DEVELOPMENT OF NEW METHODS FOR THE SYNTHESIS OF ORGANIC COMPOUNDS USING SELENIUM DIOXIDE

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IN

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BY

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OCTOBER, 2019

Dedicated To

My

Parents

Mr. Obington Marbaniang

&

Mrs. Pherida Shangpliang

Declaration

Year: 2019

I, O. Risuklang Shangpliang, hereby declare that the subject matter of the thesis entitled "***Development of New Methods for the Synthesis of Organic Compounds Using Selenium Dioxide***" is the record of works done by me under the supervision of **Prof. Bekington Myrboh**, Centre for Advanced Studies in Chemistry, School of Physical Sciences, North-Eastern Hill University. The contents of this thesis did not form basis of the award of any previous degree to me or, to the best of my knowledge, to anybody else and that the thesis has not been submitted by me for any research degree in any other University/Institute.

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(O. Risuklang Shangpliang)

Symbols/Abbreviations/Acronyms

α	Alpha
β	Beta
γ	Gamma
δ	Delta
ω	Omega
σ	Sigma
Å	Angstrom
^{o}C	Degree Celsius
%	Percentage
h	Hour
m/z	Mass by Charge Number
^{1}H NMR	Proton Nuclear Magnetic Resonance
^{13}C NMR	Carbon-13 Nuclear Magnetic Resonance
AIBN	Azobisisobutyronitrile
AcOH	Acetic Acid
ACN	Acetonitrile
$CDCl_3$	Deuterated Chloroform
Chk 1	Checkpoint Kinase 1
CSA	Camphor sulfonic acid
DABCO	1,4-diazabicyclo[2.2.2]octane
DCB	Dichlorobenzene
DCE	1,2-Dichloroethane
DCM	Dichloromethane

DMA	Dimethylacetamide
DMAP	4-dimethylaminopyridine
DMF	Dimethylforamide
DMSO	Dimethyl Sulfoxide
DMSO-d_6	Dimethyl Sulfoxide-d_6
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
ESI	Electron Spray Ionization
EWG	Electron Withdrawing Group
EtOH	Ethanol
FT-IR	Fourier Transformed Infra Red
FT-NMR	Fourier Transformed Nuclear Magnetic Resonance
GPx	Glutathione Peroxidase
HFIP	1,1,1,3,3,3-Hexafluoroisopropanol
HMPA	Hexamethylphosphoramide
HRMS	High Resolution Mass Spectra
Hz	Herzt
IR	Infra Red
LC-MS	Liquid Chromatography Mass Spectrometry
MW	Microwave
MHz	Megahertz
NCS	N-Chlorosuccinimide
NMI	N-Methylimidazole
NMP	N-Methyl-2-Pyrrolidone
ORTEP	Oak Ridge Thermal Ellipsoid Plot Program
PEG 400	Polyethylene Glycol 400

PivOH	Pivalic acid
Ppm	Parts Per Million
PTSA	*p* -Toluenesulfonic Acid
TBHP	Tetrabutyl hydroperoxide
TBAB	Tetra-*n*-Butylammonium Bromide
TBPH	Tetrabutylphosphonium Hydroxide
TCI	Tokyo Chemicals Industry
TEMDA	Tetramethylethylenediamine
TFA	Trifluoroacetic Acid
TFAA	Trifluoroacetic Anhydride
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Tetramethylsilane
UPLC-TQD	Ultra Performance Liquid Chromatography-Tandem Quadrupole
XRD	X-ray Powder Diffraction

Preface

Organic synthesis being one of the special branches of chemical synthesis of organic chemistry, plays an important role in the construction and design for the synthesis of diverse complex organic molecules with varied applications, employing simple starting organic substrate. Over the past decades, many synthetic organic chemists have been developed and design new methods of improving the existing ones that leadto the discovery of new organic compounds which have been a promising contribution to the welfare of mankind in day to day life and which it will be continued to do so in the near future.

Organic synthesis comprised of two main areas of research fields that goes hand in hand or simultaneously for accomplishing the desired purpose of compound synthesis: *total synthesis* and *methodology*.

Total synthesis is a process involving multistep reactions with relevant routes designated to synthesize a molecule. The synthesis of the complex target molecule usually can be achieved by total synthesis starting from simple and easily available starting materials. The synthesis of strychnine by Robert Burns Woodward in 1954 is one of the earliest reports on *total synthesis*. Development of new methods or improved the existing reported methods that will lead to the increase in the product yields, minimize the formation of unwanted by-products, and reduce reaction time for the synthesis of various known organic compounds or new compounds which is term as Methodology is applied and strictly followed.

Research methodologies still remain one of the promising contributions to the research fields in organic synthesis and therefore, will continue to be a burgeoning arena of synthetic organic chemistry. Amongst organic compounds, carbon-containing selenium has become the topic of research interest in the last two decades because of its wide application in organic synthesis and their biological properties.

The thesis entitled **"*Development of New Methods for the Synthesis of Organic Compounds Using Selenium Dioxide*"** comprised of five chapters.

CHAPTER 1 includes a general introduction on SeO_2 and its applications as an oxidizing agent, a catalyst and a reagent in various organic transformation reactions.

CHAPTER 2 describes the use of SeO_2 as a selenium source for the synthesis of α,α-dicarbonyl selenides. The method involves the reaction of aryl methyl ketones/heteroaryl ketones with selenium dioxide in the presence of PTSA at room temperature for 8-12 h afforded the corresponding product moderate to good yields

CHAPTER 3 described the SeO_2 mediated direct α-selenoamidation of aryl/alkyl methyl ketones with amines. It is subdivided into two parts **PART A** and **PART B**:

CHAPTER 3, PART A, described a general strategy for the preparation of *N,N*-dialkyl-2-oxo-2-arylethaneselenoamides. The single-step method involves the direct coupling of aryl methyl ketones with secondary amines and selenium dioxide in DMSO. The reactions proceeded smoothly at room temperature to provide a number of the α-oxo-selenoamides, most of which are new compounds in good to excellent yields.

CHAPTER 3, PART B, described a useful general protocol for the synthesis of hitherto unreported *α*-oxo-*N*-alkyl selenoamide from aryl methyl ketones and primary amines using selenium dioxide as a selenium source in DMSO**.** The methodology provides easy access to the selenoamides without using any catalyst, acid or base and under mild reaction conditions.

CHAPTER 4 described a method for the synthesis of 3,5-diphenyl-2*H*-1,4-selenazine by three-component condensation of aryl alkyl ketones, selenium dioxide and ammonium acetate at room temperature in DMSO as a solvent. This methodology is simple and provides a series of successfully synthesized 3,5-diphenyl-2*H*-1,4-selenazine.

CHAPTER 5 described a novel approach for the synthesis of a wide range of *α*-ketoacetals by the reaction of alkyl/aryl methyl ketones and aliphatic alcohols in presence of selenium dioxide catalyzed by *p*-toluene sulfonic acid (PTSA). This method represents a general route to obtain a wide variety of *α*-ketoacetals in a simple, rapid and practical manner. This approach is particularly attractive because of the easy availability of the starting materials, mild reaction temperature and good yields of the products. The resulting *α*-ketoacetals are of much synthetic value as organic intermediates.

Overall, this thesis described the synthetic application of SeO_2as a selenylating agent for the synthesis of an organoselenium compound *viz. α,α*-dicarbonyl selenide, selenoamide, selenazine and also as an oxidizing agent for the synthesis of *α*-ketoacetals. Most of these compounds which have been successfully synthesized are unreported. The attractiveness of these methodologies described here is the development of the new methods for the synthesis of organic compounds which are mostly new compounds

unknown and not yet reported in the literature. These methodologies can contribute to the current research, literature and its application in organic chemistry.

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CHAPTER 1

General Introduction

1.1 Selenium

Selenium is a member of the group 16 elements (O, S, Se, Te and radioactive Po), collectively known as chalcogens. Selenium is a non-metal with the symbol Se and has an atomic number 34. It was discovered in 1817 by J. J. Berzelius in the reddish deposits that was formed in the lead chambers at his sulfuric acid plant at Gripsholm in Sweden. He named the element selenium in the honor of Greek Goddess 'Selene', meaning moon.[1]

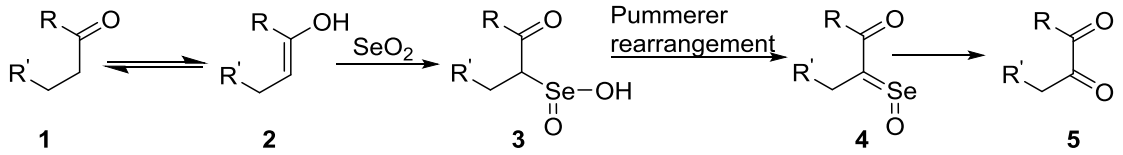
The physical and chemical properties of selenium are intermediate between those of sulfur and tellurium. Elemental selenium exists in various allotropic forms, of which three are generally known, namely two red allotropes of puckered Se_8 rings which changed on heating to the more stable grey or black trigonal selenium, which is made up of helical Se_n chains. The oxidation states of selenium range from +6 to -2. In nature, selenium is found in minerals ores, partially substituting sulfur and clausthalite (PbSe) being the most abundant selenium mineral. Industrial uses include vulcanization of rubber, in the glass industry for the manufacture of ruby-colored glass, decolorization of glass, pigments used in plastics, paints, enamels, inks and in xerography. Selenium has good photovoltaic and photoconductive properties and is extensively used in electronics, photocells, light meters and solar cells. Selenium is also used as a catalyst in the preparation of pharmaceuticals, fungicides, anti-dandruff shampoos (selenium sulfide),[2] nutritional additives, pesticide[3] and as an essential micronutrient.[4]

1.2 Selenium dioxide

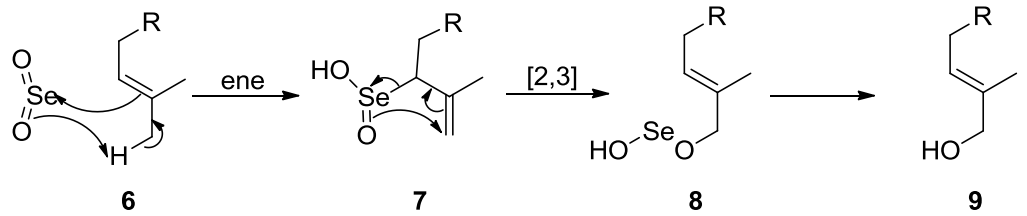
The chemistry of selenium compounds was neglected for more than a century and the entire literature comprised[5] only ~200 papers until 1920 and it was poorly appreciated until the 1970s. This slow development can be attributed to the malodorous reputation of its compounds, toxicity, and instability of certain derivatives. The unique quality of selenium reagents with wide application in organic chemistry was selenium dioxide. Selenium dioxide functions as a mild oxidizing agent over a wide temperature range and oxidations of organic compounds with this substance have been likened to auto-oxidation or peroxidation.[6] The three functional groups most subjected to oxidation with selenium dioxide are olefins, ketones and aldehydes.

1.2.1 Selenium dioxide as an oxidizing agent

The application of selenium dioxide for the oxidation of aldehydes and ketones to glyoxals and diketones **(Scheme 1.1)**,[7] and for the transformation of alkenes to allylic alcohols **(Scheme 1.2)**,[8] was first reported in the 1930s by Riley. It is also renowned as a reagent for "allylic" oxidation. However, the reaction mechanisms were not elucidated until forty years later when Sharpless *et al.* determined that both oxidations involved a seleninic acid intermediate **3** and **7**, the first reaction proceeding *via* a Pummerer rearrangement **(Scheme 1.1)**[9] and the second by an ene reaction followed by a [2,3] sigmatropic shift **(Scheme 1.2)**.[10]

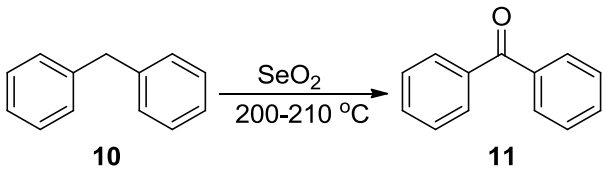


Scheme 1.1



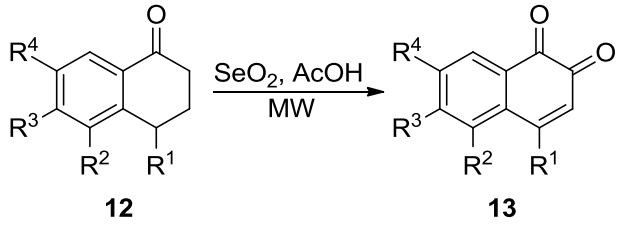
Scheme 1.2

In 1935, Lugowkin *et al*. reported the oxidation of diphenylmethane **(10)** to benzophenone **(11)** by selenium dioxide at 200-210 ^{o}C. The reaction proceeds smoothly when methylene group is flanked by two aromatic rings **(Scheme 1.3)**.[11]



Scheme 1.3

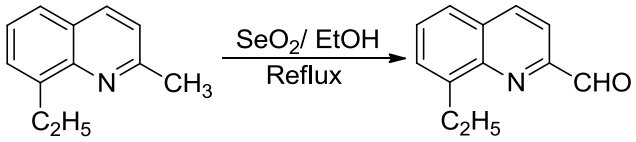
Gelman and Perlmutter reported a procedure of selective transformation of substituted 1-tetralones **(12)** to 1,2-naphthoquinones **(13)** by microwave-assisted selenium dioxide oxidation **(Scheme 1.4)**.[12]



12 **13**

Scheme 1.4

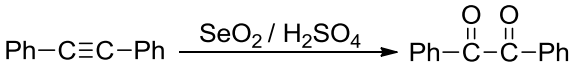
In aromatic heterocycles, the methyl group in *α*-position with respect to nitrogen is oxidized more easily. Thus, 8-ethyl-2-methylquinoline **(14)** gives selective oxidation product, aldehyde derivative **(15)**, when treated with SeO_2 **(Scheme 1.5)**.[13]



14 **15**

Scheme 1.5

Alkynes undergo oxidation with selenium dioxide to *α*-diketones. Thus, diphenylacetylene **(16)** is readily oxidized at 110 ^{o}C in the presence of selenium dioxide in a catalytic amount of sulfuric acid to benzil **(17) (Scheme 1.6)**.[14]

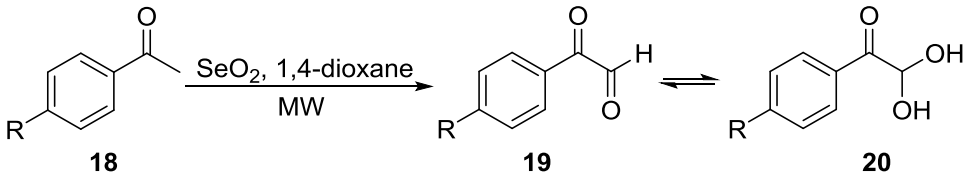


16 **17**

Scheme 1.6

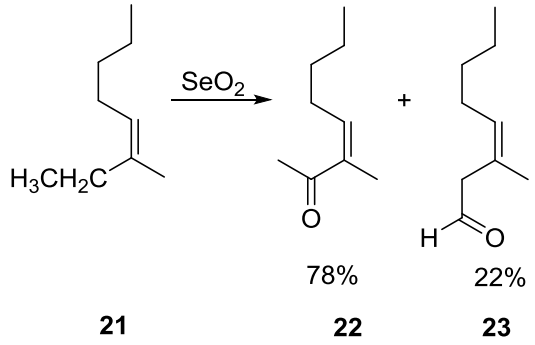
In 2011, Young *et al*. reported a convenient method for the synthesis of aryl glyoxals **(19)** by the oxidation of selenium dioxide under microwave-assisted reaction.[41] Various aryl methyl ketones **(18)** derivatives have been carried out successfully within a

short reaction time and affording the corresponding product in good yields **(Scheme 1.7)**.[15]



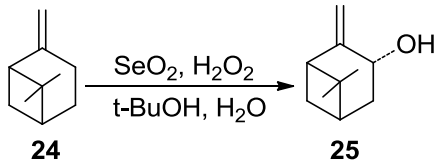
Scheme 1.7

In 1970, Rapoport and Bhalerao reported the oxidation of olefin *cis*-3-methyl-3-octene **(21)** using selenium dioxide as an oxidising agent resulted in the formation of two products. The first product **22** was formed due to oxidation of the methylene of the ethyl group (78%) and the minor product was the aldehyde **(23)** formed due to oxidation of the methyl group (22%) **(Scheme 1.8)**.[16]



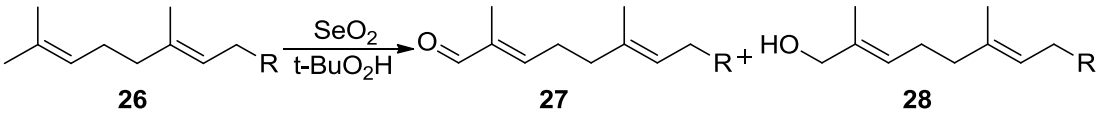
Scheme 1.8

Hartshorn and his co-workers reported a protocol for the conversion of *β*-pinene **(24)** into *trans*-pinocarveol **(25)** by oxidation with selenium dioxide **(Scheme 1.9)**.[17]



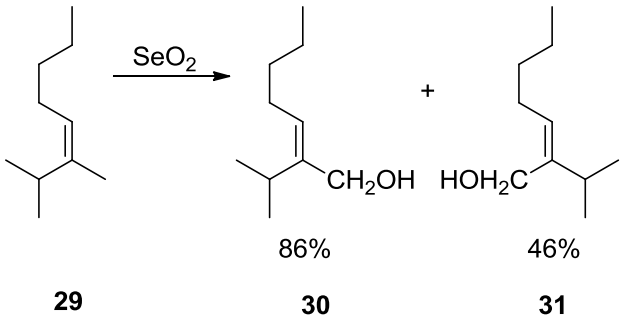
Scheme 1.9

Dickinson and group reported the oxidation of geranyl derivatives **(26)** with selenium dioxide/tertiary butyl alcohol for the synthesis of farnesyl mimics.[36] Various derivatives of *E*-geraniol **(28)** were synthesized and the products were obtained in good yields **(Scheme 1.10)**.[18]



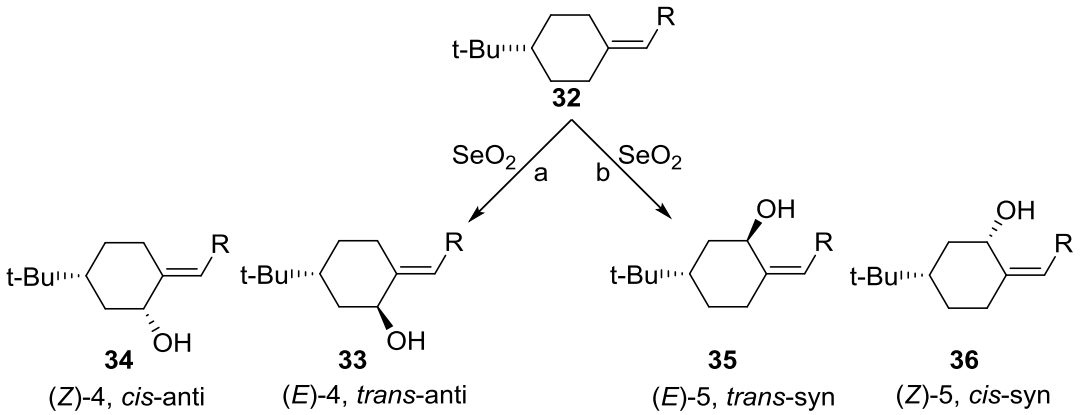
Scheme 1.10

In the case of olefins like 2,3-dimethyloct-3-ene **(29)**, the product alcohols formed due to oxidation of methyl groups. The allylic alcohols were found to be *trans* **(30)** and *cis* **(31)** with 86% and 14% yields respectively **(Scheme 1.11)**.[16]



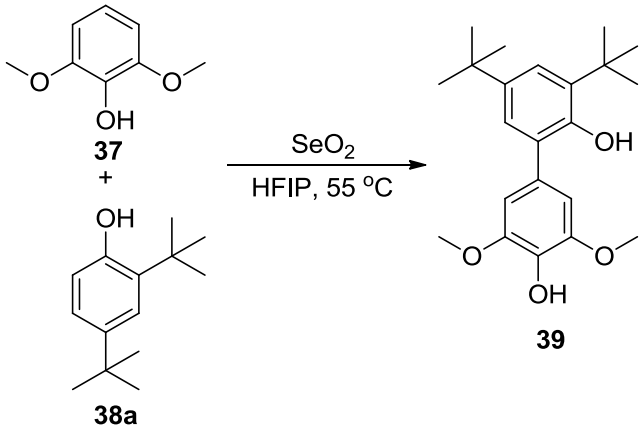
Scheme 1.11

In 2005, Park *et al*. employed selenium dioxide for the oxidation of 1-tert-butyl-4-alkylidene cyclohexanes **(32)** where allylic alcohols were isolated as a mixture of three stereoisomeric products, (*E*)-4 **(33)**, (*Z*)-4 **(34)** and (*E*)-5 **(35) (Scheme 1.12)**.[19]



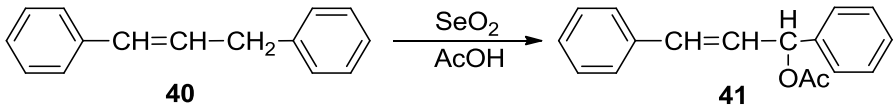
Scheme 1.12

In 2016, Waldvogel and groups reported a selenium dioxide mediated oxidative cross-coupling of phenols **(37** and **38a)** to afford an unsymmetric 2-4'-biphenols **(39)** and its derivatives in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) as a solvent **(Scheme 1.13)**.[20]



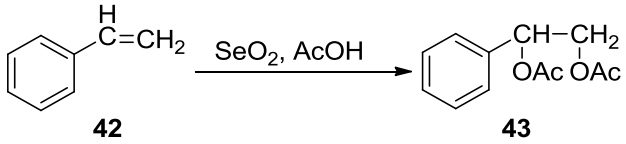
Scheme 1.13

In 1967, Schaefer *et al.* performed a study of the reaction on the oxidation of 1,3-diphenylpropene **(40)** and its derivatives. Oxidation of 1,3-diphenylpropene **(40)** with selenium dioxide in acetic acid at 115 ^{o}C gives the corresponding 1,3-diphenyl-2-propen-l-yl acetate **(41)** in good yields. The oxidation proceeds *via* the formation of a symmetrical allylic carbocation intermediate **(Scheme 1.14)**.[21]



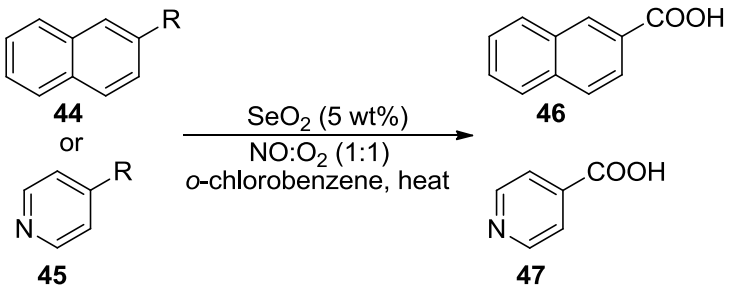
Scheme 1.14

Tsutsumi *et al*. in 1968 reported the oxidation of styrene **(42)** with selenium dioxide in the presence of glacial acetic acid. The reaction was carried out in an autoclave at 150-160 ^{o}C to give the corresponding styrene glycol diacetate **(43)** in good yields **(Scheme 1.15)**.[22]



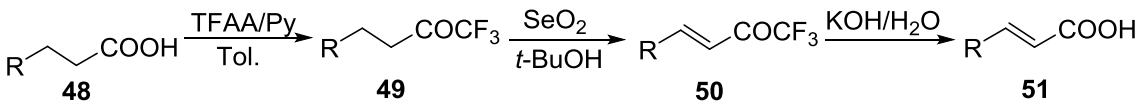
Scheme 1.15

The oxidation of the benzylic groups of alkylnaphthalene **(44)** and alkylpyridine **(45)** derivatives to the corresponding carboxylic acids **(46** and **47)** by dioxygenation which was mediated by a combination of nitrogen oxides and selenium dioxide was reported by Remias and Sen. The product was obtained in good to excellent yields **(Scheme 1.16)**.[23]



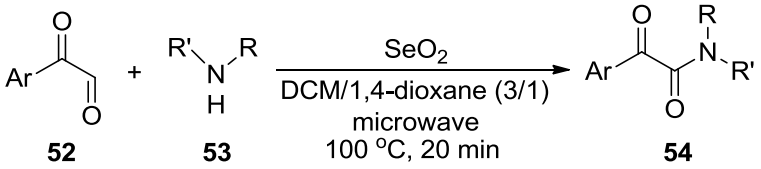
Scheme 1.16

Recently, a three-step method for the synthesis of unsaturated carboxylic acid **(51)** was reported by converting saturated carboxylic acids **(48)** to trifluoromethyl ketones **(49)** in the presence of selenium dioxide followed by hydrolysis **(Scheme 1.17)**.[24]



Scheme 1.17

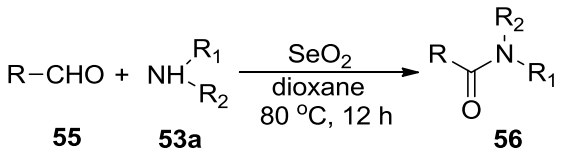
Hulme *et al*. reported the synthesis of *α*-ketoamide *via* selenium dioxide mediated oxidative amidation of arylglyoxal with secondary amines and accelerated with microwave irradiation. A series of *α*-ketoamide **(54)** from various arylglyoxal **(52)** with cyclic and acyclic secondary amine **(53)** was successfully synthesized by this method **(Scheme 1.18)**.[25]



52 **53** **54**

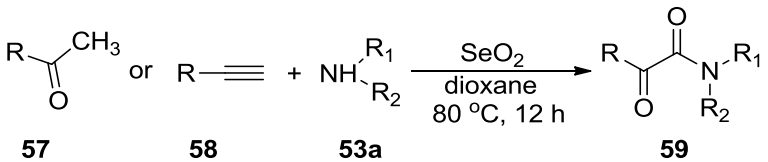
Scheme 1.18

Jain *et al.* successfully synthesized amides **(56)** from aldehydes **(55) (Scheme 1.19)** and *α*-ketoamides **(59)** from acetophenones **(57)** and phenylacetylenes (**58**) by oxidative amidation with selenium dioxide **(Scheme 1.20)**. Ketoamide derivatives of natural products 16-dehydropregnenolone acetate, pregnenolone acetate, and progesterone were also successfully synthesized.[26]



55 **53a** **56**

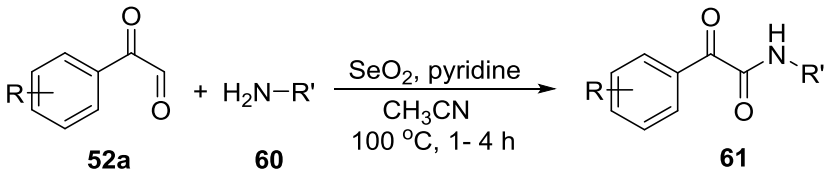
Scheme 1.19



57 **58** **53a** **59**

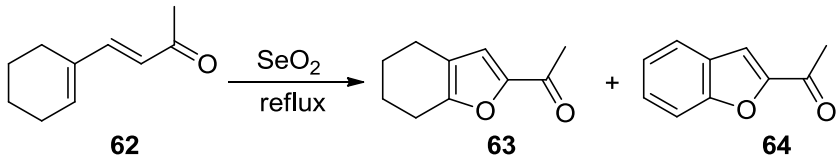
Scheme 1.20

In the above schemes (**Schemes 1.18, 1.19** and **1.20**) the primary amines and anilines failed to give the oxidized product which is probably due to their weak nucleophilicity. However, the combination of pyridine **(60**) with selenium dioxide successfully gives the oxidative coupling of 2-oxoaldehydes (**52a**) with the weak nucleophilic amines such as anilines, benzamides and sulfonamides. Initially, the reaction proceeds *via* carbonylimine formation followed by the oxidation to the carbonylamides (**61**) **(Scheme 1.21)**.[27]

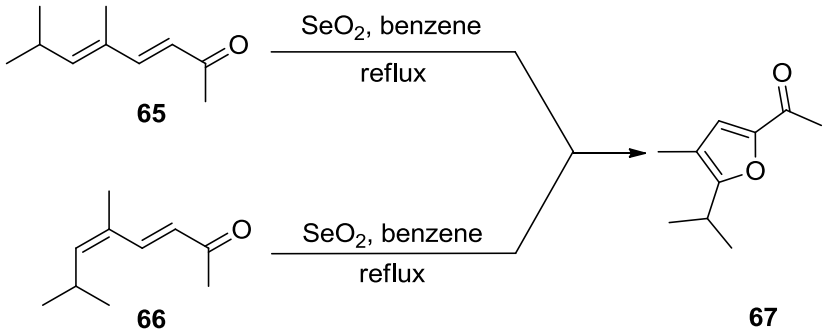


Scheme 1.21

Selenium dioxide was also found to be useful in converting conjugated dienones **(62)** to tetrahydrobenzofuran **(63)** and benzofuran **(64) (Scheme 1.22)**. Irrespective of the double bond geometry of dienones **(65** and **66)**, the reaction proceeds to produce an oxidized product, furan **(67) (Scheme 1.23)**.[28]

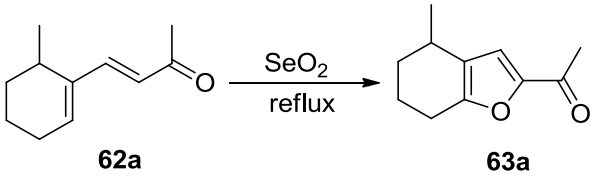


Scheme 1.22



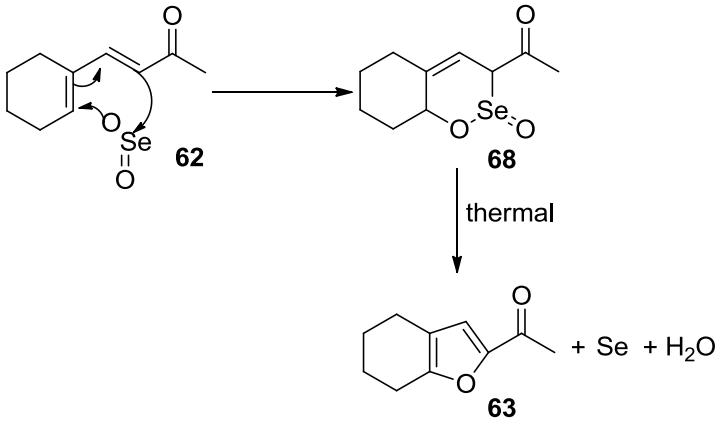
Scheme 1.23

Oxidation of *E*-4-(6-methyl-1-cyclohexenyl)-3-butene-2-one **(62a)** shows the versatility of the process. The presence of the substitution on the ring resists aromatization **(Scheme 1.24)**.[28]



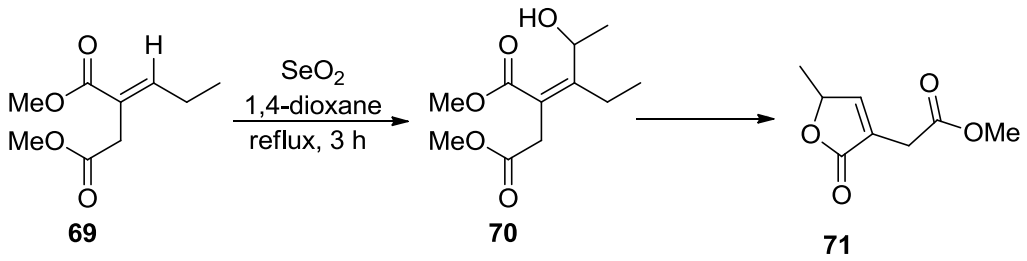
Scheme 1.24

The mechanism of the reaction shows that the formation of the selenoxo intermediate **(68)** from the step wise method by reaction of *cis*-diene **(62)** with SeO_2 is proposed from the observation that when the reaction was carried out with polar solvent such as acetic acid, the rate of the reaction increases. The selenoxo intermediate **(68)** then undergoes thermal rearrangement to give the corresponding product, furan **(63)** **(Scheme 1.25)**.[28]



Scheme 1.25

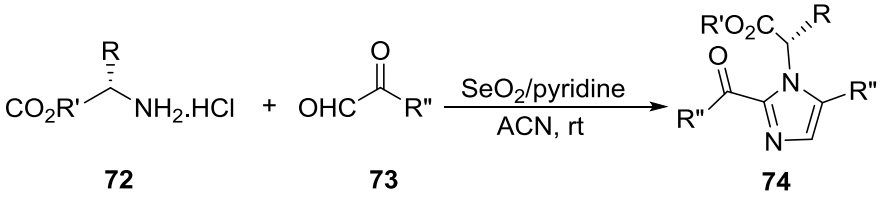
Patel *et al*. demonstrated the first (*Z*)-selective allylic alcohol formation **(70)** by selenium dioxide oxidation of dialkylalkylidenesuccinates **(69)** to accomplish the one-step synthesis of several essential butenolides **(71)** *via* an unusual *E*- to *Z*- carbon-carbon double bond isomerisation **(Scheme 1.26)**.[29]



Scheme 1.26

Padala *et al*. presented a novel amino acid substituted imidazoles **(74)** engendered from amino acid alkyl ester hydrochlorides **(72)** and 2-oxoaldehydes **(73)**, as a result of selenium dioxide promoted unconventional reaction in a basic environment and all of the reaction meticulously retained regioselectivity. The uniqueness of selenium dioxide in

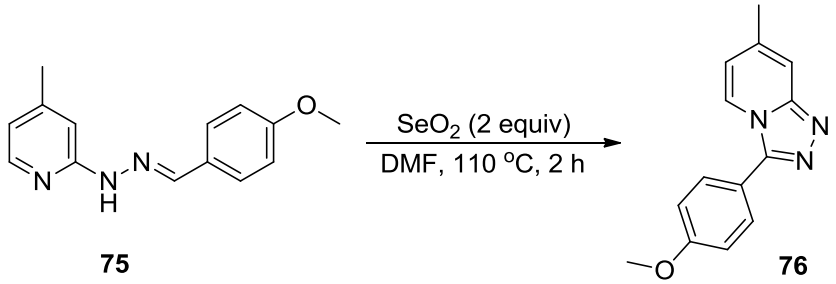
fixing two nitrogen atoms from amino acids through an *in situ* generated $ArCOCHN_1N_2$ system is the imperative feature of these reactions **(Scheme 1.27)**.[30]



72 **73** **74**

Scheme 1.27

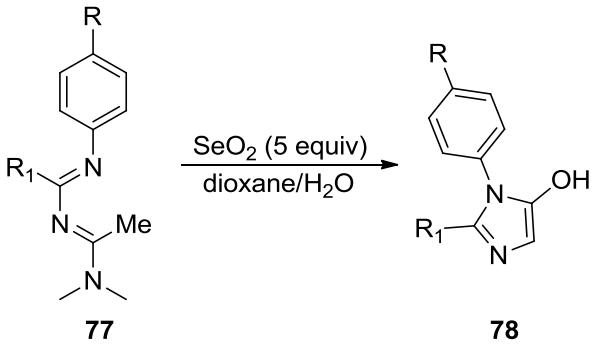
Liu and co-workers have reported that oxidation of heterocyclic-substituted hydrazones **(75)** using selenium dioxide as an oxidant led to the formation of a fused 1,2,4-triazoles **(76)** at 110 ^oC **(Scheme 1.28)**.[31]



75 **76**

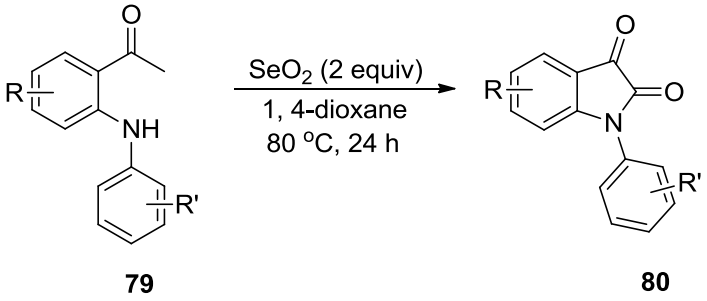
Scheme 1.28

Mahajan and co-workers reported a novel approach for the synthesis of 4-hydroxyimidazoles **(78)** *via* SeO_2 mediated oxidation of 1,3-diazabuta-1,3-dienes **(77)**.[32] Various derivatives of 4-hydroxyimidazoles have been synthesized by this method **(Scheme 1.29)**.



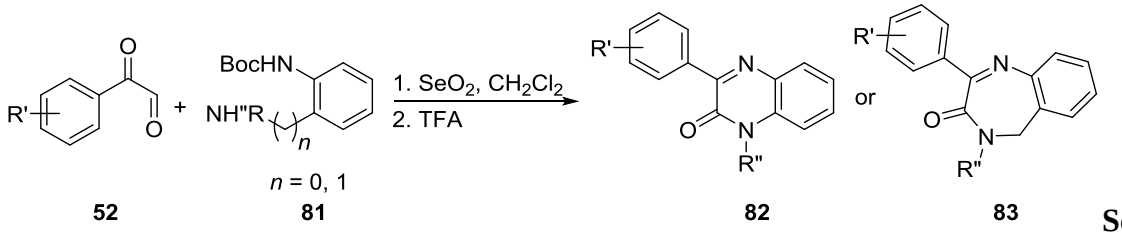
Scheme 1.29

Deng and co-workers reported the intramolecular oxidative amidation of 2-(arylamino)-acetophenones **(79)** to *N*-arylisatins **(80) (Scheme 1.30)**.[33]



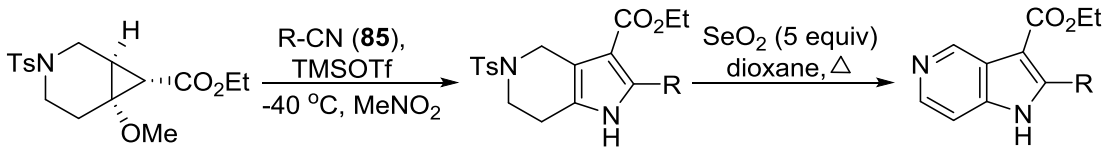
Scheme 1.30

Hulme *et al.* have reported a selenium dioxide mediated oxidative amidation of arylglyoxals **(52)** with *N*-Bocphenylenediamines **(81)** for the syntheses of quinoxalinones **(82)** and diazepinones **(83) (Scheme 1.31)**.[34]



Scheme 1.31

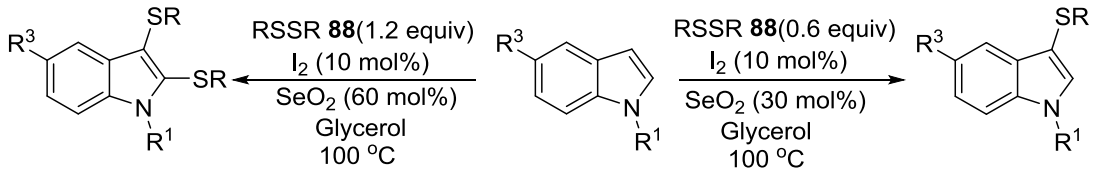
Abd Rabo Moustafa and Pagenkopf reported a [3+2] dipolar cycloaddition between 3,4-cyclopropanopiperidines **(84)** and nitriles **(85)** for the synthesis of 5-azaindoles **(87)** by SeO_2 oxidation. This two-step procedure represents a novel access to 5-azaindoles from easily available cyclopropanopiperidines **(Scheme 1.32)**.[35]



84 **86** **87**

Scheme 1.32

Recently, a selective method for the synthesis of *mono*- and *bis*-sulfenylindoles **(91** and **90)** using I_2/SeO_2 as catalyst/oxidizing agent and glycerol as the solvent was reported by Lenardão *et al*. The starting materials involved in this protocol are diorganyl disulfides **(88)** and indoles **(89)** which undergo S-S bond cleavage with the formation of new S-Csp^2 (indole) bonds **(Scheme 1.33)**.[36]

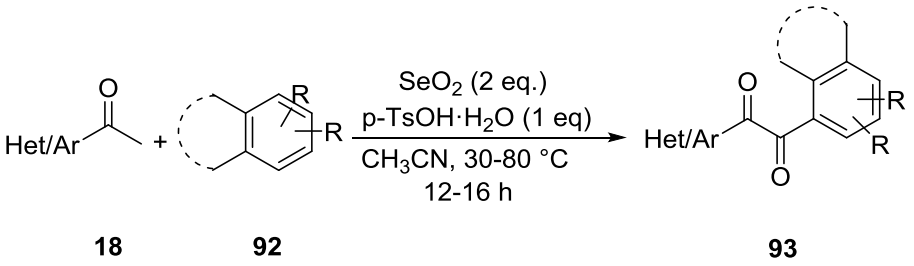


91 **89** **90**

Scheme 1.33

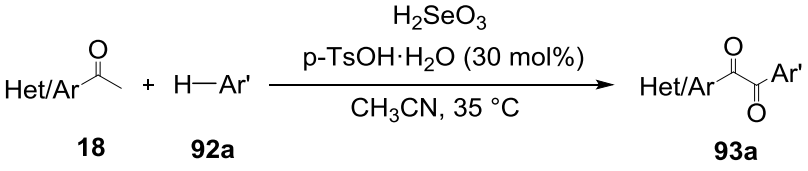
The reactive behavior of SeO_2 towards organic substrates in the presence of a Lewis acid or a Bronsted acid, however, has found few mentioned in the literature survey. In 2011, our group reported a C-C bond formation by oxidative coupling between the α-carbon atom of the aromatic ketone **(18)** with unactivated arenes **(92)** in

the presence of SeO_2 and *p*-TsOH·H_2O. A series of unsymmetrical and heteroaryl 1,2-diketones **(93)** have successfully synthesized by this protocol **(Scheme 1.34)**.[37]



Scheme 1.34

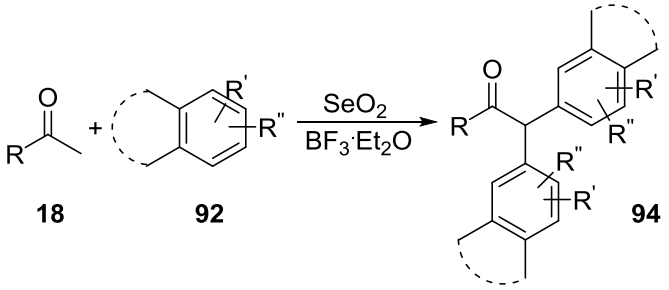
Our group has further modified the oxidative coupling for the synthesis of diketones **(93a)** by avoiding the use of *p*-TsOH·H_2O in a stoichiometric amount in the presence of H_2SeO_3 and in many instances gave better yields of the products **(93a)** as shown in **(Scheme 1.35)**.[38]



Ar = aryl, Het = heteroaryl; Ar' = benzene, toluene, xylene, anisole, naphthalene, anthracene

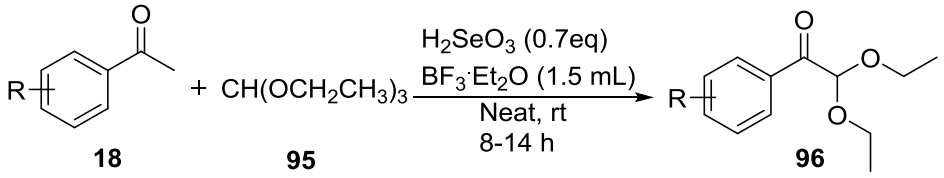
Scheme 1.35

In 2012, our group reported an efficient regio-selective protocol for the C-C bond formation by an unexpected *α,α*-diarylation **(94)** of aromatic ketones **(18)** in presence of selenium dioxide, catalyzed by boron trifluoride etherate **(Scheme 1.36)**.[39]



Scheme 1.36

In the same year, our group have successfully reported another efficient protocol for the synthesis of α-keto acetal **(96)** by the reaction of aromatic ketones **(18)** and triethyl orthoformate **(95)** in presence of selenous acid and boron trifluoride etherate **(Scheme 1.37)**.[40]



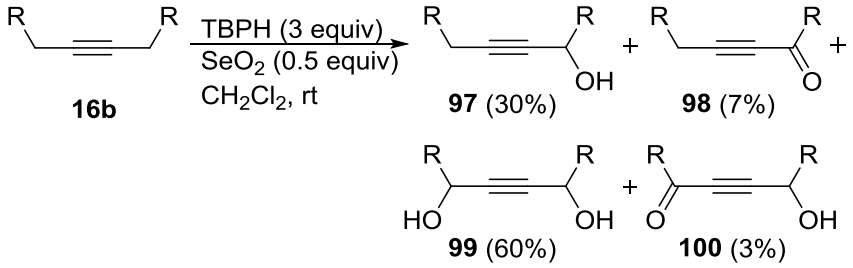
Scheme 1.37

1.2.2 Selenium dioxide as a catalyst

One of the earliest reports of the novel use of selenium dioxide as catalyst was the oxidation of acrolein to acrylic acid by hydrogen peroxide in presence of catalytic amount of selenium dioxide.[41] C. W. Smith and co-worker again reported a novel use of selenium dioxide as catalyst for the ring contraction of cycloalkanones to cycloalkane carboxylic acids in presence of hydrogen peroxide as the oxidizing agent.[42] Since then, several workers have reported similar oxidation reactions where selenium dioxide

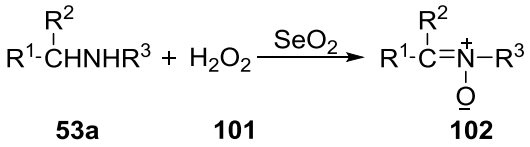
function as a catalyst. For example, the hydroxylation[43a] and oxidation[43b] of olefins with peroxide in the presence of selenium dioxide as a catalyst.

In 1979, Sharpless *et al*. described the oxidation of acetylenes **(16b)** catalyzed by selenium dioxide in the presence of a *tert*-butylhydroperoxide[44] which gave a mixture of *α,α'*-dioxygenated products **99** and **100** and the expected mono-oxygenated products **97** and **98 (Scheme 1.38)**.



Scheme 1.38

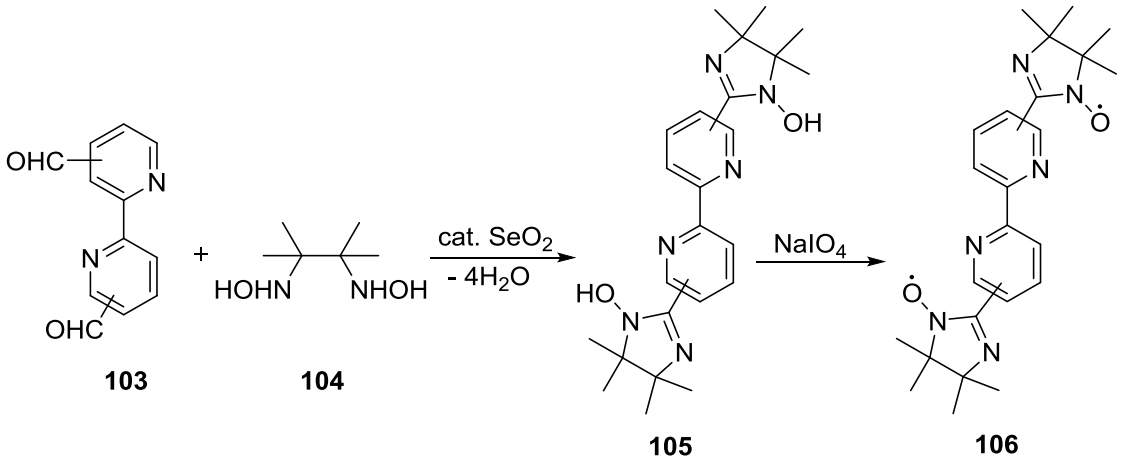
In 1987, Murahashi *et al*. reported an efficient selenium dioxide-catalyzed oxidation of secondary amines **(53a)** with hydrogen peroxide **(101)** to give nitrones **(102)** which are versatile synthetic intermediates **(Scheme 1.39)**.[45]



Scheme 1.39

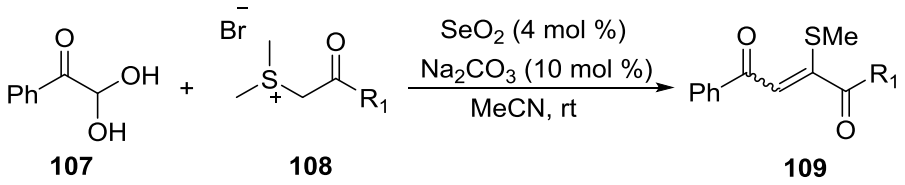
Ulrich and Ziessel presented a mild and selective synthesis of a novel family of oligopyridine based imino-nitroxide biradicals **(106)** catalyzed by selenium dioxide. The bis-*N*-hydroxyimidazolidines **(105)** were prepared in good yields (40-90%) by multiple

condensation of *N*-*N*'-dihydroxy-2,3-diamino-2,3-dimethylbutane **(104)** with the formyl compounds **(103)** in methanol using selenium dioxide as catalyst **(Scheme 1.40)**.[46]



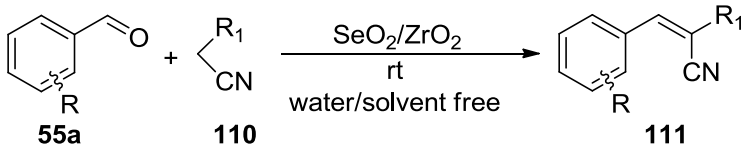
Scheme 1.40

Shao and Li have reported an efficient protocol for the condensations of glyoxal hydrate **(107)** with sulfonium salts **(108)**. The method involves the use of a catalytic amount of SeO_2 in the presence of Na_2CO_3 and acetonitrile as a solvent **(Scheme 1.41)**.[47]



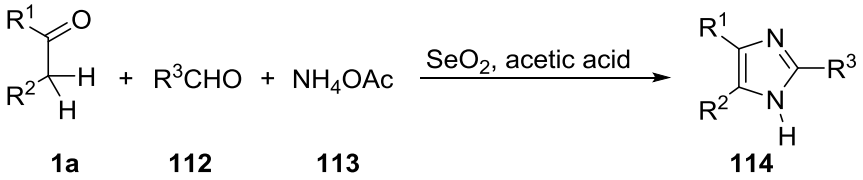
Scheme 1.41

Banothu *et al*. reported the selenium dioxide promoted zirconia (SeO_2/ZrO_2) catalyst for the synthesis of alkenes derivatives **(111)** by Knoevenagel condensation of aromatic aldehyde **(55a)** with active methylene **(110)** compounds in water medium and solvent-free conditions **(Scheme 1.42)**.[48]



Scheme 1.42

Jeena and Mazibuko described selenium dioxide/acetic acid catalyzed one-pot conversion of α-methylene ketones **(1a)**, aldehyde **(112)** with ammonium acetate **(113)** to Lophine derivatives **(114)** *via* Domino multi-component reaction **(Scheme 1.43)**.[49]

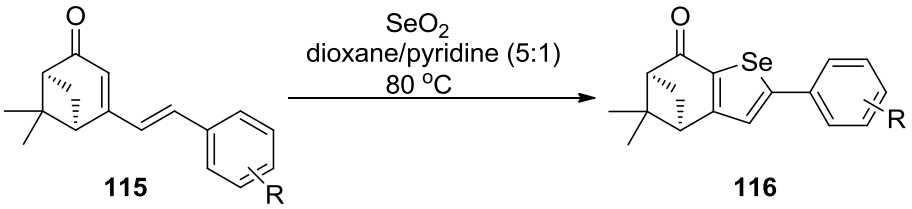


Scheme 1.43

1.2.3 Selenium dioxide as a reagent

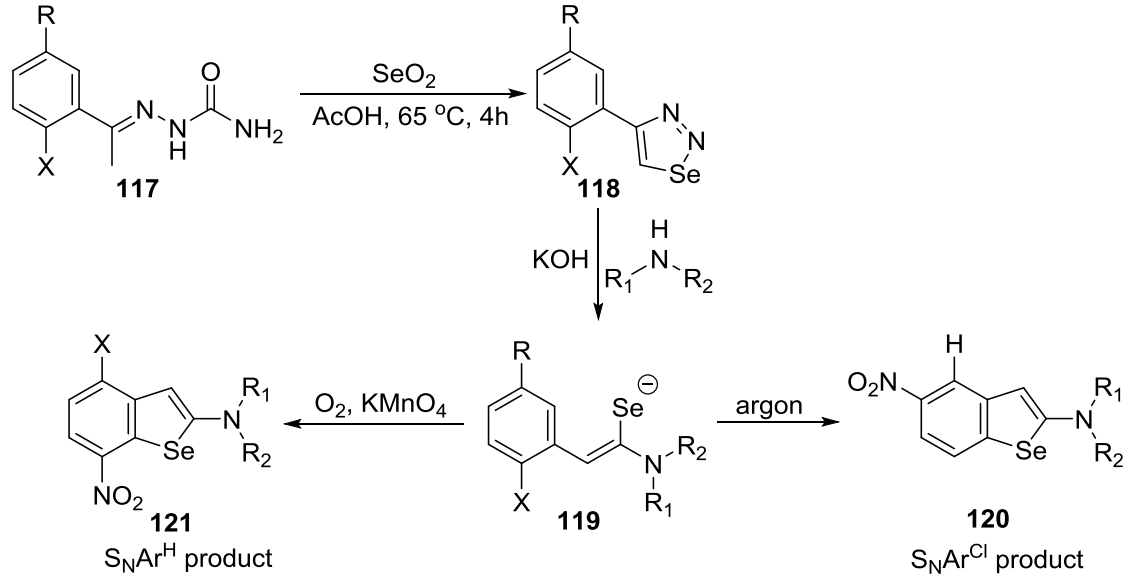
Selenium dioxide has recently emerged as a stable, useful and readily available selenylating reagent in the synthesis of organoselenium compounds.

