dharpure, R. G. Bhat, *Tetrahedron*

Lett., **2018**, *59*, 4076-4079; (d) L V. R. Babu Syamala, T. M. Khopade, P. K. Warghude, R. G. Bhat. *Tetrahedron Lett*., **2019**, *60*, 88-91; (e) T. M. Khopade, P. K. Warghude, T. B. Mete, R. G. Bhat. *Tetrahedron Lett*., **2019**, *60*, 197-200; (f) T. M. Khopade, P. K. Warghude, A. D. Sonawane, R. G. Bhat. *Org. Biomol. Chem.*, **2019**, *17*, 561-566.

27 F. Pesciaioli, F. De Vincentiis, P. Galzerano, G. Bencivenni, G. Bartoli, A. Mazzanti, P. Melchiorre, *Angew. Chem. Int. Ed*., **2008**, *47*, 8703-8706.