In 2002, Lee *et al*. reported an efficient method for the synthesis of selenophenes. The synthesis of selenophenes **(116)** was carried out in one-step procedure from the reaction of selenium dioxide with 1,3-dienes **(115)** *via* [4+2] cycloadditions **(Scheme 1.44)**.[50]



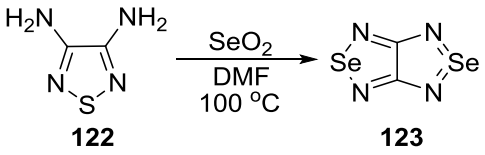
Scheme 1.44

Androsov and group successfully synthesized benzo[*b*]selenophenes starting from semicarbazones **(117)** of acetophenones with selenium dioxide to give 1,2,3-selenadiazoles **(118)** and further in the presence of strong nucleophile (alkyl amines) and base it undergo ring opening to form eneselenolates **(119)**. Further, the presence of a nitro group which is an electron-withdrawing on the aromatic ring leads to a cyclized benzo[*b*]selenophenes **(120)** under an oxygen-free atmosphere. However, when an oxidant ($KMnO_4$) is present, the eneselenolates **(119)** undergo oxidative nucleophilic substitution *via* S_NAr^H pathway benzo[*b*]selenophenes **(121)** was formed selectively under the oxidative conditions **(Scheme 1.45)**.[51]



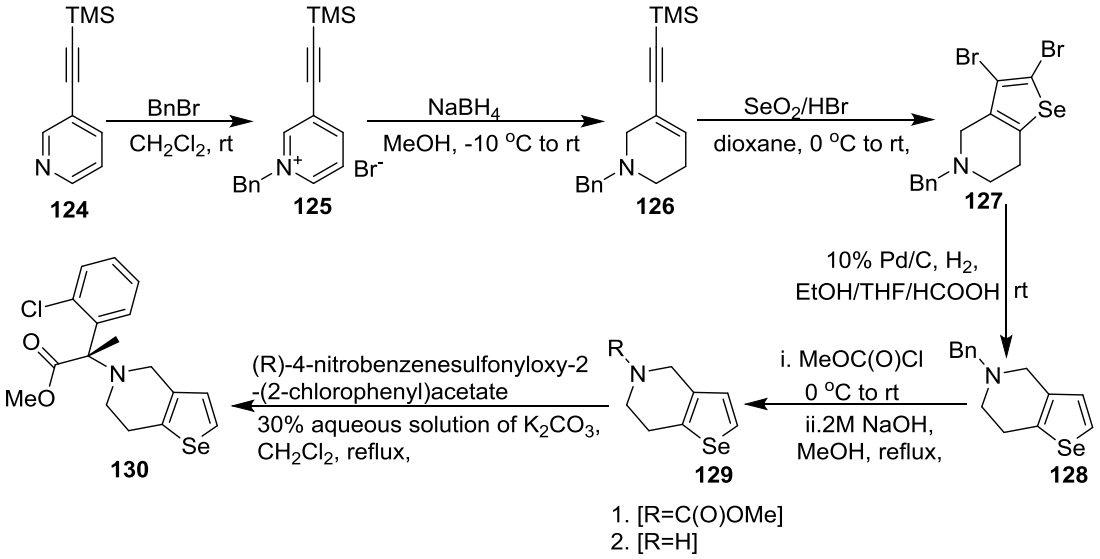
Scheme 1.45

The direct synthesis of fused 1,2,5-selenadiazoles **(123)** from 1,2,5-thiadiazoles **(122)** was reported by Konstantinova *et al*. In these reactions, transformation was undergoing two processes in the same pot formation of a 1,2,5-selenadiazole **(123)** ring *via* condensation of a *vic*-diamine with SeO_2, and exchange of the sulfur atom in the 1,2,5-thiadiazoles **(122)** ring with a selenium atom **(Scheme 1.46)**.[52]



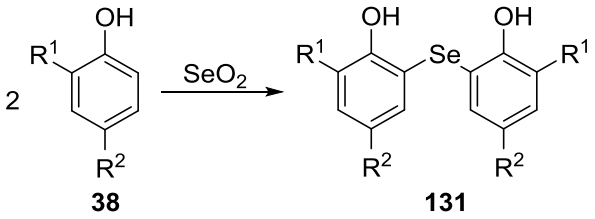
Scheme 1.46

In 2016 Arsenyan *et al.* developed a synthetic procedure for the preparation of selenopheno[2,3-*c*]dihydropyridines **(127)** which is a convenient protocol for the synthesis of (*S*)-Clopidogrel selenium analog **(130) (Scheme 1.47)**.[53]



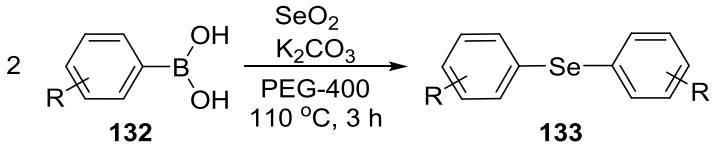
Scheme 1.47

In 2016, Waldvogel *et al.* reported the synthesis of diaryl selenides **(131)** employing selenium dioxide in pyridine as a solvent. This protocol allows the conversion of a broad substrate scope of different phenols **(38) (Scheme 1.48)**.[54]



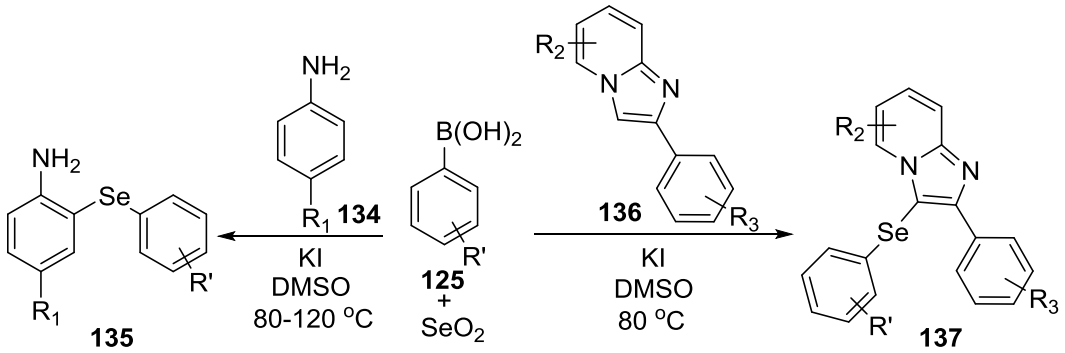
Scheme 1.48

Kumar *et al.* reported a transition metal-free protocol for the preparation of diaryl selenium **(133)** compound from selenium dioxide in the presence of eco-friendly solvent PEG-400.[55]



Scheme 1.49

Recently, in 2019, Zhou *et al.* reported the synthesis of ArSe-substituted aniline **(135)** and 2-phenylimidazo[1,2-*a*]pyridine **(137)** derivatives using selenium dioxide as a selenium source under mild and environmentally friendly conditions **(Scheme 1.50)**.[56]



Scheme 1.50

The importance of selenium chemistry in organic synthesis has led us to further exploit the synthetic applicability of selenium compounds particularly selenium dioxide. Hence, in the next four chapters, we will be describing the synthetic applications of selenium dioxide for the synthesis of various important synthetic intermediates which serve as building blocks in organic synthesis and some of the unreported compounds which have been successfully synthesized.

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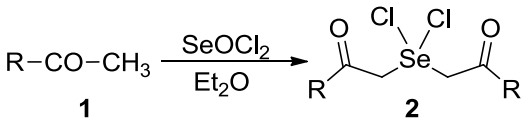
CHAPTER 2

Selenium Dioxide as a Selenium Source for the Synthesis of α,α-Dicarbonyl Selenides

2.1 Introduction

The C-Se bond is considered as an important linkage in organic compounds[1, 2] and is widely found in biological molecules, drug candidates and even functional organic materials.[3-5] The synthesis of compounds with a C-Se bond has attracted attention for many years. Over the past decades, many synthetic methods have been developed to construct various organoselenium compounds with potential biological activities.[6-11] Amongst the C-Se bond skeleton, *α,α*-dicarbonyl selenides are key intermediate for the synthesis of selenophene,[12] seleno alkynes,[13] selenadiazepine and pyridazine.[14] As per our literature survey, only a few methods have been reported for the synthesis of *α,α*-dicarbonyl selenides.[12, 14-17]

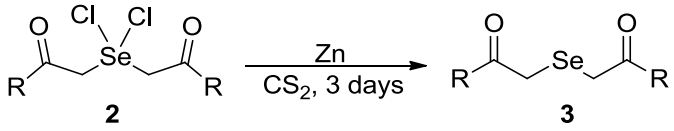
The first method was reported by Nelson and Jones in 1930, for the synthesis of dichloro selenodiketones **(2)** by the reaction of ketones **(1)** with selenium oxychloride in anhydrous ether. The dichloride product described as more or less unstable and moisture-sensitive **(Scheme 2.1)**.[15]



1 **2**

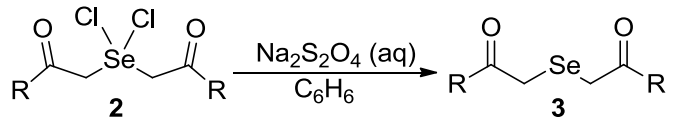
Scheme 2.1

In 1972, Ajello reported a procedure for the synthesis of *α,α*-dicarbonyl selenides **(3)** starting from dichloro selenodiketones **(2)** with Zn powder in excess of carbon disulfide under reflux for 3 days **(Scheme 2.2)**.[14]



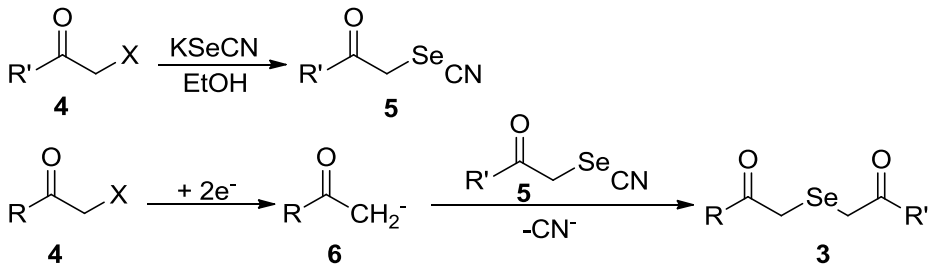
Scheme 2.2

In 1987, Nakayama and his co-workers successfully reported a method for the synthesis of *α,α*-dicarbonyl selenides **(3)** by portion-wise addition of dichloro selenodiketones **(2)** to a two-phase mixture of sodium dithionite and benzene at room temperature **(Scheme 2.3)**.[12]



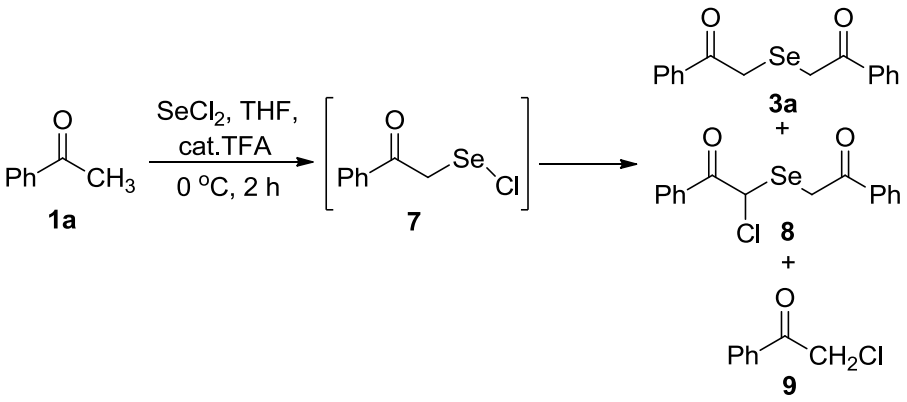
Scheme 2.3

Barba *et al.* reported the synthesis of *α,α*-dicarbonyl selenides **(3)** by the reaction of electrogenerated enolate **(6)** over *α*-carbonyl selenocyanates **(5) (Scheme 2.4)**.[16]



Scheme 2.4

In 2013, Braverman *et al.* performed the reaction of selenium dichloride with acetophenone **(1a)** in presence catalytic amount of TFA at low temperature which gave a mixture of two selenides **(3a, 8)** and a by-product **9 (Scheme 2.5)**.[17]

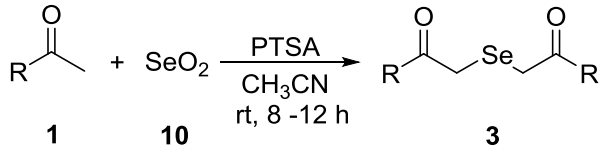


Scheme 2.5

These methods, however, are air and moisture sensitive and involved multi-steps procedure, giving multiple products that naturally limit their scope of applications. Thus, the development of new synthetic methods using easily available starting materials in one-step process and under mild reaction conditions would have significant synthetic value.

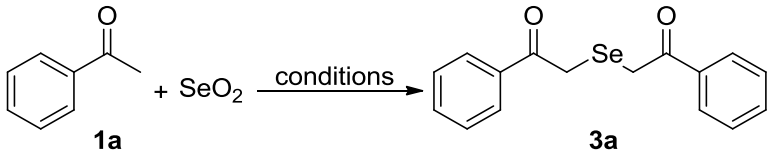
2.2 Results and Discussion

Based on our previous work where selenium dioxide was employed only as an oxidizing agent,[18-21] in this chapter we demonstrated the reaction where selenium dioxide acts as a selenylating agent. We have thus established a method for the synthesis of *α,α*-dicarbonyl selenides starting from substituted acetophenones/heteroaryl ketones **(1)** in presence of easily available selenium dioxide (SeO_2) and *p*-toluenesulfonic acid (PTSA) **(Scheme 2.6)**.



Scheme 2.6 Synthesis of *α,α*-dicarbonyl selenides

Table 2.1.Optimization of reaction conditions[a]



entry	acid/equiv	solvent	time (h)	yield (%)
1	PTSA/0.3	CH_3CN	8	35
2	**PTSA/0.5**	**CH_3CN**	8	**69**
3	PTSA/1.0	CH_3CN	8	71
4	BF3·Et2O/0.5	CH_3CN	8	60
5	CH_3COOH/0.5	CH_3CN	8	0

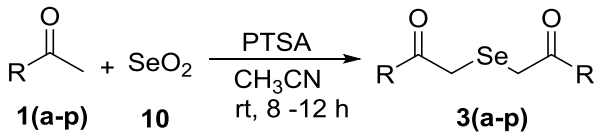
[a]Reaction conditions: ketones **(1)** (1.0 mmol), SeO_2 (0.5 mmol), solvent (1mL)

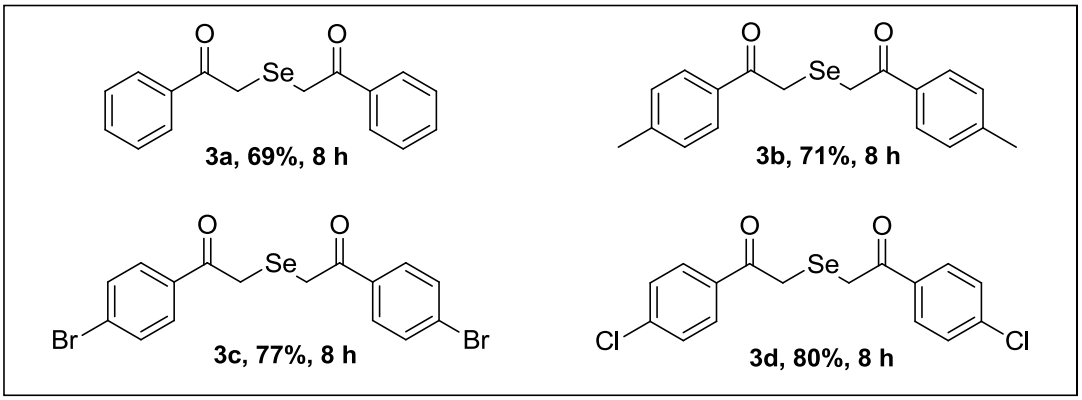
Initially, when a mixture of acetophenone **(1a**, 0.115 mL, 1.0 mmol, 1 equiv**)**, selenium dioxide (55 mg, 0.5 mmol, 0.5 equiv) and PTSA (570 mg, 0.3 mmol, 0.3 equiv) in CH_3CN as a solvent was allowed to stir at room temperature for 8 h the reaction product **3a** was formed in 35% yield **(Table 2.1, entry 1)**. The optimized condition was obtained when the reaction was carried out with 0.5 equiv of PTSA

which gave the product at 69% yield. Next, the reaction was carried out with different acids such as $BF_3 \cdot EtO_2$ which resulted in even less yield of the product **(Table 2.1, entry 4)** and with CH_3COOH, the desired product was not formed **(Table 2.1, entry 5)**.

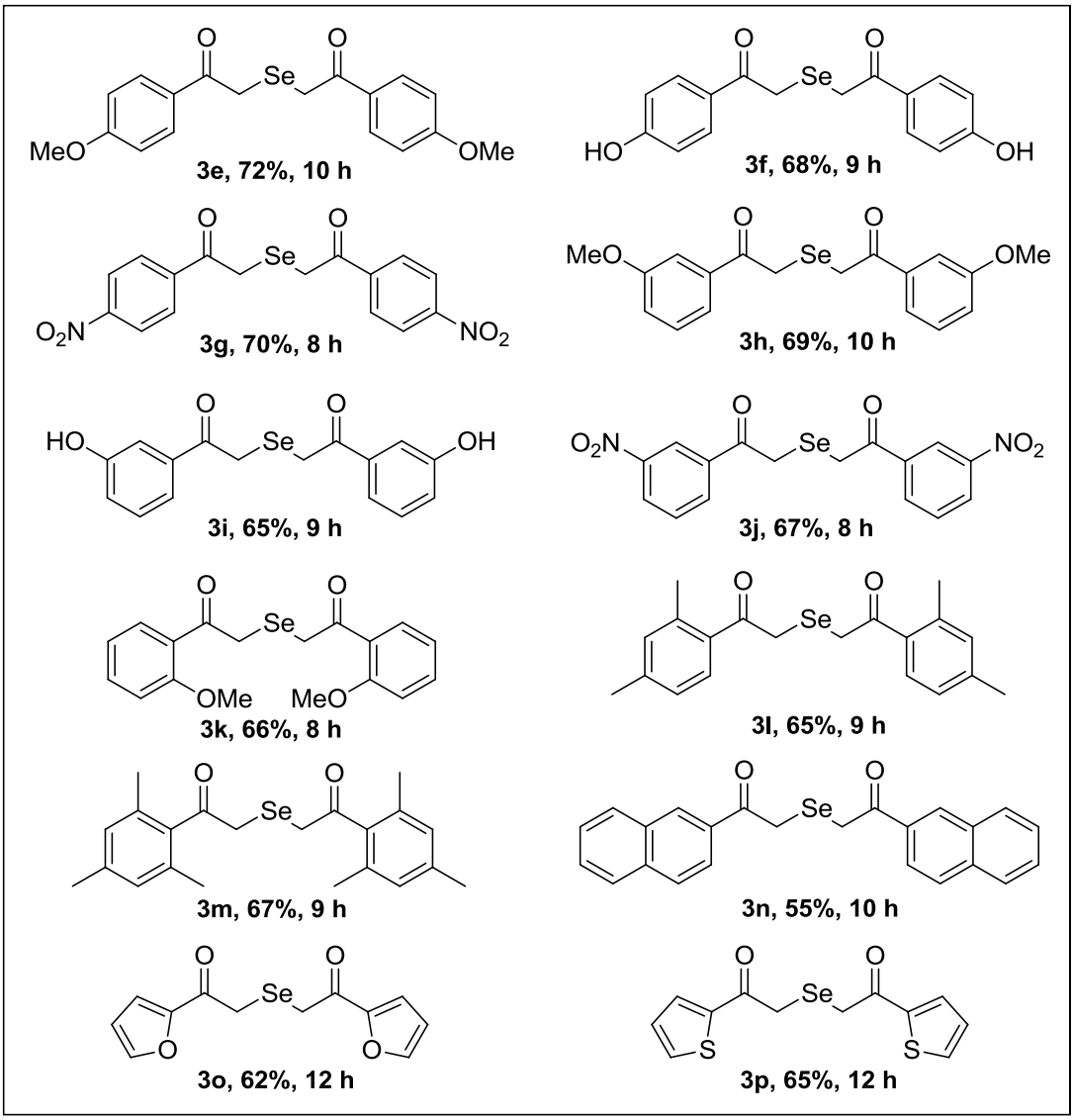
Under the optimized reaction conditions, the scope of the reaction of aryl methyl ketones was explored. Aryl methyl ketones bearing electron-donating **(**e.g., **1b**, 4-Me; **1e**, 4-OMe; **1f**, 4-OH; **1h**, 3-OMe; **1i**, 3-OH; **1k**, 2-OMe**)** or electron-withdrawing **(**e.g., **1g**, 4-NO_2; **1j**, 3-NO_2**)** substituent in the ring were successfully converted to the corresponding products **3b**, **3e-k** in moderate to good yields **(**65-80%**)**. The reaction also proceeded very well with halogenated aryl methyl ketone (**3c**, 4-Br; **3d**, 4-Cl), which afforded the desired products in good yields **(3c**, 77%; **3d**, 80%**)**.

Scheme 2.7 Substrate scope of aryl methyl ketones[a]





[a] Reaction conditions: ketones (**1)** (1.0 mmol) , SeO_2 (0.5mmol), solvent (1 mL), room temperature.



a

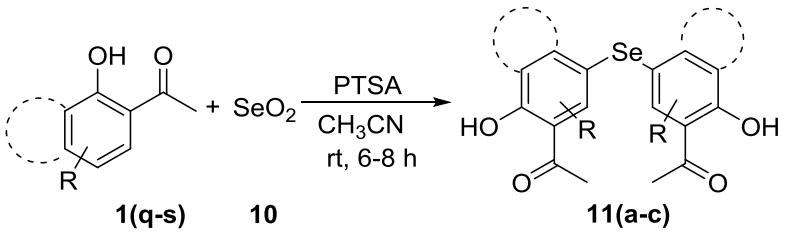
Reaction conditions: ketones (**1)** (1.0 mmol) , SeO_2 (0.5mmol), solvent (1 mL), room temperature.

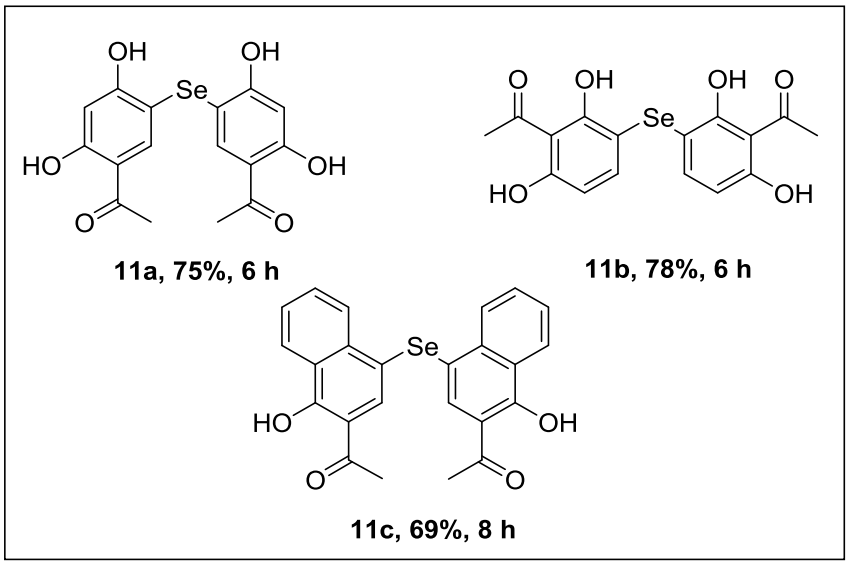
The scope of the reaction was also extended to *di*- and *tri*-substituted acetophenones which gave the desired products **(3l**, 65%; **3m**, 67%**)** in moderate yield. Similarly sterically hindered 2-acetyl naphthalene **(1j)**, readily gave the corresponding product in satisfactory yield **(3n**; 55%**)**.

To test the generality of the method, the reaction was further extended to the heteroaryl methyl ketones **1o-p**. Heteroaryl methyl ketones such as 2-arylfuran **(1o)** and 2-arylthiophene **(1p)** were allowed to react with selenium dioxide, the reaction

proceeds smoothly to give the desired products **(3o**, 62%; **3p**, 65%**)** in moderate yields.

Scheme 2.8 Substrate scope of aryl methyl ketones[a]

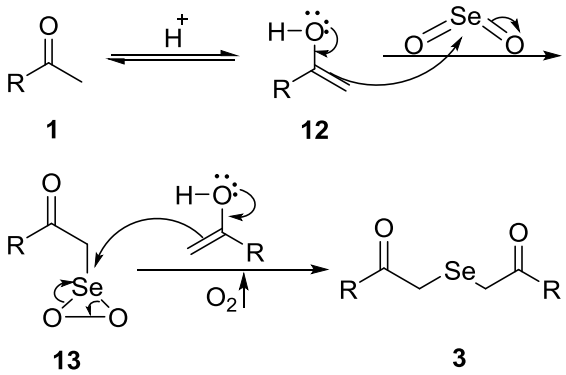




[a]Reaction conditions: ketones **(1)** (1.0 mmol) , SeO_2 (0.5 mmol), solvent (1 mL), room temperature.

It is interesting to note that when the reaction was carried out with 2-hydroxy acetophenone derivatives **(1q, 1r, 1s)**, the expected product **3** was not obtained instead selenium directly attaches itself to the aromatic carbons to give diaryl selenides **(11)** in good yields **(11a**, 75%; **11b**, 78%; **11c**, 69%**)**. This is expected due to the presence of a *para*-directing hydroxyl group **(Scheme 2.8)**.

Scheme 2.9 Plausible mechanism



The probable mechanism of the reaction may be depicted as in **Scheme 2.9**. Enolization of the ketone **(1)** in the presence of *p*-toluenesulfonic acid monohydrate is the first step followed by reaction with selenium dioxide to generate the intermediate **13**. The propensity of the Se to get reduced to its lower oxidation state results in a facile nucleophilic attack on the Se, leading to the formation of the product **3** with the elimination of oxygen.

In conclusion, we have developed a method for the synthesis of *α,α*-dicarbonyl selenides from aryl methyl ketones using selenium dioxide as a selenium source. The method is simple and proceeds under mild reaction conditions at room temperature. Moreover, the starting materials employed in this method are easily available which adds to the overall synthetic significance of this procedure.

2.3 Experimental Section

General Methods

All reagents were purchased from Sigma Aldrich, TCI Chemicals and Alfa Aesar and were used without further purification unless noted. Melting points were recorded by open capillary tube method and are uncorrected. IR spectra were recorded on a Perkin Elmer Spectrum 400 FTIR instrument. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance II-400 spectrometer in $CDCl_3$ and DMSO-d_6 with TMS as internal standard. ^{77}Se NMR spectra were recorded on Mercury Plus 300Hz NMR Spectrometer in ppm using Me_2Se as internal standard. Mass spectral data were obtained with a Waters UPLC-TQD mass spectrometer (ESI-MS). All reactions were monitored by thin layer chromatography (TLC) using pre-coated aluminium sheets (silica gel 60 F_{254} 0.2-mm thickness). Column chromatography was carried out on silica gel (100-200 mesh) and Flash chromatography was carried out on silica gel (230-400 mesh).

X-ray Crystallography

The crystallographic data of compound **3e**, **11a**, and **11c (Table 2.2-2.4)** were collected at 293(3) K with Agilent Xcalibur, Eos, Gemini diffractometer using graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å) source. The data was collected and reduced in CrysAlis PRO (Agilent, 2013) software and cell refinement was done in CrysAlis PRO software.[22] The absorption was corrected by multi-scan methods. Using Olex2,[23] the structure was solved with the ShelXS[24] structure solution program using direct Methods and refined with the ShelXL[25] refinement package using Least Squares. All non-hydrogen atoms were refined anisotropically.

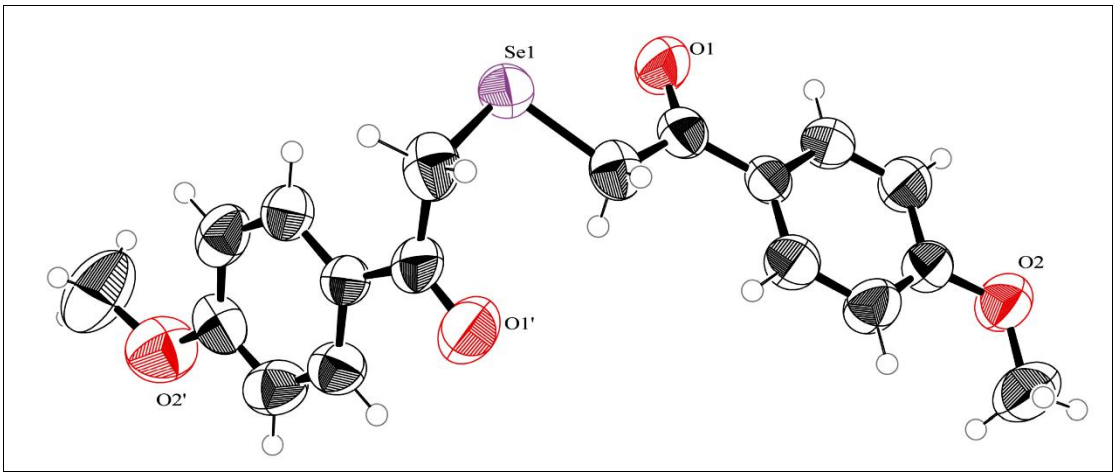


Figure 2.1 ORTEP Image of **3e** showing thermal ellipsoids at 50% probability level.

Table 2.2 X-ray crystallography data for compound **3e** (**CCDC1957504**)

Empirical formula	$C_{18}H_{18}O_4Se$	
Formula weight	377.28	
Temperature	291.63(10)K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 16.4491(12) Å	α= 90°.
	b = 11.6935(9) Å	β = 97.934(7)°.
	c = 8.7784(7) Å	γ = 90°.
Volume	1672.3(2)Å^3	
Z	4	
Density (ρ_{calc})	1.498 g/cm^3	
Absorption coefficient (μ)	2.262 mm^{-1}	
F (000)	768	
2Θ range for data collection	6.096 to 57.388°.	
Index ranges	$-21 \leq h \leq 21, -9 \leq k \leq 15, -8 \leq l \leq 11$	
Reflections collected	8281	
Independent reflections	3830 [R_{int} = 0.0352]	
Data / restraints / parameters	3830/ 2 / 217	
Goodness-of-fit on F^2	1.016	
Final R indices [I≥2σ(I)]	R_1 = 0.0514, wR_2 = 0.0994	
R indices (all data)	R_1 = 0.1110, wR_2 = 0.1218	

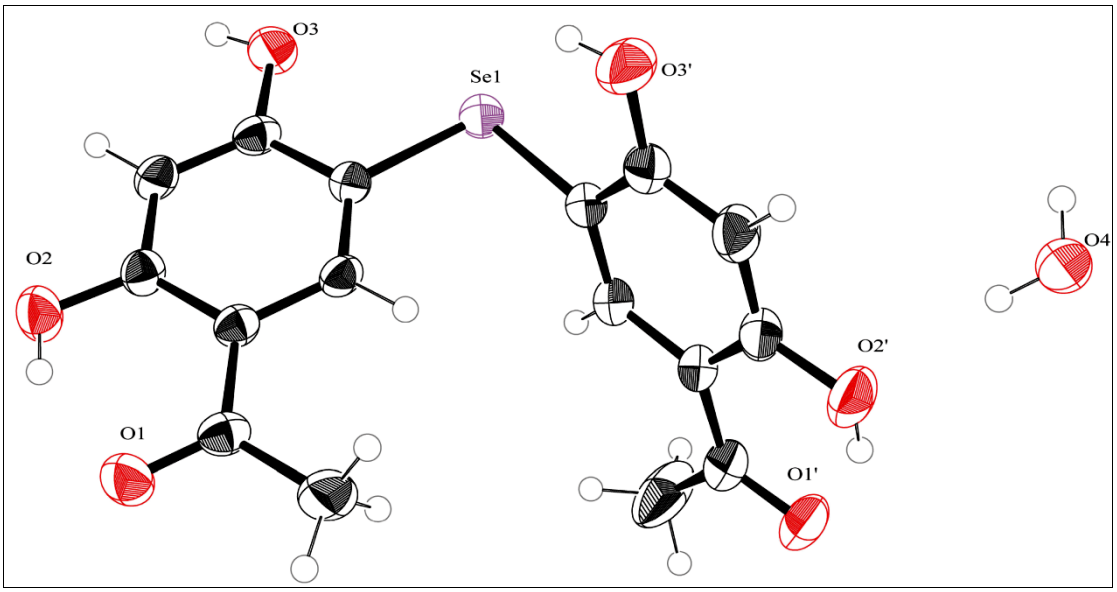


Figure 2.2 ORTEP Image of **11a** showing thermal ellipsoids at 50% probability level.

Table 2.3 X-ray crystallography data for compound **11a** (**CCDC1957503**)

Empirical formula	$C_{16}H_{14}O_6Se$, H_2O	
Formula weight	399.25	
Temperature	295.2(7) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 8.4119(9) Å	α= 76.416 (8)°.
	b = 9.3391(8) Å	β = 94.076 (11)°.
	c = 11.6187(12)Å	α = 69.771(8)°.
Volume	806.36(15)$Å^3$	
Z	2	
Density (calculated)	1.644 g/cm^3	
Absorption coefficient (μ)	2.364 mm^{-1}	
F (000)	404	
2Θ range for data collection	6.402 to 57.244°.	
Index ranges	$-11 \leq h \leq 11$, $-12 \leq k \leq 12$, $-15 \leq l \leq 9$	
Reflections collected	5857	
Independent reflections	3610 [R_{int} = 0.0250]	
Data / restraints / parameters	3610 / 0 / 226	
Goodness-of-fit on F^2	1.051	
Final R indices [I≥2σ(I)]	R_1 = 0.0360, wR_2 = 0.0759	
R indices (all data)	R_1 = 0.0469, wR_2 = 0.0811	

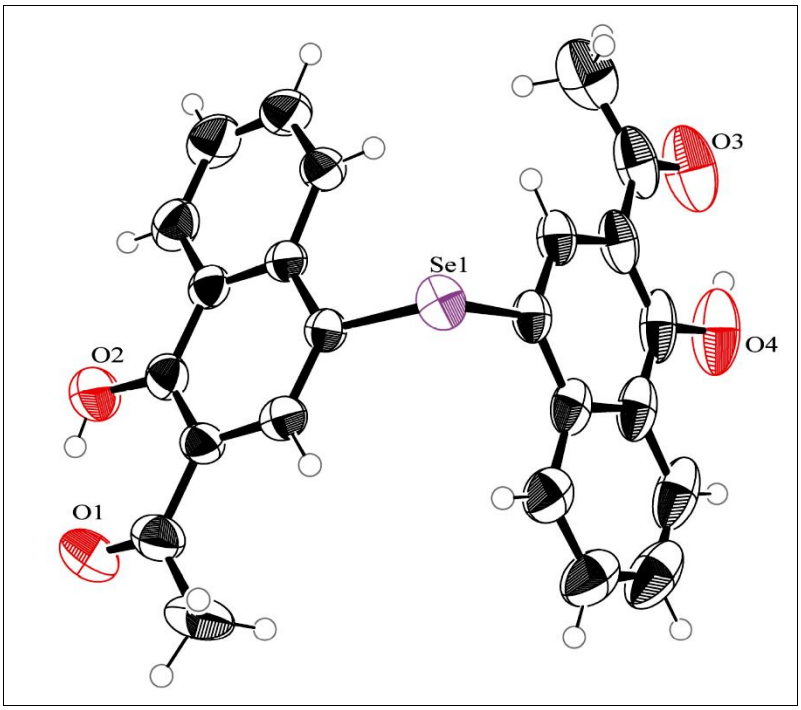


Figure 2.3 ORTEP Image of **11c** showing thermal ellipsoids at 50% probability level.

Table 2.4 X-ray crystallography data for compound **11c** (**CCDC1957502**)

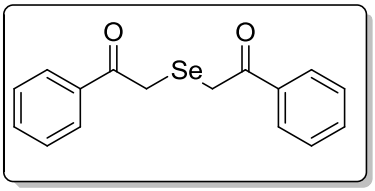
Empirical formula	$C_{24}H_{18}O_4Se$	
Formula weight	449.34	
Temperature	293.0 (2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	a = 9.7473(4) Å	α= 90°.
	b = 15.1937(6) Å	β = 99.666 (4)°.
	c = 13.3176(6)Å	α = 90°.
Volume	1944.30 (14) $Å^3$	
Z	4	
Density (ρ_{calc})	1.535 g/cm^3	
Absorption coefficient (μ)	1.960 mm^{-1}	
F (000)	912	
2Θ range for data collection	6.196 to 57.506°.	
Index ranges	$-13 \leq h \leq 13, -19 \leq k \leq 14, -17 \leq l \leq 12$	
Reflections collected	9960	
Independent reflections	4442 [R_{int} = 0.0270]	
Data / restraints / parameters	4442 / 0 / 266	
Goodness-of-fit on F^2	1.034	
Final R indices [I≥2σ(I)]	R_1 = 0.0372, wR_2 = 0.0749	
R indices (all data)	R_1 = 0.0630, wR_2 = 0.0864	

***General experimental procedure for synthesis of dicarbonyl selenides*:**

A mixture of aryl methyl ketones **(1)** (1.0 mmol, 1equiv) and selenium dioxide **(10)** (55 mg, 0.5 mmol, 0.5 equiv) in acetonitrile (1 ml) as a solvent was stirred for 5 minutes then followed by the addition of PTSA (95 mg, 0.5 mmol, 0.5 equiv) and the reaction mixture was allowed to stir for 8-12 hrs at room temperature. After completion, the reaction mixture was diluted with ethyl acetate and was filtered through a celite. The combined filtrate was washed with a saturated aqueous sodium bicarbonate solution followed by brine. The separated organic layer was dried over anhydrous sodium sulfate and concentrated. The compound was purified by flash chromatography on a silica gel (320-400 mesh) using ethyl acetate/hexane as eluent.

Spectroscopic analytical data

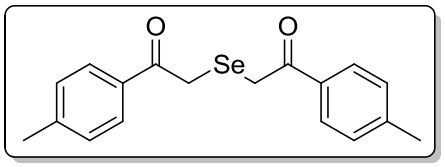
2, 2'-selenobis(1-phenylethanone) (3a):



Yellow solid; yield: 69%; MP: 56-58 ^{o}C

IR (KBr film): 3059, 3012, 2959, 2904, 1658, 1594, 1387, 1277, 1182, 1162, 706, 683 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91-7.49 (m, 10H), 3.92 (s, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.0, 135.2, 133.3, 129.1, 128.8, 28.7 ppm; ^{77}Se NMR (57.25 MHz, CDCl3) δ 217.140. MS (ES^+) calcd for $C_{16}H_{14}O_2Se$ 318.0, found *m/z* 318.9 $[M + H]^+$, 341.0 $[M + Na]^+$.

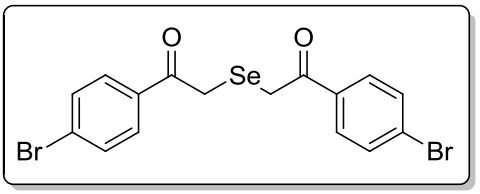
2,2'-selenobis(1-(p-tolyl)ethanone) (3b):



Yellow solid; yield: 71%; MP: 98-100 ^{o}C

IR (KBr film) 3096, 3062, 2916, 1658, 1603, 1418, 1279, 1007 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8 Hz, 4H), 7. 19 (d, J = 8 Hz, 4H), 3.89 (s, 4H), 2.34 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.8, 144.4, 132.7, 129.1, 28.9, 21.7 ppm; ^{77}Se NMR (57.25 MHz, $CDCl_3$) δ 219.914. MS (ES^+) calcd for $C_{18}H_{18}O_2Se$ 346.04, found *m/z* 347.0$[M + H]^+$.

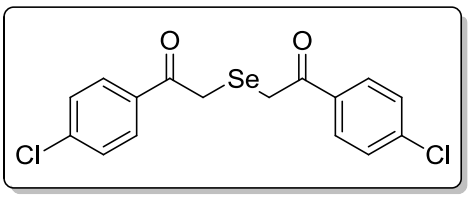
2,2'-selenobis(1-(p-bromophenyl)ethanone) (3c):



Yellow solid; yield: 77%; Mp: 91-93 ^{o}C

IR (KBr): 3043, 3013, 2933, 1664 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 8.4 Hz, 4H), 7.54 (d, J = 8.4 Hz, 4H), 3.86 (s, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.0, 135.4, 131.7, 129.1, 127.3, 28.6 ppm; MS (ES^+) calcd for $C_{16}H_{12}Br_2O_2Se$ 475.9, found *m/z* 476.9 $[M + H]^+$, 498.9 $[M + Na]^+$.

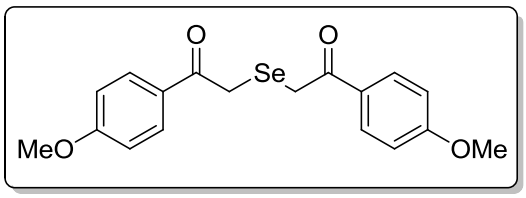
2,2'-selenobis(1-(4-chlorophenyl)ethanone) (3d):



Light yellow solid; yield: 80%, MP: 108-110 ^{o}C

IR (KBr film): 3436, 2934, 2898, 1663, 1590, 1396, 1281, 1094, 814 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 8.8 Hz, 4H), 7.44 (d, J = 8.8 Hz, 4H), 3.94 (s, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.7, 140.0, 133.4, 130.1, 129.0, 28.5 ppm; MS (ES^+) calcd for $C_{16}H_{12}Cl_2O_2Se$ 385.9 , found *m/z* 386.9 $[M + H]^+$.

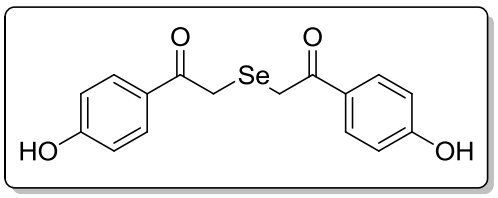
2,2'-selenobis(1-(4-methoxyphenyl)ethan-1-one) (3e):



Yellow solid; yield: 72%; Mp: 85-87 ^{o}C

IR (KBr film): 3056, 2949, 2841, 1659, 1599, 1508, 1421, 1311, 1282, 1256, 1167, 840 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 8.8 Hz, 4H), 6.86 (d, J = 8.8 Hz, 4H), 3.88 (s, 4H), 3.80 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.9, 163.7, 131.1, 130.5, 113.8, 55.5, 28.5 ppm; MS (ES^+) calcd for $C_{18}H_{18}O_4Se$ 378.03, found *m/z* 379.0 $[M + H]^+$.

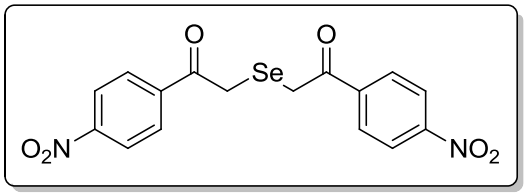
2,2'-selenobis(1-(4-hydroxyphenyl)ethanone) (3f):



Yellow solid; yield: 68%; Mp: 89-91 ^{o}C

IR (KBr film): 3365, 3149, 3064, 2970, 2816, 1667, 1647, 1574, 1437, 1378, 1240, 828 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.84 (s, 1H), 7.77 (d, J = 8.4 Hz, 4H), 6.80 (d, J = 8.4 Hz, 4H), 3.86 (s, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.6, 167.3, 135.9, 131.5, 120.3, 33.2 ppm; MS (ES^+) calcd for $C_{16}H_{14}O_4Se$ 350.0, found *m/z* 351.0 $[M + H]^+$, 373.0 $[M + Na]^+$.

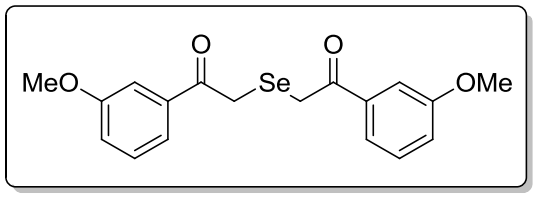
2,2'-selenobis(1-(4-nitrophenyl)ethanone) (3g):



Light yellow solid; yield: 70%, MP: 119-121 ^{o}C

IR (KBr film): 3116, 2928, 2857, 1707, 1605, 1523, 1351, 1092, 855 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.26 (d, J = 8.4 Hz, 4H), 8.05 (d, J = 8.4 Hz, 4H), 3.94 (s, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.8, 150.5, 139.6, 129.7, 124.0, 28.7 ppm; MS (ES^+) calcd for $C_{18}H_{18}O_4Se$ 407.99, found m/z 431.0 $[M + Na]^+$.

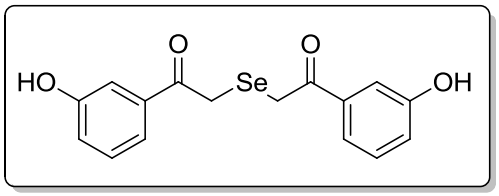
2,2'-selenobis(1-(3-methoxyphenyl)ethanone) (3h):



Oil; yield: 69%

IR (KBr film): 3003, 2938, 2836, 1669, 1596, 1431, 1277, 1021 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (t, 2H), 7.31 (d, J = 8.4 Hz, 2H), 7.28 (s, 2H), 7.05 (d, J = 7.6 Hz, 2H), 3.90 (s, 4H), 3.78 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.9, 159.9, 136.6, 129.7, 121.3, 120.1, 112.8, 55.4, 28.6 ppm; MS (ES^+) calcd for $C_{18}H_{18}O_4Se$ 378.04 , found m/z 378.9 $[M + H]^+$, 400.9 $[M + Na]^+$.

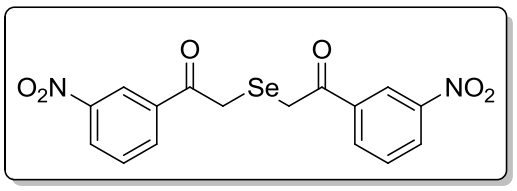
2,2'-selenobis(1-(3-hydroxyphenyl)ethan-1-one) (3i):



Oil; yield: 65%

IR (KBr film): 3439, 2926, 1656, 1583, 1450, 1291 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (s, 2H), 7.32 (d, J = 8 Hz, 2H), 7.20 (t, J = 7.6Hz, 2H), 6.98 (d, J = 8.4 Hz, 2H), 3.88 (s, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.7, 162.4, 141.3, 134.4, 125.6, 124.4, 119.9, 33.6 ppm; MS (ES^+) calcd for $C_{16}H_{14}O_4Se$ 350.01, found *m/z* 351.0 $[M + H]^+$.

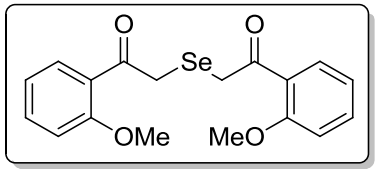
2,2'-selenobis(1-(3-nitrophenyl)ethanone) (3j):



Oil; yield: 67%

IR (KBr film): 3087, 2926, 2870, 1677, 1530, 1350, 1262, 1083, 717 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 2H), 8.38 (d, J = 8.4 Hz, 2H), 8.23 (d, J =7.6 Hz, 2H), 7.65 (t, J = 7.6 Hz, 2H), 3.97 (s, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.3, 148.4, 135.2, 134.2, 130.1, 127.8, 123.5, 28.5 ppm; MS (ES^+) calcd for $C_{16}H_{12}N_2O_6Se$ 407.9, found *m/z* 409.0 $[M + H]^+$.

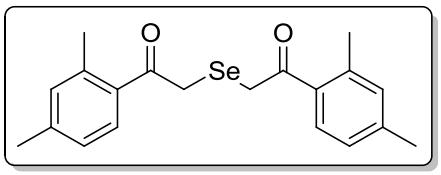
2,2'-selenobis(1-(2-methoxyphenyl)ethanone) (3k):



Yellow solid; yield: 66%; MP: 104-106 ^{o}C

IR (KBr film): 3433,3067, 2939, 2837, 1650, 1647, 1595, 1482, 1450, 1297, 1248, 1137, 1011, 759 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 7.2 Hz, 2H), 7.40 (t, J = 7.2 Hz, 2H), 6.94 (t, J = 7.2 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 3.86 (s, 4H), 3.83 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.7, 157.6, 133.0, 130.4, 119.7, 110.5, 54.5, 32.6 ppm; MS (ES^{+}) calcd for $C_{18}H_{18}O_4Se$ 378.04, found *m/z* 378.9 $[M + H]^{+}$, 400.9 $[M + Na]^{+}$.

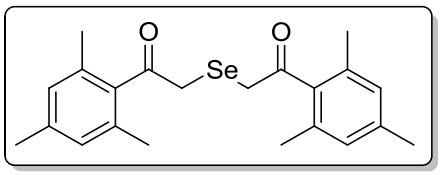
2,2'-selenobis(1-(2,4-dimethylphenyl)ethan-1-one) (3l):



Oil; yield: 65%

IR (KBr film): 3012, 2961, 2921, 2866, 1667, 1610, 1564, 1496, 1447, 1380, 1289, 1262, 1235, 1000, 824, 765 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, J = 7.8 Hz, 2H), 7.069 (s, 2H), 7.05 (d, J = 7.8 Hz, 2H), 3.89 (s, 4H), 2.49 (s, 6H), 2.33 (s, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.9, 142.6, 139.8, 133.4, 133.1, 129.6, 126.4, 31.5, 21.7, 21.6 ppm; MS (ES^{+}) calcd for $C_{20}H_{22}O_2Se$ 374.08, found *m/z* 375.2 $[M + H]^{+}$.

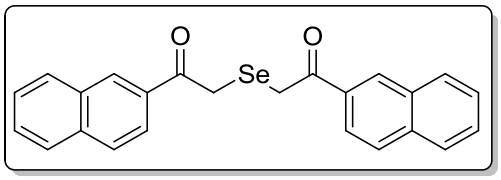
2,2'-selenobis(1-mesitylethanone) (3m):



Oil; yield: 67%

IR (KBr film): 2953, 2910, 2849, 1668, 1549, 1432, 1324, 1267, 1059, 717 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.66 (s, 4H), 3.88 (s, 4H), 2.16 (s, 12H), 2.12 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.4, 138.7, 136.4, 133.8, 128.2, 28.1, 24.3, 21.5, 20.4 ppm; MS (ES^+) calcd for $C_{22}H_{26}O_2Se$ 402.1, found *m/z* 403.0 $[M + H]^+$.

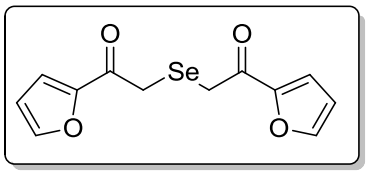
2,2'-selenobis(1-(naphthalen-2-yl)ethanone) (3n):



Oil; yield: 55%

IR (KBr film): 3060, 2938, 2917, 2852, 1669, 1524, 1405, 1342, 1265, 1038 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 2H), 7.76-7.24 (m, 12H), 3.89 (s, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.0, 136.2, 132.6, 130.8, 129.7, 129.1, 128.8, 127.8, 127.1, 124.5, 28.2 ppm; MS (ES^+) calcd for $C_{24}H_{18}O_2Se$ 418.0, found *m/z* 441.0 $[M + Na]^+$.

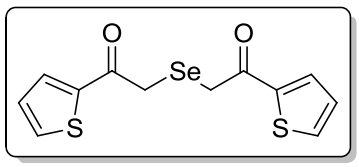
2,2'-selenobis(1-(furan-2-yl)ethanone) (3o):



Oil; yield: 62%

IR (KBr film): 3132, 2926, 2853, 1657, 1567, 1464, 1388, 1298, 1038, 766 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53-6.50 (m, 6H), 3.75 (s, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.1, 150.8, 147.0, 118.5, 112.6, 27.6 ppm; MS (ES^+) calcd for $C_{12}H_{10}O_4Se$ 297.97, found *m/z* 320.8 $[M + Na]^+$.

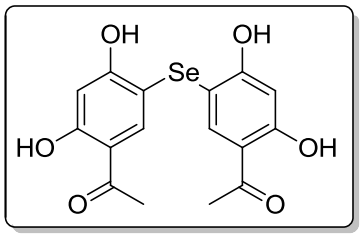
*ele**2,2'-selenobis(1-(thiophen-2-yl)ethanone) (3p):***



Oil; yield: 65%

IR (KBr film): 3099, 2924, 2853, 1647, 1517, 1413, 1354, 1284, 1237, 1060, 858, 727 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 3.2 Hz, 2H), 7.61 (d, J = 4.8 Hz, 2H), 7.08 (t, J = 4.4 Hz, 2H), 3.85 (s, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.5, 142.5, 134.7, 133.2, 128.4, 28.7 ppm; MS (ES^+) calcd for $C_{12}H_{10}O_2S_2Se$ 329.92, found *m/z* 352.8 $[M + Na]^+$.

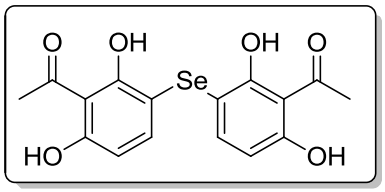
1,1'-(selenobis(2,4-dihydroxy-5,1-phenylene))diethanone (11a) :



Yellow solid; yield: 75%; Mp: 112-114 ^{o}C

IR (KBr film): 3530, 3385, 3069, 2922, 1606, 1481, 1423, 1370, 1271, 1147 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.46 (s, 2H), 10.52 (s, 2H), 7.63 (s, 2H), 6.37 (s, 2H), 2.35 (s, 6H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 202.7, 169.5, 168.6, 142.4, 119.1, 112.4, 107.6, 30.9 ppm; MS (ES^{+}) calcd for $C_{16}H_{14}O_6Se$ 381.9, found *m/z* 382.9 $[M + H]^{+}$.

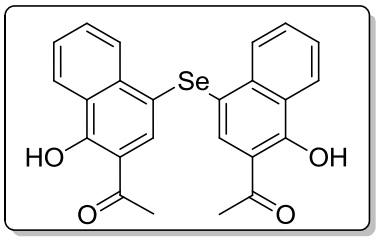
1,1'-(selenobis(2,6-dihydroxy-3,1-phenylene))diethanone (11b) :



Yellow solid; yield: 78%, Mp:108-110 ^{o}C

IR (KBr film): 3316, 3008, 2928, 2853, 1621,1586, 1420, 1368, 1217, 1043cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.74 (s, 2H), 11.00 (s, 2H), 7.21 (d, J = 8.4 Hz, 2H), 6.33 (d, J = 8.4 Hz, 2H), 2.65 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$: DMSO-d_6) δ 205.1, 162.6, 160.9, 141.5, 109.6, 108.4, 106.1, 32.9 ppm; MS (ES^{+}) calcd for $C_{16}H_{14}O_6Se$ 381.9, found *m/z* 382.9 $[M + H]^{+}$.

1,1'-(selenobis(1-hydroxynaphthalene-4,2-diyl))diethanone (11c):



Yellow solid; yield: 69%; Mp: 96-98 ^{o}C

IR (KBr film): 3319, 3056, 2926, 2855, 1620, 1574, 1499, 1375, 1234 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ13.970 (s, 2H), 8.42 (d, J = 8 Hz, 2H), 8.24 (d, J = 8.4 Hz, 2H), 7.82 (s, 2H), 7.71 (t, J = 7.4 Hz, 2H), 7.58 (t, J = 7.4 Hz, 2H), 2.42 (s, 6H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 204.4, 161.4, 136.6, 132.2, 131.2, 126.8, 126.6, 125.1, 124.3, 117.4, 113.6, 26.7 ppm; MS (ES^{+}) calcd for $C_{24}H_{18}O_4Se$ 450.0, found m/z 451.1 $[M + H]^{+}$.

2.4 Representative Spectra

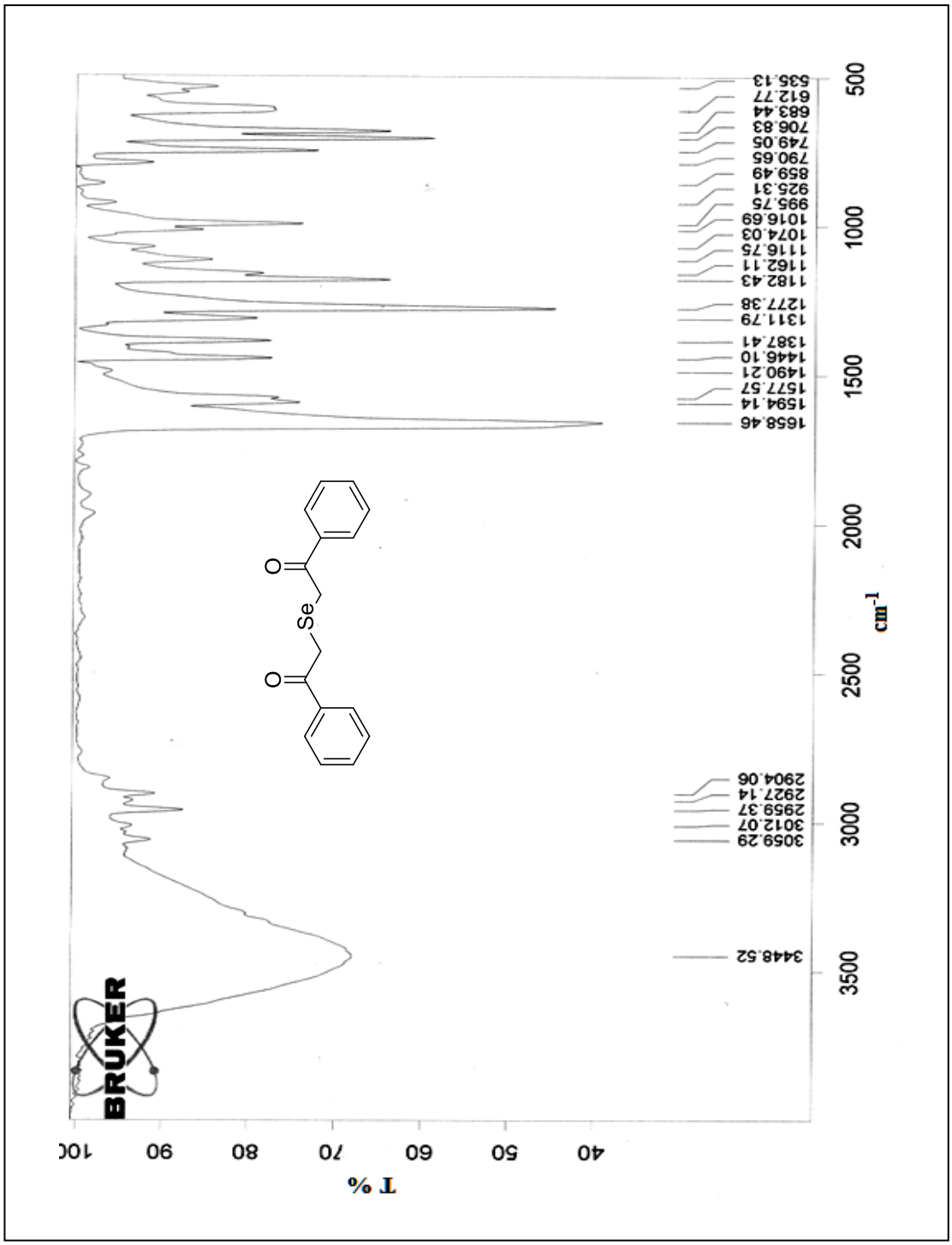


Figure 2.4 IR spectrum of 2,2'-selenobis(1-phenylethanone) **(3a)**

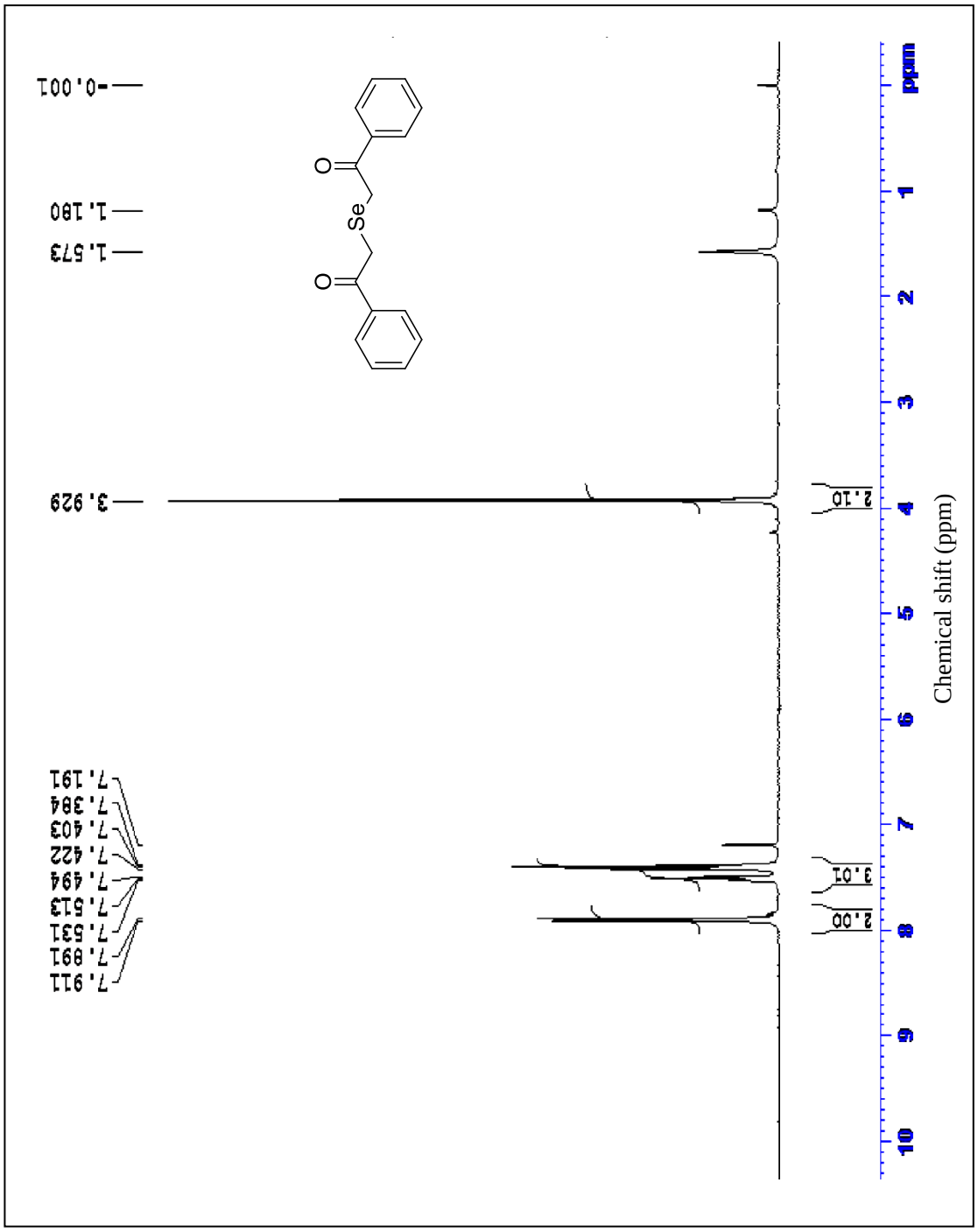


Figure 2.5 ^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of 2,2'-selenobis(1-phenylethanone) **(3a)**

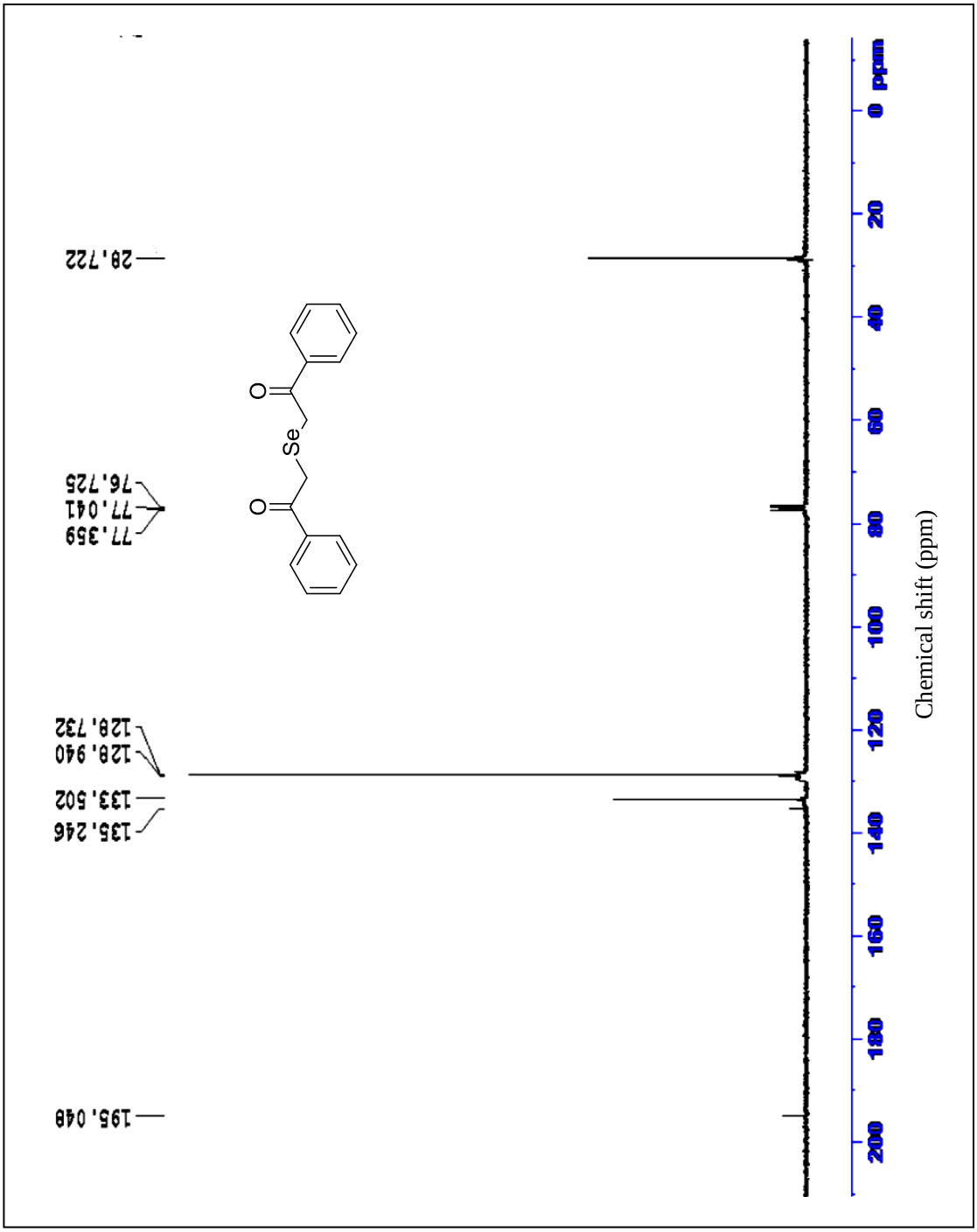


Figure 2.6 ^{13}C NMR ($CDCl_3$, 100 MHz) spectrum of 2,2'-selenobis(1-phenylethanone) **(3a)**

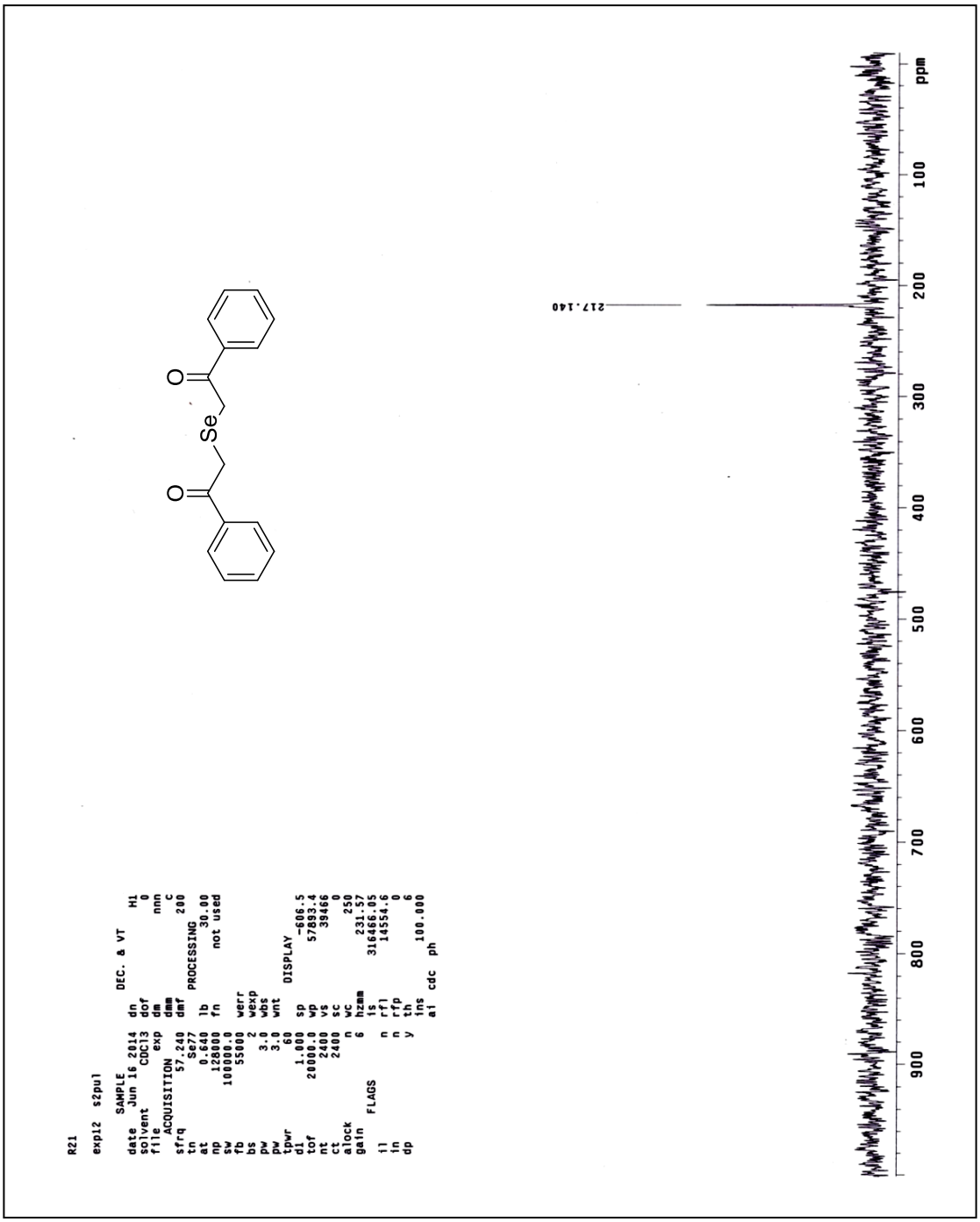


Figure 2.7 ^{77}Se NMR (CDCl3, 57.25 MHz) spectrum of 2,2'-selenobis(1-phenylethanone) **(3a)**

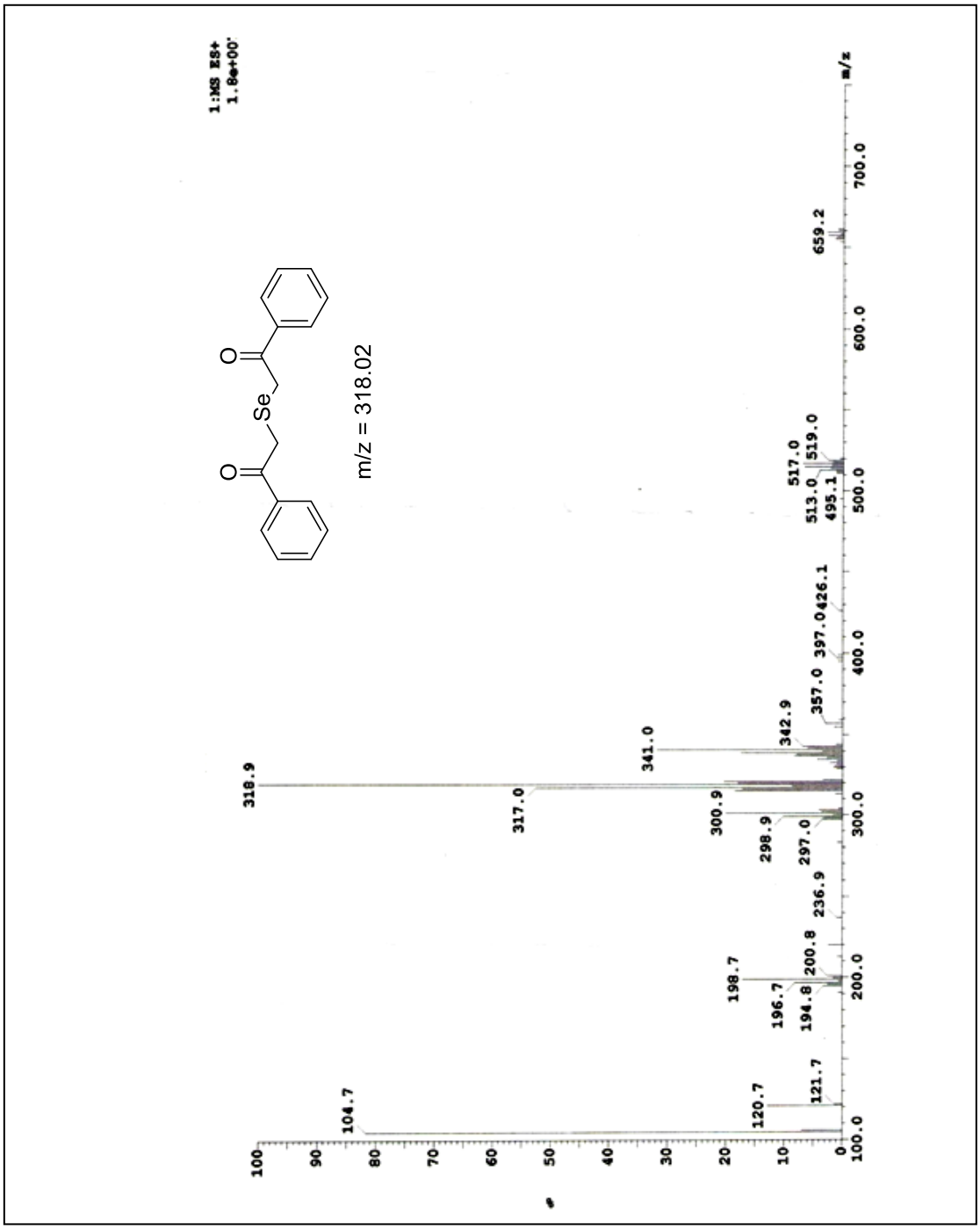


Figure 2.8 Mass spectrum of 2,2'-selenobis(1-phenylethanone) **(3a)**

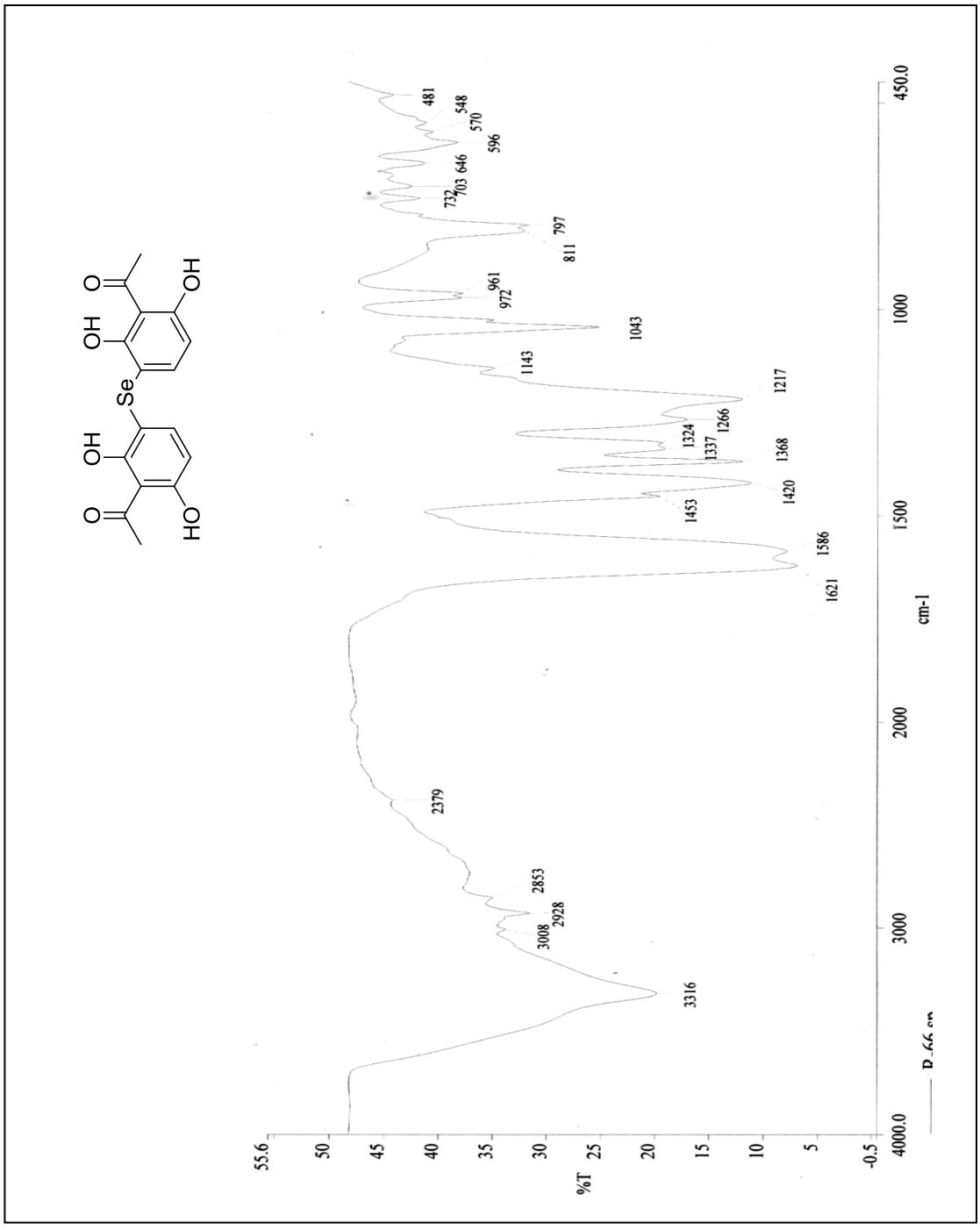


Figure 2.9 IR spectra for 1,1'-(selenobis(2,6-dihydroxy-3,1-phenylene))bis(ethan-1-one) **(11b)**

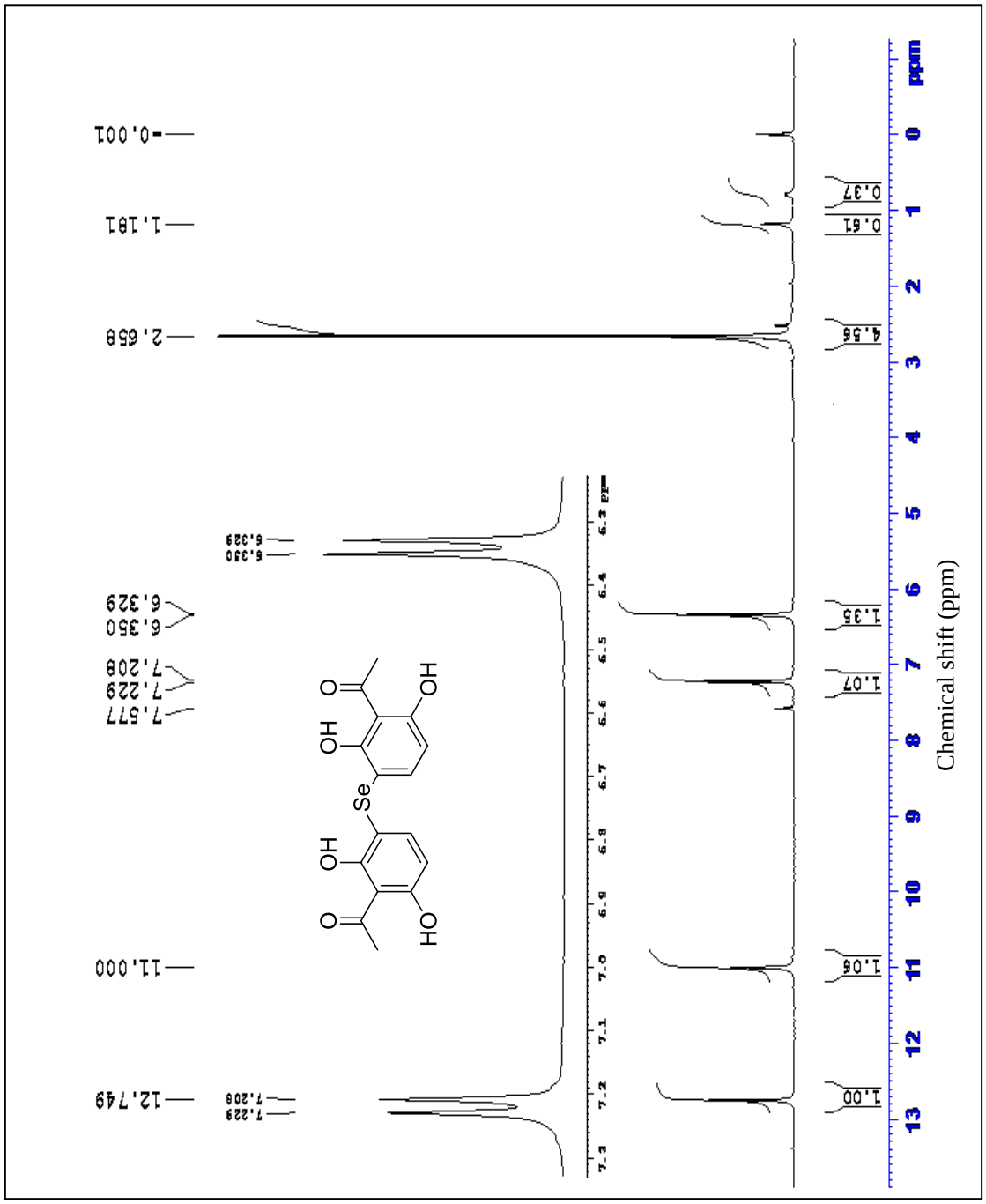


Figure 2.10 ^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of 1,1'-(selenobis(2,6-dihydroxy-3,1-phenylene))bis(ethan-1-one) **(11b)**

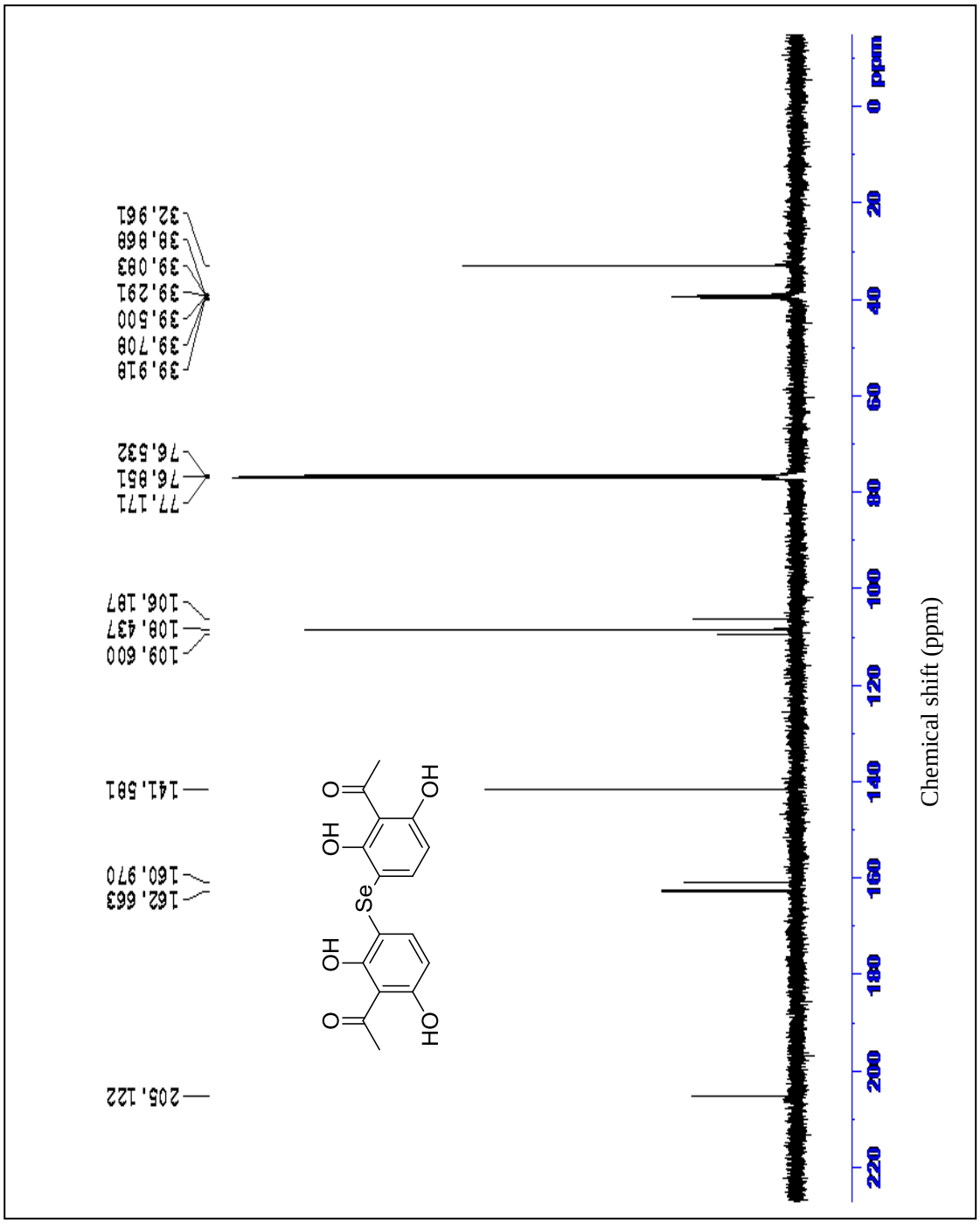


Figure 2.11 ^{13}C NMR ($CDCl_3$+DMSO d_6, 100 MHz) spectrum of 1,1'-(selenobis(2,6-dihydroxy-3,1-phenylene))bis(ethan-1-one)**(11b)**

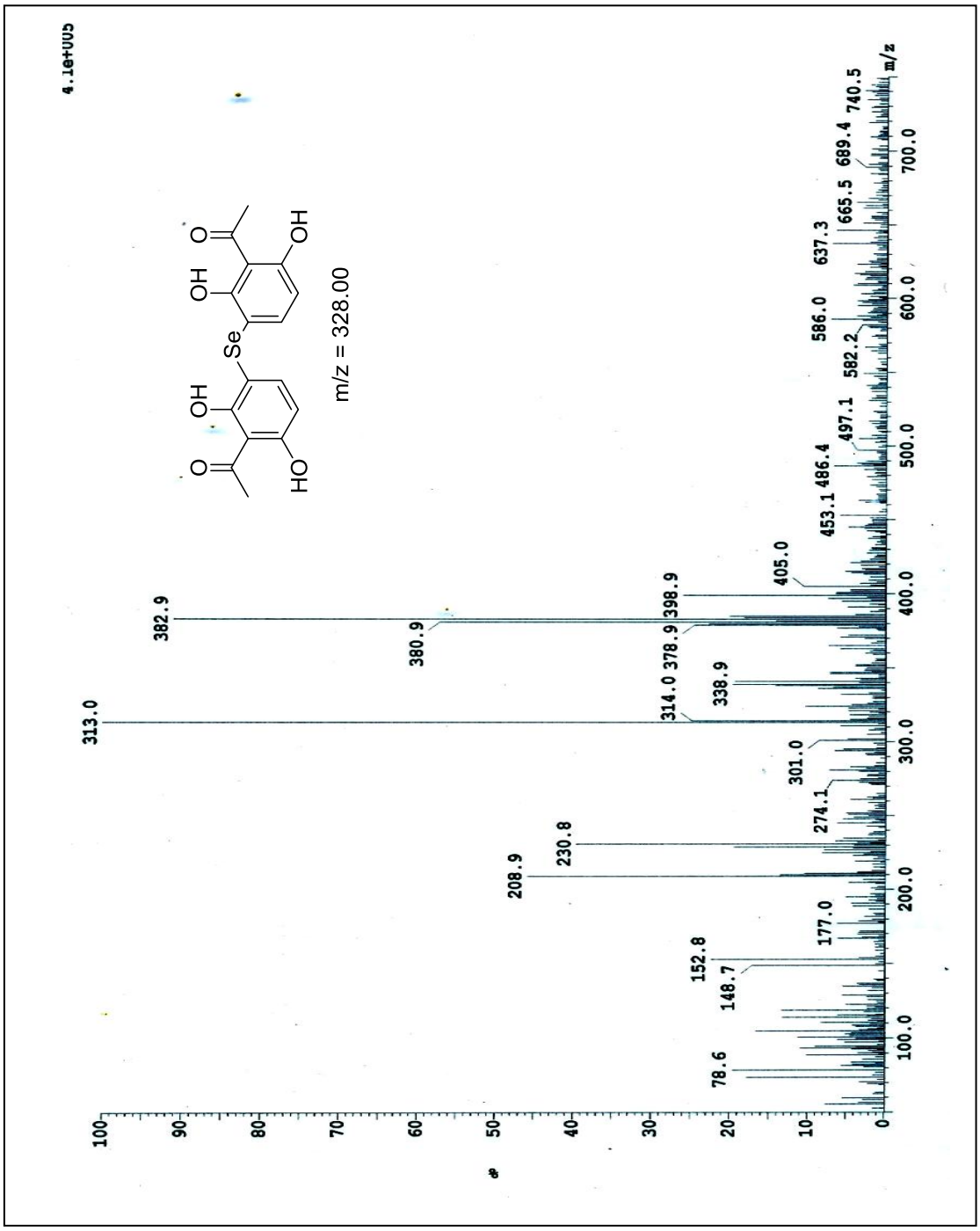


Figure 2.12 Mass spectrum of 1,1'-(selenobis(2,6-dihydroxy-3,1phenylene))bis(ethan-1-one) **(11b)**

2.5 References

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CHAPTER 3A

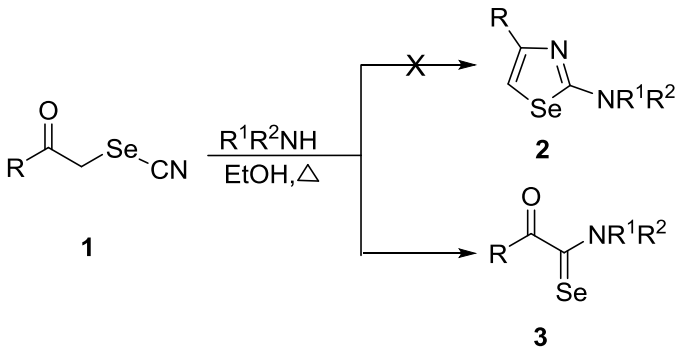
Selenium Dioxide as an Alternative Reagent for the Direct α-Selenoamidation of Aryl Methyl Ketones

[#]O. Risuklang Shangpliang *et al*. *J. Org. Chem*. **2018**, *83*, 5829.

3A.1 Introduction

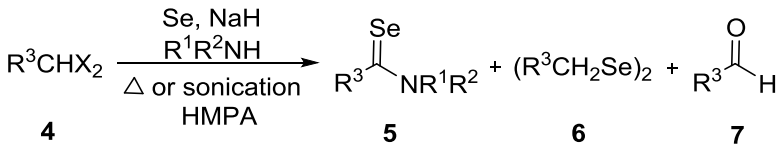
During the past decade, organoselenium compounds have attracted much attention in the field of synthetic chemistry because of their interesting biological activities[1, 2] and also as important reaction intermediates.[3] Selenoamides[4] constitute a class of organoselenium compounds which have been considered to be important precursors for the synthesis of various selenium-containing heterocycles[5] and as pharmaceutical agents.[6] The *α*-oxo-selenoamides having C=Se bond formation attached directly to the *α*-carbon of the C=O group are not very common and as per our literature survey, only few methods are available for their synthesis.[7-9]

Hartmann and Zhou reported a transformation reaction of *ω*-selenocyanato acetophenones with secondary aliphatic amines to corresponding aryl selenoamides instead of the expected 2-amino-4-aryl-selenazoles. The unexpected formation of *N*,*N*-disubstituted aryl selenoamides **(3)** can be explained that the secondary amine which is used as a reagent reacts with *ω*-selenocyanato acetophenones **(1)**, not at the CN triple bond of the selenocyanato group, but at their methylene groups **(Scheme 3A.1)**.[7]



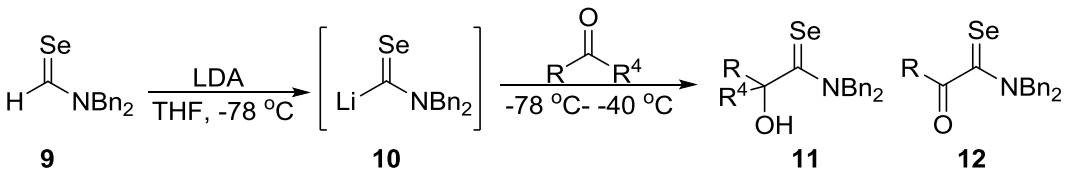
Scheme 3A.1

Takikawa and co-workers reported the synthesis of selenoamides **(5)** by the treatment of dihalomethane derivatives **(4)** with elemental selenium in the presence of a strong base NaH with an excess amount of an amine in HMPA as a solvent **(Scheme 3A.2)**.[8]



Scheme 3A.2

Recently, Murai *et al.* reported a protocol for the synthesis of *α*-oxo-selenoamides **(12)** from the reaction of selenocarbamoyllithiums **(10)** with carbonyl compounds and under an inert atmosphere in two steps procedure **(Scheme 3A.3)**.[9]

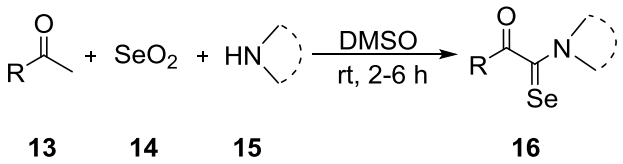


Scheme 3A.3

In all of the above methods, the selenylating agents are themselves multi-step synthetic intermediates. Although these methods are quite effective, the use of strong base, harsh reaction conditions and multiple-step procedure severely limit their scope of application. Hence, a new methodology for an efficient synthesis of selenoamides starting from easily available starting materials and under mild reaction conditions is highly desirable.

3A.2 Results and Discussion

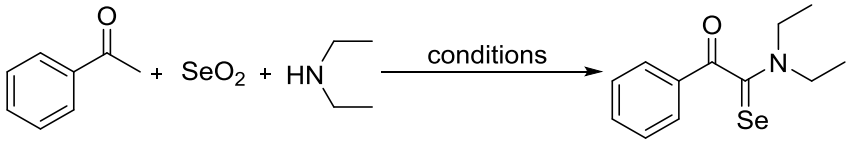
As a part of our effort towards the synthetic application of selenium dioxide, in this chapter we report the synthesis of α-selenoamidation starting from aryl methyl ketones with secondary amines at room temperature without using any catalyst, acid or base **(Scheme 3A.4)**.



Scheme 3A.4 Synthesis of selenoamides.

Initially, when acetophenone **(13a)**, (0.116 mL, 1.0 mmol, 1 equiv**)** was treated with selenium dioxide **(14)**, (110 mg, 1.0 mmol, 1 equiv**)** and diethylamine **(15a)**, (0.107 mL, 1.0 mmol, 1 equiv) at room temperature for 8 h the reaction product **16a** was formed in 30% yield **(Table 3A.1, entry 1)**. Our efforts to optimize the reaction by varying the stoichiometry of the amine showed no improvement in the product yield **(Table 3A.1, entries 2-3)**. The optimized condition was achieved when the reaction was carried out using dimethyl sulfoxide as the solvent which resulted in the formation of **16a** in 65% yield in 2 h **(Table 3A.1, entry 4)**. Further attempts to improve the efficiency of the reaction by varying the amount of amine and using different solvents, provided no significant result **(Table 3A.1, entries 5-11)**.

Table 3A.1 Optimization of the reaction conditions[a]



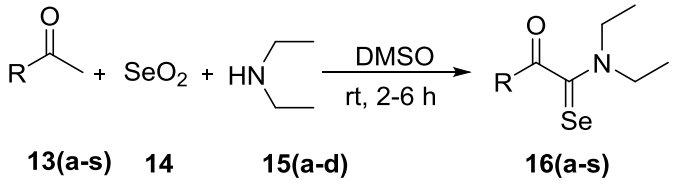
13a **14** **15a** **16a**

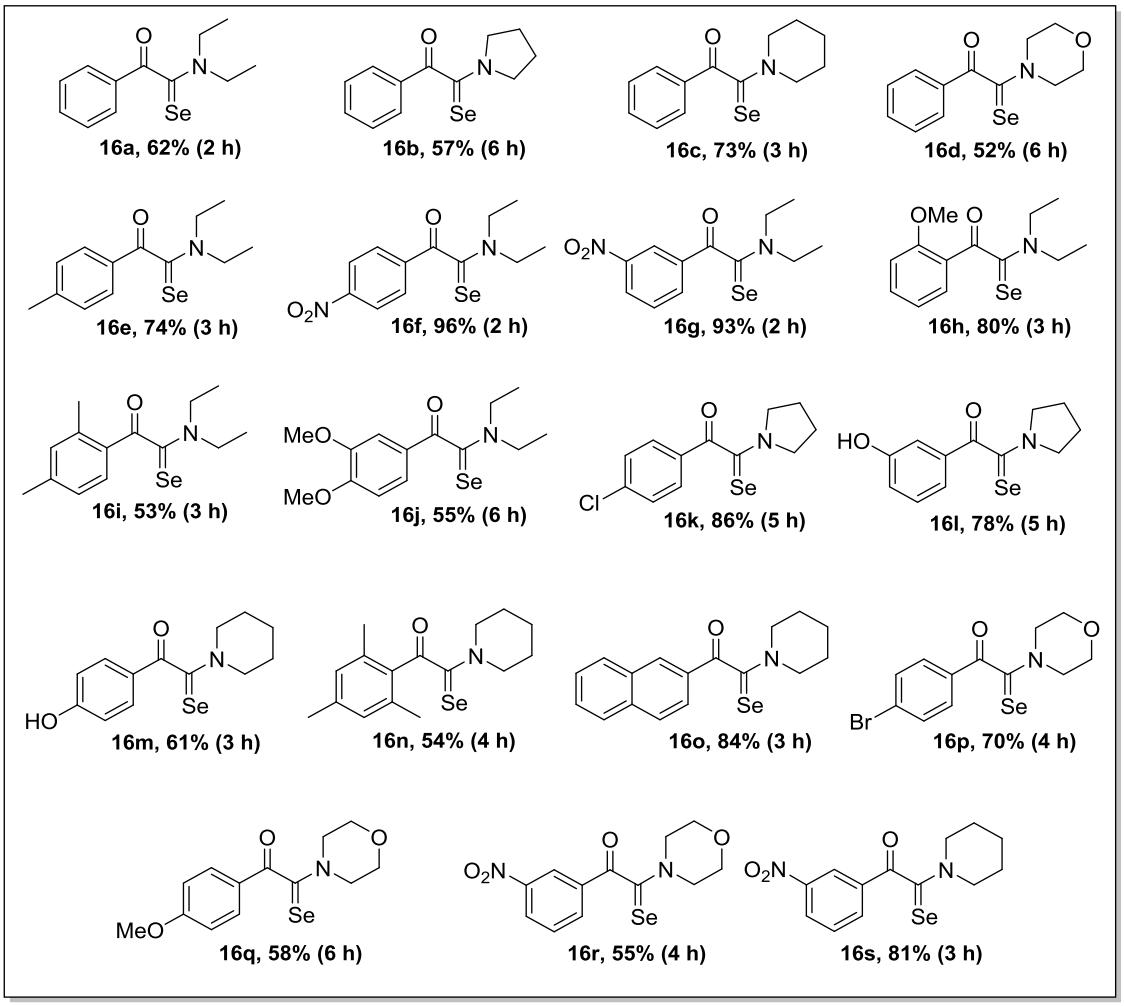
entry	Substrate 13a (equiv)	Solvent	t (h)	Yield(%)[b]
1	1	-	8	30
2	1.5	-	8	44
3	2	-	8	45
4	**1**	**DMSO**	**2**	**65**
5	1.25	DMSO	2.5	63
6	1.5	DMSO	2.5	65
7	1	H_2O	12	0
8	1	EtOH	12	0
9	1	DCM	12	20
10	1	CH_3CN	12	35
11	1	THF	12	0

[a]Reaction conditions: ketone **(13a)** (1.0 mmol), SeO_2 (1.0 mmol), solvent (0.5 mL), room temperature. [b]Isolated yields.

Under the optimized reaction conditions, the scope of the reaction of aryl methyl ketones and amines was investigated. Firstly, we carried out the reaction of aromatic ketones with different amines. Secondary amines such as diethylamine **(15a)**, pyrrolidine **(15b)**, piperidine **(15c)** and morpholine **(15d)** reacted favorably to give their corresponding products **(16a**, 62%; **16b**, 57%; **16c**, 73%; **16d**, **52**%**)** in moderate to good yields. It was observed that reactions with diethylamine **(15a)** and piperidine **(15c)** were more effective than with pyrrolidine **(15b)** and morpholine **(15d)**, which is probably due to the weaker nucleophilicity of the latter. Secondly, substituted aromatic ketones having electron-donating **13b** (*p*-Me), **13e** (*o*-OMe), **13i** (*m*-OH), **13j** (*p*-OH), **13n** (*p*-OMe) and electron-withdrawing groups **13c** (*p*-NO_2), **13d** (*m*-NO_2), **13h** (*p*-Cl), **13m** (*p*-Br) were allowed to react with the amines **(15a-15d)**. Despite the electronic effects of the substituents of the benzene ring of ketones, the reactions proceeded smoothly to give the desired products **(16e**,74%; **16f**, 96%; **16g**, 93%; **16h**, 80%; **16k**, 86%; **16l**, 78%; **16m**, 61%; **16p**, 70%; **16q**, 58%; **16r**, 55%; **16s**, 81%**)** in good yields. The scope of the reaction was also extended to *di*- and *tri*-substituted acetophenones which also gave the corresponding products **(16i**, 53%; **16j**, 55%; **16n**, 54%**)** in satisfactory yields **(Scheme 3A.5**).

Scheme 3A.5 Substrate scope of aryl methyl ketones[a]





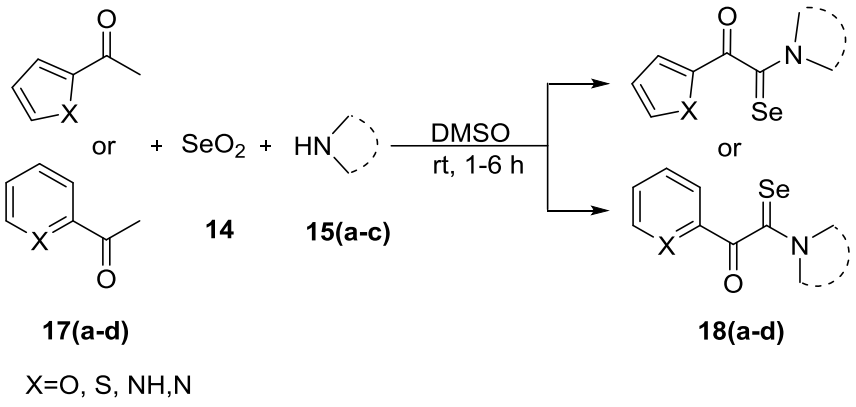
[a]Reaction conditions: ketones **(13)** (1.0 mmol) , SeO_2 (1.0 mmol), solvent (0.5 mL), room temperature.

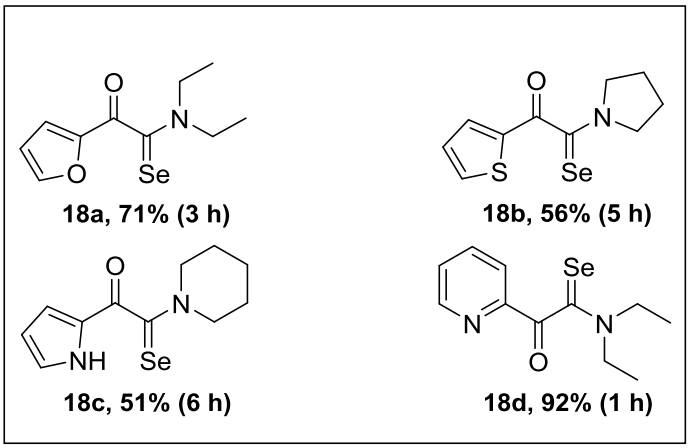
The procedure was also found to work well for ketones with extended aromatic ring such as 2-acetylnaphthalene **(13l)** to give the corresponding product **(16o**, 84%**)** in good yield **(Scheme 3A.5)**. The solid products formed well-defined

crystals and their XRD data **(16f, 16h, 16o, 16r)** further confirmed the structures of the synthesized compounds.

To further strengthen the generality of the method, the reaction was further extended to the heteroaryl ketones **(17)**. Thus, when 2-acetylfuran **(17a)**, 2-acetylthiophene **(17b)**, 2-acetylpyrrole **(17c)** and 2-acetylpyridine **(17d)** were allowed to react with diethylamine **(15a)**, pyrrolidine **(15b)**, piperidine **(15b)** and diethylamine **(15a)** respectively and their corresponding products **(18a**, 71%; **18b**, 56%; **18c**, 51%; **18d**, 92%**)** were obtained in good yields **(Scheme 3A.6)**.

Scheme 3A.6 Substrate scope of heteroaryl methyl ketones[a]

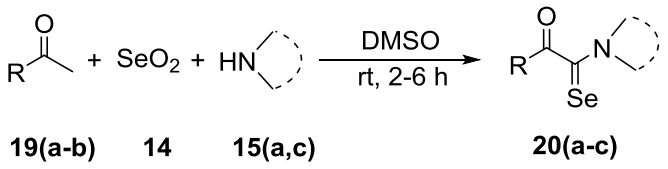




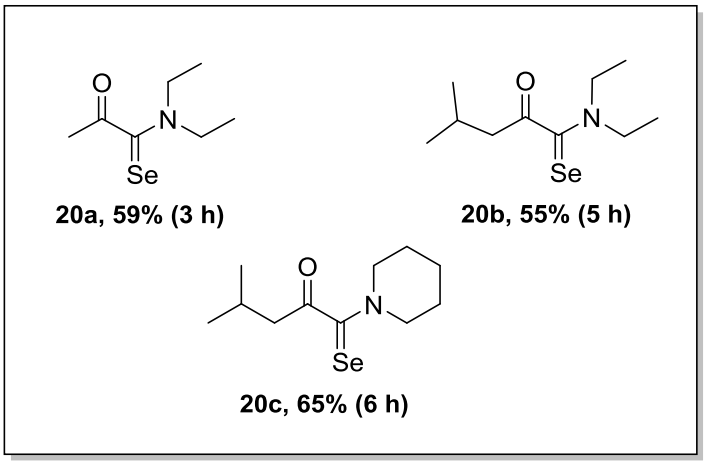
[a]Reaction conditions: ketones **(17)** (1.0 mmol), SeO_2 (1.0 mmol), solvent (0.5 mL), room temperature. [b]Isolated yields.

The scope of the reactions was further explored with aliphatic ketones **(19)**. To our surprise, when the reaction of aliphatic ketones such as acetone **(19a)** and isobutyl methyl ketone **(19b)** was allowed to react with diethylamine **(15a)** and piperidine **(15c)** the reaction proceeded well to give the corresponding products **20a-c** in a satisfactory yield (55-65%) **(Scheme 3A.7)**.

Scheme 3A.7 Substrate scope of alkyl methyl ketones[a]



19(a-b) **14** **15(a,c)** **20(a-c)**

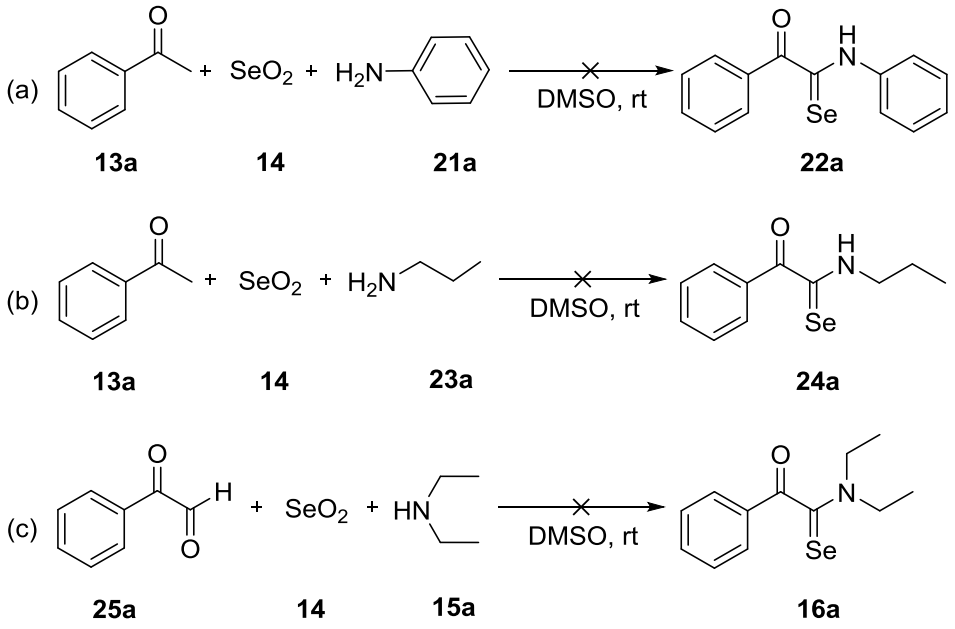


[a]Reaction conditions: ketones **(19)** (1.0 mmol), SeO_2 (1.0 mmol), solvent (0.5 mL), room temperature.

The reaction could proceed only with aliphatic secondary amines **(Scheme 3A.8)**. When acetophenone **(13a)** was allowed to react with aniline **(21a)** under the same reaction conditions, formation of the expected product was not observed **(Scheme 3A.8)**. This may probably be due to the resonance effect of the aromatic ring which renders the reaction unreactive. Similarly, when aliphatic primary amine, *n*-propyl amine **(23a)** was allowed to react with acetophenone **(13a)** at room

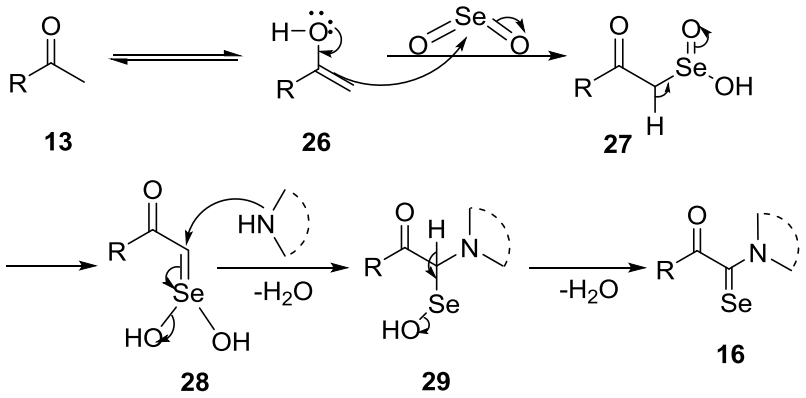
temperature, no reaction takes place. However, at elevated temperature, TLC of the reaction mixture after 1 h displayed formation of multiple products. Further to establish whether phenyl glyoxal **(25a)**, the well-known oxidation product of acetophenone **(13a)** with SeO_2, is involved in the reaction, we carried out the reaction using glyoxal **(25a)** with selenium dioxide under the same reaction conditions. The formation of the expected product was, however, not observed **(Scheme 3A.8)**.

Scheme 3A.8 Control experiment



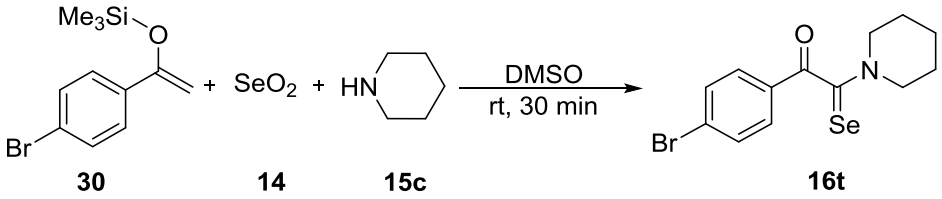
The probable mechanism of the reaction may be depicted as in **Scheme 3A.9**. The reaction of the enolized ketone **(13)** with selenium dioxide to generate the intermediate **28**,[10a] a potential umpolung of the aryl ketone[11] is believed to be the first step. Subsequent nucleophilic attack by the secondary amine on the α-carbon resulted in the intermediate **29**. The propensity of Se to get reduced to its lower oxidation state resulted in the deprotonation of the α-hydrogen and loss of another molecule of water leading to the formation of the product **16**.

Scheme 3A.9 Plausible mechanism



The reaction mechanism proposed above was further strengthened by the fact that the *O*-silyl vinyl ether **(30)** derived from *p*-bromoacetophenone when reacted with piperidine **(15c)** gave the expected 1-(4-bromophenyl)-2-(piperidin-1-yl)-2-selenoxoethanone **(16t)** in 94% yield **(Scheme 3A.10)**.

Scheme 3A.10 Synthesis of 1-(4-bromophenyl)-2-(piperidin-1-yl)-2-selenoxoethanone **(16t)**



In conclusion, we have demonstrated the application of SeO_2 as a unique selenium source for the synthesis of *α*-oxoselenoamides from aryl methyl ketones and amines. The method is simple and provides an efficient approach to selenoamide compounds without using any catalyst, acid or base. The reaction proceeds smoothly under mild reaction conditions at room temperature. Moreover, the direct use of the easily available starting materials adds to the overall synthetic significance of this procedure.

3A.3 Experimental Section

General Methods

All chemicals were purchased from Sigma Aldrich, Merck, Alfa Aesar, TCI Chemicals and were used without further purification unless noted. Melting points were recorded by open capillary tube method and are uncorrected.IR spectra were recorded on a Perkin Elmer Spectrum 400 FTIR instrument, and the frequencies are expressed in cm^{-1}. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance II-400 spectrometer in $CDCl_3$ and DMSO-d_6 (Chemical shifts are recorded in ppm with TMS as internal standard). ^{77}Se NMR spectra were recorded on Mercury Plus 300Hz NMR Spectrometer in ppm using Me_2Se as internal standard. Mass spectral data were obtained with a Waters UPLC-TQD mass spectrometer (ESI-MS). Elemental analyses (C, H, N) were carried out on Perkin Elmer 2400 Series II. All reactions were monitored by thin layer chromatography (TLC) using pre-coated aluminium sheets (silica gel 60 F_{254} 0.2-mm thickness). Flash chromatography was carried out on silica gel (230-400 mesh).

X-Ray Crystallography

The crystallographic data of compound was recorded using Agilent Xcalibur, Eos, Gemini diffractometer equipped with a graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å) source. The data was collected and reduced in CrysAlis PRO (Agilent, 2015) software and cell refinement was done in CrysAlis PRO software. The absorption was corrected by multi-scan methods. Using Olex2,[12] the structure was solved by Direct Methods using the ShelXS structure solution program and refined by Least Squares using of ShelXL-2015.[13,14] All non-hydrogen atoms were refined anisotropically.

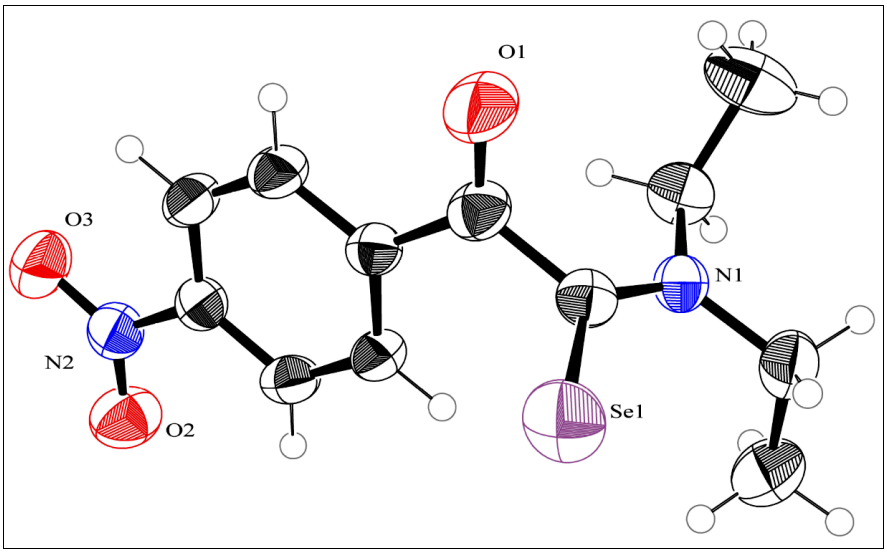


Figure 3A.1 ORTEP diagram of **16f** (**CCDC 1573439**) with 50% ellipsoid contour probability.

Table 3A.2 Crystal data and structure refinement for compound **16f**

Empirical formula	$C_{12}H_{14}N_2O_3Se$
Formula weight	313.22
Temperature	295.6(3) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell dimensions	
	a = 7.1388(7) Å α = 90°
	b = 18.695(2) Å β = 104.938(10) °
	c = 10.5157(13) Å γ = 90°
Volume	1356.0(3) $Å^3$
Z	4
Density (calculated)	1.5341 g/cm^3
Absorption coefficient	2.771 mm^{-1}
F(000)	632.0
Theta range for data collection	6.22 to 52.74°
Index ranges	$-9 \leq h \leq 8$, $-23 \leq k \leq 25$, $-5 \leq l \leq 13$
Reflections collected	5246
Independent reflections	2756 [R(int) = 0.0255, Rσ = 0.0547]
Data / restraints / parameters	2756/0/164
Goodness-of-fit on F^2	1.041
Final R indexes [I>=2σ (I)]	R_1 = 0.0445, wR_2 = 0.0853
Final R indexes [all data]	R_1 = 0.0790, wR_2 = 0.1000

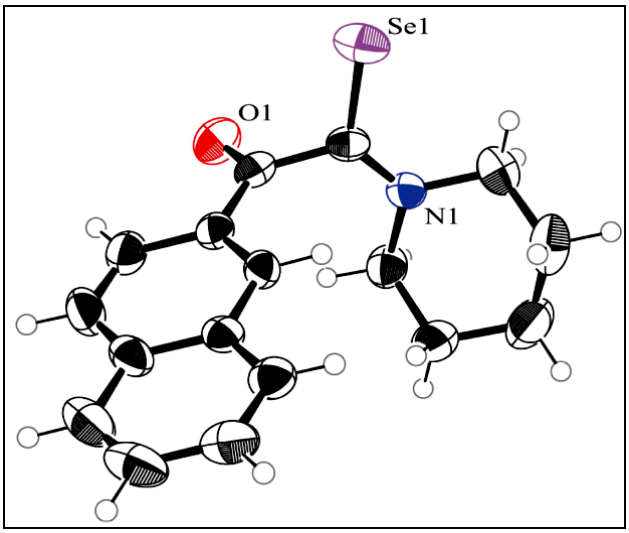


Figure 3A.2 ORTEP diagram of **16o** (**CCDC 1573436**) with 50% ellipsoid contour probability.

Table 3A.3 Crystal data and structure refinement for compound **16o**

Empirical formula	$C_{17}H_{17}NOSe$	
Formula weight	330.29	
Temperature	293.95(10) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions		
	a = 11.6786(8) Å	α = 90°
	b = 10.5551(6) Å	β = 108.536(8) °
	c = 12.611(1) Å	γ = 90°
Volume	1473.90(19) $Å^3$	
Z	1	
Density (calculated)	1.4884 g/cm^3	
Absorption coefficient	2.542 mm^{-1}	
F(000)	671.9	
Theta range for data collection	6.94 to 52.74°	
Index ranges	$-15 \leq h \leq 9$, $-7 \leq k \leq 14$, $-16 \leq l \leq 17$	
Reflections collected	5797	
Independent reflections	2992 [R(int) = 0.0216, Rσ =0.0435]	
Data / restraints / parameters	2992/0/180	
Goodness-of-fit on F^2	1.018	
Final R indexes [I>=2σ (I)]	R_1 = 0.0370, wR_2 = 0.0766	
Final R indexes [all data]	R_1 = 0.0575, wR_2 = 0.0870	

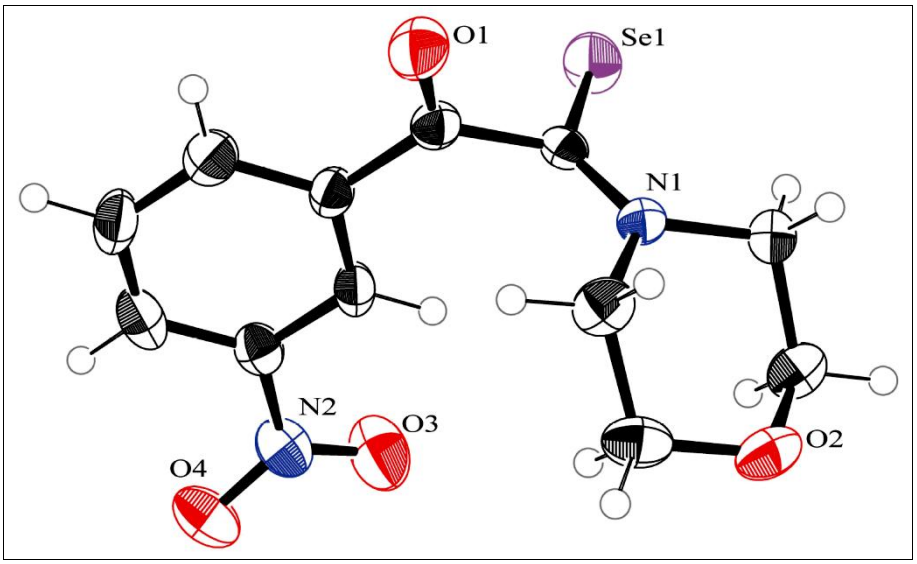


Fig 3A.3 ORTEP diagram of **16r** (**CCDC 1573438**) with 50% ellipsoid contour probability.

Table 3A.4 Crystal data and structure refinement for compound **16r**

Empirical formula	$C_{12}H_{12}N_2O_4Se$	
Formula weight	327.20	
Temperature	292.8(3) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions		
	a = 7.3382(5) Å	α = 90°
	b = 11.3020(6) Å	β = 102.411(7) °
	c = 16.1309(9) Å	γ = 90°
Volume	1306.58(14) $Å^3$	
Z	4	
Density (calculated)	1.6632 g/cm^3	
Absorption coefficient	2.885 mm^{-1}	
F(000)	656.0	
Theta range for data collection	6.74 to 52.74°	
Index ranges	$-6 \le h \le 9$, $-15 \le k \le 7$, $-20 \le l \le 13$	
Reflections collected	3606	
Independent reflections	2281 [R(int) = 0.0196, Rσ =0.0443]	
Data / restraints / parameters	2281/0/171	
Goodness-of-fit on F^2	1.057	
Final R indexes [I>=2σ (I)]	R_1 = 0.0332, wR_2 = 0.0675	
Final R indexes [all data]	R_1 = 0.0465, wR_2 = 0.0731	

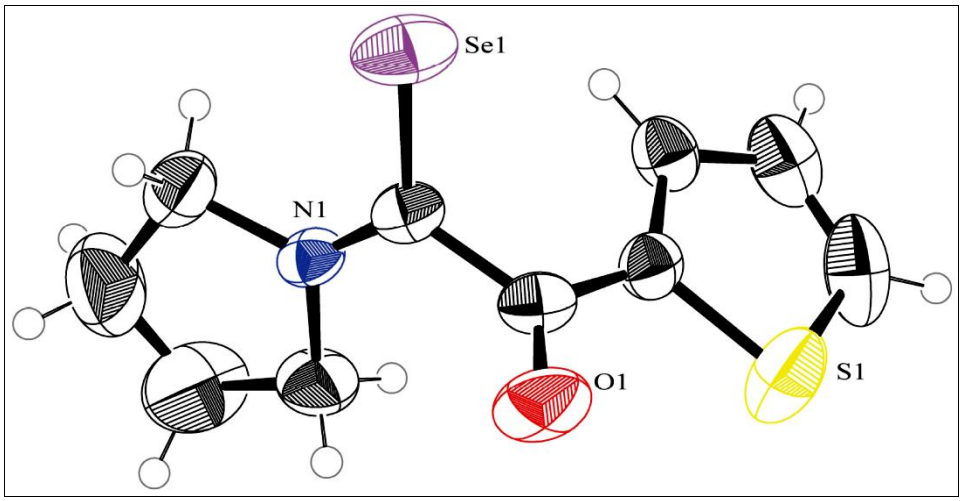


Fig 3A.4 ORTEP diagram of **18b** (**CCDC 1573440**) with 50% ellipsoid contour probability.

Table 3A.5 Crystal data and structure refinement for compound **18b**

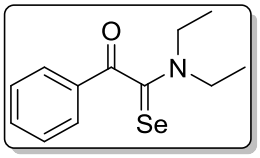
Empirical formula	$C_{10}H_{11}NOSSe$	
Formula weight	272.23	
Temperature	294.4(3) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions		
	a = 10.079(2) Å	α = 90°
	b = 9.9043(12) Å	β = 107.125(19) °
	c = 11.9050(19) Å	γ = 90°
Volume	1135.7(3) $Å^3$	
Z	4	
Density (calculated)	1.5920 g/cm^3	
Absorption coefficient	3.457 mm^{-1}	
F(000)	544.4	
Theta range for data collection	7.52 to 52.74°	
Index ranges	$-13 \leq h \leq 13$, $-11 \leq k \leq 13$, $-16 \leq l \leq 13$	
Reflections collected	4591	
Independent reflections	2312 [R(int) = 0.0432, Rσ =0.0823]	
Data / restraints / parameters	2312/0/126	
Goodness-of-fit on F^2	1.028	
Final R indexes [I>=2σ (I)]	R_1 = 0.0615, wR_2 = 0.1371	
Final R indexes [all data]	R_1 = 0.1099, wR_2 = 0.1661	

General procedure for the synthesis of α-oxo selenoamides:

To a stirring mixture of aryl or heteroaryl methyl ketones **(13, 17 or 19)** (1.0 mmol) and selenium dioxide (1.0 mmol, 1 equiv) in DMSO (0.5 mL) amine **(15)** (1.0 mmol) was added. The reaction was allowed to stir for 2-6 h at room temperature. After completion, the reaction was diluted with ethyl acetate (10 mL) and washed with brine (2×10 mL). The organic layer was separated, dried over anhydrous $NaSO_4$ and the solvent removed using rotatory evaporator. The compound was then purified by flash chromatography on silica gel (230-400 mesh) using ethyl acetate/hexane as eluent.

Spectroscopic analytical data

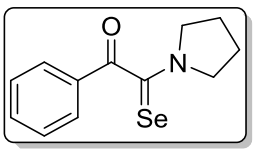
N, N-diethyl-2-oxo-2-phenylselenoacetamide (16a):



Oil; yield: 62%

IR (KBr): 3054, 2978, 2935, 2873, 1658, 1518, 1448, 1286, 1241, 1074, 1053, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 6.8 Hz, 2H), 7.51 (t, J = 7.2 Hz, 1H), 7.40 (t, J = 7.2 Hz, 2H), 4.11 (d, J = 6.8 Hz , 2H), 3.43 (q, J = 7.2 Hz, 2H), 1.40 (t, J = 6.8 Hz, 3H), 1.17 (t, J = 7.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.4, 188.4, 133.9, 133.4, 129.7, 128.7, 49.4, 47.8, 13.2, 11.2 ppm; MS (ES^+) calcd for $C_{12}H_{15}NOSe$ 269.0, found *m/z* 270.2 $[M + H]^+$.

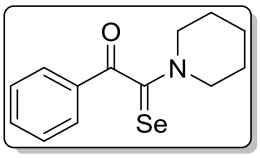
1-phenyl-2-(pyrrolidin-1-yl)-2-selenoxoethanone (16b):



Orange solid; yield: 57%; Mp: 59-61 ^{o}C

IR (KBr): 3077, 2980, 2931, 2883, 1693, 1589, 1570, 1488, 1403, 1286, 1200, 1092, 1015 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96-7.94 (m, 2H), 7.54-7.50 (m, 1H), 7.42-7.37 (m, 2H), 3.87-3.83 (m, 2H), 3.34-3.31 (m, 2H), 2.08-2.01 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 189.9, 134.2, 132.6, 130.0, 128.8, 54.4, 52.6, 26.3, 23.8 ppm; MS (ES^+) calcd for $C_{12}H_{13}NOSe$ 267.0, found *m/z* 268.2 $[M + H]^+$; Anal. calcd for $C_{12}H_{13}NOSe$: C, 54.14; H, 4.92; N, 5.26. Found: C, 54.17; H, 4.85; N, 5.29.

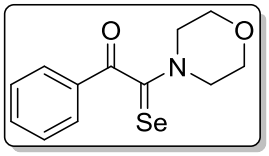
1-phenyl-2-(piperidin-1-yl)-2-selenoxoethanone (16c):



Yellow solid; yield: 73%; Mp: 74-76 ^{o}C

IR (KBr): 3065, 2935, 2853, 1658, 1523, 1449, 1241, 1226, 1001 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 7.2 Hz, 2H), 7.52 (t, J = 7.6 Hz, 1H), 7.41 (t, J = 8 Hz, 2H), 4.30 (t, J = 5.6 Hz , 2H), 3.46 (t, J = 5.2 Hz, 2H), 1.83 (quin, J = 5.6 Hz, 2H), 1.72 (quin, J = 5.6 Hz, 2H), 1.57(s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.1, 188.8, 134.0, 133.3, 129.6, 128.8, 54.6, 52.0, 26.3, 25.3, 23.8 ppm; MS (ES^+) calcd for $C_{13}H_{15}NOSe$ 281.0, found *m/z* 282.0 $[M + H]^+$; Anal. calcd for $C_{13}H_{15}NOSe$: C, 55.72; H, 5.40; N, 5.00. Found: C, 55.79; H, 5.36; N, 5.03.

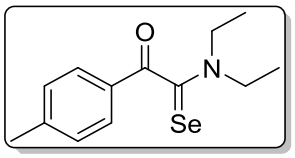
1-morpholino-2-phenylethane-1, 2-dione (16d):



Orange solid; yield: 52%; Mp: 103-105 ^{o}C

IR (KBr): 3054, 2967, 2851, 1649, 1511, 1448, 1275, 1264, 1105, 1019 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97-7.95 (m, 2H), 7.56-7.52 (m, 1H), 7.42 (t, J = 8 Hz, 2H), 4.38 (t, J = 4.8 Hz , 2H), 3.89 (t, J = 4.8 Hz, 2H), 3.64 (t, J = 4.4 Hz, 2H), 3.51 (t, J = 4.8 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.0, 188.9, 134.3, 133.2, 129.7, 128.9, 66.3, 66.2, 53.6, 50.8 ppm; MS (ES^+) calcd for $C_{12}H_{13}NO_2Se$ 283.0, found *m/z* 284.2 $[M + H]^+$; Anal. calcd for $C_{12}H_{13}NO_2Se$: C, 51.07; H, 4.64; N, 4.96. Found: C, 51.04; H, 4.67; N, 4.99.

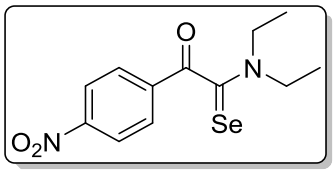
N, N-diethyl-2-oxo-2-(p-tolyl)ethaneselenoamide (16e):



Oil; yield: 74%

IR (KBr): 3028, 2977, 2935, 2873, 1654, 1605, 1570, 1513, 1447, 1381, 1286, 1250, 1178, 1072 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 4.09 (s, 2H), 3.42 (q, J = 7.2 Hz, 2H), 2.34 (s, 3H), 1.39 (t, J = 7.2 Hz, 3H), 1.17 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.6, 188.4, 145.0, 130.8, 129.9, 129.4, 49.3, 47.8, 21.8, 13.2, 11.2 ppm; MS (ES^+) calcd for $C_{13}H_{17}NOSe$ 283.0, found *m/z* 284.2 $[M + H]^+$; Anal. calcd for $C_{13}H_{17}NOSe$: C, 55.32; H, 6.07; N, 4.96. Found: C, 55.38; H, 6.03; N, 4.91.

N, N-diethyl-2-(4-nitrophenyl)-2-oxoethaneselenoamide (16f):



Orange solid; yield: 94%; Mp: 123-125 ^{o}C

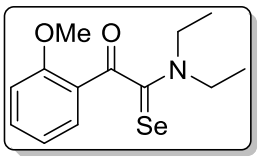
IR (KBr): 3103, 2978, 2939, 1670, 1526, 1436, 1346, 1244, 1201, 1074 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J = 8.8 Hz, 2H), 8.11 (d, J = 9.2 Hz, 2H), 4.11 (q, J = 7.2 Hz, 2H), 3.47 (q, J = 7.6 Hz, 2H), 1.42 (t, J = 7.2 Hz, 3H), 1.21 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.5, 183.6, 149.3, 137.8, 129.7, 122.7, 48.6, 47.1, 12.4, 10.2 ppm; ^{77}Se NMR (57.25 MHz, $CDCl_3$) δ 681.631; MS (ES^+) calcd for $C_{12}H_{14}N_2O_3Se$ 314.0, found *m/z* 337.3 $[M + Na]^+$.

N, N-diethyl-2-(3-nitrophenyl)-2-oxoethaneselenoamide (16g):

Orange solid; yield: 96%; Mp: 198-200 ^{o}C

IR (KBr): 3082, 2979, 2937, 2874, 1664, 1644, 1532, 1437, 1350, 1290, 1238, 1097, 703 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.36-8.27 (m, 2H), 7.61 (t, *J* = 8.0, 1H), 4.12 (q, *J* = 7.2 Hz, 2H), 3.47 (q, *J* = 7.2 Hz, 2H), 1.43 (t, *J* = 7.2 Hz, 3H), 1.22 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.3, 184.6, 148.3, 135.4, 135.1, 129.9, 127.8, 124.3, 49.7, 48.2, 13.5, 11.3 ppm; MS (ES$^+$) calcd for $C_{12}H_{14}N_2O_3Se$ 314.0, found *m/z* 315.4 $[M + H]^+$; Anal. calcd for $C_{12}H_{14}N_2O_3Se$: C, 46.02; H, 4.51; N, 8.94. Found: C, 46.10; H, 4.45; N, 8.89.

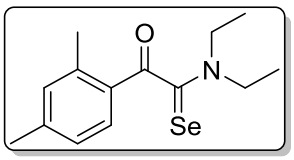
N, N-diethyl-2-(2-methoxyphenyl)-2-oxoethaneselenoamide (16h):



Orange solid; yield: 80%; Mp: 113-115 ^{o}C

IR (KBr): 3076, 2982, 2940, 2838, 1637, 1597, 1537, 1437, 1383, 1297, 1281, 1112, 1015, 760 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 2, 2 Hz, 1H), 7.48-7.44 (m, 1H), 7.03- 6.99 (m, 1H), 6.88 (d, *J* = 8.4, 1H), 4.02 (q, *J* = 6.8 Hz, 2H), 3.75 (s, 3H), 3.47 (q, *J* = 6.8 Hz, 2H) , 1.36 (t, *J* = 7.2 Hz, 3H), 1.24 (t, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.4, 186.2, 157.7, 134.2, 130.7, 123.2, 120.2, 111.3, 54.5, 48.3, 46.3, 11.6, 9.9 ppm; ^{77}Se NMR (57.25 MHz, $CDCl_3$) δ 525.721; MS (ES$^+$) calcd for $C_{13}H_{17}NO_2Se$ 299.04, found *m/z* 300.2 $[M + H]^+$.

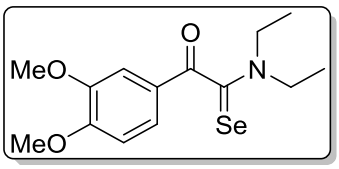
2-(2, 4-dimethylphenyl)-N, N-diethyl-2-oxoethaneselenoamide (16i):



Oil; yield: 53%

IR (KBr): 3077, 2980, 2931, 2883, 1693, 1589, 1570, 1488, 1403, 1286, 1200, 1092, 1015 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 7.6 Hz, 1H), 7.02 (s, 1H), 6.97 (d, J = 8.4 Hz, 1H), 4.09 (q, J = 6.8 Hz, 2H), 3.47 (q, J = 6.8 Hz, 2H), 2.58 (s, 3H), 2.28 (s, 3H), 1.39 (t, J = 7.2 Hz, 3H), 1.21 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.0, 189.8, 143.9, 141.9, 133.4, 131.9, 129.4, 126.3, 49.4, 47.9, 22.1, 21.5, 13.1, 11.1 ppm; MS (ES^+) calcd for $C_{14}H_{19}NOSe$ 297.0, found *m/z* 298.2 $[M + H]^+$; Anal. calcd for $C_{14}H_{19}NOSe$: C, 56.76; H, 6.46; N, 4.73. Found: C, 56.73; H, 6.48; N, 4.70.

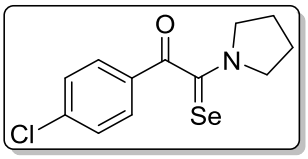
2-(3, 4-dimethoxyphenyl)-N, N-diethyl-2-oxoethaneselenoamide (16j):



Yellow solid; yield: 55%; Mp: 125-127 ^{o}C

IR (KBr): 3077, 2980, 2931, 2883, 1693, 1589, 1570, 1488, 1403, 1286, 1200, 1092, 1015 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.49 (m, 2H), 6.81 (d, J = 8.4 Hz, 1H), 4.11 (s, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 3.43 (q, J = 7.6 Hz, 2H), 1.40 (t, J = 6.8 Hz, 3H), 1.19 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.5, 187.0, 152.9, 148.1, 125.2, 124.3, 110.0, 109.2, 55.1, 55.0, 48.3, 46.8, 12.2, 10.2 ppm; ^{77}Se NMR (57.25 MHz, $CDCl_3$): δ 638.233; MS (ES^+) calcd for $C_{14}H_{19}NO_3Se$ 329.0, found *m/z* 330.2 $[M + H]^+$; Anal. calcd for $C_{14}H_{19}NO_3Se$: C, 51.22; H, 5.83; N, 4.27. Found: C, 51.33; H, 5.78; N, 4.29.

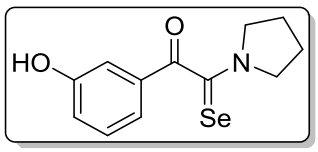
1-(4-chlorophenyl)-2-(pyrrolidin-1-yl)-2-selenoxoethanone (16k):



Yellow solid; yield: 86%; Mp: 143-145 ^{o}C

IR (KBr): 3060, 2964, 2874, 1656, 1586, 1514, 1445, 1262, 1158, 1090 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.8 Hz, 2H), 3.85 (t, J = 6.8 Hz, 2H), 3.33 (t, J = 5.6 Hz, 2H), 2.09-2.03 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.7, 188.4, 140.6, 131.4, 131.3, 129.1, 54.5, 52.6, 26.3, 23.8 ppm; ^{77}Se NMR (57.25 MHz, $CDCl_3$) δ 692.568; MS (ES^+) calcd for $C_{12}H_{12}ClNOSe$ 300.9, found *m/z* 302.1 $[M + H]^+$.

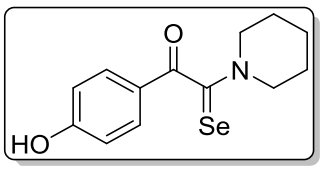
1-(3-hydroxyphenyl)-2-(pyrrolidin-1-yl)-2-selenoxoethanone (16l):



Oil; yield: 78%

IR (KBr): 3309, 3060, 2982, 2950, 2873, 1661, 1596, 1527, 1445, 1291, 1207, 1153, 1056 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.42 (m, 2H), 7.23 (t, J = 8.0 Hz, 1H), 7.01-6.98 (m,1H), 6.78 (s, 1H), 3.84 (t, J = 7.2 Hz, 2H), 3.32 (t, J = 6.8, Hz, 2H), 2.06-2.01 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.8, 190.1, 156.6, 133.5, 130.1, 122.2, 122.1,116.2, 54.6, 52.9, 26.2, 23.8 ppm; MS (ES^+) calcd for $C_{12}H_{13}NO_2Se$ 283.0, found *m/z* 284.2 $[M + H]^+$. Anal. calcd for $C_{12}H_{13}NO_2Se$: C, 51.07; H, 4.64; N, 4.96. Found: C, 51.11; H, 4.60; N, 4.92.

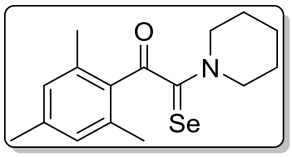
1-(4-hydroxyphenyl)-2-(piperidin-1-yl)-2-selenoxoethanone (16m):



Yellow solid; yield: 61%; Mp: 148-150 ^{o}C

IR (KBr): 3433, 3165, 2948, 2937, 2861, 1651, 1609, 1539, 1435, 1313, 1281, 1242, 1115, 1002, 614 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 8.4 Hz, 2H), 6.97 (s, 1H), 6.77 (d, J = 8.4 Hz, 2H), 4.27 (s, 2H), 3.46 (s, 2H), 1.80-1.18 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.2, 188.0, 163.5, 132.3, 124.4, 116.0, 54.4, 51.8, 26.4, 25.5, 23.5 ppm; MS (ES^+) calcd for $C_{13}H_{15}NO_2Se$ 297.0, found *m/z* 298.2 $[M + H]^+$. Anal. calcd for $C_{13}H_{15}NO_2Se$: C, 52.71; H, 5.10; N, 4.73. Found: C, 52.77; H, 5.07; N, 4.71.

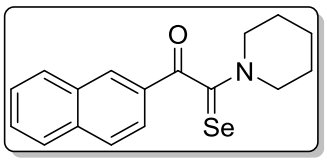
1-mesityl-2-(piperidin-1-yl)-2-selenoxoethanone (16n):



Orange solid; yield: 54%; Mp: 93-95 ^{o}C

IR (KBr): 3021, 2943, 2925, 2856, 1644, 1608, 1518, 1442, 1377, 1235, 1221, 1113, 1001 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 (s, 2H), 4.24 (t, J = 5.6 Hz, 2H), 3.77 (t, J = 6.0 Hz, 2H), 2.66 (s, 6H), 2.22 (s, 3H), 1.81-1.77 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.6, 189.9, 140.5, 136.4, 136.2, 129.4, 54.7, 53.7, 26.1, 25.4, 24.0, 21.2, 20.3 ppm; MS (ES^+) calcd for $C_{16}H_{21}NOSe$ 323.0, found *m/z* 324.3 $[M + H]^+$. Anal. calcd for $C_{16}H_{21}NOSe$: C, 59.62; H, 6.57; N, 4.35. Found: C, 59.70; H, 6.51; N, 4.38.

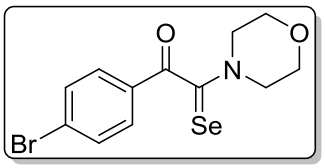
1-(naphthalen-2-yl)-2-(piperidin-1-yl)-2-selenoxoethanone (16o):



Yellow solid; yield: 84%; Mp: 140-142 ^{o}C

IR (KBr): 3060, 2938, 2917, 2852, 1644, 1628, 1513, 1445, 1352, 1290, 1213, 1188, 1108 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 7.99 (dd, J = 2.0, 1.6 Hz, 1H), 7.89-7.79 (m, 3H), 7.56-7.46 (m, 2H), 4.35 (t, J = 5.6 Hz, 2H), 3.49 (s, 2H), 1.86 (quint, J = 5.6 Hz, 2H), 1.72 (quint, J= 5.6 Hz, 2H), 1.58 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.1, 188.9, 136.0, 132.4, 132.0, 130.6, 129.6, 129.1, 128.7, 127.9, 127.0, 124.4, 54.7, 52.1, 26.3, 25.4, 23.8 ppm; ^{77}Se NMR (57.25 MHz, $CDCl_3$) δ 605.130; MS (ES^{+}) calcd for $C_{17}H_{17}NOSe$ 331.0, found *m/z* 332.2 $[M + H]^{+}$.

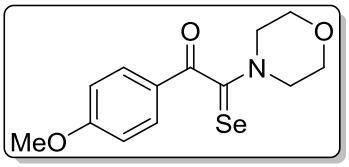
1-(4-bromophenyl)-2-morpholino-2-selenoxoethanone (16p):



Yellow solid; yield: 70%; Mp: 177-179 ^{o}C

IR (KBr): 3059, 2966, 2914, 2856, 1654, 1584, 1505, 1435, 1398, 1271, 1231, 1115 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.23 (d, J = 8.8 Hz, 2H), 7.13 (d, J = 8.8 Hz, 2H), 3.68 (s, 2H), 3.22 (t, J = 4.8 Hz, 2H), 2.94 (s, 4H), ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 197.3, 186.8, 132.1, 132.0, 131.1, 128.5, 65.6, 65.5, 53.7, 50.7 ppm; ^{77}Se NMR (57.25 MHz, $CDCl_3$) δ 663.013; MS (ES^{+}) calcd for $C_{12}H_{12}BrNO_2Se$ 360.9, found *m/z* 362.2 $[M + H]^{+}$. Anal. calcd for $C_{12}H_{12}BrNO_2Se$: C, 39.91; H, 3.35; N, 3.88. Found: C, 39.94; H, 3.29; N, 3.81.

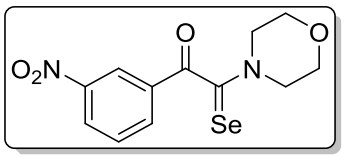
1-(4-methoxyphenyl)-2-morpholino-2-selenoxoethanone (16q):



Yellow solid; yield: 58%; Mp: 172-174 ^{o}C

IR (KBr): 2994, 2975, 2932, 2851, 1650, 1593, 1519, 1441, 1316, 1264, 1234, 1161, 1112, 1023 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 8.8 Hz, 1H), 6.89 (d, J = 8.8 Hz, 1H), 4.37 (t, J = 4.8 Hz,2H), 3.88 (t, J = 5.2 Hz, 2H), 3.81 (s, 3H), 3.63 (s, 2H), 3.51 (s, 2H) ppm; ^{13}C NMR (100 MHz, $DMSOd_6$) δ 198.6, 187.4, 164.0, 131.8, 125.4, 114.4, 65.6, 65.5, 55.7, 53.5, 50.6 ppm; MS (ES^{+}) calcd for $C_{13}H_{15}NO_3Se$ 313.0, found *m/z* 314.2 [M + H]$^{+}$.

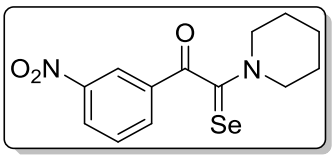
2-morpholino-1-(3-nitrophenyl)-2-selenoxoethanone (16r):



Orange solid; yield: 55%; Mp: 196-198 ^{o}C

IR (KBr): 3071, 2976, 2921, 2862, 1661, 1612, 1529, 1460, 1355, 1259, 1230, 1107, 1020, 703 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$+DMSO-d_6 1:4) δ 8.65 (s, 1H), 8.49 (d, J = 7.6 Hz, 1H), 8.36 (d, J = 8 Hz, 1H), 7.85 (t, J = 8.0 Hz, 1H), 4.35 (t, J = 4.4 Hz, 2H), 3.88 (t, J = 4.8 Hz, 2H), 3.64 (s, 2H), 3.63 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6 1:4) δ 196.3, 185.0, 148.0, 135.3, 134.4, 130.8, 128.2, 123.2, 65.7, 65.5, 53.8, 50.8 ppm; MS (ES^{+}) calcd for $C_{12}H_{12}N_2O_4Se$ 328.0, found *m/z* 351.2 [M + Na]$^{+}$.

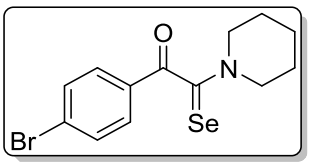
1-(3-nitrophenyl)-2-(piperidin-1-yl)-2-selenoxoethanone (16s):



Yellow solid; yield: 81%; Mp: 115-117 ^{o}C

IR (KBr): 3082, 2956, 2923, 2857, 1664, 1533, 1444, 1351, 1278, 1223, 1091, 704 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.36- 8.29 (m, 2H) 7.62 (t, J = 8.0 Hz, 1H), 4.31 (t, J = 5.6 Hz, 2H), 3.50 (t, J = 5.6 Hz, 2H), 1.86 (quint, J = 5.2 Hz, 2H), 1.76 (quint, J = 5.2 Hz, 2H), 1.62 (quint, J = 5.2 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.1, 184.0, 147.4, 134.4, 133.9, 129.0, 126.9, 123.2, 53.9, 51.2, 25.5, 24.4, 22.8 ppm; MS (ES^{+}) calcd for $C_{13}H_{14}N_2O_3Se$ 326.0, found *m/z* 327.2 [M + H]$^{+}$; Anal. calcd for $C_{13}H_{14}N_2O_3Se$: C, 48.01; H, 4.34; N, 8.61. Found: C, 48.11; H, 4.30; N, 8.65.

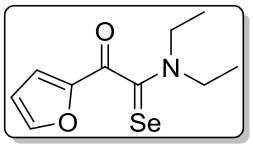
1-(4-bromophenyl)-2-(piperidin-1-yl)-2-selenoxoethanone (16t):



Orange solid; yield: 94%; Mp: 138-140 ^{o}C

IR (KBr): 3076, 2936, 2856, 1662, 1579, 1519, 1438, 1221, 1005 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85 (d, J = 8.4 Hz, 2H), 7.79 (d, J = 8.8 Hz, 2H), 4.29 (t, J = 4.8 Hz , 2H), 3.54 (t, J = 4.8 Hz, 2H), 1.78-1.68 (m, 4H), 1.72 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 195.2, 186.1, 131.6, 131.5, 130.5, 127.8, 53.8, 50.9, 25.4, 24.5, 22.4 ppm; MS (ES^{+}) calcd for $C_{13}H_{14}BrNOSe$ 358.9, found *m/z* 359.9 [M + H]$^{+}$. Anal. calcd for $C_{13}H_{14}BrNOSe$: C, 43.48; H, 3.93; N, 3.90. Found: C, 43.53; H, 3.89; N, 3.94.

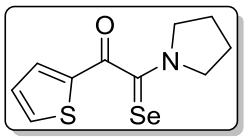
N, N-diethyl-2-(furan-2-yl)-2-oxoethaneselenoamide (18a):



Oil; yield: 71%

IR (KBr): 3077, 2980, 2931, 2883, 1693, 1589, 1570, 1488, 1403, 1286, 1200, 1092, 1015 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 0.8, 0.8 Hz, 1H), 7.24 (dd, *J* = 0.8, 0.8 Hz, 1H), 6.50 (dd, *J* = 1.6, 1.6 Hz, 1H), 4.05 (q, *J* = 7.2 Hz, 2H), 3.47 (q, *J* = 6.8 Hz, 2H), 1.36 (t, *J* = 7.2 Hz, 3H), 1.19 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.1, 177.2, 149.6, 147.8, 121.2, 112.7, 49.3, 48.2, 13.2, 11.0 ppm; MS (ES^+) calcd for $C_{10}H_{13}NO_2Se$ 259.0, found *m/z* 260.2 $[M + H]^+$; Anal. calcd for $C_{10}H_{13}NO_2Se$: C, 46.52; H, 5.08; N, 5.43. Found: C, 46.56; H, 5.01; N, 5.49.

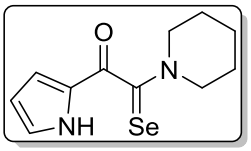
2-(pyrrolidin-1-yl)-2-selenoxo-1-(thiophen-2-yl)ethanone (18b):



Orange solid; yield: 56%; Mp: 89-91 ^{o}C

IR (KBr): 3076, 2978, 2923, 2868, 1639, 1523, 1445, 1405, 1271, 1124 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (dd, *J* = 1.2, 1.2 Hz, 1H), 7.66 (dd, *J* = 1.2, 1.2 Hz, 1H), 7.07 (dd, *J* = 4.0, 4.0 Hz, 1H), 3.83-3.79 (m, 2H), 3.42-3.37 (m, 2H), 2.07-2.03 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.5, 183.4, 139.7, 136.1, 136.0, 128.5, 54.7, 52.7, 26.3, 23.9 ppm; ^{77}Se NMR (57.25 MHz, $CDCl_3$) δ 698.543; MS (ES^+) calcd for $C_{10}H_{11}NOSSe$ 272.9, found *m/z* 274.1 $[M + H]^+$.

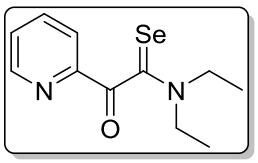
2-(piperidin-1-yl)-1-(1H-pyrrol-2-yl)-2-selenoxoethanone (18c):



Yellow solid; yield: 51%; Mp: 142-144 ^{o}C

IR (KBr): 3270, 2936, 2867, 1611, 1520, 1400, 1240, 1099 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.22 (s, 1H), 7.26-7.24 (m, 1H), 6.87-6.85 (m, 1H), 6.30-6.28 (m, 1H), 4.24 (s, 2H), 3.58 (t, J = 5.6 Hz, 2H), 1.81-1.70 (m, 4H), 1.57 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 197.2, 179.9, 128.2, 127.9, 119.7, 111.1, 54.3, 52.1, 26.5, 25.5, 23.5 ppm; MS (ES^{+}) calcd for $C_{11}H_{14}N_2OSe$ 270.0, found *m/z* 271.0 $[M + H]^{+}$.

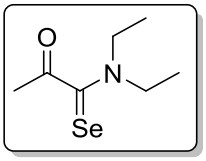
N, N-diethyl-2-oxo-2-(pyridin-2-yl)ethaneselenoamide (18d):



Orange solid; yield: 92%; Mp: 79-81 ^{o}C

IR (KBr): 3049, 2983, 2944, 2873, 1667, 1532, 1433, 1270, 1205, 1074 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70-8.68 (m, 1H), 8.10-8.02 (m, 2H), 7.66-7.62 (m, 1H), 4.09 (q, J = 7.2 Hz , 2H), 3.57 (q, J = 7.2 Hz, 2H), 1.35 (t, J = 7.2 Hz, 3H), 1.20 (t, J = 7.2 Hz, 3H ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 200.1, 186.4, 152.1, 149.8, 138.1, 128.2, 124.1, 50.2, 47.7, 13.4, 11.5 ppm; MS (ES^{+}) calcd for $C_{11}H_{14}N_2OSe$ 270.0, found *m/z* 271.0 $[M + H]^{+}$.

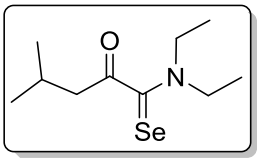
N, N-diethyl-2-oxopropaneselenoamide (20a):



Oil; yield; 59%

IR (KBr film): 2969, 2932, 2816, 1657, 1523, 1467, 1354, 1271, 1072 cm-1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.94 (q, J = 7.2Hz, 2H), 3.44 (q, J = 7.2Hz, 2H), 2.51 (s, 3H), 1.31-1.22 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.18, 198.21, 48.13, 47.18, 27.07, 12.63, 10.15 ppm; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_7H_{13}NOSeNa$ 230.0060; found 230.0059.

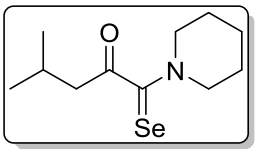
N, N-diethyl-4-methyl-2-oxopentaneselenoamide (20b):



Oil; yield; 55%

IR (KBr film): 2960, 2856, 1661, 1537, 1382, 1288, 1087 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.94 (q, J = 7.2Hz, 2H), 3.42 (q, J = 7.2Hz, 2H), 2.791 (d, J = 6.8Hz, 2H), 2.28-2.18 (m, 1H),1.30-1.22 (m, 6H), 0.93 (d, J = 6.4, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.8, 198.3, 47.9, 47.8, 47.1, 22.9, 21.4,12.5, 10.12 ppm; MS (ES^+) calcd for $C_{10}H_{19}NOSe$ 249.0, found *m/z* 250.0 $[M + H]^+$.

4-methyl-1-(piperidin-1-yl)-1-selenoxopentan-2-one (20c):



Oil; yield; 65%

IR (KBr film): 2974, 2892, 1641, 1479, 1379, 1230, 1036 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.13 (t, J = 4.8 Hz, 2H), 3.47 (t, J = 6 Hz, 2H), 2.75 (d, J = 6.8 Hz, 2H), 2.27-2.18 (m, 1H), 1.74-1.56 (m, 6H), 0.93 (d, J = 6.4Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.5, 198.5, 53.2, 51.3, 47.9, 25.5, 24.1, 22.9, 22.8, 21.5 ppm; MS (ES^+) calcd for $C_{11}H_{19}NOSe$ 261.0, found *m/z* 262.0 $[M + H]^+$.

3A.4 Representative Spectra

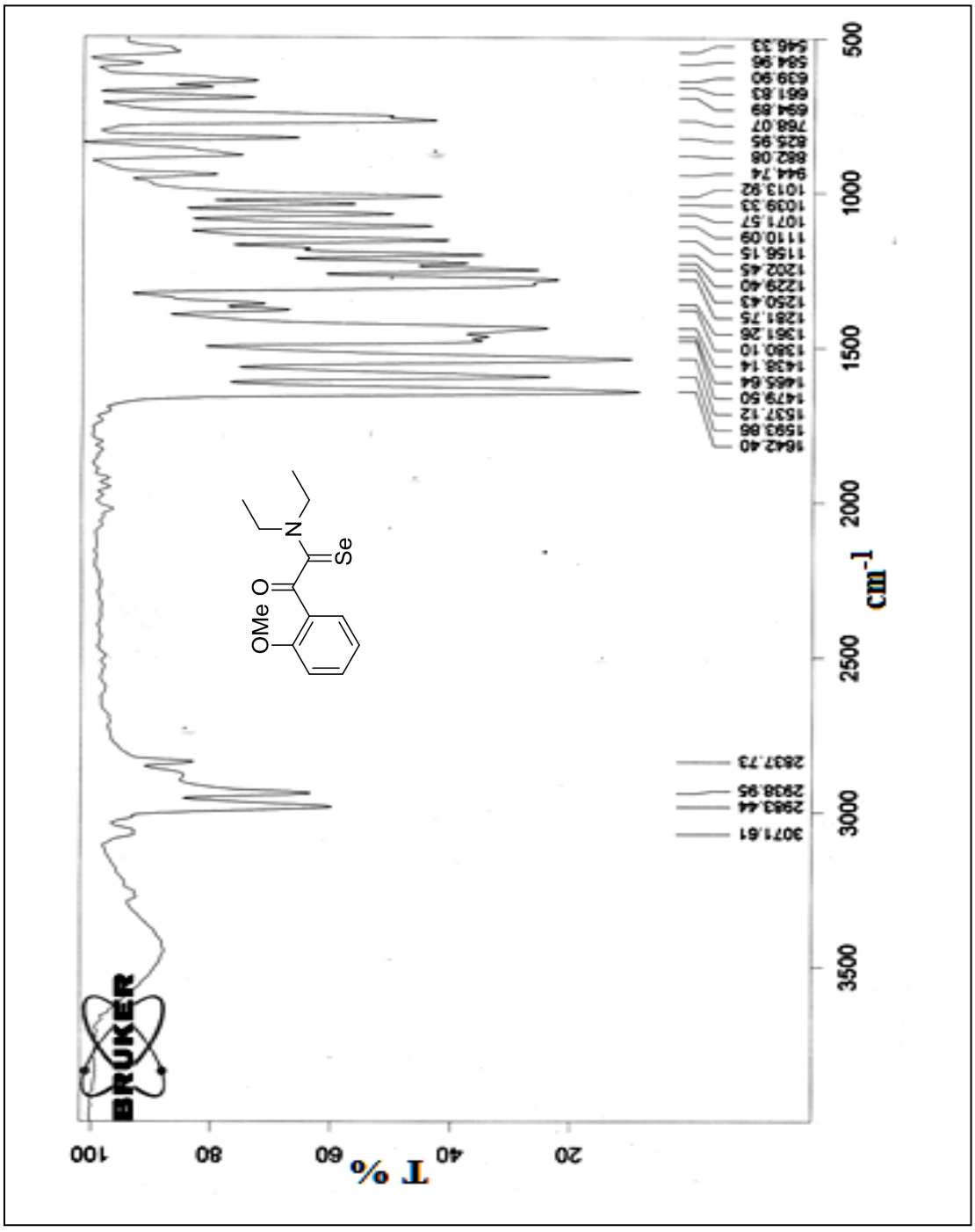


Figure 3A.5 IR spectrum of *N*,*N*-diethyl-2-(2-methoxyphenyl)-2 oxoethaneselenoamide **(16h)**

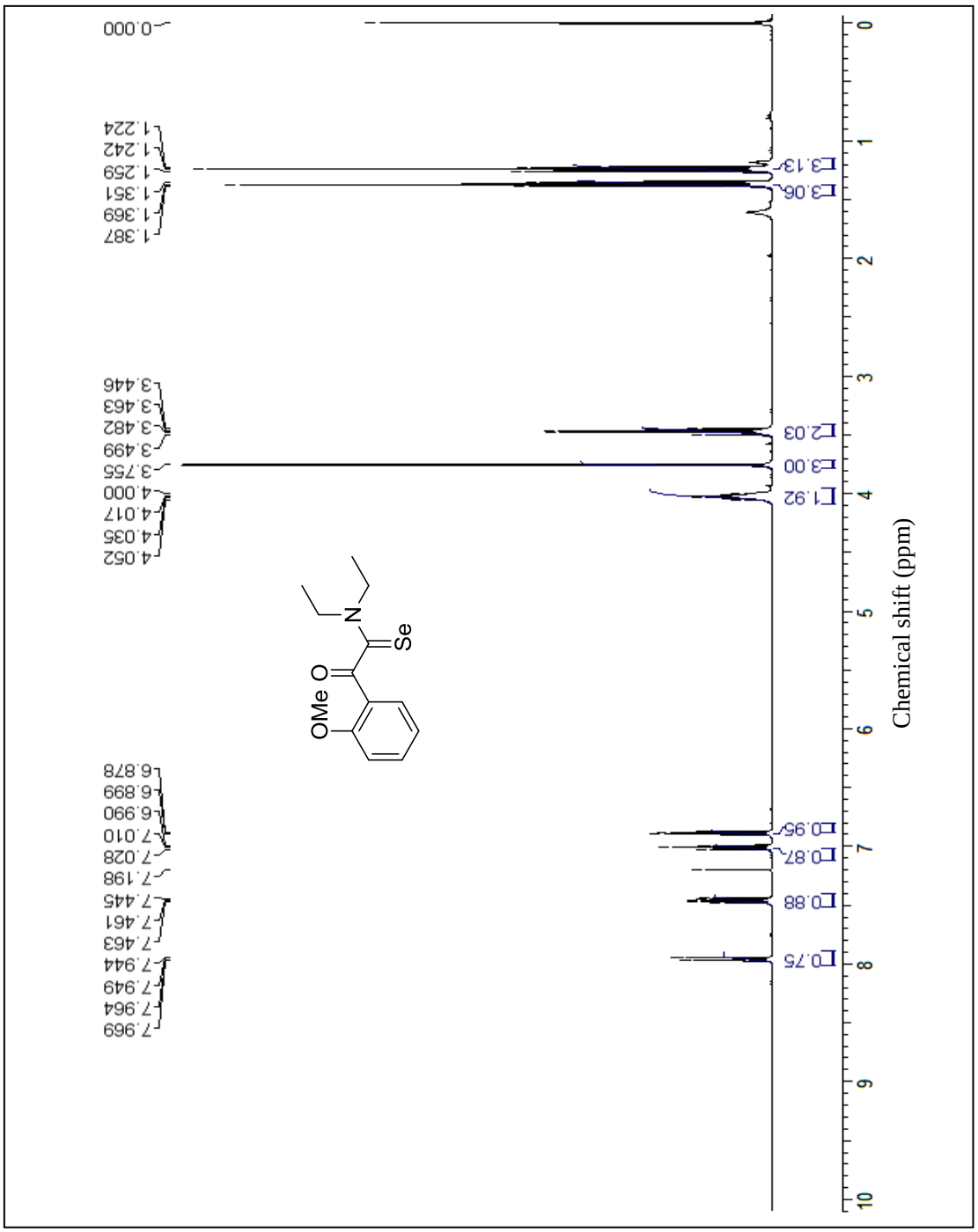


Figure 3A.6 ^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of *N*,*N*-diethyl-2-(2-methoxyphenyl)-2-oxoethaneselenoamide **(16h)**

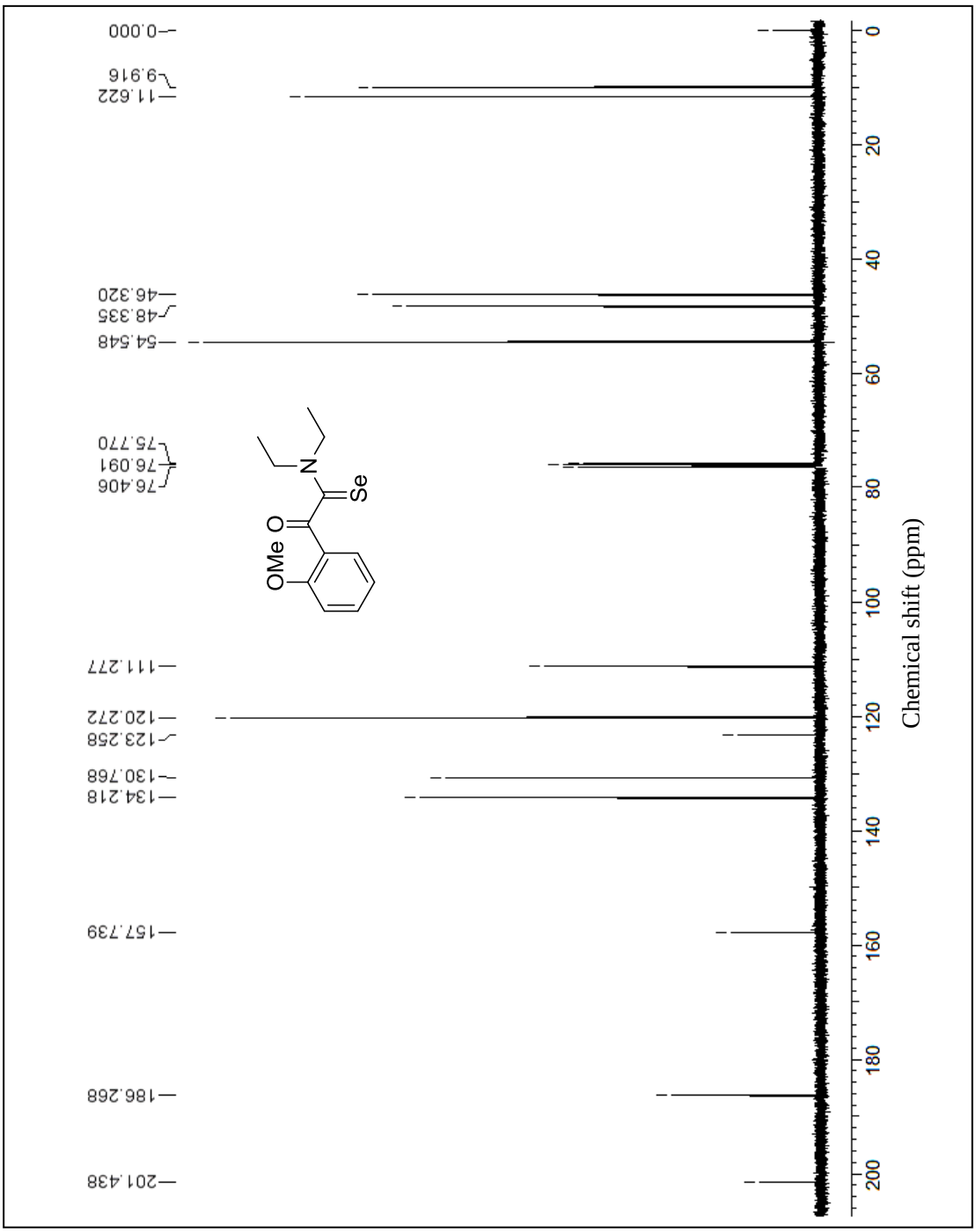


Figure 3A.7 ^{13}C NMR ($CDCl_3$, 100 MHz) spectrum of *N*,*N*-diethyl-2-(2-methoxyphenyl)-2-oxoethaneselenoamide **(16h)**

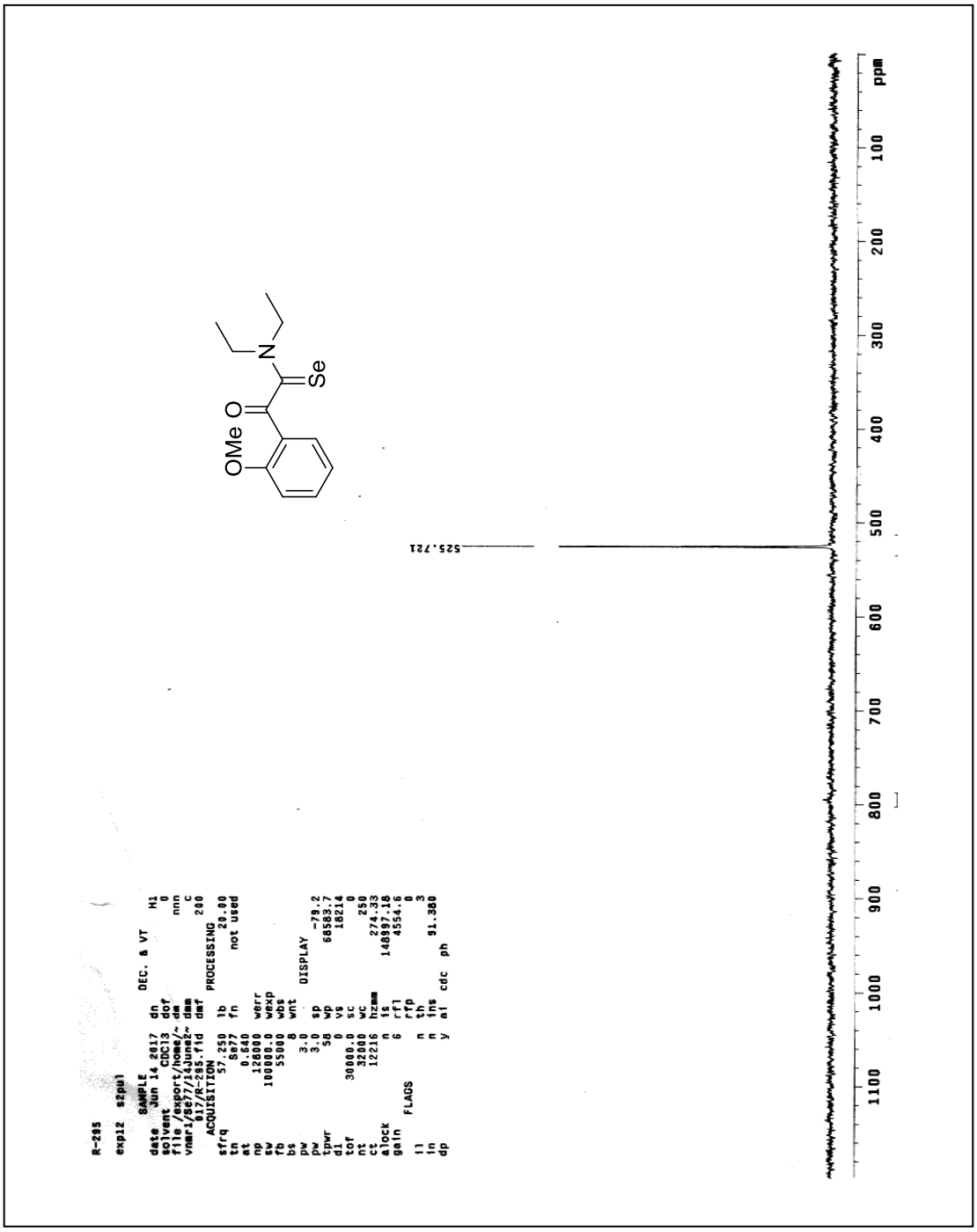


Figure 3A.8 ^{77}Se NMR ($CDCl_3$, 57.25 MHz) spectrum of *N*, *N*-diethyl-2-(2-methoxyphenyl)-2-oxoethaneselenoamide **(16h)**

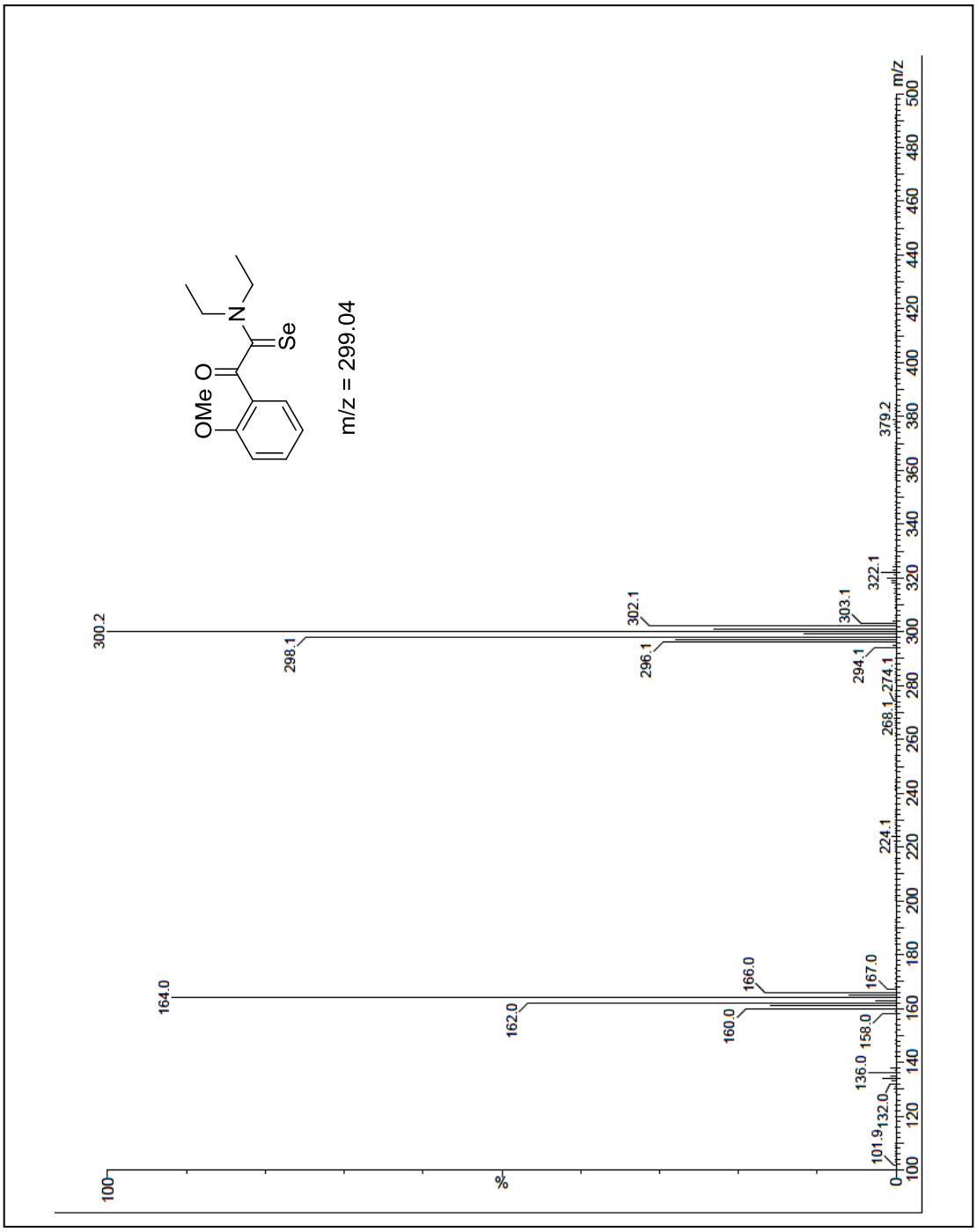


Figure 3A.9 Mass spectrum of *N, N*-diethyl-2-(2-methoxyphenyl)-2-oxoethaneselenoamide **(16h)**

3A.5 References:

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CHAPTER 3B

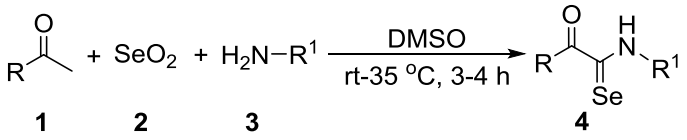
Synthesis of α-xo-N-alkyl Selenoamides by a Three-Component Reaction involving Aromatic Ketones, Selenium Dioxide and Primary Amines

3B.1 Introduction

The development of novel and an efficient methods for the synthesis of selenoamides has been the subject of recent research interest, because of selenium-containing skeletons C=Se bonds are widely spread as an important moiety in many biologically active compounds, pharmaceutical agents[1-3] and as well as a versatile intermediate in organic synthesis.[4-5] Various methods have been reported for the synthesis of selenoamides.[6-9] However, for *α*-oxo-selenoamides having C=Se bond which attached to the *α*-carbon of the C=O group are not very common and hence it has been a challenge to many synthetic organic chemists. From our literature survey, only a few methods could be garnered which described their synthesis.[10-12] In the previous chapter, we have demonstrated the protocol for the direct *α*-selenoamidation of aryl methyl ketones with secondary amines. As a part of our continuation of the previous work,[13] our literature survey has further revealed that the used of primary amines in the synthesis of the above class of compounds has not been reported. In this chapter, the first method for the synthesis, isolation and characterization of the so far unreported *α*-oxo-*N*-alkyl selenoamides is disclosed.

3B.2 Results and Discussion

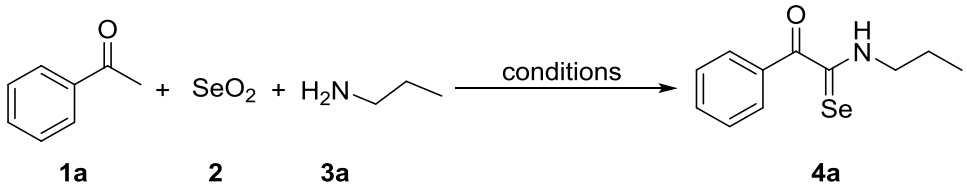
In this context and in the frame of our current research interest, herein we report the synthesis of *α*-oxo-*N*-alkyl selenoamides **(4)** from aryl methyl ketones **(1)** with primary amines **(3)** using selenium dioxide **(2)** as a selenium source **(Scheme 3B.1)**.



Scheme 3B.1

Our investigation started with the reaction of readily available acetophenone **(1a)**, selenium dioxide **(2)** and *n*-propylamine **(3a)** as a model substrate the detailed investigations of which are summarized in **Table 3B.1**. Our initial effort of reacting acetophenone **(1a)**, (0.116 mL, 1.0 mmol, 1 equiv) with selenium dioxide **(2)**, (110 mg, 1.0 mmol, 1 equiv) and *n*-propylamine **(3a)**, (0.82 mL, 1 mmol, 1 equiv) at room temperature for 10 minutes yielded no result. When the temperature was raised to 35 ^{o}C for 4 h, only trace amount of the product **4a** was obtained **(Table 3B.1, entry 1)**. Raising the temperature to 60 ^{o}C resulted in a mixture of products which could not be isolated. At this point we reasoned that using a suitable reaction medium might allow the reaction to proceed the way we wanted. Their action was performed under solvent condition and the first solvent we chose was DMSO. Thus, when the reaction was carried out in DMSO at room temperature we were gratified to observe a slight increase in the yield of the product **(Table 3B.1, entry 2)**. Changing the stoichiometry of the amine and the solvent resulted in increased product yield **(Table 3B.1, entries 3-5)**. Our effort to optimize the reaction using different solvents such as H_2O, EtOH, DCM were screened, but either the desired product was not formed **(Table 3B.1, entries 6-7)** or the desired product was obtained in low yield **(Table 3B.1, entry 8)**. The optimized condition was achieved when the reaction was carried out using stoichiometric amount of amine with DMSO as a solvent **(Table 3B.1, entry 4)**.

Table 3B.1 Optimization of the reaction conditions[a]



1a **2** **3a** **4a**

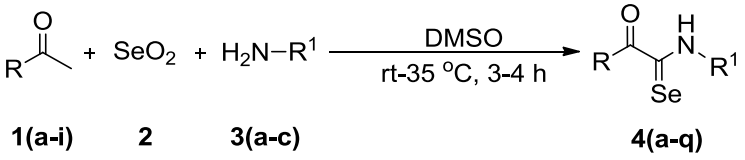
entry	substrate 3a (equiv)	solvent	t (h)	yield(%)
1	1	-	8	Trace
2	1	DMSO	8	20
3	2	DMSO	4	34
4	**3**	**DMSO**	**4**	**55**
5	4	DMSO	4	53
6	3	H_2O	4	0
7	3	EtOH	4	0
8	3	DCM	4	trace

[a]Reaction conditions: ketones **(1)** (1.0 mmol), SeO_2 **(2)** (1.0 mmol), solvent (1mL) at rt-35 ^oC

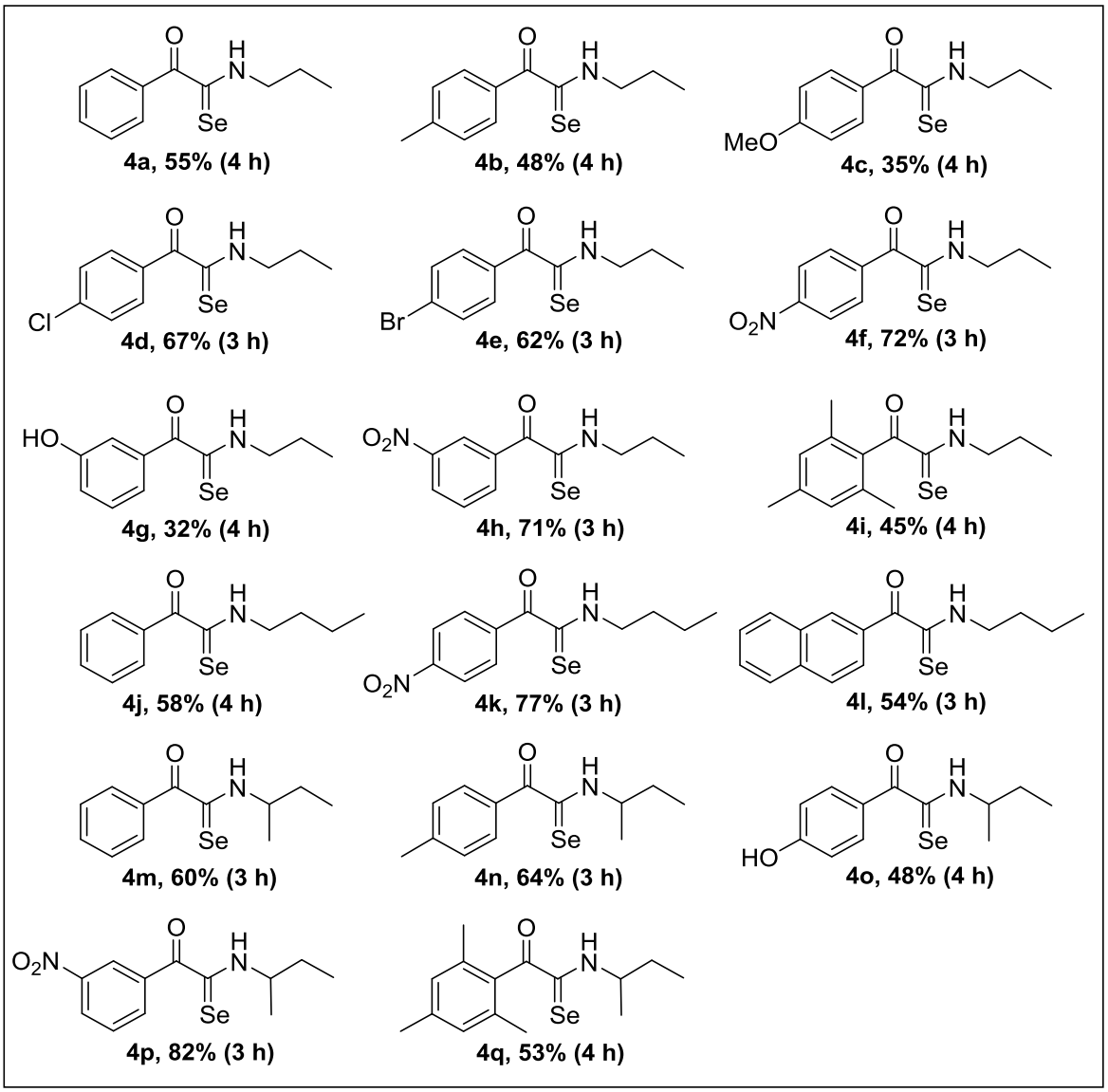
With the optimal reaction conditions in hands, the scope of the reaction with various aryl methyl ketones **(1)** and amines **(3)** was evaluated. First, we carried out the reaction of aryl methyl ketones **(1)** with *n*-propylamine **(3a)**. Aryl methyl ketones containing both electron-donating and electron-withdrawing groups at different positions in the aromatic ring were allowed to react with *n*-propylamine **(3a)**. The reaction proceeded as expected and readily afforded the corresponding *α*-oxo-*N*-alkyl selenoamides **4a-h** in moderate to good yields (32%-72%) **(Scheme 3B.2)**. Aryl methyl ketones containing a variety of functional groups such as methyl **(1b)**,

methoxy **(1c)**, chloro **(1d)**, bromo **(1e)**, nitro **(1f** and **1h)** and hydroxyl **(1g** and**1k)**, were well tolerated in this reaction. In fact we were pleased to observe that even *tri*-substituted acetophenones **(1i)** was well tolerated in this reaction and gave the corresponding 2-mesityl-2-oxo-*N*-propylethaneselenoamide **(4i)** in 45% yield **(Scheme 3B.2)**. Secondly, the reaction was performed with different primary amines such as long-chain *n*-butylamine **(3b)** and branch chain *sec*-butylamine **(3c)**. Acetophenone **(1a)** and *p*-nitro acetophenone **(1f)** were allowed to react with *n*-butylamine **(3b)** and the reaction underwent smoothly to furnish the corresponding **4j** and **4k** in 58% and 77% yields respectively **(Scheme 3B.2)**. Further, the reaction was performed with extended rings such as 2-acetyl naphthalene **(1j)** and the desired product **4l** was obtained in a satisfactory yield (54%). Furthermore, the reaction was extended with branch *sec*-butylamine **(3c)** and irrespective of the bulky nature of the amines, the expected *N*-(sec-butyl)-2-oxo-selenoamides **4m-q** were obtained in moderate to good yields(38%-82%).The reaction was also extended to heteroaryl methyl ketones including 2-acetyl furan **(1l)** and 2-acetylthiophene **(1m)**, however, the reaction failed to give the desired product, presumably due to the weak nucleophilicity of the primary amine.

Scheme 3B.2 Substrate scope of aryl methyl ketones[a]



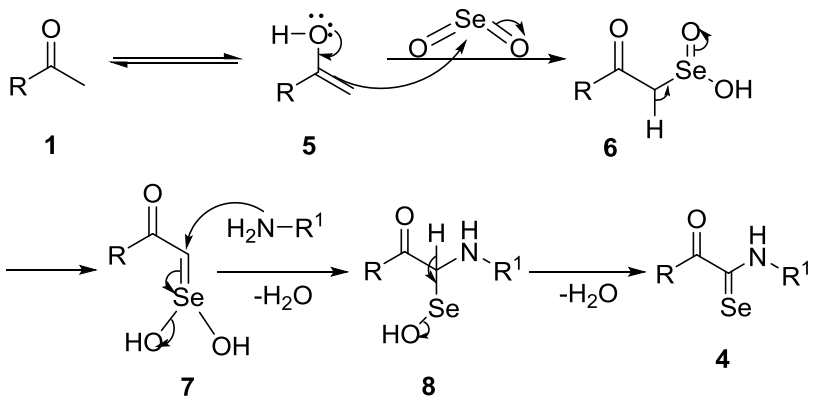
1(a-i) **2** **3(a-c)** **4(a-q)**



[a]Reaction conditions: ketones **(1)** (1.0 mmol), SeO_2 **(2)** (1.0 mmol), solvent (1 mL) at rt-35 °C

The probable mechanism of the reaction may be depicted as in **Scheme 3B.3**. The first step is the enolization of ketone **(1)** which is followed by the reaction with selenium dioxide **(2)** to generate the intermediate **7**.[13a] The intermediate **7** undergo a nucleophilic attack by the primary amine on the *α*-carbon leading to the intermediate **8**. The propensity of Se to get reduced to its lower oxidation state resulted in the deprotonation of the *α*-hydrogen with the elimination of another molecule of water resulted in the formation of the product **4**.

Scheme 3B.3 Plausible mechanism



In conclusion, an efficient and useful general protocol for the synthesis of hitherto unreported *α*-oxo-*N*-alkyl selenoamides has been developed from readily available aryl methyl ketones, primary amines and selenium dioxide. This methodology employed selenium dioxide as a selenium source. The attractiveness of the method is further augmented by the fact that the reaction proceeds without using any catalyst, acid or base and under mild reaction conditions. To the best of our knowledge, this is a first report where primary amines react with aryl methyl ketones to yield *α*-oxo-*N*-alkyl selenoamides in presence of selenium dioxide.

3B.3 Experimental Section

General Methods

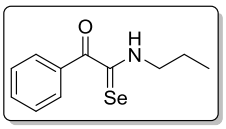
All reagents were purchased from Sigma Aldrich, TCI Chemicals and Alfa Aesar were used without further purification unless noted. IR spectra were recorded on a Perkin Elmer Spectrum 400 FTIR instrument. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance II-400 spectrometer in $CDCl_3$ with TMS as internal standard. Mass spectral data were obtained with a Waters UPLC-TQD mass spectrometer (ESI-MS). High-resolution mass spectra (ESI-HRMS) were recorded on MaXis (Bruker Daltonics, Bremen, Germany) time of flight (TOF) mass spectrometer. All reactions were monitored by thin-layer chromatography (TLC) using pre-coated aluminium sheets (silica gel 60 F_{254} 0.2-mm thickness). Column chromatography was carried out on silica gel (100-200 mesh) and Flash chromatography was carried out on silica gel (230-400 mesh).

General procedure for α-oxo-N-alkyl selenoamides

To a stirring mixture of aryl methyl ketones **(1)** (1.0 mmol) and selenium dioxide **(2)** (111 mg, 1.0 mmol, 1 equiv) in DMSO (1 mL), amine **(3)** (3.0 mmol, 3 equiv) was added dropwise. The reaction was allowed to stir at room temperature for 10 minutes and then increase to 35 ^{o}C for 3-4 h. After completion, the reaction was diluted with ethyl acetate (10 mL) and washed with brine (2x10 mL). The organic layer was separated, dried over anhydrous $NaSO_4$ and the solvent removed using rotatory evaporator. The compound was then purified by flash chromatography on silica gel (230-400 mesh) using ethyl acetate/hexane as eluent.

Spectroscopic analytical data

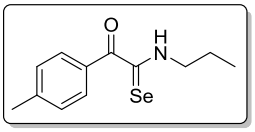
***2-oxo-2-phenyl-N-propylethaneselenoamide (4a)*:**



Oil; yield: 55%

IR (KBr film): 3222, 3057, 2963, 2932, 2874, 1658, 1541, 1450, 1407, 1238 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.08 (s, 1H), 7.93 (d, J = 7.2 Hz, 2H), 7.48 (t, J = 7.2 Hz, 1H), 7.34 (t, J = 7.6 Hz, 2H), 3.66 (q, J = 6.8 Hz, 2H), 1.84-1.75 (m,2H), 0.99 (t, J =7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.3, 189.8, 133.8, 133.7, 130.4, 128.0, 50.1, 20.8, 11.4 ppm; HRMS (ESI) *m/z*: $[M + Na]^+$calcd for $C_{11}H_{13}NOSeNa$ 278.0060; found 278.0069.

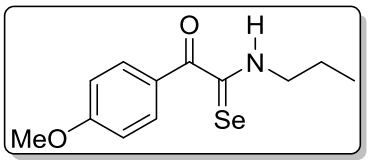
***2-oxo-N-propyl-2-(p-tolyl)ethaneselenoamide(4b)*:**



Oil; yield: 48%

IR (KBr film): 3282, 3063, 2963, 2930, 2870, 1644, 1547, 1535, 1404, 1378, 1251 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 (s, 1H), 7.84 (d, J = 8.0 Hz, 2H), 7.12 (d, J = 8.0 Hz, 2H), 3.68-3.63 (m, 2H), 2.32 (s, 3H), 1.83-1.74 (m, 2H), 0.99 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.2, 189.1, 144.0, 130.0, 129.6, 127.9, 49.1, 20.8, 19.8, 10.5 ppm; HRMS (ESI) *m/z*: $[M + Na]^+$calcd for $C_{12}H_{15}NOSeNa$ 292.0217; found 292.0221.

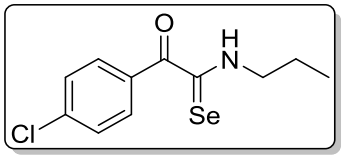
***2-(4-methoxyphenyl)-2-oxo-N-propylethaneselenoamide (4c)*:**



Oil; yield: 35%

IR (KBr film): 3234, 3053, 3006, 2963, 2933, 2874, 1656, 1597, 1510,1357, 1260, 1170 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 (s, 1H), 7.95 (d, *J* = 8.8 Hz, 2H), 6.80 (d, *J* = 9.2Hz, 2H), 3.79 (s, 3H), 3.69-3.64 (m, 2H), 1.83-1.74(m, 2H), 0.99 (t, *J* = 7.6Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.1, 189.0, 163.7, 132.5, 125.6, 113.1, 55.0, 49.6, 20.4, 11.0 ppm; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{12}H_{15}NO_2SeNa$ 308.0166, found 308.0158.

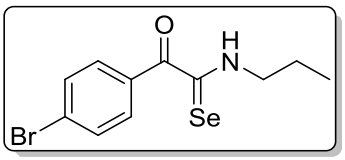
***2-(4-chlorophenyl)-2-oxo-N-propylethaneselenoamide (4d)*:**



Oil; yield: 67%

IR (KBr film): 3270, 3039, 2964, 2932, 2874, 1656, 1588, 1554, 1402, 1240, 1090 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (s, 1H), 7.92 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 3.64 (t, *J* = 7.2 Hz, 2H), 1.83-1.74 (m, 2H), 0.99 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.2, 188.2, 140.0, 132.9, 132.6, 131.9, 49.3, 20.9, 11.5 ppm; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{11}H_{12}ClNOSeNa$ 311.9670, found 311.9665.

***2-(4-bromophenyl)-2-oxo-N-propylethaneselenoamide (4e)*:**

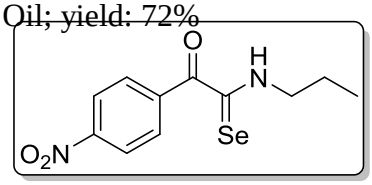


Oil; yield: 62%

IR (KBr film): 3265, 3087, 2963, 2929, 2872, 1653,1584, 1558, 1401, 1237, 1070 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.99 (s, 1H), 7.86 (d, J = 8.8 Hz, 2H), 7.49 (d, J = 8.8 Hz, 2H), 3.66-3.61 (m, 2H), 1.84-1.75 (m, 2H), 1.00 (t, J = 7.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.4, 187.2, 132.0, 130.9, 130.3, 128.7, 49.4, 19.8, 10.4 ppm; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{11}H_{12}BrNOSeNa$ 355.9165, found 355.9170.

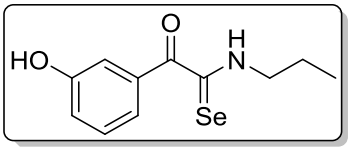
***2-(4-nitrophenyl)-2-oxo-N-propylethaneselenoamide (4f)*:**

Oil; yield: 72%



IR (KBr film): 3266, 3054, 2960, 2931, 2873, 1669, 1552, 1531, 1461, 1386, 1252, 1064 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.24 (s, 1H), 8.18 (d, J = 9.2 Hz, 2H), 8.09 (d, J = 9.2 Hz, 2H), 3.65-3.60 (m, 2H), 1.87-1.77 (m, 2H), 1.01 (t, J = 7.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.1, 185.9, 149.5, 139.6, 130.7, 122.4, 49.9, 20.3, 11.0 ppm; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{11}H_{12}N2O_3SeNa$ 322.9911, found 322.9905.

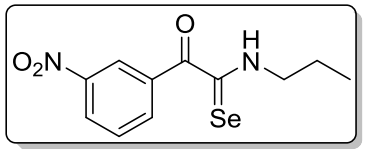
***2-(3-hydroxyphenyl)-2-oxo-N-propylethaneselenoamide (4g)*:**



Oil; yield: 32%

IR (KBr film): 3230,3058, 2960, 2929, 2873, 1638, 1570, 1407, 1270, 1168 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.11 (s,1H), 7.41-6.92 (m, 4H), 5.70 (s, 1H), 3.61(t, J = 7.2 Hz, 2H), 1.79-1.69 (m, 2H), 0.96 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.0, 185.7, 156.8, 134.3, 129.5, 122.4, 122.3, 116.8, 50.1, 20.8, 11.5 ppm; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{11}H_{13}NO_2SeNa$ 294.0009, found 294.0002.

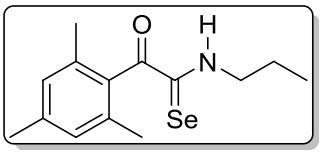
***2-(3-nitrophenyl)-2-oxo-N-propylethaneselenoamide (4h)*:**



Oil; yield: 71%

IR (KBr film): 3263, 3083, 2962, 2933, 2875, 1668, 1550, 1527, 1454, 1352, 1252 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 (s,1H), 8.79 (s, 1H), 8.32-8.29 (m, 2H), 7.55 (t, J = 8 Hz, 1H), 3.66-3.61(m, 2H), 1.87-1.78 (m, 2H), 1.02 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.2, 185.0, 146.5, 135.3, 134.8, 127.9, 126.4, 124.2, 49.5, 19.8, 10.5 ppm; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{11}H_{12}N_2O_3SeNa$ 322.9911, found 322.9911.

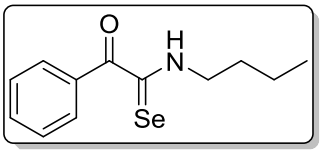
***2-mesityl-2-oxo-N-propylethaneselenoamide (4i)*:**



Oil; yield: 45%

IR (KBr film): 3295, 2963, 2926, 2872, 1672, 1609, 1516, 1455, 1380, 1242 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.48 (s, 1H), 6.76 (s, 2H), 3.53-3.48 (m, 2H), 2.23 (s, 3H), 2.07 (s, 6H), 1.84-1.75 (m, 2H), 0.99 (t, J = 7.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.64, 193.34, 138.82, 135.41, 133.54, 50.11, 20.78, 20.33, 19.16, 11.06 ppm; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{14}H_{19}NOSeNa$ 320.0530, found 320.0528.

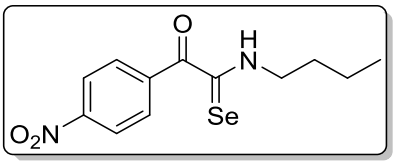
***N-butyl-2-oxo-2-phenylethaneselenoamide (4j)*:**



Oil; yield: 58%

IR (KBr film): 3251, 3057, 2957, 2930, 2869, 1658, 1539, 1449, 1260 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.08 (s, 1H), 7.95 (d, J = 7.2 Hz, 2H), 7.48 (t, J = 7.6 Hz, 1H), 7.34 (t, J = 7.6 Hz, 2H), 3.69 (q, J = 7.2 Hz, 2H), 1.78-1.70 (m, 2H), 1.46-1.38 (m, 2H), 0.92 (t, J =7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.1, 188.7, 132.7, 130.1, 129.4, 127.0, 47.1, 28.5, 19.2, 12.7 ppm; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{12}H_{15}NOSeNa$ 292.0217, found 292.0210.

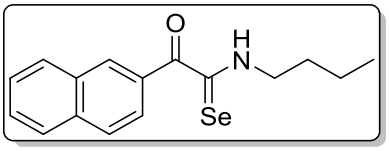
***N-butyl-2-(4-nitrophenyl)-2-oxoethaneselenoamide (4k)*:**



Oil; yield: 77%

IR (KBr film): 3243, 3054, 2960, 2932, 2870, 1669, 1523, 1344 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.26 (s, 1H), 8.14 (d, J = 8.8 Hz, 2H), 8.10 (d, J = 8.8 Hz, 2H), 3.75-3.70 (m, 2H), 1.97-1.87 (m, 2H), 1.45-1.39 (m, 2H), 0.98 (t, J = 7.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.1, 184.9, 148.4, 138.5, 129.7, 121.4, 46.9, 27.6, 19.8, 12.0 ppm; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{12}H_{14}N_2O_3SeNa$ 337.0067, found 337.0065.

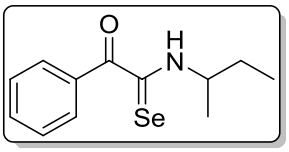
***N-butyl-2-(naphthalen-2-yl)-2-oxoethaneselenoamide (4l*):**



Oil; yield: 54%

IR (KBr film): 3229,3051, 2963, 2930, 2870, 1654, 1563, 1378, 1245, 1179 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.25 (s, 1H), 8.12-7.42 (m, 7H), 3.82 (q, J = 6 Hz, 2H), 1.72-1.65 (m, 2H), 1.27-1.18 (m, 2H), 0.79 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.1, 185.7, 134.4, 133.2, 133.0, 132.3,128.9. 128.3, 128.0, 127.9, 127.1, 123.9, 48.6, 29.8, 20.4, 13.8 ppm; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{16}H_{17}NOSeNa$ 342.0373, found 342.0367.

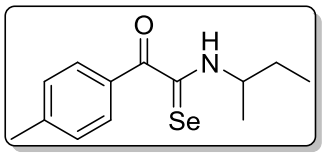
***N-(sec-butyl)-2-oxo-2-phenylethaneselenoamide (4m*)**:



Oil; yield: 60%

IR (KBr film): 3278, 3027, 2946, 2901, 2850, 1626, 1543, 1508, 1397, 1223; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1H), 7.94 (d, J = 7.2 Hz, 2H), 7.49 (t, J = 7.2 Hz, 1H), 7.35 (t, J = 7.6 Hz, 2H), 4.67-4.58 (m, 1H), 1.78-1.66 (m,2H),1.32 (d, J = 6,4 Hz, 3H), 0.96 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.8, 189.8, 134.8, 134.7, 131.4, 129.0, 56.4, 28.1 21.8, 11.1 ppm; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{12}H_{15}NOSeNa$ 292.0217, found 292.0214.

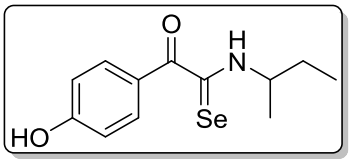
***N-(sec-butyl)-2-oxo-2-(p-tolyl)ethaneselenoamide (4n)*:**



Oil; yield: 64%

IR (KBr film): 3281,3058, 2965, 2929, 2873, 1646, 1541,1522, 1412, 1258 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (s, 1H), 7.83 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 4.67-.60 (m, 1H), 2.33 (s, 3H), 1.82-1.62 (m, 2H), 1.30 (d, J = 6.4 Hz, 3H), 0.96 (t, J =7.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.9, 189.9, 145.0, 131.1, 130.6, 128.9, 55.4, 28.1, 21.8, 18.2, 10.3 ppm; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{13}H_{17}NOSeNa$ 306.0373, found 306.0365.

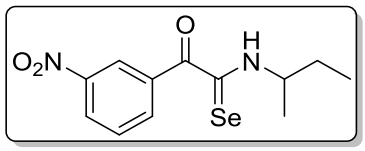
***N-(sec-butyl)-2-oxo-2-(p-tolyl)ethaneselenoamide (4o)*:**



Oil; yield: 48%

IR (KBr film): 3269, 3051, 2960, 2935, 2886, 1658, 1582, 1550, 1399, 1281, 1080 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.55(s, 1H), 7.90 (d, J = 8.0 Hz, 2H), 6.73 (d, J = 8.0 Hz, 2H), 4.63 (s, 1H), 1.80-1.63 (m, 2H), 1.30 (d, J = 6.8 Hz, 3H), 0.96 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.6, 188.4, 161.9, 131.8, 123.7, 114.6, 54.3, 26.9, 17.2, 9.5 ppm; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{12}H_{15}NO_2SeNa$ 308.0166, found 308.0169.

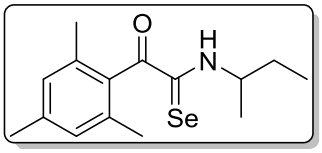
N-(sec-butyl)-2-(3-nitrophenyl)-2-oxoethaneselenoamide (4p):



Oil; yield: 82%

IR (KBr film): 3247, 3057, 2962, 2931, 2878, 1663, 1527, 1404, 1335 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.91 (s,1H), 8.78 (s, 1H), 8.32-8.28 (m, 2H), 7.55 (t, J = 7.6 Hz, 1H), 4.61-4.56 (m, 1H), 1.82-1.68 (m, 2H), 1.38 (d, J = 6.4Hz, 3H), 0.98 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.4, 186.1, 147.5, 136.2, 135.8, 129.0, 127.4, 125.1, 55.7, 28.1, 18.1, 10.3 ppm; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{12}H_{14}N_2O_3SeNa$ 337.0067, found 337.0055.

***N-(sec-butyl)-2-mesityl-2-oxoethaneselenoamide (4q*)**:



Oil; yield: 53%

IR (KBr film): 3290, 2957, 2929, 2869, 1670, 1604, 1518, 1454, 1344, 1265, 1170 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.217 (s,1H), 6.767(s, 2H), 4.477-4.375(m, J = 6 Hz, 1H), 2.23(s, 3H),2.08(s, 6H),1.82-1.62 (m, 2H), 1.30(d, J = 6.4Hz, 3H) 0.94 (t, J = 7.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.3, 192.8, 139.3, 136.0, 134.0, 128.0, 55.6, 28.0, 21.2, 19.6, 18.0, 10.3 ppm; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{15}H_{21}NOSeNa$ 334.0686, found 334.0678.

3B.4 Representative Spectra

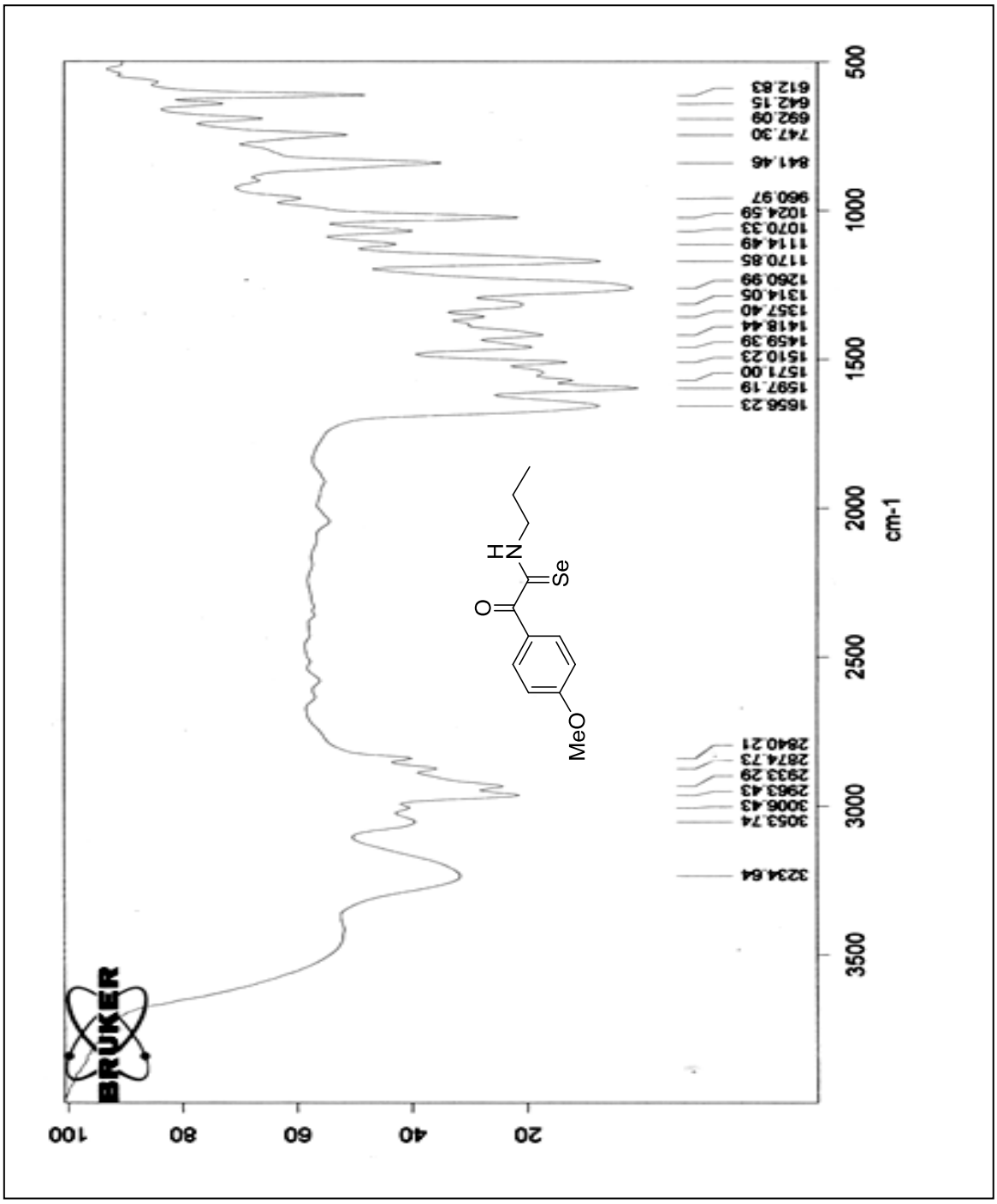


Figure 3B.1 IR spectrum of 2-(4-methoxyphenyl)-2-oxo-*N*-propylethaneselenoamide **(4c)**

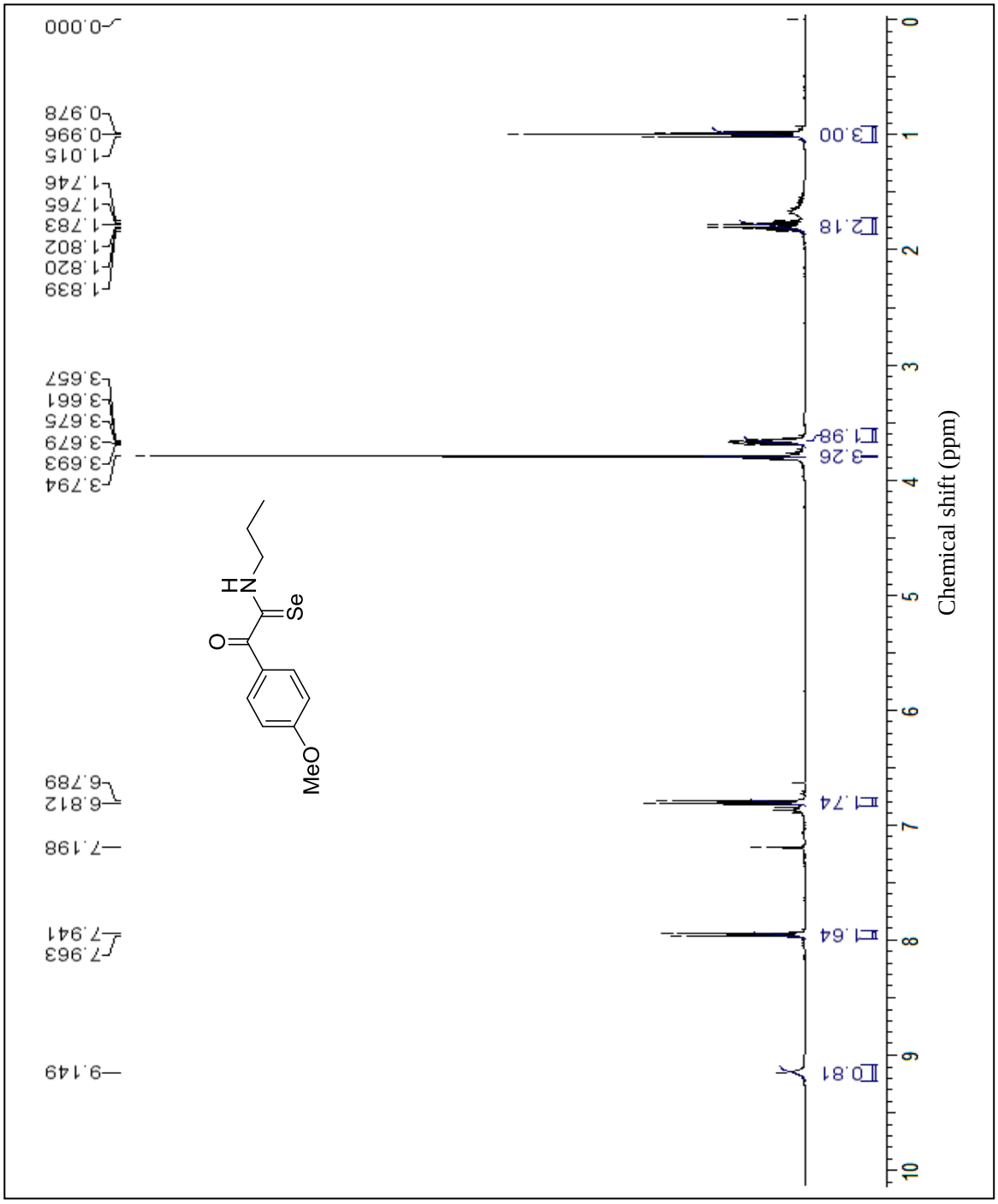


Figure 3B.2 ^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of 2-(4-methoxyphenyl)-2-oxo-*N*-propylethaneselenoamide **(4c)**

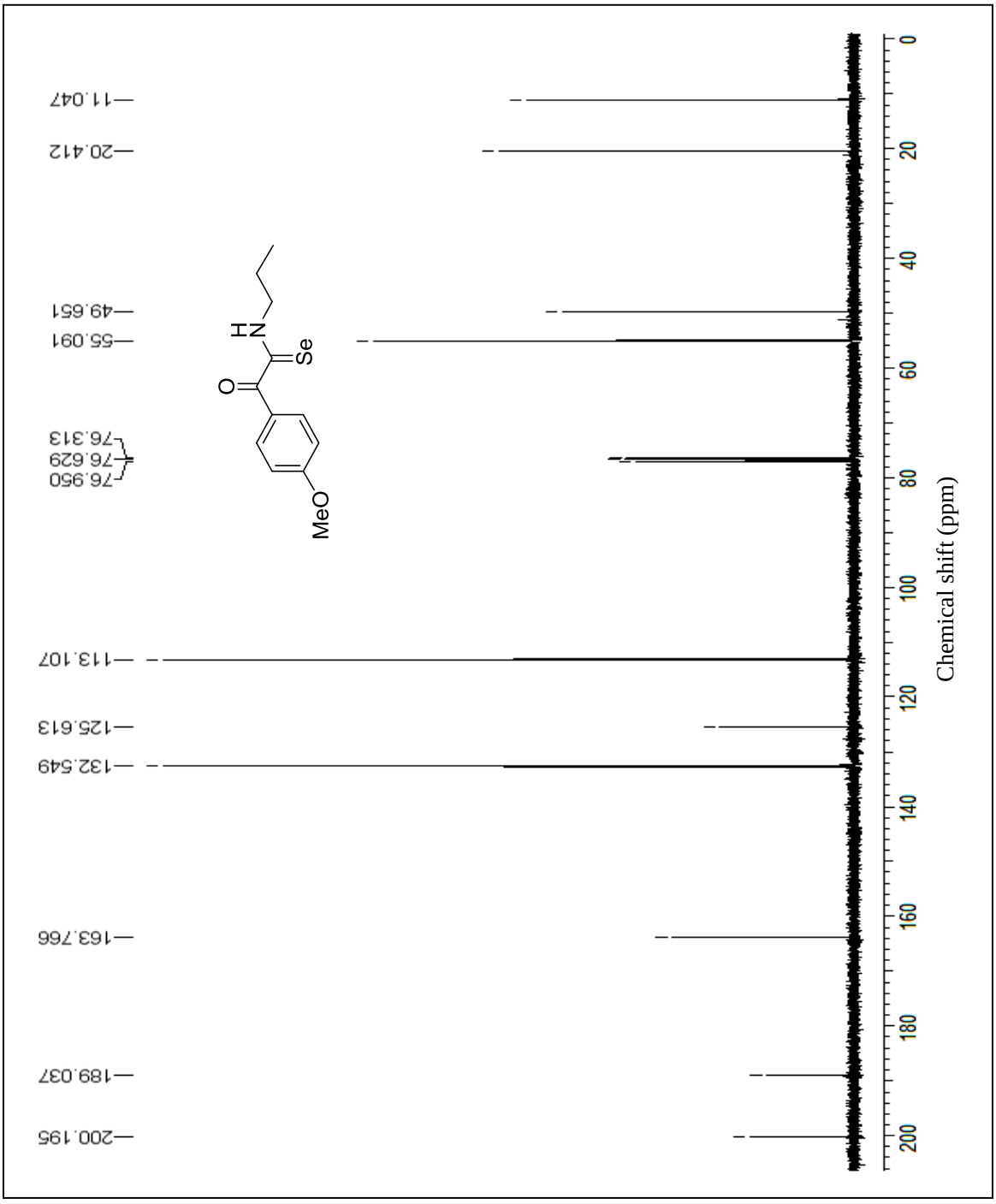


Figure 3B.3 ^{13}C NMR ($CDCl_3$, 100 MHz) spectrum of 2-(4-methoxyphenyl)-2-oxo-*N*propylethaneselenoamide **(4c)**

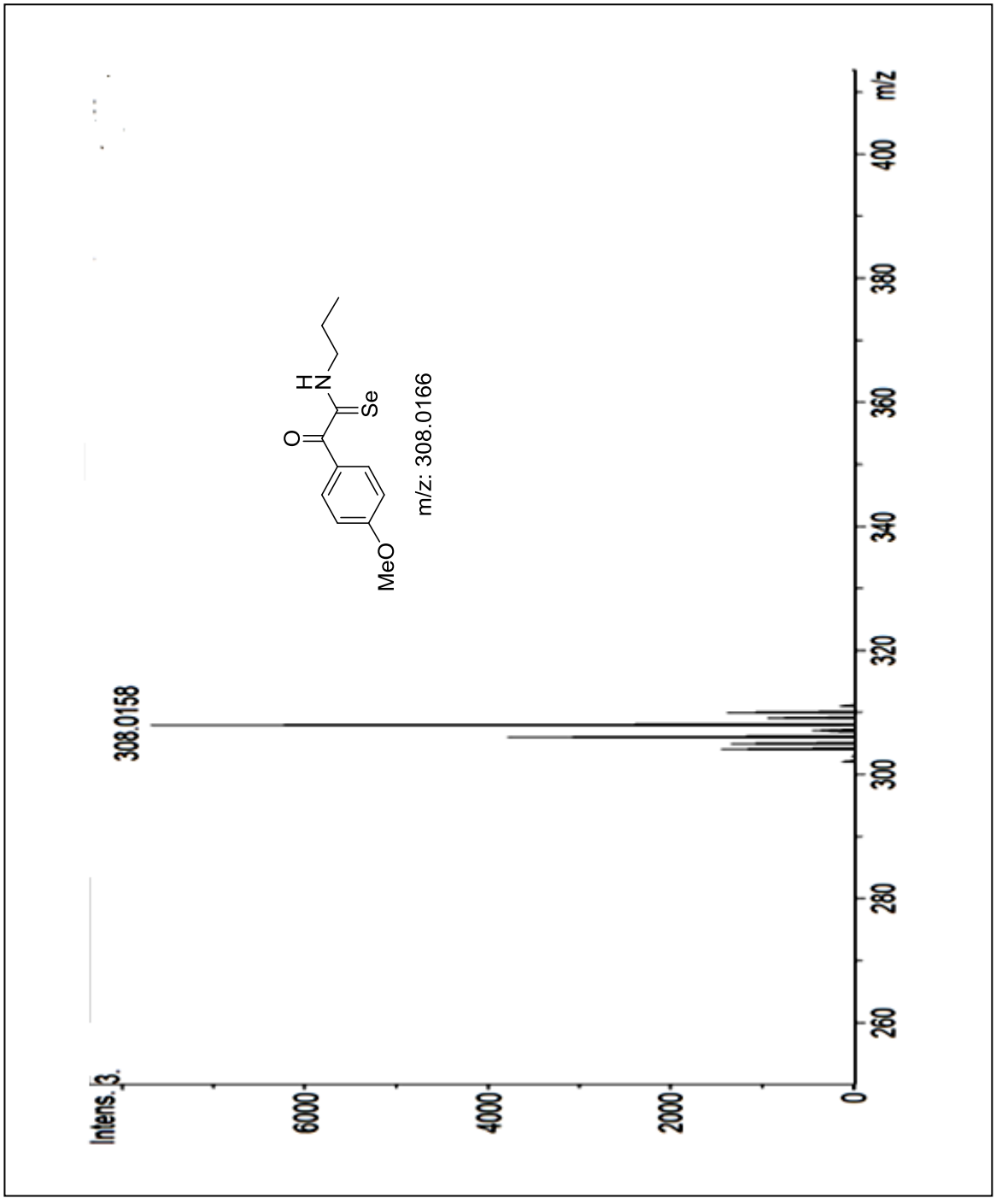


Figure 3B.4 Mass spectrum of 2-(4-methoxyphenyl)-2-oxo-*N*-propylethaneseleno amide **(4c)**

3B.5 References

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CHAPTER 4

Direct Synthesis of 1,4-Selenazines by Reaction of Aryl Alkyl Ketones with Selenium Dioxide in the Presence of Ammonium Acetate

4.1 Introduction

Heterocycles containing selenium atoms occupy a special place among organoselenium compounds. Although numerous reviews on various aspects of the chemistry of organoselenium compounds have been published during the last two decades, survey of the literature on organoselenium heterocycles is restricted to pre-1985.[1] Selenium-containing heterocycles represent an interesting class of compounds in the field of medicinal chemistry as well as in materials sciences.[2] Based on the advantages related to the presence of selenium in the heterocyclic ring and its biological importance, their synthetic methodologies has grown from the 1980's when Ebselen, the synthetic selenium-containing heterocycle was found to have a potential antioxidant properties.[3] The selenium-containing scaffolds like ebselen,[4] selenadiazoles,[5] seleno-chromenes,[6] selenium-embedded polysaccharide-protein complexes[7] and benzoselenophene fused imidazopyridines[8] have received much attention for their unique pharmacological properties.

1, 4-Selenazine is a class of selenium containing heterocycles that constitutes an important intermediate in organic synthesis and also exhibit potential for various biological properties such as antifungal activity,[9] antimicrobial photosensitizer,[10] antioxidant[11] and anti-Alzheimer's.[11] **Figure 4.1** represents some of the biologically active molecules containing the 1,4-selenazine moiety. 1,4-selenazine is also used as a chromophore for photosensitization of ruthenium nitrosyls complexes.[12] In spite of their importance, however, relatively few studies have been reported on the synthesis of 1, 4-selenazine.[9-15]

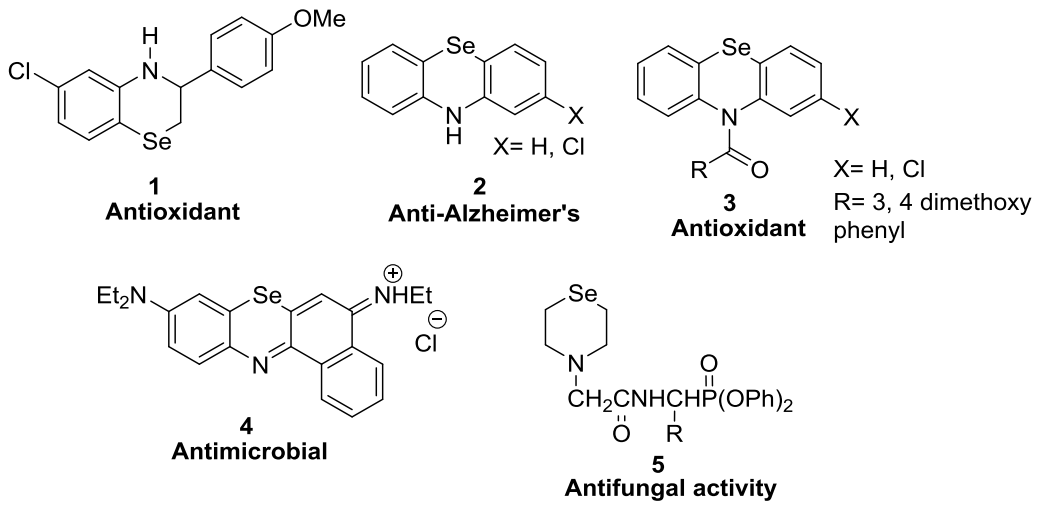
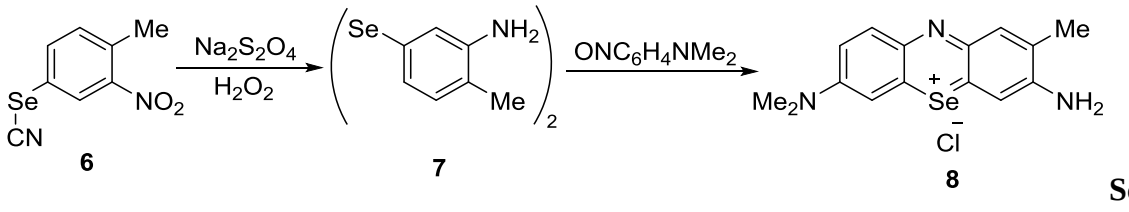


Figure 4.1 Medicinal importance of 1, 4-selenazine scaffolds

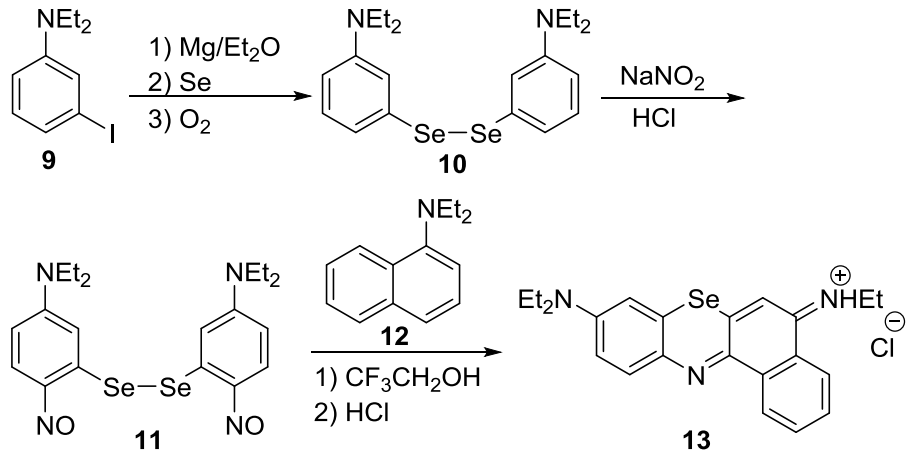
One of the first examples for the synthesis of 1, 4-selenazine was by reduction of 4-methyl-3-nitrophenylselenocyanate **(6)** with sodium dithionate followed by oxidation with H_2O_2 which gave bis-(4-methyl-3-aminophenyl)diselenide **(7)**. Cyclization of the latter with *N*,*N*-dimethylamino-*p*-nitrosoaniline hydrochloride gave **8.**[13]



Scheme 4.1

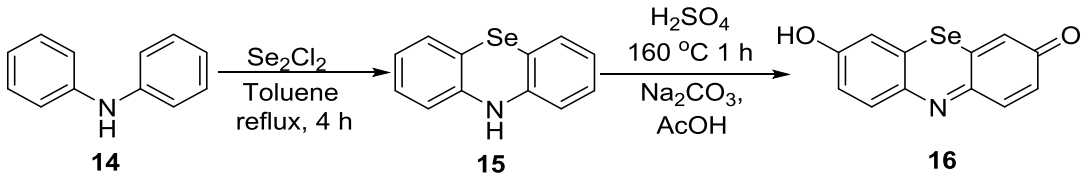
The preparation of 5-ethylamino-9-diethylaminobenzo[*a*]phenoselenazinium chloride (EtNBSe) was successfully achieved and reported by Hamblin *et al.* starting from the Grignard reagent derived from 3-iodo-*N*,*N*-diethylaniline **(9)** to give the diselenide **(10)** by reaction with selenium powder followed by oxidation. The diselenide **(10)** on treatment with nitrous acid gave dinitrosodiselenide **(11)** which further condense

with N-ethyl-1-naphthylamine **(12)** gave the corresponding EtNBSe **(13)** in good yields.[10]



Scheme 4.2

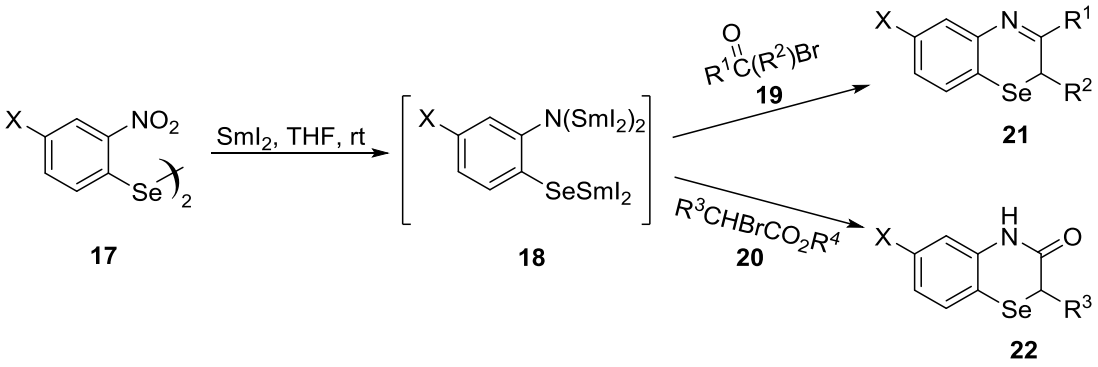
In 2009, Mascharak *et al*. reported the synthesis of the selenium-containing dye selenophore **(16)** from phenoselenazine **(15)** which was obtained from the reaction of diphenylamine **(14)** with Se_2Cl_2 in toluene.[12]



Scheme 4.3

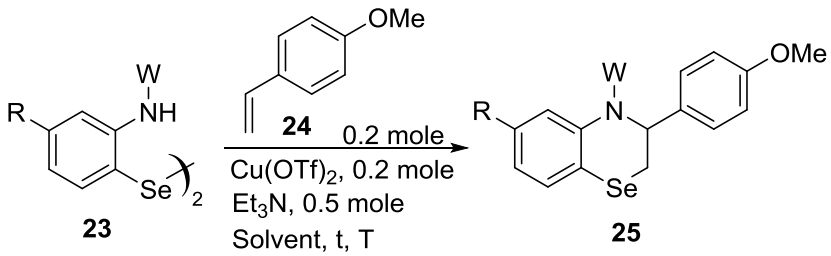
The reaction of bis(o-nitrophenyl)diselenides **(17)** with SmI_2 led to the reduction of nitro groups and reductive cleavage of the Se-Se bonds which give the intermediate **18**. The intermediate **18** undergo further reaction with α-bromoketones **(19)** and α-bromocarboxylic acid derivatives **(20)** to afford the desired 2*H*-1,4-benzoselenazines

(21) and 2*H*-1,4-benzo-selenazin-3(4*H*)-ones **(22)** respectively which was successfully achieved by Zhang and his co-workers.[14]



Scheme 4.4

Recently, in 2016 Viglianisi *et al.* reported one-pot access to benzo[*b*] [1,4]selenazines **(25)** from 2-amino aryl diselenides **(23)** with electron rich dienophiles using stoichiometric amount of $Cu(OTf)_2$. In this procedure, the synthesis of selenazines was achieved with a wide substrate scope by using different dienophiles such as styrene **(24)**, enol ethers, vinyl amides, and 1, 3-dienes which give a good yield of the products. A preliminary investigation of few selected selenazine for the GPx-like activity was also described.[15]

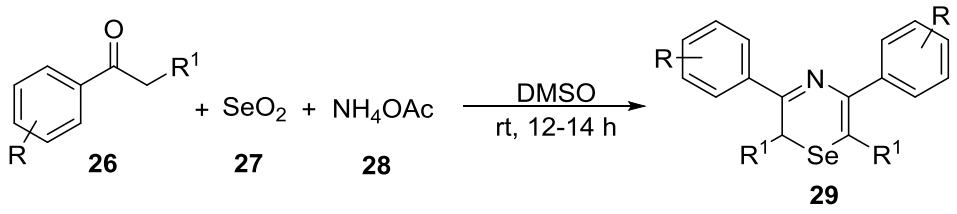


Scheme 4.5

Hence, the development of new selenium-containing heterocycles is highly desirable and has attracted the attention of many researchers due to their versatility as building blocks as well as important pharmaceuticals. As per to our literature survey, there is no reported method for the synthesis of 3,5-diphenyl-2*H*-1,4-selenazine derivatives. In this chapter, we wish to report the synthesis of 3,5-diphenyl-2*H*-1,4-selenazine starting from aryl alkyl ketones with selenium dioxide and ammonium acetate *via* a one-step process.

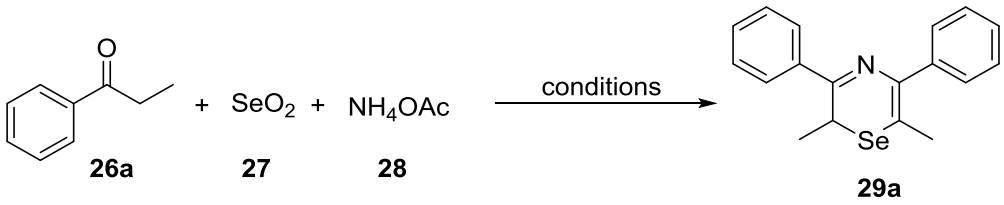
4.2 Results and Discussion

Based on our ongoing study on the synthetic utility of selenium dioxide for C-Se bond formation, we have developed a method for the synthesis of 3,5-diphenyl-2*H*-1,4-selenazine and its derivatives by three-component condensation of aryl alkyl ketones **(26)**, selenium dioxide **(27)** and ammonium acetate **(28)** at room temperature in DMSO as a solvent **(Scheme 4.6)**.



Scheme 4.6

Table 4.1 Optimization of the reaction conditions[a]



entry	substrate **3a** (equiv)	solvent	t (h)	yield (%)
1	1	DMSO	12	trace
2	2	DMSO	12	25
3	3	DMSO	12	40
4	**4**	**DMSO**	**12**	**59**
5	5	DMSO	12	60
6	4	Toluene	12	0
7	4	H_2O	12	0
8	4	EtOH	12	0

[a]Reaction conditions: ketone **(26)** (1.0 mmol), SeO_2 (0.5mmol), solvent (1 mL), room temperature.

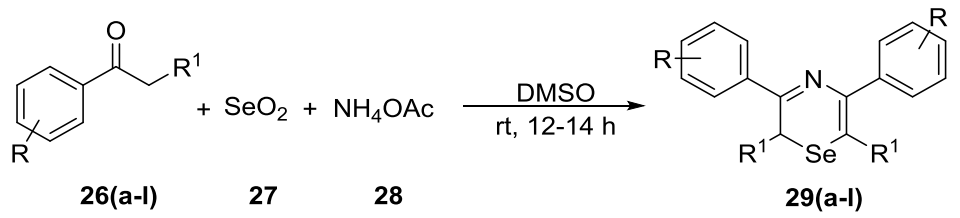
To initiate our investigation, we choose the readily available propiophenone **(26a)** as a model substrate for the proposed reaction cascade. Our initial effort in reacting propiophenone **(26a)** (1.0 mmol, 1 equiv), SeO_2 **(27)** (0.5 mmol, 0.5 equiv) and NH_4OAc **(28)** (1.0 mmol, 1.0 equiv) in DMSO (1 mL) at room temperature for 12 h, the corresponding product **29a** was obtained only in trace amount **(Table 4.1, entry 1)**.

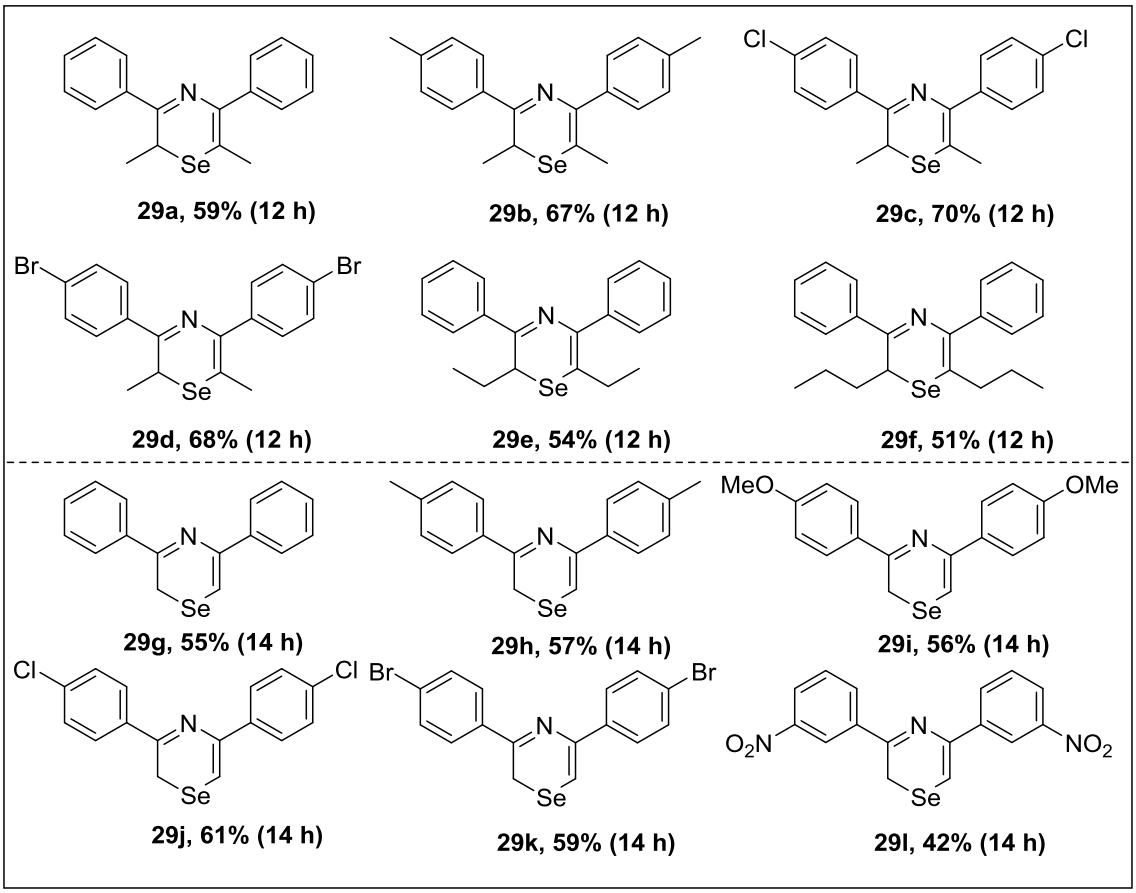
Furthermore, the isolated yield of **29a** was improved, when the reaction mixture was carried out in a stoichiometric amount of the ammonium acetate **(28) (Table 4.1, entries 2-5)**. To improve the yield of the product, the reaction was further carried out with different solvent and DMSO was found to be the best for the formation of **29a** to 59 % yield, whereas toluene, H_2O and ethanol failed to give the desired product **(Table 4.1, entries 6-8)**. However, after optimization, it was found that the optimal yield of the product **29a** was obtained when the reaction was performed with a stoichiometric amount of ammonium acetate **(28)** (4.0 equiv) in DMSO as a solvent **(Table 4.1, entry 4)**.

Having the optimized reaction conditions in hand, the substrate scope of the reaction with respect to various aryl alkyl ketones was investigated. First, we carried out the reaction with propiophenones and its derivatives. As shown in Scheme 2, Propiophenones bearing unsubstituted **(26a)**, *p*-Me **(26b)**, *p*-Cl **(26c)** and *p*-Br **(26d)** readily delivered the corresponding products **(29a**, 59%; **29b**, 67%; **29c**, 70%; **29d**, 68%**)** in moderate to good yields. It was observed that propiophenones bearing electron-withdrawing groups provided better yields comparatively. Further, the scope of the reaction was extended to long-chain alkyl such as butyrophenone **(26e)** and valerophenone **(26f)** which also successfully gave the desired products **29e**, **29f** in 54% and 51% yields respectively. From the results obtained it was found that with long-chain alkyl groups the product yield is lower, probably the result of steric hindrance. Secondly, to test the generality of the reaction, aryl methyl ketones such as acetophenone **(26g)**, *p*-Me **(26h)**, *p*-OMe **(26i)**, *p*-Cl **(26j)**, *p*-Br **(26k)** and *m*-NO_2 **(26l)** were allowed to react with ammonium acetate **(Scheme 4.7)**. Irrespective of the presence of electron-donating or electron-withdrawing at different position in the phenyl ring, the reaction were well

tolerated to furnished the corresponding products **(29g**, 55%; **29h**, 57%; **29i**, 56%; **29j**, 61%; **29k**, 59%; **29l**, 42%**)** in a satisfactory yields. It may be noted that the reaction with propiophenones **(26a-f)** gives better yields and proceeds cleanly as compared to acetophenones **(26g-l)**.

Scheme 4.7 Substrate scope of aryl alkyl ketones[a]

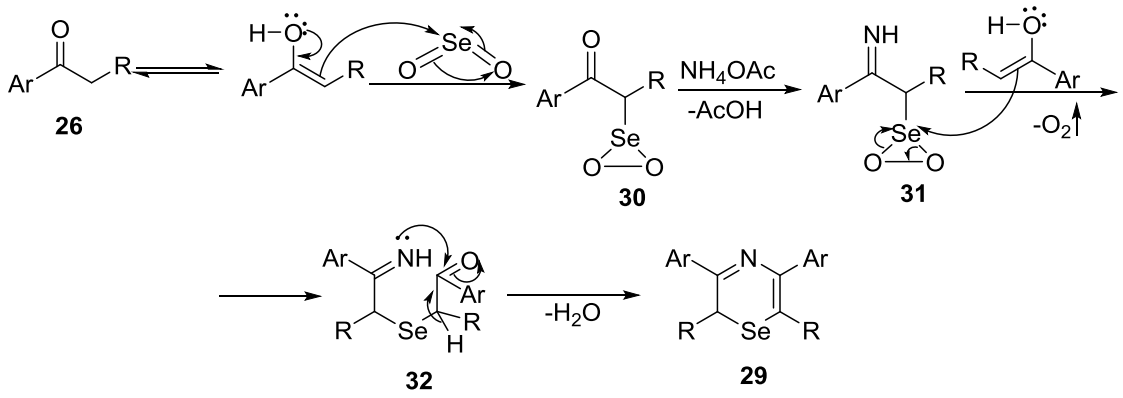




[a]Reaction conditions: ketone **(26)** (1.0 mmol), SeO_2 (0.5mmol), solvent (1 mL),room temperature.

The plausible mechanism is depicted in **Scheme 4.8**. The first step is the enolization of ketones **(26)** followed by the reaction with selenium dioxide **(27)** to generate selenium intermediate **30**. The intermediate **30** undergoes reaction with ammonium acetate **(28)** to give imine intermediate **31**. Another molecule of ketone **(26)** undergoes a nucleophilic attack on the selenium of the imine intermediate **32** which followed by cyclization leading to the formation of the product **29** with the elimination of a water molecule.

Scheme 4.8 Plausible mechanism



In summary, we have established a one-pot method for the synthesis of 1, 4-selenazine from aryl alkyl ketones, selenium dioxide and ammonium acetate. The procedure is simple and proceeds smoothly at room temperature. The attractiveness of this methodology is by the fact that the reaction proceeds without any catalyst, acid or base and the starting materials are cheap and easily available.

4.3 Experimental Section

General Methods

All reagents were purchased from Sigma Aldrich, TCI Chemicals and Alfa Aesar and were used without further purification unless noted. Melting points were recorded by open capillary tube method and are uncorrected. IR spectra were recorded on a Perkin Elmer Spectrum 400 FTIR instrument and the frequencies are expressed in cm^{-1}. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance II-400 spectrometer in $CDCl_3$ with TMS as internal standard. ^{77}Se NMR spectra were recorded on Mercury Plus 300Hz NMR Spectrometer in ppm using Me_2Se as internal standard. Mass spectral data were obtained with a Waters UPLC-TQD mass spectrometer (ESI-MS). High-resolution mass spectra (ESI-HRMS) were recorded on Agilent 6520Q-Tof (ESI-HRMS and APCI-HRMS) mass spectrometer. All reactions were monitored by thin layer chromatography (TLC) using pre-coated aluminium sheets (silica gel 60 F_{254} 0.2-mm thickness). Column chromatography was carried out on silica gel (100-200 mesh) and Flash chromatography was carried out on silica gel (230-400 mesh).

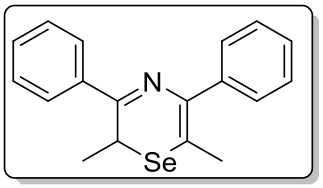
General procedure for the synthesis of 1, 4-selenazine

A mixture of aryl alkyl ketones **(26)** (1.0 mmol, 1 equiv), selenium dioxide **(27)** (55 mg, 0.5 mmol) in DMSO (1 mL) was stirred followed by the addition of ammonium acetate **(28)** (308 mg, 4.0 mmol, 4 equiv). The reaction was allowed to stir for 12-14 h at room temperature. After completion the reaction was diluted with ethylacetate (10 mL) and washed with brine (2x10 mL). The organic layer was separated, dried over anhydrous $NaSO_4$ and concentrated using rotatory evaporator. The compound was then

purified by flash chromatography on silica gel (230-400 mesh) using ethylacetate/hexane as eluent.

Spectroscopic analytical data

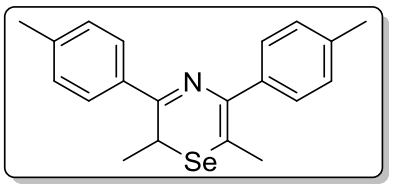
***2, 6-dimethyl-3, 5-diphenyl-2H-1, 4-selenazine (29a)*:**



Oil; yield: 59%

IR (KBr): 3057, 3024, 2953, 2905, 2849, 1563, 1441, 1330, 765, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96-7.94 (m, 2H), 7.58 (d, *J* = 7.2 Hz, 2H), 7.39-7.32 (m, 5H), 7.24 (t, *J* = 7.6, 7.2 Hz, 1H), 4.14 (q, *J* = 7.2, 6.8 Hz, 1H), 2.24 (s, 3H), 1.51 (d, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.6, 142.2, 138.4, 137.0, 129.9, 128.8, 128.5, 128.0, 127.3, 127.0, 110.7, 25.6, 21.3, 16.6 ppm; ^{77}Se NMR (57.25 MHz, CDCl3) δ 276.219; HRMS (ESI) calcd for $C_{18}H_{17}NSe$ 327.0526, found *m/z* 328.0596 $[M + H]^+$.

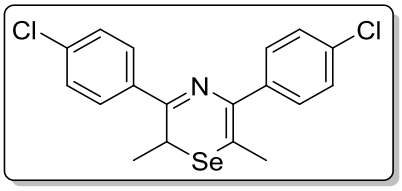
***2, 6-dimethyl-3, 5-di-p-tolyl-2H-1,4-selenazine (29b)*:**



Oil; yield: 67%

IR (KBr): 3076, 2986, 2930, 2871, 1566, 1440, 1371, 1289, 1211, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8 Hz, 2H), 7.49 (d, *J* = 7.6 Hz, 2H), 7.18-7.12 (m, 4H), 4.11 (q, *J* = 6.8, 7.2 Hz, 1H), 2.31 (s, 3H), 2.29 (s, 3H), 2.22 (s, 3H), 1.43 (d, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.7, 142.1, 140.2, 136.7, 135.6, 134.3, 129.3, 128.8, 128.7, 127.3, 109.4, 25.6, 21.47, 21.4, 21.3, 16.7 ppm; MS (ES^+) calcd for $C_{20}H_{21}NSe$ 355.0, found *m/z* 356.0 $[M + H]^+$.

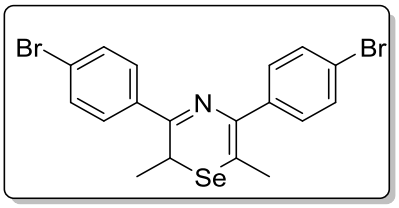
3,5-bis(4-chlorophenyl)-2,6-dimethyl-2H-1,4-selenazine (29c):



Oil; yield: 70%

IR (KBr): 3085, 2970, 2952, 1572, 1559, 1458, 1363, 1278, 1119, 681 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 8.8 Hz, 2H), 7.51-7.33 (m, 6H), 4.08 (q, J = 7.2 Hz, 1H), 2.32 (s, 3H), 1.42 (d, J = 7.6 Hz , 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0, 140.0, 138.0, 136.5, 133.7,133.0, 128.3, 127.7, 127.2, 126.9, 111.1, 24.4, 20.1, 15.5 ppm; MS (ES+) calcd for $C_{18}H_{15}Cl_2NSe$ 394.7.02, found *m/z* 395.9 $[M + H]^+$.

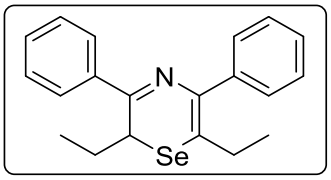
***3,5-bis(4-bromophenyl)-2,6-dimethyl-2H-1,4-selenazine (29d)*:**



Oil; yield: 68%

IR (KBr): 3088, 2986, 2929, 2871, 1572, 1526, 1450, 1371, 1200, 1109, 691 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 8.4 Hz, 2H), 7.76 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 8.8 Hz, 2H), 7.52 (d, J = 8.4 Hz, 2H), 4.26 (q, J = 7.2 Hz, 1H), 2.23 (s, 3H), 1.49 (d, J = 6.8Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.7, 142.1, 138.3, 136.8, 132.8, 132.5, 130.4, 127.9, 126.0, 122.9, 111.4, 25.9, 21.7, 16.8 ppm; MS (ES+) calcd for $C_{18}H_{15}Br_2NSe$ 484.8, found *m/z* 485.9 $[M + H]^+$.

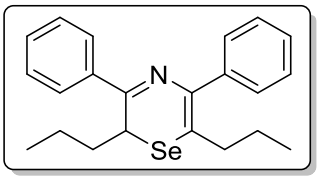
***2, 6-diethyl-3, 5-diphenyl-2H-1,4-selenazine (29e)*:**



Oil; yield: 54%

IR (KBr): 3093, 2967, 2889, 1557, 1436, 1345, 1265, 703 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93-7.18 (m, 10H), 3.95 (t, *J* = 7.6 Hz, 1H), 2.60-2.40 (m, 2H), 1.74-1.61 (m, 2H), 1.14 (t, *J* = 7.6, 7.2 Hz, 3H), 0.94 (t, J = 7.6, 6.8, 3H)) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.2, 142.2, 138.9, 137.5, 132.8, 129.9, 128.7, 128.5, 128.1, 127.5, 119.2, 40.5, 33.1, 27.2, 21.8, 15.70 ppm; MS (ES^+) calcd for $C_{20}H_{21}NSe$ 355.0, found *m/z* 356.1 $[M + H]^+$.

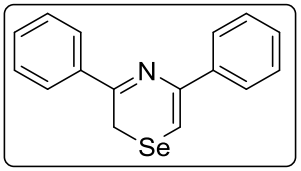
***3,5-diphenyl-2,6-dipropyl-2H-1,4-selenazine (29f)*:**



Oil; yield: 51%

IR (KBr): 3099, 2976, 2928, 1571, 1555, 1437, 1311, 1209, 667 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91-7.23 (m, 10H), 3.89 (t, *J* = 7.6 Hz, 1H), 2.71-2.52 (m, 2H), 1.95-1.48 (m, 6H), 1.18-0.93 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9, 146.1, 136.4, 135.3, 129.0, 127.2, 127.1, 126.8, 126.7, 119.9, 40.3, 33.2, 27.3, 24.5, 21.9, 15.2, 12.1 ppm; MS (ES+) calcd for $C_{22}H_{25}NSe$ 383.1, found *m/z* 384.0 $[M + H]^+$.

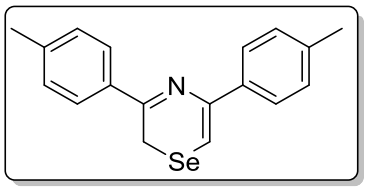
***3,5-diphenyl-2H-1,4-selenazine (29g)*:**



Yellow solid; yield: 55%, Mp: 42-44 ^{o}C

IR (KBr): 3101, 2985, 2967, 2887, 1569, 1449, 1397, 1283, , 678cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03-8.01 (m, 2H), 7.77 (d, *J* = 7.6, 2H), 7.42-7.22 (m, 5H), 6.72 (s, 1H), 3.31 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.8, 146.0, 137.5, 136.2, 129.3, 127.6, 127.4, 126.9, 126.6, 99.4, 14.6 ppm; MS (ES+) calcd for $C_{16}H_{13}NSe$ 299.0, found *m/z* 322.9 $[M + Na]^+$.

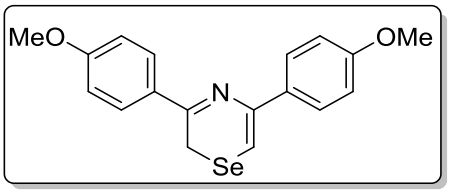
***3,5-di-p-tolyl-2H-1,4-selenazine (29h)*:**



Yellow solid; yield: 57%, Mp: 51-53 ^{o}C

IR (KBr): 3098, 2952, 2857, 1572, 1449, 1402, 1376, 1252, 659 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.4 Hz, 2H), 7.61 (d, *J* = 8 Hz, 2H), 7.27-7.22 (m, 4H), 6.71 (s, 1H), 3.28 (s, 2H), 2.28 (s, 3H), 2.23 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.4, 146.1, 139.2, 135.7, 134.6, 133.3, 128.3, 127.8, 127.7, 126.3, 101.1, 21.4, 21.3, 15.7 ppm; MS (ES^+) calcd for $C_{18}H_{17}NSe$ 327.0, found *m/z* 328.1 $[M + H]^+$.

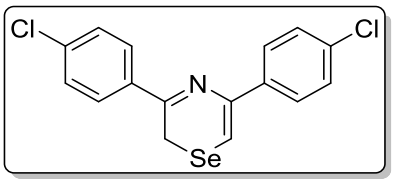
***3, 5-bis(4-methoxyphenyl)-2H-1,4-selenazine (29i)*:**



Yellow solid; yield: 56%, Mp: 60-62 ^{o}C

IR (KBr): 3095, 2978, 2942, 2886, 1564, 1520, 1441, 1389, 1202, 707 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 8.8 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 7.01 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.4 Hz, 2H), 6.82 (s, 1H), 3.85 (s, 3H), 3.26 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 159.2, 148.4, 146.3, 130.21, 128.9, 127.8, 126.6, 114.4, 114.2, 55.3, 15.8 ppm; MS (ES^{+}) calcd for $C_{18}H_{17}NO_2Se$ 359.0, found *m/z* 382.0 $[M + Na]^{+}$.

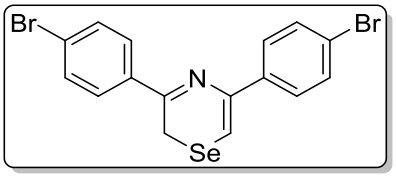
***3,5-bis(4-chlorophenyl)-2H-1,4-selenazine (29j)*:**



Yellow solid; yield: 61%, Mp: 45-47 ^{o}C

IR (KBr): 3034, 2954, 2898, 1563, 1547, 1447, 1340, 1291, 1108, 1006, 670 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 8.8 Hz, 2H), 7.38 (d, J = 8 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 6.72 (s, 1H), 3.26 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.6, 146.0, 136.8, 136.6, 135.4,133.5, 129.2, 128.9, 128.6, 126.6, 101.6, 15.5 ppm; MS (ES+) calcd for $C_{16}H_{11}Cl_2NSe$ 366.9, found *m/z* 390.1 $[M + Na]^{+}$.

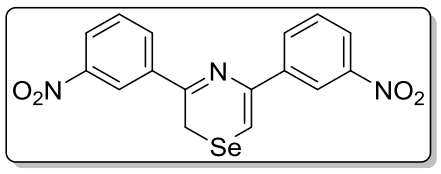
***3,5-bis(4-bromophenyl)-2H-1,4-selenazine (29k)*:**



Yellow solid; yield: 59%, Mp: 41-43 ^{o}C

IR (KBr): 3103, 2978, 2939, 1670, 1526, 1436, 1346, 1244, 1201, 1069, 677 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 8.8 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 6.74 (s, 1H), 3.26 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7, 146.1, 137.3, 135.9, 131.9, 131.5, 129.5, 126.9, 125.1, 121.7, 101.8, 15.4 ppm; MS (ES+) calcd for $C_{16}H_{11}Br_2NSe$ 456.8, found *m/z* 457.9 $[M + H]^+$.

***3,5-bis(3-nitrophenyl)-2H-1,4-selenazine (29l)*:**



Yellow solid; yield: 42%, Mp: 56-58 ^{o}C

IR (KBr): 3081, 2987, 2886, 1568, 1516, 1442, 1362, 1269, 1214, 1074, 712 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.71 (s, 1H), 8.47 (s, 1H), 8.36-8.01 (m, 4H), 7.57 (t, J = 8.4 Hz, 1H), 7.44 (t, J = 8.4 Hz, 1H), 6.93 (s, 1H), 3.31 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 146.3, 145.0, 139.7, 138.5, 133.8, 131.1, 129.9, 129.4, 125.1, 122.7, 122.4, 120.2, 105.7, 15.7 ppm; MS (ES+) calcd for $C_{16}H_{11}N_3O_4Se$ 388.9, found *m/z* 389.9 $[M + H]^+$.

4.4 Representative Spectra

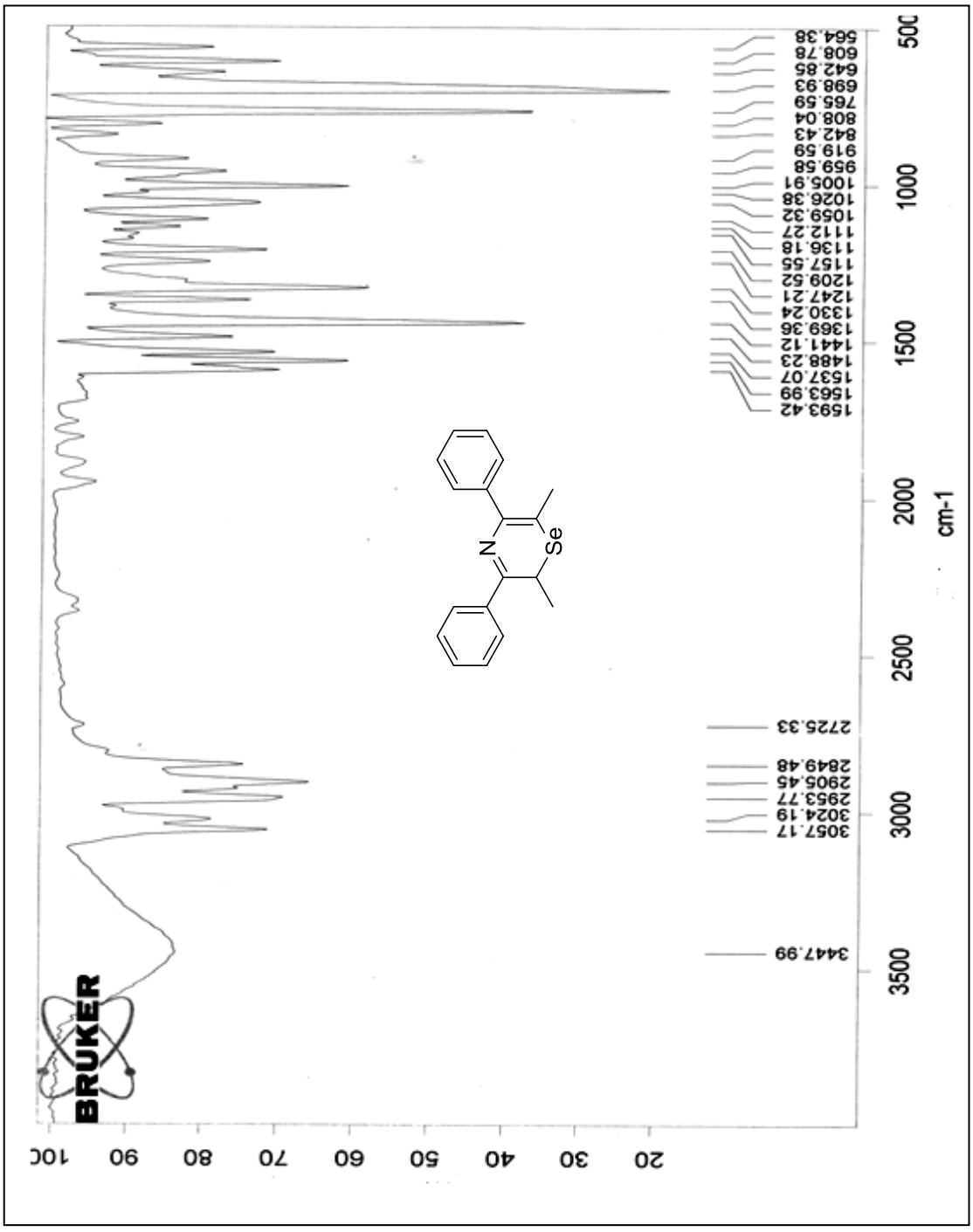


Figure 4.2 IR spectrum of 2,6-dimethyl-3,5-diphenyl-2*H*-1,4-selenazine **(29a)**

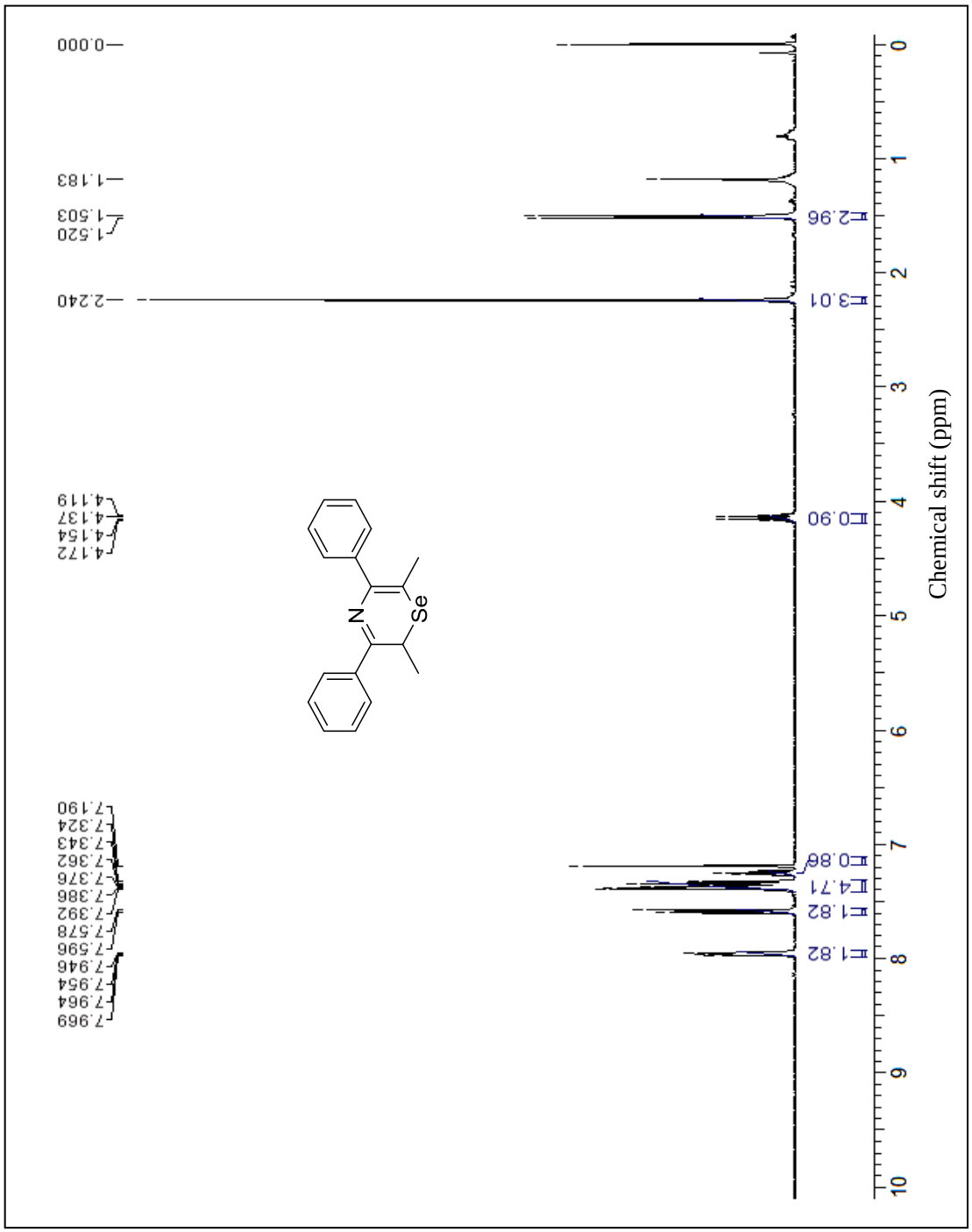


Figure 4.3 ^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of 2,6-dimethyl-3,5-diphenyl-2*H*-1,4-selenazine **(29a)**

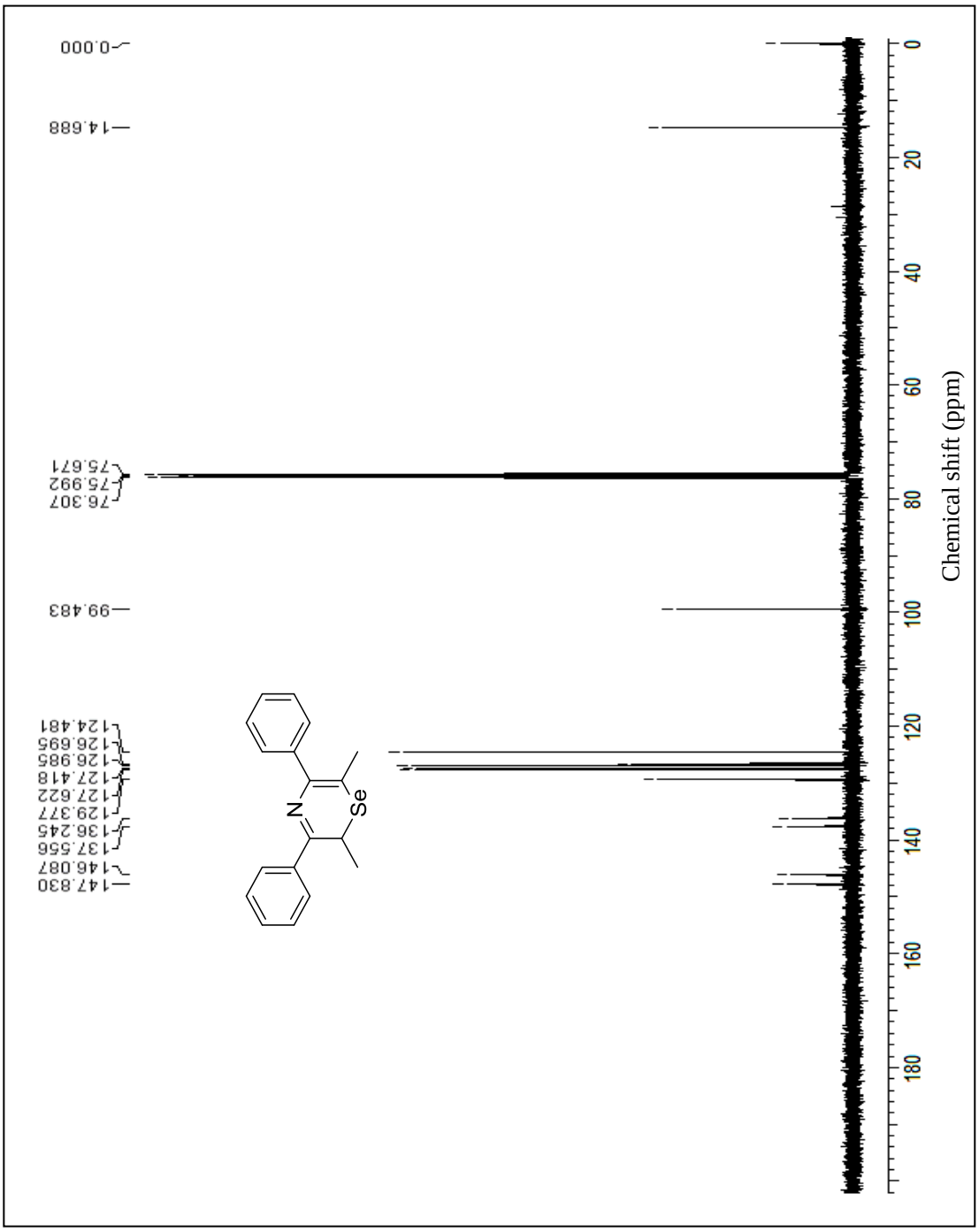


Figure 4.4 ^{13}C NMR ($CDCl_3$, 100 MHz) spectrum of 2,6-dimethyl-3,5-diphenyl-2*H*-1,4-selenazine **(29a)**

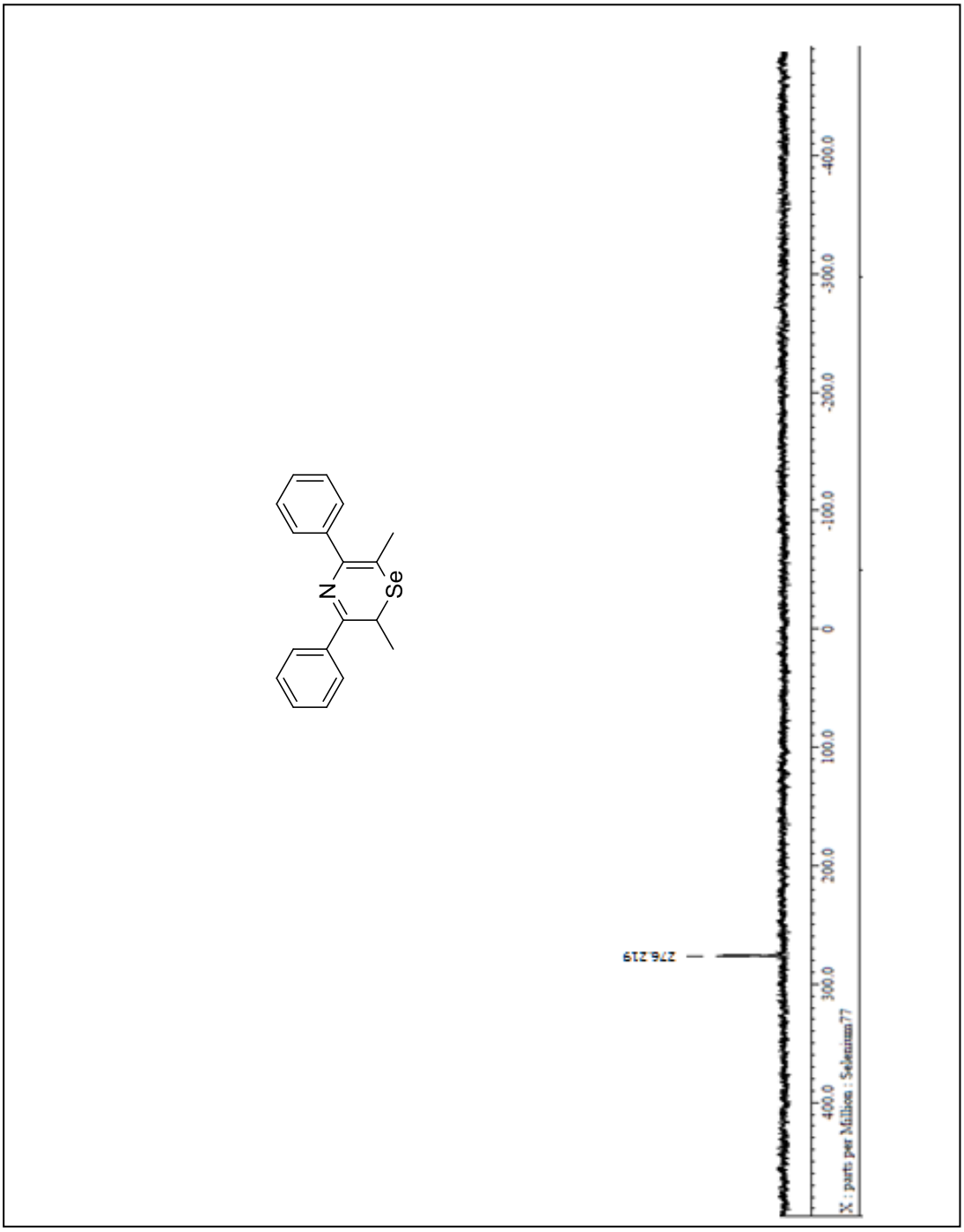


Figure 4.5 [77] Se NMR spectrum ($CDCl_3$, 57.25 MHz) of 2,6-dimethyl-3,5-diphenyl-2*H*-1,4-selenazine **(29a)**

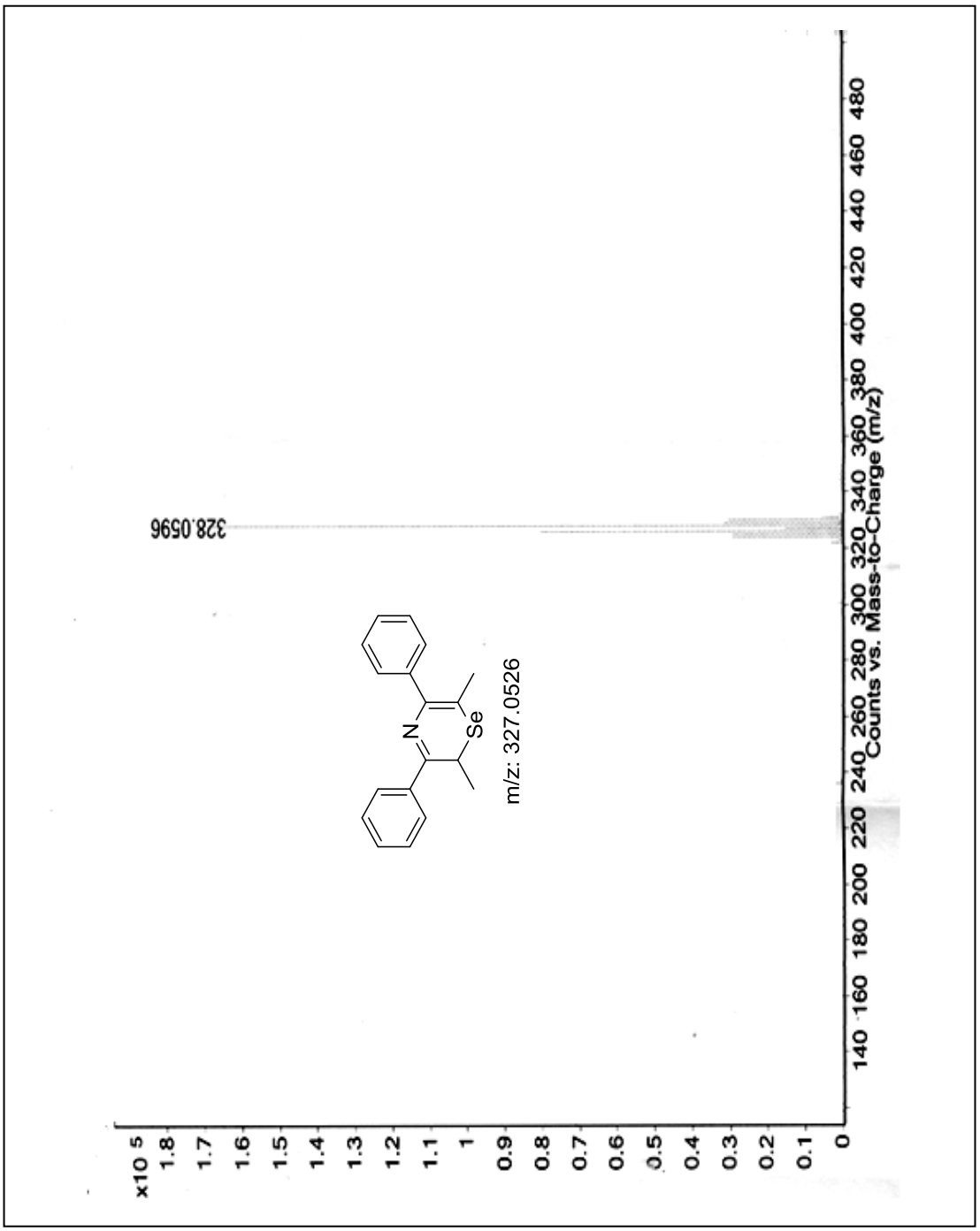


Figure 4.6 Mass spectrum of 2,6-dimethyl-3,5-diphenyl-2*H*-1,4-selenazine **(29a)**

4.5 References

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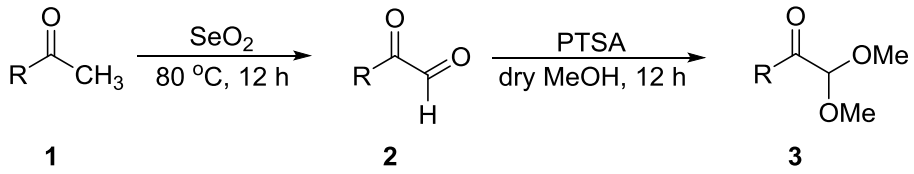
CHAPTER 5

PTSA-Catalyzed Reaction of Alkyl/Aryl Methyl Ketones with Aliphatic Alcohols in the Presence of Selenium Dioxide: A Protocol for the Generation of an α-Ketoacetals Library

5.1 Introduction

α-ketoacetals are important functional moieties and are useful building blocks in organic synthesis. They are useful intermediates in that they provide an array of functional groups which are extremely valuable in organic synthesis. For instance the *α*-ketoacetals are key intermediates in the synthesis of various biologically active compounds, such as chiral *α*-hydroxy acetals,[1] chiral *α*-amino acetals,[2] chiral auxiliaries,[3] cyanosilylation[4] and also for the construction of important heterocycles.[5] Several methods have been described for the preparation of *α*-ketoacetals.[5-9]

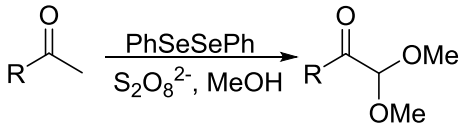
Goswami *et al.* reported the synthesis of aliphatic *α*-ketoacetals **(3)** starting from ketones **(1)** *via* a two-step procedure using SeO_2 **(Scheme 5.1)**.[5a-b]



1 **2** **3**

Scheme 5.1

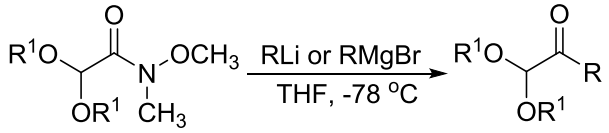
Tiecco and co-workers reported the synthesis of *α*-ketoacetals **(3)** catalyzed by diphenyl diselenide and an excess of ammonium peroxydisulfate under reflux conditions **(Scheme 5.2)**.[7]



1 **3**

Scheme 5.2

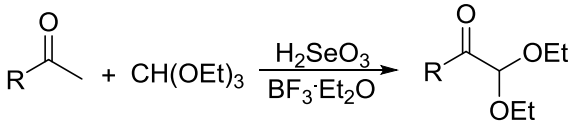
Ayala-Mata and group employed Weinreb amides **(4)** as a starting material for the synthesis of *α*-ketoacetals **(3) (Scheme 5.3)**.[8]



4 **3**

Scheme 5.3

More recently, we have reported the synthesis of phenylglyoxal diethylacetals **(3)** *via* the reaction of aromatic ketones **(1)** with triethylorthoformate **(5)** in presence of H_2SeO_3 catalyzed by $BF_3 \cdot Et_2O$ **(Scheme 5.4)**.[9]



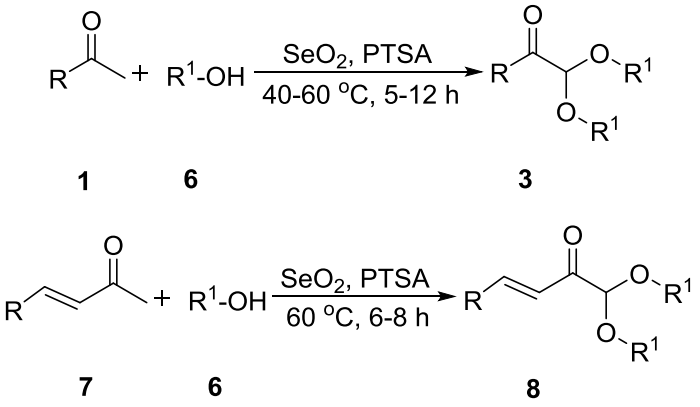
1 **5** **3**

Scheme 5.4

This method, though simple, is limited by the use of triethylorthoformate **(7)** as the sole source of alkoxide nucleophile. Generally, most of the other reported methods involved multistep reactions. Besides, the high cost of the reagents, coupled with sensitive reaction conditions limit their scope of applications. Development of an alternative method for the synthesis of *α*-ketoacetals with wide substrate scope starting from simple and easily available starting materials would, therefore, be a welcome addition to synthetic organic chemists.

The reactive behavior of SeO_2 towards organic substrates in presence of a Lewis acid or a strong organic acid, however, has found few in the literature study. Earlier we reported an efficient regio-selective protocol for the C-C bond formation by an unexpected *α,α*-diarylation of aromatic ketones in presence of selenium dioxide, catalyzed by boron trifluoride etherate.[10] This unusual reactivity of SeO_2 towards aromatic ketones in presence of a Lewis acid prompted us to explore its reactions with organic substrates by varying the nature of the acid and the solvent used. Since then, we have further demonstrated this unique reactivity of SeO_2 with aromatic ketones by changing the acid catalyst and/or the solvent used, leading to the formation of important organic intermediates.[11]

As part of our ongoing investigation on the synthetic utility of selenium dioxide,[9-11] we wish to report here an efficient general method for the synthesis of *α*-ketoacetals **(3)** from a wide range of ketones **(1** and **7)** and alcohols **(6)** in presence of SeO_2 catalyzed by PTSA **(Scheme 5.5)**.

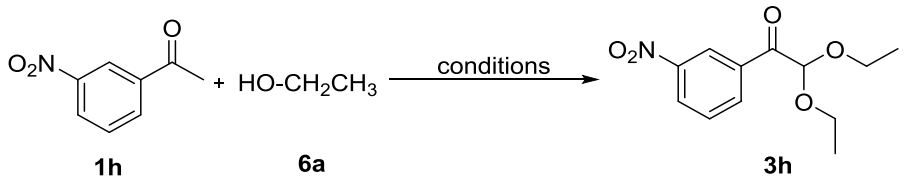


Scheme 5.5

5.2 Results and Discussion

Initially, when a mixture of 1-(3-nitrophenyl)ethanone **(1h)** (165 mg, 1.0 mmol, 1equiv), ethanol **(6a)** (1 mL), SeO_2 (55 mg, 0.5 mmol 0.5 equiv) and PTSA (95 mg, 0.5 mmol, 0.5 equiv) was stirred at room temperature for 12 h, only trace amount of the product **3h** was formed as observed by TLC **(Table 5.1, Entry 1)**. When the reaction temperature was raised to 60 °C for 8 h, the yield increased to 52% **(Table 5.1, Entry 2)**. Any further increase in the temperature did not increase the yield of the product **3h**. Further, optimization of the reactions by varying the number of equivalents of selenium dioxide and PTSA **(Table 5.1, Entry 2-6)** were carried out. It was found that (77 mg, 0.7 mmol, 0.7 equiv) of SeO_2 and (190 mg, 1.0 mmol, 1.0 equiv) of PTSA gave optimum yield of the product (85%) **(Table 5.1, Entry 4)**. To establish whether PTSA is unique to this reaction, other organic acids such as TFA and CH_3COOH were employed and in both cases the desired product was not formed. It may be noted that the use of either SeO_2 or PTSA alone failed to give the desired product.

Table 5.1 Optimization of the reaction conditions[a]



1h **6a** **3h**

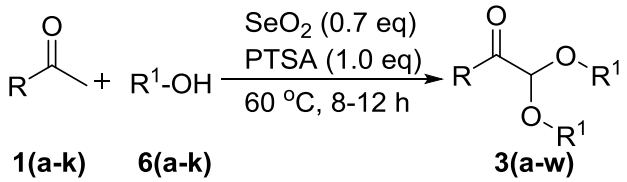
entry	oxidant (equiv)	catalyst (equiv)	temperature ^{o}C	*t* (h)	yield (%)[b]
1	SeO_2 (0.5)	PTSA (0.5)	rt	12	trace
2	SeO_2 (0.5)	PTSA (0.5)	60	8	52
3	SeO_2(0.5)	PTSA (1.0)	60	12	61
4	**SeO_2 (0.7)**	**PTSA (1.0)**	**60**	**8**	**85**
5	SeO_2 (0.7)	PTSA (1.0)	80	8	83
6	SeO_2 (1.0)	PTSA (1.0)	60	8	86

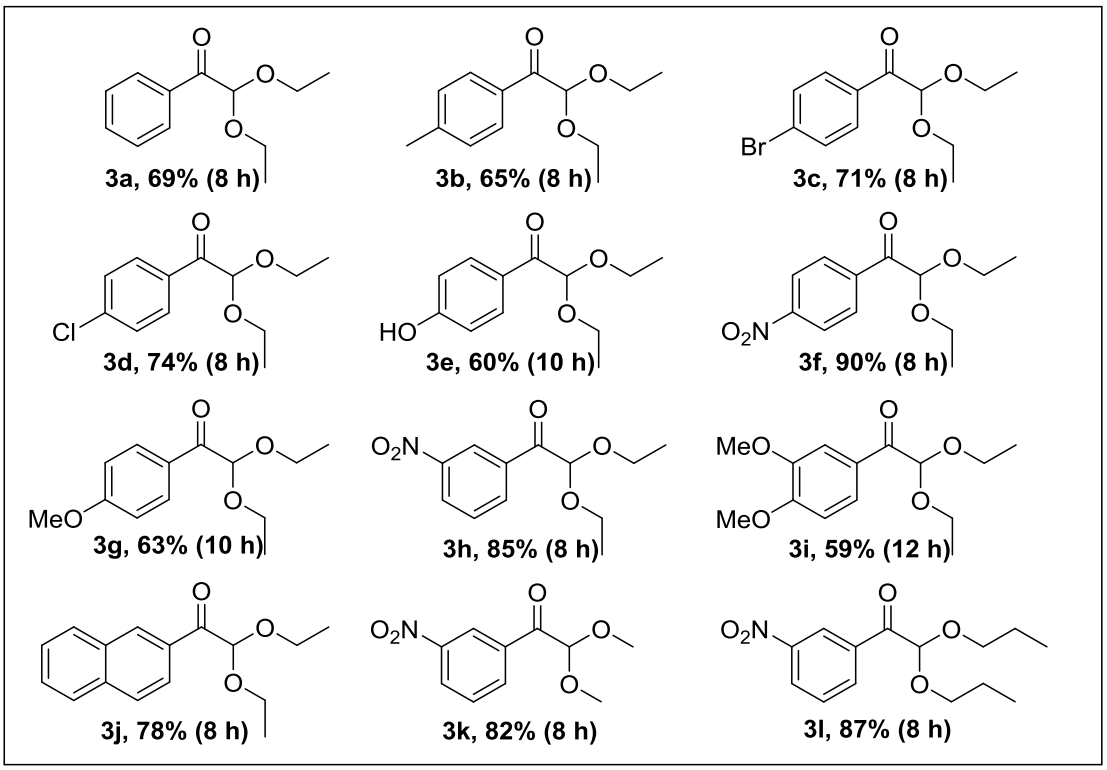
[a]Reaction conditions: ketones **(1)** (1.0 mmol), ethanol **(6)** (1 mL). [b]Yields.

With the optimized conditions in hand, the scope and the generality of the reaction of aryl methyl ketones with alcohols were investigated. First, the reaction demonstrated wide substrate scope in terms of the aromatic ketone **(1a-j)** with ethanol **(6a) (Scheme 5.6)**. Aryl methyl ketones bearing electron-neutral (4-H), electron-donating (e.g., 4-Me, 4-OH, 4-OMe, 3, 4-$(OMe)_2$) or electron-withdrawing (e.g., 3-NO_2, 4-NO_2) substituent in the ring were successfully converted to the corresponding products **3a-b**, **3e-f** and **3g-i** in moderate to good yields (59-90%). The procedure was also found

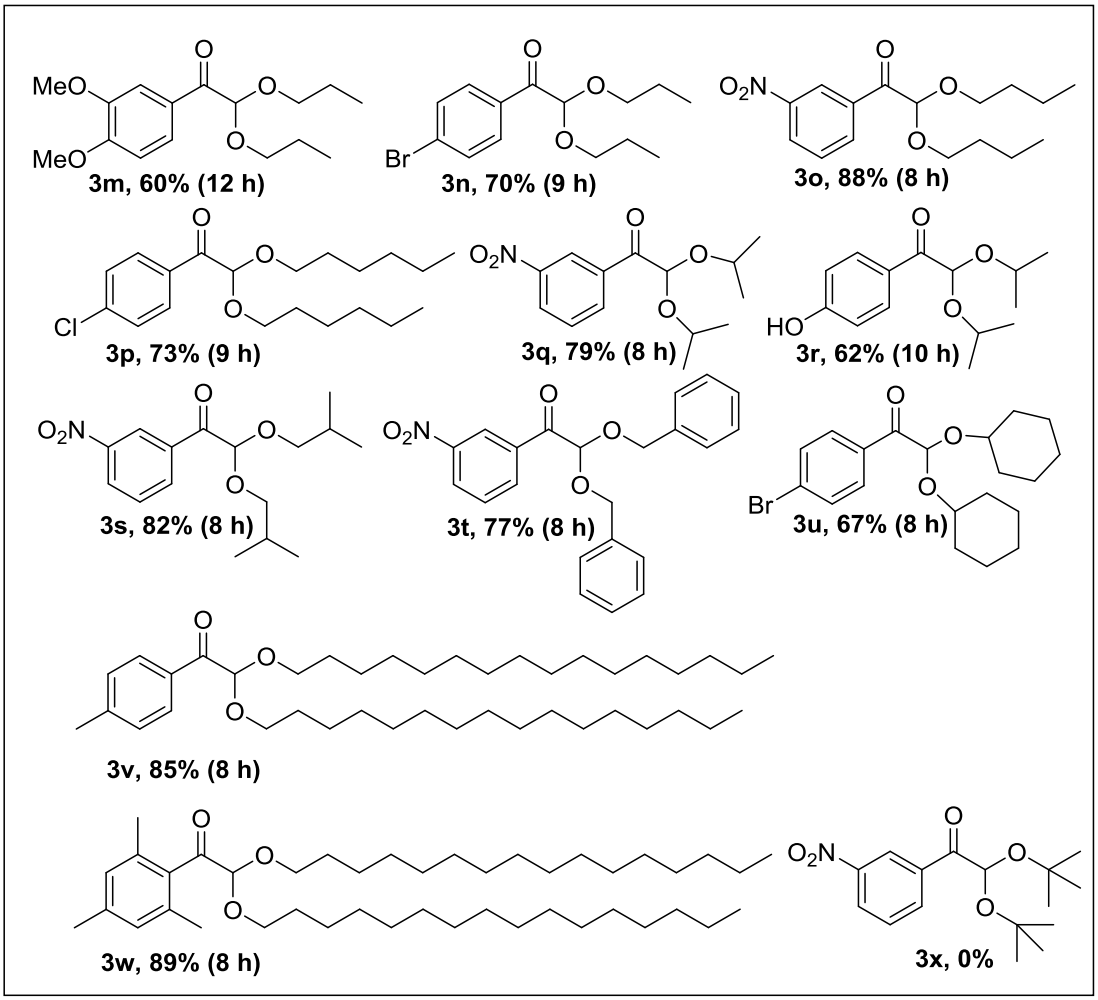
to be compatible with halogenated aryl methyl ketone (4-Br, 4-Cl), which gave the desired products in good yields **(3c**, 71%; **3d**, 74%**)**. The scope of the reaction was also extended to sterically hindered 2-acetyl naphthalene **(1j)**, which readily yielded product **3j** in 78% yield.

Scheme 5.6 Scope of aryl methyl ketones that couple with alcohols[a]





[a]Reaction conditions: ketones **(3)** (1.0 mmol), alcohols **(6)** (1 mL), SeO_2 (0.7 equiv), PTSA (1.0 equiv) at 60 °C, 8-12 h.



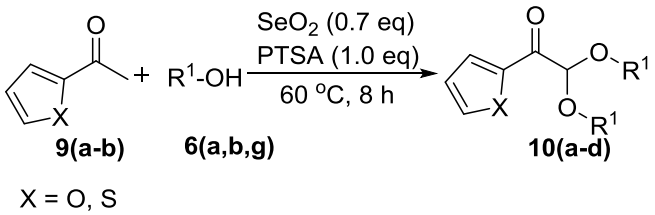
[a]Reaction conditions: ketones **(3)** (1.0 mmol), alcohols **(6)** (1 mL), SeO_2 (0.7 equiv), PTSA (1.0 equiv) at 60 °C, 8-12 h.

Secondly, homologs of alcohol from the aliphatic series **(Scheme 5.6)** were randomly selected. Both primary and secondary aliphatic alcohols easily undergo double nucleophilic attack on the *α*-carbon atom of the ketone to give the desired products **3k-w** in moderate to good yields (60−89%). Methanol **(6b)**, 1-propanol **(6c)**, 1-butanol **(6d)**, 1-hexanol **(6e)**, benzyl alcohol **(6f)**, *iso*-butanol **(6g)** readily reacted with aryl methyl ketones bearing electron-withdrawing group (3-NO_2), electron-donating groups (3,4-$(OMe)_2$), halogenated aryl methyl ketones (4-Br, 4-Cl) to give the corresponding products **3k-p** and **3s-t** in moderate to good yields (60-88%). Ordinarily, one would have

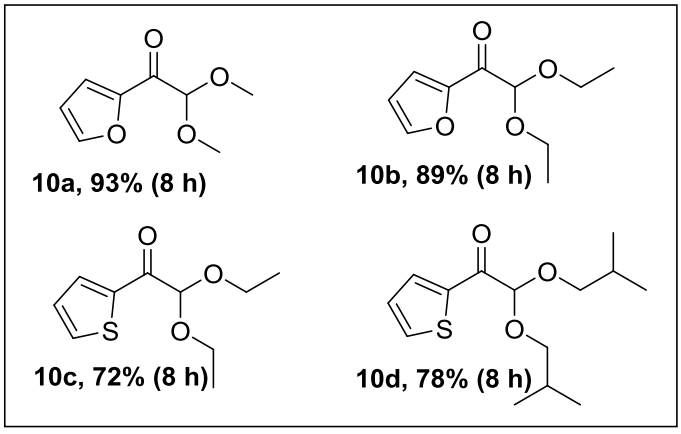
expected that long chain aliphatic alcohol would not react because of steric consideration. Surprisingly, however, the reaction with cetyl alcohol **(6h)** proceeded cleanly in 8 h to give excellent yields of the desired product (**3v**, 85%; **3w**, 89%). Similarly, secondary alcohols such as *iso*-propanol **(6i)** and cyclohexanol **(6j)** also reacted smoothly to give the corresponding products **3q-r** and **3u** in satisfactory yields (62-79%). However, tertiary aliphatic alcohol **(6k)** failed to react evidently due to the bulky nature of the substituent adjacent to the reacting nucleophile **3x**.

The methodology was further extended to the reaction of hetero-aryl methyl ketones **(9)** with aliphatic alcohol **(6)** which effortlessly gave the desired products **10a-d** in moderate to good yields (72-93%) **(Scheme 5.7)**.

Scheme 5.7 Scope of heteroaryl methyl ketones that couple with alcohols[a]



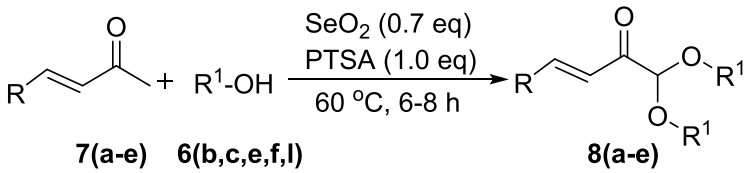
9(a-b) **6(a,b,g)** **10(a-d)**

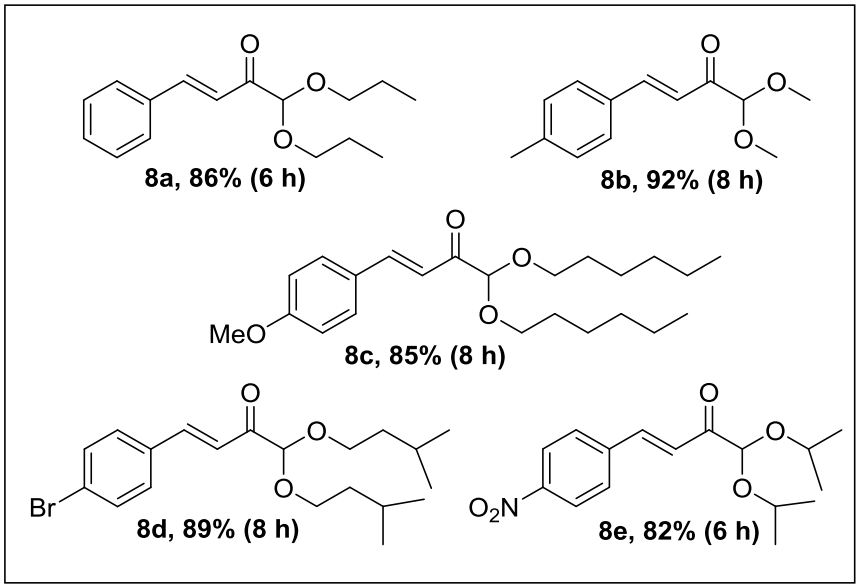


[a]Reaction conditions: ketones **(9)** (1.0 mmol), alcohol **(6)** (1 mL), SeO_2 (0.7 equiv), PTSA (1.0 equiv) at 60 °C, 8 h.

To further explore the efficacy of the method, reactions of substituted benzylidine acetones **(7)** with alcohols **(6)** were performed **(Scheme 5.8)**. Benzylidine acetone bearing electron neutral (4-H), electron donating (e.g. 4-Me, 4-OMe), electron withdrawing (4-NO_2) or halogenated group (4-Br), all gave the expected products **8a-e** in good yield (82-92%).

Scheme 5.8 Scope of *α,β*-unsaturated ketones that couple with alcohols[a]



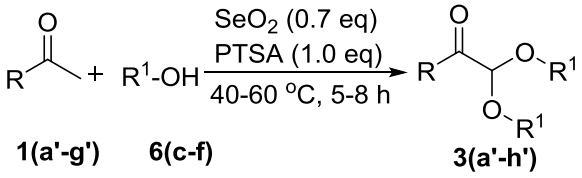


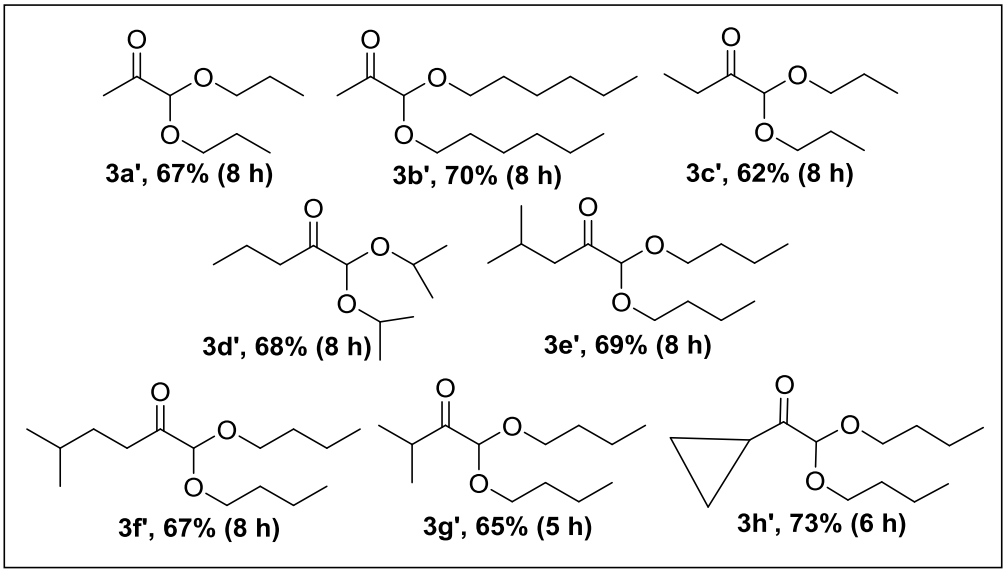
[a]Reaction conditions: ketones **(7)** (1.0 mmol), alcohols **(6)** (1 mL), SeO_2 (0.7 equiv), PTSA (1.0 equiv) at 60 °C, 6-8 h.

Having met with unprecedented success in the above reactions, we finally turned to the aliphatic ketones **(1)**. We were delighted to note that the method continues to hold good with representative examples of cyclic and acyclic aliphatic ketones **(Scheme 5.9)**. Reaction with aliphatic ketones such as acetone **(1a′),** ethyl methyl ketone **(1b′)**,

pentanone **(1c′)** proceeded as expected to give the corresponding products **3a′-d′** in moderate yield (62-70%). Reaction with branched aliphatic ketones such as *iso*-butyl methyl ketone **(1d′),** *iso*-pentyl methyl ketone **(1e′)** also gave the desired products (**3e′**, 69%; **3f′**, 67%) in good yields. Similarly, secondary aliphatic ketones 3-methyl-2-butanone **(1f′)** and the strained cyclopropyl ketone **(1g′)** afforded the desired products **3g′** and **3h′** in 65% and 73% yields respectively.

Scheme 5.9 Scope of aliphatic ketones that couple with alcohols[a]



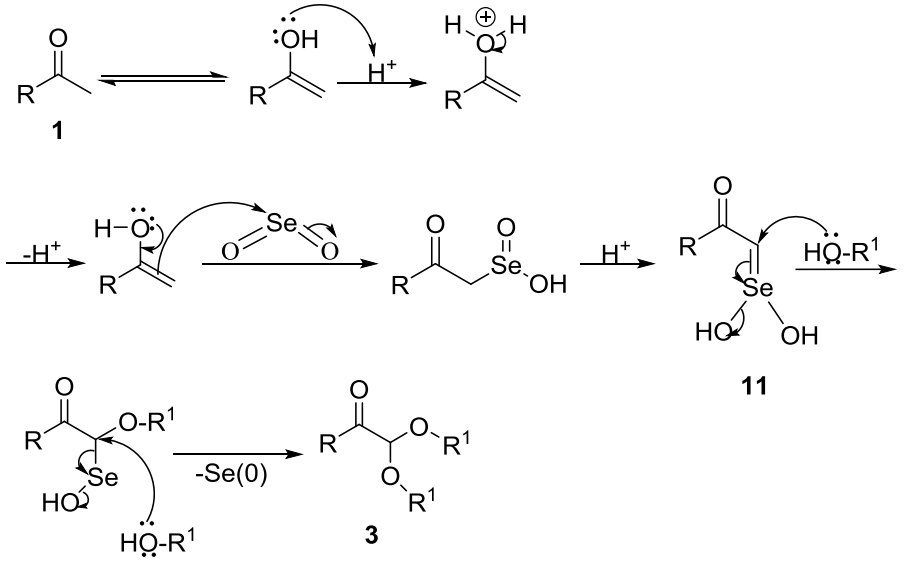


[a]Reaction conditions: ketones **(1)** (1.0 mmol), alcohol **(6)** (1 mL), SeO_2 (0.7 equiv), PTSA (1.0 equiv), 40-60 °C, 5-8 h.

Previously, we had proposed the reactions to proceed *via* the intermediate **11 (Scheme 5.10)** where precipitation of elemental selenium occurred. In the present work particularly, the precipitation of elemental selenium was clean with no formation of

colloidal Se. Although we have not succeeded in isolating the intermediate **11** so far, evidently the mechanism follow the same route as reported in our previous work **(Scheme 5.10)**.[9, 10]

Scheme 5.10 Plausible mechanism



In conclusion, we have developed a simple and an efficient approach for the synthesis of *α*-ketoacetals from aryl/alkyl methyl ketones with aliphatic alcohols in the presence of selenium dioxide and PTSA. The methodology further demonstrates its generality for a diversity-oriented synthesis of novel *α*-ketoacetals library. The reactions exhibited wide substrate tolerance in both the reactants. The easy availability of the reactants used coupled with the simplicity of the reaction procedure involved will certainly make this methodology a more attractive and viable alternative.

5.3. Experimental Section

General Methods

All reagents were purchased from Sigma Aldrich, TCI Chemicals and Alfa Aesar and were used without further purification unless noted. Melting points were recorded by open capillary tube method and are uncorrected. IR spectra were recorded on a Perkin Elmer Spectrum 400 FTIR instrument. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance II-400 spectrometer in $CDCl_3$ with TMS as internal standard. Mass spectral data were obtained with a Waters UPLC-TQD mass spectrometer (ESI-MS). Elemental analyses were carried out on Perkin Elmer 2400 Series II. High-resolution mass spectra (ESI-HRMS) were recorded on MaXis (Bruker Daltonics, Bremen, Germany) time of flight (TOF) mass spectrometer. All reactions were monitored by thin layer chromatography (TLC) using pre-coated aluminium sheets (silica gel 60 F_{254} 0.2-mm thickness). Column chromatography was carried out on silica gel (100-200 mesh) and Flash chromatography was carried out on silica gel (230-400 mesh).

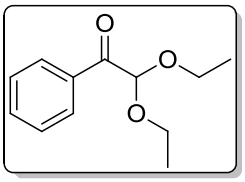
General procedure for the synthesis of compounds 3, 8, and 10:

A mixture of ketones **(1, 7** and **9)** (1.0 mmol), selenium dioxide (77 mg, 0.7 mmol, 0.7 equiv), PTSA (190 mg, 1.0 mmol, 1.0 equiv) and alcohol **6** (1 mL) was allowed to stir at 40-60 ^{o}C for 5-12 hours. When a thick precipitate of elemental selenium settled at the bottom of the flask which was then filtered off, washed with ethyl acetate (2 x 10 mL) and the combined filtrate was transferred to a separating funnel, washed with conc. sodium bicarbonate solution (2x10 mL) followed by brine (2x10 mL). The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude mass

was purified by column chromatography using silica gel (100-200 mesh) or flash chromatography using silica gel (230-400 mesh) and ethyl acetate-hexane as the eluent.

Spectroscopic analytical data

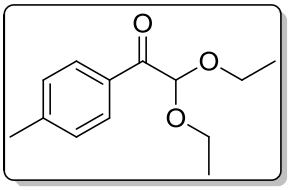
2, 2-diethoxy-1-phenylethanone (3a)*:*



Oil; yield: 69%

IR (KBr film): 3064, 2979, 2883, 1686, 1599, 1449, 1360, 1266, 1119, 1062 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17-7.43 (m, 5H), 5.29 (s, 1H), 3.80-3.62 (m, 4H), 1.25 (t, J = 7.2 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.0, 133.7 133.4, 129.7, 128.3, 102.3, 63.1, 15.2 ppm; MS (ES^+) for $C_{12}H_{16}O_3$ 208.1, found *m/z* 231.2 $[M + Na]^+$.

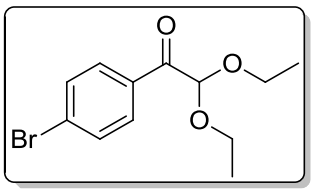
2, 2-diethoxy-1-(p-tolyl)ethanone (3b)*:*



Oil; yield: 65%

IR (KBr film): 3030, 3004, 2922, 2870, 1682, 1606, 1574, 1428, 1405, 1358, 1268, 1181, 1122, 1018 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 8.0 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 5.21 (s, 1H), 3.71-3.53 (m, 4H), 2.33 (s, 3H) 1.17 (t, J = 7.2 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.6, 143.3, 130.2, 128.8, 128.0, 101.2, 62.0, 20.7, 14.1 ppm; MS (ES^+) for $C_{13}H_{18}O_3$ 222.1, found *m/z* 245.1 $[M + Na]^+$.

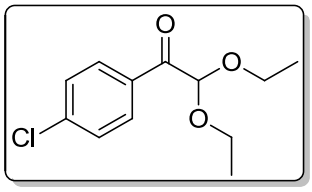
***1-(4-bromophenyl)-2, 2-diethoxyethanone (3c)**:*



Oil; yield: 71%

IR (KBr film): 3094, 2979, 2931, 2883, 1693, 1585, 1484, 1400, 1287, 1118, 1070, 1011 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H), 5.10 (s, 1H), 3.73-3.52 (m, 4H), 1.16 (t, J = 7.2 Hz, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.2, 132.2, 131.6, 131.4, 128.7, 103.0, 63.5, 15.2 ppm; MS (ES^+) for $C_{12}H_{15}BrO_3$ 286.0, found *m/z* 309.1 $[M + Na]^+$.

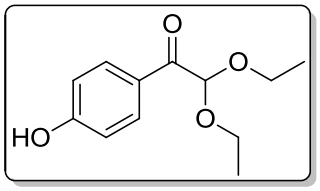
***1-(4-chlorophenyl)-2, 2-diethoxyethanone (3d)**:*



Oil; yield: 74%

IR (KBr film): 3077, 2980, 2931, 2883, 1693, 1589, 1570, 1488, 1403, 1286, 1200, 1092, 1015 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 8.8 Hz, 2H), 7.35 (d, J = 8.8 Hz, 2H), 5.10 (s, 1H), 3.73-3.52 (m, 4H), 1.17 (t, J = 7.2 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.0, 139.9, 131.8, 131.3, 128.6, 103.0, 63.5, 15.1 ppm; MS (ES^+) for $C_{12}H_{15}ClO_3$ 242.0, found *m/z* 265.2 $[M + Na]^+$.

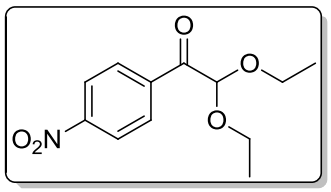
***2,2-diethoxy-1-(4-hydroxyphenyl)ethanone (3e)**:*



Oil; yield: 60%

IR (KBr film): 3330, 2982, 2935, 2896, 1675, 1602, 1515, 1443, 1372, 1290, 1164, 1056 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.8 Hz, 2H), 7.66 (s br, 1H), 6.83 (d, J = 8.8 Hz, 2H), 5.28 (s, 1H), 3.68-3.54 (m, 4H), 1.15 (t, J = 7.2 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.4, 161.8, 133.0, 132.4, 116.1, 115.5, 101.2, 62.8, 15.1 ppm; MS (ES^+) for $C_{12}H_{16}O_4$ 224.1, found *m/z* 225.0 $[M+H]^+$, 247.0 $[M + Na]^+$.

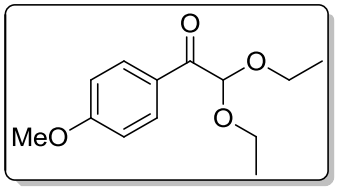
***2,2-diethoxy-1-(4-nitrophenyl)ethanone (3f)**:*



Oil; yield: 90%

IR (KBr film): 3107, 3051, 2978, 2939, 2903, 1702, 1603, 1528, 1481, 1370, 1345, 1329, 1278, 1109, 1053, 1017 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, J = 8.8 Hz, 2H), 8.21 (d, J = 8.8 Hz, 2H), 5.07 (s, 1H), 3.78-3.54 (m, 4H), 1.18 (t, J = 7.2 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.7, 150.3, 138.0, 131.0, 123.3, 103.7, 64.1, 15.1 ppm; MS (ES^+) for $C_{12}H_{15}NO_5$ 253.1, found *m/z* 276.1 $[M + Na]^+$.

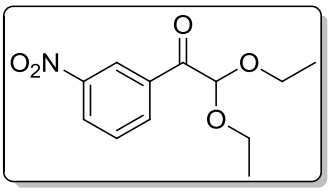
***2,2-diethoxy-1-(4-methoxyphenyl)ethanone (3g)**:*



Oil; yield: 63%

IR (KBr film): 2978, 2935, 2896, 2844, 1679, 1601, 1575, 1511, 1460, 1422, 1308, 1260, 1173, 1114, 1062, 1029 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 5.17 (s, 1H), 3.80 (s, 3H), 3.71-3.53 (m, 4H), 1.17 (t, J = 7.2 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.7, 163.7, 132.1, 130.6, 113.5, 102.5, 63.0, 55.4, 15.2 ppm; MS (ES^+) for $C_{13}H_{18}O_4$ 238.1, found *m/z* 261.1 $[M + Na]^+$.

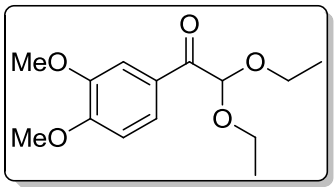
***2, 2-diethoxy-1-(3-nitrophenyl)ethanone (3h)**:*



Oil; yield: 85%

IR (KBr film):3088, 2980, 2935, 2885, 1703, 1614, 1580, 1534, 1478, 1441, 1351, 1271, 1228, 1062 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (s, 1H), 8.43 (d, J = 7.6 Hz, 1H), 8.34 (d, J = 8.0 Hz, 1H), 7.58 (t, J = 8 Hz, 1H), 5.09 (s, 1H), 3.80-3.55 (m, 4H), 1.19 (t, J = 7.2 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.0, 148.1, 135.6, 134.6, 129.4, 127.5, 125.0, 103.5, 64.1, 15.1 ppm; MS (ES^+) for $C_{12}H_{15}NO_5$ 253.1, found *m/z* 276.1 $[M + Na]^+$.

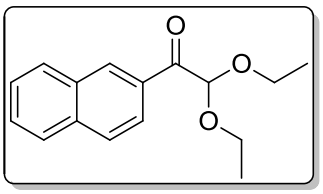
2, 2-diethoxy-1-(3,4-dimethoxyphenyl)ethanone (3i):



Oil; yield: 59%

IR (KBr film): 2977, 2935, 2844, 1681, 1595, 1515, 1464, 1421, 1343, 1273, 1229, 1174, 1121, 1060, 1023 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 8.4 Hz, 1H), 7.59 (s, 1H), 6.82 (d, J = 8.8 Hz, 1H), 5.19 (s, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.72-3.54 (m, 4H), 1.18 (t, J = 7.2 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.6, 153.5, 148.7, 126.7, 124.8, 123.2, 111.4, 109.9, 102.4, 63.0, 56.0, 55.9, 15.2 ppm; MS (ES^+) for $C_{14}H_{20}O_5$ 268.1, found *m/z* 269.7 $[M + H]^+$; HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{14}H_{20}O_5Na$ 291.1208, found 291.1209.

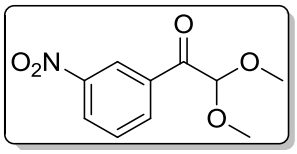
2, 2-diethoxy-1-(naphthalen-2-yl)ethanone (3j):



Oil; yield: 78%

IR (KBr film): 3059, 2977, 2882, 1681, 1627, 1597, 1468, 1438, 1361, 1281, 1115, 1061 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.08-7.45 (m, 6H), 5.34 (s, 1H), 3.76-3.59 (m, 4H), 1.19 (t, J = 7.2 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.0, 132.0, 128.6, 128.5, 128.4, 128.1, 127.7, 126.6, 124.9, 123.8, 102.4, 63.1, 15.2 ppm; MS (ES^+) for $C_{16}H_{18}O_3$ 258.1, found *m/z* 281.0 $[M + Na]^+$.

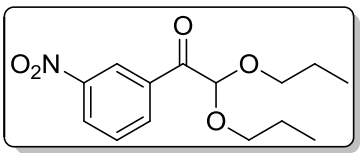
***2, 2-dimethoxy-1-(3-nitrophenyl)ethanone (3k)**:*



Oil; yield: 82%

IR (KBr film): 3088, 2942, 2837, 1697, 1615, 1532, 1351, 1192, 1093 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.90 (s, 1H), 8.40-8.32 (m, 2H), 7.60 (t, J = 8.0 Hz, 1H), 5.03 (s, 1H), 3.46 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.5, 148.2, 135.4, 134.6, 129.6, 127.7, 124.8, 104.8, 55.4 ppm; MS (ES^+) for $C_{10}H_{11}NO_5$ 225.0, found *m/z* 248.0 $[M + Na]^+$.

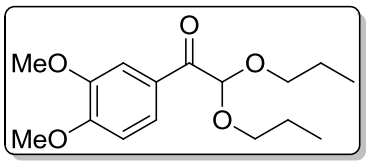
***2, 2-dipropoxy-1-(3-nitrophenyl)ethanone (3l)**:*



Oil; yield: 87%

IR (KBr film): 3120, 2967, 2937, 2878, 1702, 1615, 1534, 1477, 1438, 1350, 1300, 1267, 1191, 1122, 1100, 1071 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.97 (s, 1H), 8.43 (d, J = 7.6 Hz, 1H), 8.34 (d, J = 8.0 Hz, 1H), 7.58 (t, J = 8.0 Hz, 1H), 5.05 (s, 1H), 3.69-3.45 (m, 4H), 1.62-1.53 (m, 4H), 0.84 (t, J = 7.2 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.1, 148.1, 135.6, 134.6, 129.4, 127.5, 125.1, 104.2, 70.4, 22.9, 10.5 ppm; MS (ES^+) for $C_{14}H_{19}NO_5$ 281.1, found *m/z* 299.0 $[M+NH_4]^+$; HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{14}H_{19}NO_5Na$ 304.1161, found 304.1158.

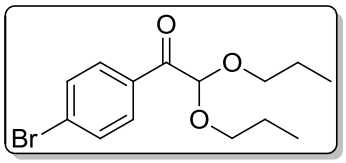
***1-(3, 4-dimethoxyphenyl)-2, 2-dipropoxyethanone (3m)**:*



Oil; yield: 60%

IR (KBr film): 2964, 2939, 2877, 1680, 1595, 1515, 1464, 1421, 1344, 1273, 1228, 1119, 1069, 1024 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 8.4 Hz, 1H), 7.61 (s, 1H), 6.82 (d, J = 8.8 Hz, 1H), 5.14 (s, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.61-3.43 (m, 4H), 1.61-1.52 (m, 4H), 0.84 (t, J = 7.2 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.7, 152.5, 147.6, 125.7, 123.9, 110.6, 108.9, 102.2, 68.3, 55.0, 54.9, 21.9, 9.5 ppm; MS (ES^+) for $C_{16}H_{24}O_5$ 296.1, found *m/z* 297.2 $[M+H]^+$; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{16}H_{24}O_5Na$ 319.1521, found 319.1523.

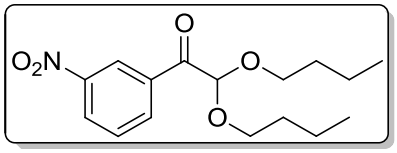
***1-(4-bromophenyl)-2,2-dipropoxyethanone (3n)**:*



Oil; yield: 70%

IR (KBr film): 2965, 2935, 2877, 1690, 1586, 1483, 1396, 1265, 1116, 1071, 1010 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 8.8 Hz, 2H), 7.59 (d, J = 9.2 Hz, 2H), 5.13 (s, 1H), 3.69-3.48 (m, 4H), 1.67-1.58 (m, 4H), 0.90 (t, J = 7.6 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.2, 131.2, 130.8, 130.5, 128.8, 102.7, 68.8, 21.8, 9.5 ppm; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{14}H_{19}BrO_3Na$ 337.0415, found 337.0411.

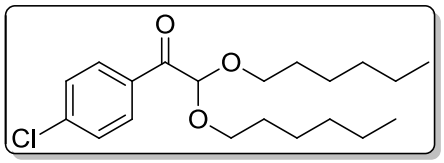
2, 2-dibutoxy-1-(3-nitrophenyl)ethanone (3o):



Oil; yield: 88%

IR (KBr film): 3087, 2960, 2935, 2874, 1702, 1614, 1580, 1534, 1466, 1350, 1299, 1269, 1228, 1125, 1073 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (s, 1H), 8.42 (d, *J* = 7.6 Hz, 1H), 8.34 (d, *J* = 7.6 Hz, 1H), 7.58 (t, *J* = 8.0 Hz, 1H), 5.03 (s, 1H), 3.73-3.48 (m, 4H), 1.56-1.49 (m, 4H), 1.33-1.24 (m, 4H), 0.82 (t, *J* = 7.2 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.1, 148.1, 135.6, 134.6, 129.4, 127.5, 125.1, 104.3, 68.5, 31.6, 19.1, 13.7 ppm; MS (ES^+) for $C_{16}H_{23}NO_5$ 309.1, found *m/z* 309.0 $[M]^+$; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{16}H_{23}NO_5Na$ 332.1474, found 332.1736.

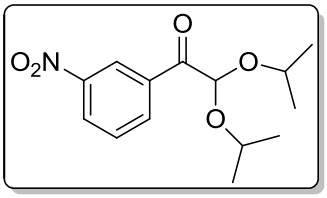
1-(4-chlorophenyl)-2, 2-bis(hexyloxy)ethanone (3p):



Oil; yield: 73%

IR (KBr film): 3136, 2956, 2932, 2861, 1694, 1589, 1401, 1385, 1284, 1192, 1121, 1092 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 5.04 (s, 1H), 3.64-3.43 (m, 4H), 1.55-1.48 (m, 4H), 1.27-1.17 (m, 12H), 0.78 (t, *J* = 7.2 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.1, 139.8, 131.8, 131.3, 128.5, 103.6, 68.1, 31.4, 29.5, 25,6, 22.5, 13.9 ppm; MS (ES^+) for $C_{20}H_{31}ClO_3$ 354.2, found *m/z* 377.3 $[M + Na]^+$; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{20}H_{31}ClO_3Na$ 377.1859, found 377.1856.

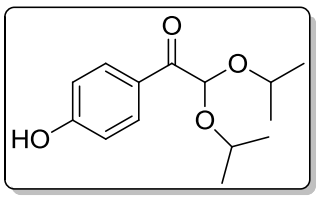
2, 2-diisopropoxy-1-(3-nitrophenyl)ethanone (3q):



Oil; yield: 79%

IR (KBr film): 3088, 2977, 2934, 2892, 1703, 1615, 1580, 1535, 1467, 1438, 1378, 1351, 1320, 1269, 1180, 1122, 1099, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.01 (s, 1H), 8.47 (d, J = 7.6 Hz, 1H), 8.32 (d, J = 8.4 Hz, 1H), 7.56 (t, J = 8.0 Hz, 1H), 5.07 (s, 1H), 3.94-3.85 (m, 2H), 1.22 (d, J = 6.0 Hz, 6H) 1.07 (d, J = 6.0 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.7, 148.0, 136.1, 134.4, 129.2, 127.3, 125.5, 102.2, 71.0, 22.9, 22.2 ppm; MS (ES^+) for $C_{14}H_{19}NO_5$ 281.1, found *m/z* 299 $[M + NH_4]^+$; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{14}H_{19}NO_5Na$ 304.1161, found 304.1162.

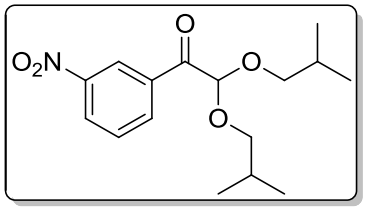
1-(4-hydroxyphenyl)-2, 2-diisopropoxyethanone (3r):



Oil; yield: 62%

IR (KBr film): 3339, 2975, 2933, 1674, 1602, 1582, 1515, 1443, 1438, 1383, 1288, 1241, 1171, 1119, 1038 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 5.20 (s, 1H), 3.97-3.90 (m, 12H), 1.24 (d, J = 6.0 Hz, 6H) 1.14 (d, J = 6.0 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.6, 161.3, 133.2, 126.2, 115.4, 101.6, 70.5, 23.1, 22.5 ppm; MS (ES^+) for $C_{14}H_{20}O_4$ 252.1, found *m/z* 275.0 $[M + Na]^+$; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{14}H_{20}O_4Na$ 275.1259, found 275.1257.

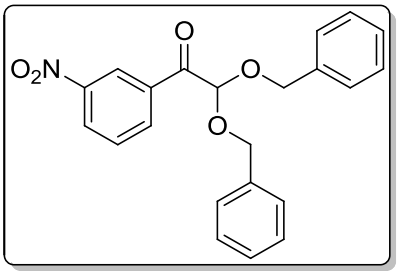
2, 2-diisobutoxy-1-(3-nitrophenyl)ethanone (3s):



Oil; yield: 82%

IR (KBr film): 3090, 2960, 2875, 1703, 1615, 1580, 1536, 1472, 1438, 1349, 1301, 1266, 1055 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (s, 1H), 8.43 (d, J = 7.6 Hz, 1H), 8.34 (d, J = 9.2 Hz, 1H), 7.58 (t, J = 8.0 Hz, 1H), 4.99 (s, 1H), 3.50-3.25 (m, 4H), 1.88-1.78 (m, 2H), 0.83 (t, J = 6.4 Hz, 12H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.0, 148.0, 135.6, 134.5, 129.3, 127.5, 125.2, 104.8, 75.5, 28.5, 19.2, 19.1 ppm; MS (ES^+) for $C_{16}H_{23}NO_5$ 309.1, found *m/z* 327.1 $[M + NH_4]^+$. HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{16}H_{23}NO_5Na$ 332.3518, found 332.3514.

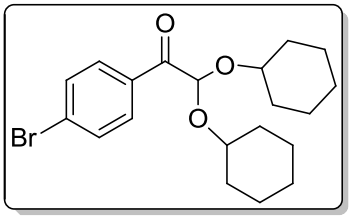
2, 2-bis(benzyloxy)-1-(3-nitrophenyl)ethanone (3t):



Oil; yield: 77%

IR (KBr film): 3088, 3034, 2931, 2874, 1698, 1614, 1580, 1532, 1497, 1454, 1350, 1257, 1124, 1101 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 8.37 (d, J = 7.6 Hz, 1H), 8.32 (d, J = 8.0 Hz, 1H), 7.54 (t, J = 8.0 Hz, 1H), 7.24 (s, 10H), 5.26 (s, 1H), 4.72-4.58 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.6, 148.1, 136.3, 135.5, 134.6, 129.5, 128.6, 128.3, 128.2, 127.6, 125.0, 101.6, 70.0 ppm; MS (ES^+) for $C_{22}H_{19}NO_5$ 377.13, found *m/z* 395.42 $[M+ NH_4]^+$.

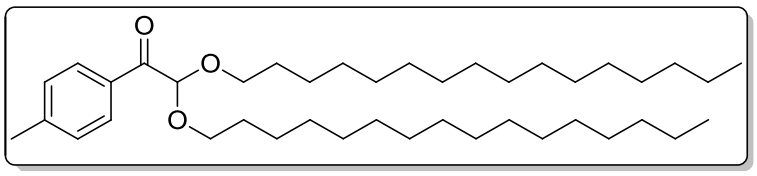
***1-(4-bromophenyl)-2, 2-bis(cyclohexyloxy)ethanone (3u)**:*



White solid; yield: 67%. Mp: 47-49 ^{o}C

IR (KBr film): 2933, 2856, 1689, 1585, 1449, 1281, 1117, 1038 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 8.8 Hz, 2H), 7.50 (d, J = 8.8 Hz, 2H), 5.10 (s, 1H), 3.57-3.50 (m, 2H), 1.86-1.09 (m, 20H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.3, 132.0, 131.9, 131.4, 128.4,102.2, 76.4, 32.9, 32.2, 25.4 ppm; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{20}H_{27}BrO_3Na$ 417.1041, found 417.1034.

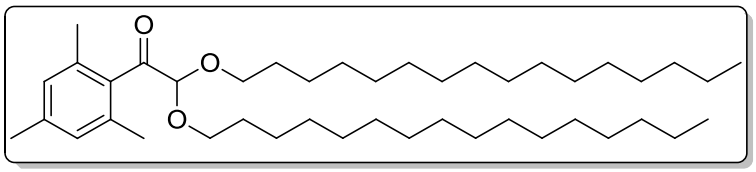
***2, 2-bis(hexadecyloxy)-1-(p-tolyl)ethanone (3v)**:*



White solid; yield: 85%. Mp: 43-45 ^{o}C

IR (KBr film): 3054, 2955, 2917, 2850, 1689, 1605, 1471, 1242, 1132, 1041 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8Hz, 2H), 5.15 (s, 1H), 3.62-3.45 (m, 4H), 2.33 (s, 3H), 1.52 (quint, J = 6.8Hz, 4H), 1.22-1.16 (m, 52H), 0.80 (t, J = 6.8Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.8, 144.2, 131.2, 129.9, 129.0,102.6, 67.6, 31.9, 29.72, 29.70, 29.68, 29.64, 29.61, 29.5, 29.38, 29.33, 26.0, 22.7, 21.7, 14.1 ppm; MS (ES^+) for $C_{41}H_{74}O_3$ 614.5, found *m/z* 615.8 $[M + H]^+$. Anal. Calcd for $C_{41}H_{74}O_3$: C, 80.07; H, 12.13; O, 7.80. Found: C, 80.21; H, 12.35; O, 7.75.

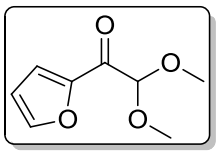
***2, 2-bis(hexadecyloxy)-1-mesitylethanone (3w)**:*



White solid; yield: 89%. Mp: 29-3 ^{o}C

IR (KBr film): 2954, 2918, 2851, 1721, 1611, 1469, 1127, 1052 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (s, 2H), 4.87 (s, 1H), 3.66-3.43 (m, 4H), 2.19 (s, 3H), 2.14 (s, 6H), 1.49 (quint, J = 6.8Hz, 4H), 1.24-1.18 (m, 52H), 0.80 (t, J = 6.8Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.7, 138.5, 136.7, 133.9, 128.2,102.2, 68.1, 31.9, 29.72, 29.70, 29.69, 29.67, 29.64, 29.61, 29.59, 29.3, 25.9, 22.7, 21.0, 19.5, 14.1 ppm; Anal. Calcd for $C_{43}H_{78}O_3$: C, 80.31; H, 12.23; O, 7.46. Found: C, 80.53; H, 12.25; O, 7.49; HRMS data could not be generated due to solubility problem.

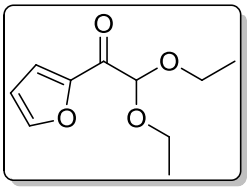
***1-(furan-2-yl)-2, 2-dimethoxyethanone (10a)**:*



Oil; yield: 93%

IR (KBr film): 3138, 2942, 2837, 1688, 1565, 1466, 1396, 1273, 1131, 1066 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 1.2 Hz, 1H), 7.38 (d, J = 3.2 Hz, 1H), 6.49 (dd, J = 1.6 Hz, 1H), 5.03 (s, 1H), 3.40 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.2, 148.9, 146.6, 120.1, 111.2, 101.1, 53.3 ppm; MS (ES^{+}) for $C_8H_{10}O_4$ 170.0, found *m/z* 193.1 $[M + Na]^{+}$.

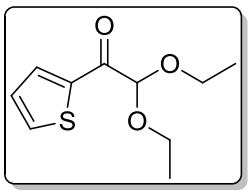
***2, 2-diethoxy-1-(furan-2-yl)ethanone (10b)**:*



Oil; yield: 89%

IR (KBr film): 3139, 2980, 2935, 2887, 1681, 1565, 1465, 1394, 1306, 1268, 1228, 1125, 1061 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 1.6 Hz, 1H), 7.43 (d, *J* = 3.6 Hz, 1H), 6.48 (dd, *J* = 1.6 Hz, *J* = 2.0 Hz, 1H), 5.08 (s, 1H), 3.74-3.55 (m, 4H), 1.19 (t, *J* = 6.8 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.0, 147.4, 121.2, 112.2, 101.2, 63.0, 15.1 ppm; MS (ES^+) for $C_{10}H_{14}O_4$ 198.1, found *m/z* 199.0 $[M + H]^+$.

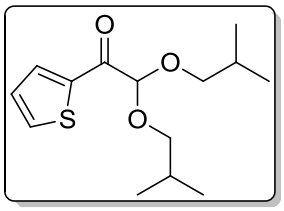
***2, 2-diethoxy-1-(thiophen-2-yl)ethanone (10c)**:*



Oil; yield: 72%

IR (KBr film): 3102, 2979, 2931, 2883, 1670, 1509, 1413, 1363, 1323, 1288, 1240, 1115, 1059 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 3.6 Hz, 1H), 7.60 (d, *J* = 4.8 Hz, 1H), 7.07 (t, *J* = 4.8 Hz, 1H), 5.06 (s, 1H), 3.74-3.56 (m, 4H), 1.20 (t, *J* = 7.2 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.7, 139.6, 134.8, 134.6, 128.0, 102.2, 63.1, 15.1 ppm; MS (ES^+) for $C_{10}H_{14}O_3S$ 214.0, found *m/z* 236.7 $[M + Na]^+$.

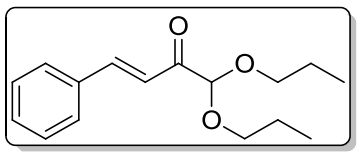
***2, 2-diisobutoxy-1-(thiophen-2-yl)ethanone (10d)**:*



Oil; yield: 78%

IR (KBr film): 3104, 2960, 2874, 1670, 1517, 1414, 1366, 1288, 1124, 1055 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, J = 1.2, 0.8 Hz, 1H), 7.60 (dd, J = 0.8, 1.2 Hz, 1H), 7.07-7.05 (m, 1H), 4.96 (s, 1H), 3.43-3.26 (m, 4H), 1.90-1.80 (m, 2H), 0.86-0.83 (m, 12H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.8, 138.6, 133.8, 133.4, 126.9, 102.4, 73.4, 27.5, 18.3, 18.2 ppm. MS (ES^+) for $C_{14}H_{22}O_3S$ 270.1, found *m/z* 293.0 $[M + Na]^+$; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{14}H_{22}O_3SNa$ 293.1187, found 293.1186.

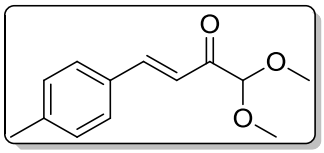
***(E)-4-phenyl-1, 1-dipropoxybut-3-en-2-one (8a)**:*



Oil; yield: 86%

IR (KBr film): 3061, 3028, 2966, 2935, 2876, 1697, 1610, 1453, 1317, 1070 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 16.4 Hz, 1H), 7.53-7.31 (m, 5H), 7.03 (d, J = 16 Hz, 1H), 4.73 (s, 1H), 3.60-3.41 (m, 4H), 1.64-1.55 (m, 4H), 0.88 (t, J = 7.6 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.3, 144.7, 134.6, 130.6, 128.8, 128.5, 120.8, 102.8, 69.2, 22.9, 10.5 ppm; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{16}H_{22}O_3Na$ 285.1467, found 285.1463.

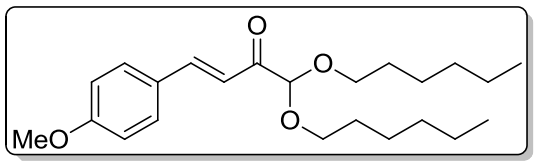
***(E)-1, 1-dimethoxy-4-(p-tolyl)but-3-en-2-one (8b)**:*



Oil; yield: 92%

IR (KBr film): 2996, 2935, 2834, 1696, 1602, 1512, 1321, 1183, 1068 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 16.4 Hz, 1H), 7.43 (d, J = 8 Hz, 2H), 7.13 (d, J = 8 Hz, 2H), 6.96 (d, J = 16 Hz, 1H), 4.68 (s, 1H), 3.38 (s, 6H), 2.30 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.8, 144.2, 140.4, 130.7, 128.6, 127.7, 118.6, 102.6, 53.3, 20.5 ppm; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{13}H_{16}O_3Na$ 243.0997, found 243.0995.

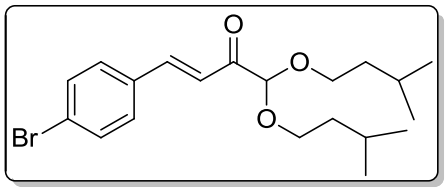
***(E)-1, 1-bis(hexyloxy)-4-(4-methoxyphenyl)but-3-en-2-one (8c)**:*



Oil; yield: 85%

IR (KBr film): 2956, 2931, 2863, 1694, 1596, 1512, 1463, 1256, 1174, 1066 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 16 Hz, 1H), 7.48 (d, J = 8.4 Hz, 2H), 6.90 (d, J = 16.4 Hz, 1H), 6.83 (d, J = 8.8 Hz, 2H), 4.71 (s, 1H), 3.77 (s, 3H), 3.61-3.44 (m, 4H), 1.56 (quin, J = 6.8 Hz, 4H), 1.33-1.19 (m, 12H), 0.80 (t, J = 6.8 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.3, 161.7, 144.5, 130.3, 127.4, 118.5, 114.3, 102.8, 67.5, 55.3, 31.5, 29.6, 25.5, 22.5, 14.0 ppm; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{23}H_{36}O_4Na$ 399.2511, found 399.2515.

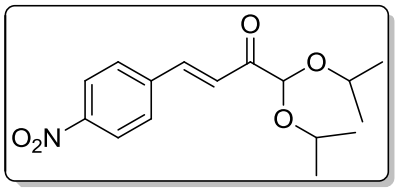
***(E)-4-(4-bromophenyl)-1, 1-bis(isopentyloxy)but-3-en-2-one (8d)**:*



Oil; yield: 89%

IR (KBr film): 2958, 2872, 1700, 1610, 1486, 1313, 1165, 1068 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 16 Hz, 1H), 7.45 (d, J = 8.8 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 6.99 (d, J = 16.4 Hz, 1H), 4.68 (s, 1H), 3.67-3.48 (m, 4H), 1.70-1.59 (m, 2H), 1.46 (q, J = 6.8 Hz, 6H), 0.84 (d, J = 2 Hz, 6H), 0.82 (d, J = 2.4 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.0, 142.2, 132.5, 131.1, 128.8, 123.9, 120.2, 101.9, 65.1, 37.3, 23.9, 21.5 ppm; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{30}BrO_3$ 397.1378, found 397.1343.

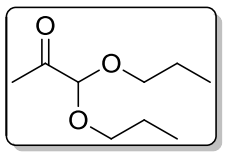
***(E)-1, 1-diisopropoxy-4-(4-nitrophenyl)but-3-en-2-one (8e)**:*



Oil; yield: 82%

IR (KBr film): 3110, 2974, 2932, 2897, 1700, 1616, 1519, 1345, 1107, 1041 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 8.8 Hz, 2H), 7.72-7.66 (m, 3H), 7.14 (d, J = 16 Hz, 1H), 4.74 (s, 1H), 3.91-3.79 (m, 2H), 1.21 (d, J = 6 Hz, 6H), 1.11 (d, J = 6.4 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.0, 147.5, 140.1, 139.9, 128.0, 123.4, 123.0, 99.6, 69.5, 21.9, 21.3 ppm; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{16}H_{21}NO_5Na$ 330.1317, found 330.1316.

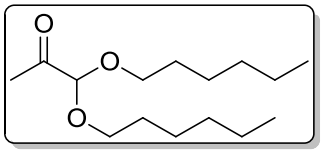
***1, 1-dipropoxypropan-2-one (3a')**:*



Oil; yield: 67%

IR (KBr film): 2967, 2937, 2879, 1734, 1462, 1381, 1354, 1255, 1111, 1072 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.44 (s, 1H), 3.56-3.35 (m, 4H), 2.13 (s, 3H), 1.61-1.52 (m, 4H), 0.87 (t, J = 7.2 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.4, 102.0, 68.4, 23.5, 21.9, 9.5 ppm; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_9H_{18}O_3Na$ 197.1154, found 197.1146 .

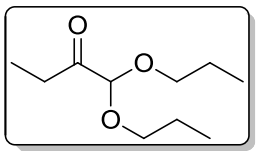
1, 1-bis(hexyloxy)propan-2-one (3b'):



Oil; yield: 70%

IR (KBr film): 2957, 2932, 2865, 1733, 1464, 1353, 1114, 1071 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.42 (s, 1H), 3.58-3.38 (m, 4H), 2.12 (s, 3H), 1.53 (quin, J = 6.8 Hz, 4H), 1.26 (m, 12H), 0.81 (t, J = 6.4 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.3, 103.0, 67.8, 31.5, 29.5, 25.6, 24.4, 22.5, 13.9 ppm; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{15}H_{30}O_3Na$ 281.2093, found 281.2084 .

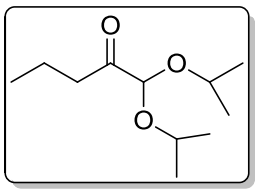
1, 1-dipropoxybutan-2-one (3c′):



Oil; yield: 62%

IR (KBr film): 2968, 2938, 2878, 1730, 1601, 1461, 1381 1258, 1103, 1074 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.48 (s, 1H), 3.55-3.34 (m, 4H), 2.54 (q, J = 7.6 Hz, 2H), 1.56 (m, 4H), 0.98 (t, J = 7.2Hz, 3H), 0.87 (t, J = 7.6 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.0, 102.9, 69.4, 30.1, 22.8, 10.5, 6.9 ppm; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{10}H_{20}O_3Na$ 211.1310, found 211.1309.

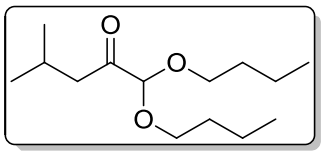
1, 1-diisopropoxypentan-2-one (3d′)*:*



Oil; yield: 68%

IR (KBr film): 2971, 2932, 2877, 1726, 1463, 1378, 1104, 1029 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.50 (s, 1H), 3.82-3.73 (m, 2H), 2.51 (t, J = 7.2 Hz, 2H), 1.57-1.48 (m, 2H), 1.16 (d, J = 6.4 Hz, 6H), 1.08 (d, J = 6 Hz, 6H), 0.85 (t, J = 7.2 Hz,3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.0, 99.7, 69.0, 36.6, 21.8, 21.2, 15.4, 12.7 ppm; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{11}H_{22}O_3Na$ 225.1467, found 225.1459.

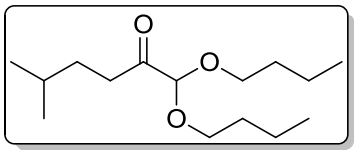
***1, 1-dibutoxy-4-methylpentan-2-one (3e')**:*



Oil; yield: 69%

IR (KBr film): 2960, 2935, 2873, 1729, 1465, 1073 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.41 (s, 1H), 3.58-3.37 (m, 4H), 2.38 (d, J = 6.8 Hz, 2H), 2.14-2.04 (m, 1H), 1.55-1.48 (m, 4H), 1.36-1.27 (m, 4H), 0.87-0.83 (m, 12H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.8, 102.2, 66.5, 44.6, 30.7, 22.6, 21.5, 18.2, 12.8 ppm; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{14}H_{28}O_3Na$ 267.1936, found 267.1929.

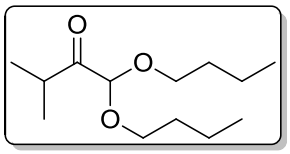
***1, 1-dibutoxy-5-methylhexan-2-one (3f')**:*



Oil; yield: 67%

; IR (KBr film): 2960, 2935, 2873, 1729, 1467, 1074 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.45 (s, 1H), 3.59-3.37 (m, 4H), 2.50 (t, J = 7.6 Hz, 2H), 1.55-1.48 (m, 4H), 1.36-1.27 (m, 4H), 0.87-0.81 (m, 12H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.6, 102.1, 66.5, 44.6, 33.7, 30.6, 26.6, 21.3, 18.2, 12.8 ppm; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{15}H_{30}O_3Na$ 281.2093, found 281.2087.

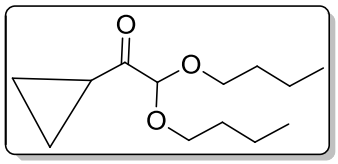
1, 1-dibutoxy-3-methylbutan-2-one (3g'):



Oil; yield: 65%

IR (KBr film): 2963, 2935, 2873, 1727, 1465, 1157, 1074 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.57 (s, 1H), 3.58-3.38 (m, 4H), 3.04-2.93 (m, 1H), 1.52 (m, 4H), 1.32 (m, 4H), 1.02 (d, J = 6.4 Hz, 6H), 0.85 (t, J = 7.2 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.6, 102.3, 67.3, 35.3, 31.7, 19.2, 18.3, 13.7 ppm; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{13}H_{26}O_3Na$ 253.1780, found 253.1774.

2, 2-dibutoxy-1-cyclopropylethanone (3h'):



Oil; yield: 73%

IR (KBr film): 3009, 2960, 2935, 2873, 1713, 1462, 1385, 1161, 1070 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.61 (s, 1H), 3.59-3.42 (m, 4H), 2.32-2.26 (m, 1H), 1.55-1.48 (m, 4H), 1.58-1.51 (m, 4H), 1.38-1.29 (m, 4H), 1.02-0.98 (m, 2H), 0.91-0.84 (m, 8H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.3, 101.6, 66.1, 30.7, 18.2, 15.2, 12.8, 10.8 ppm; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{13}H_{24}O_3Na$ 251.1623, found 251.1614.

5.4 Representative Spectra

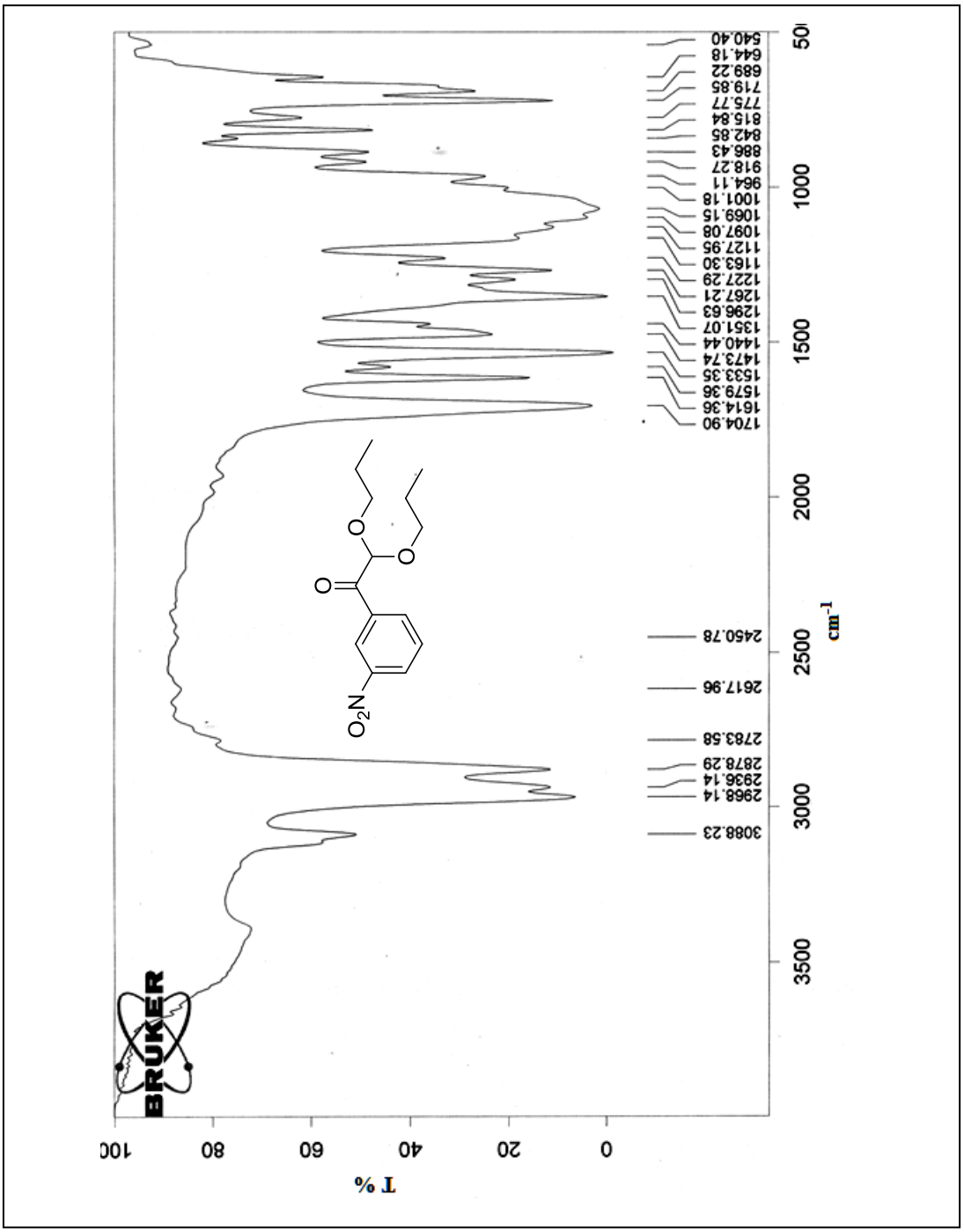


Figure 5.1 IR spectra for 1-(3-nitrophenyl)-2,2-dipropoxyethan-1-one **(3l)**

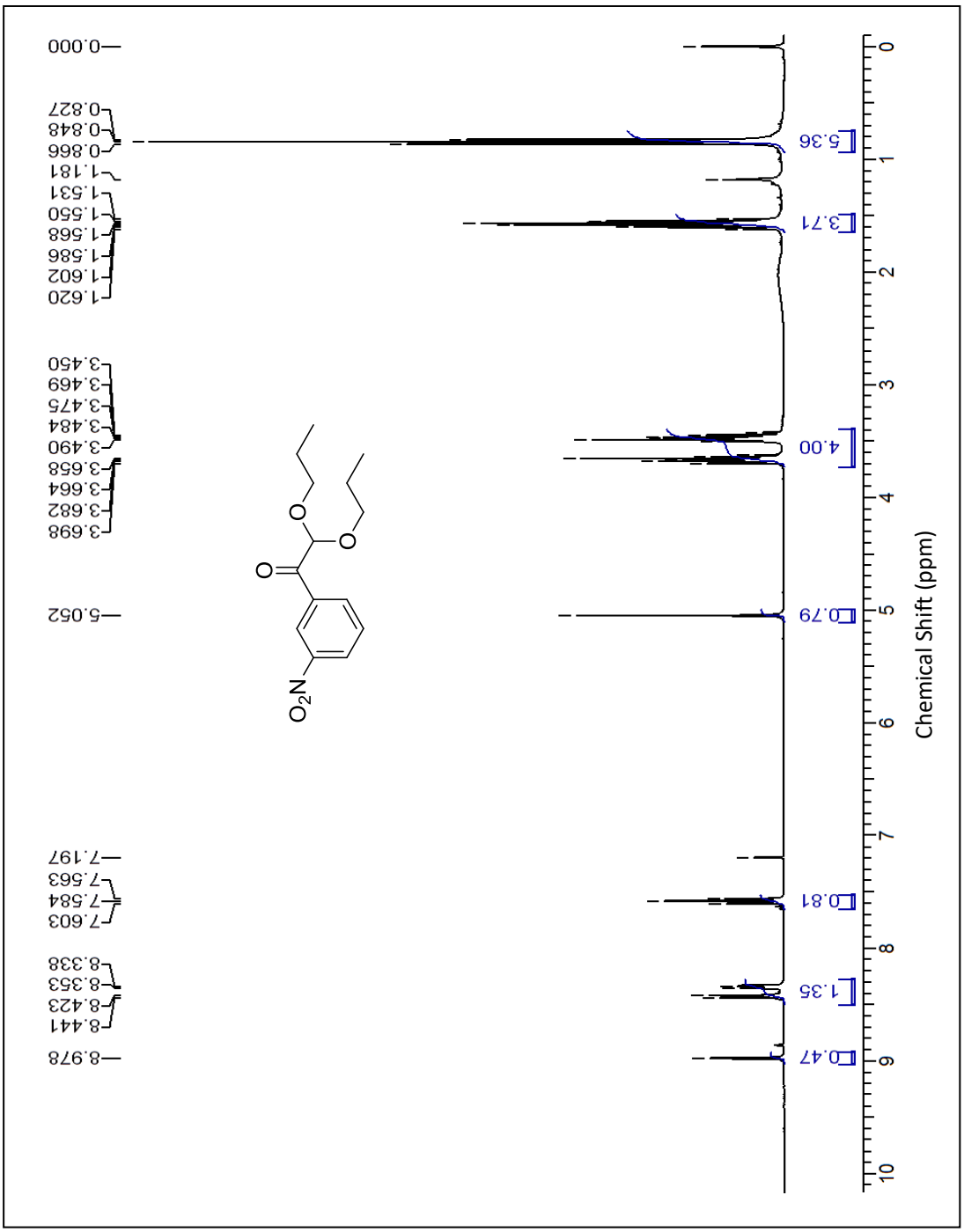


Figure 5.2 ^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of 1-(3-nitrophenyl)-2,2-dipropoxyethanone **(3l)**

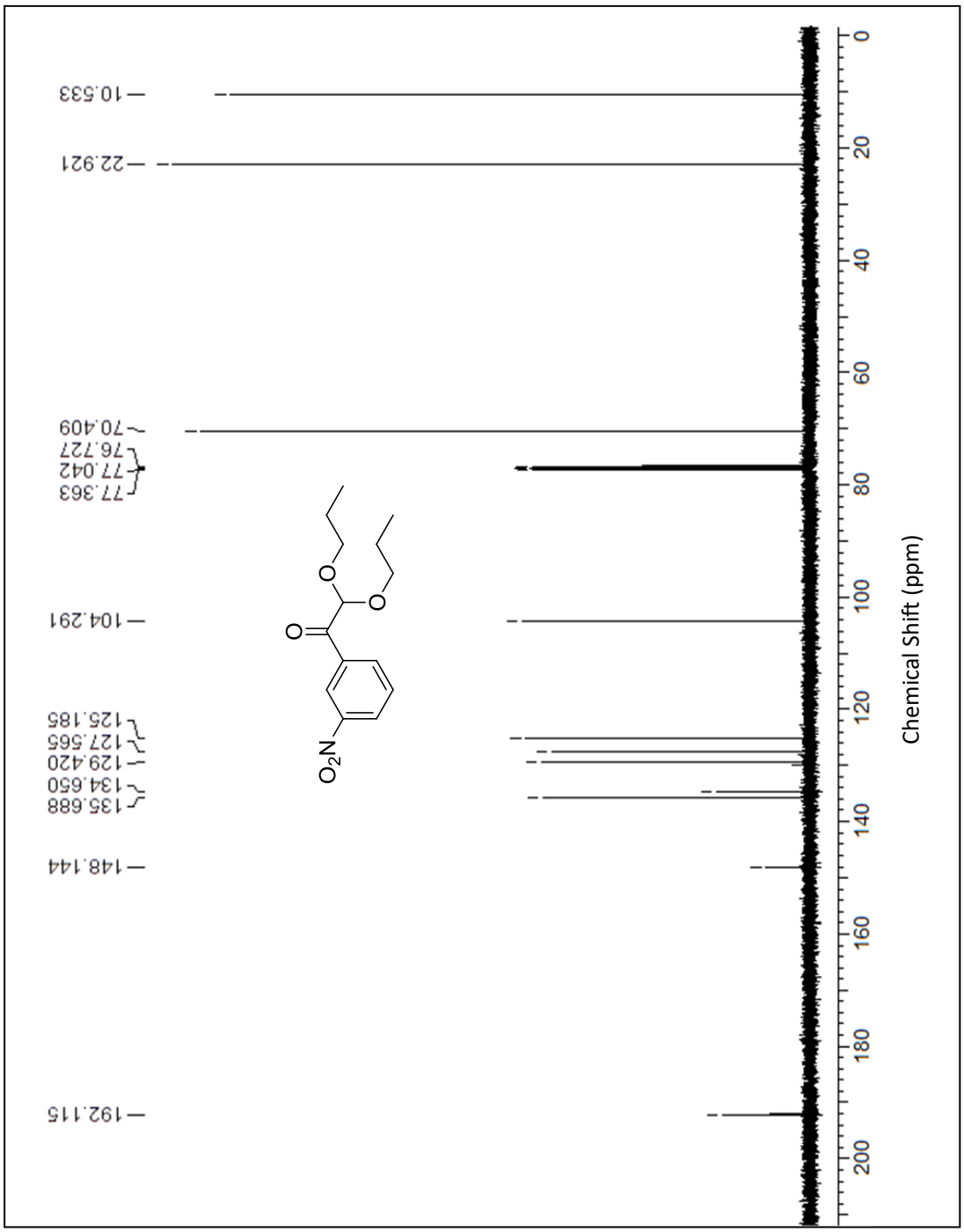


Figure 5.3 ^{13}C NMR ($CDCl_3$, 100 MHz) spectrum of 1-(3-nitrophenyl)-2,2-dipropoxyethanone **(3l)**

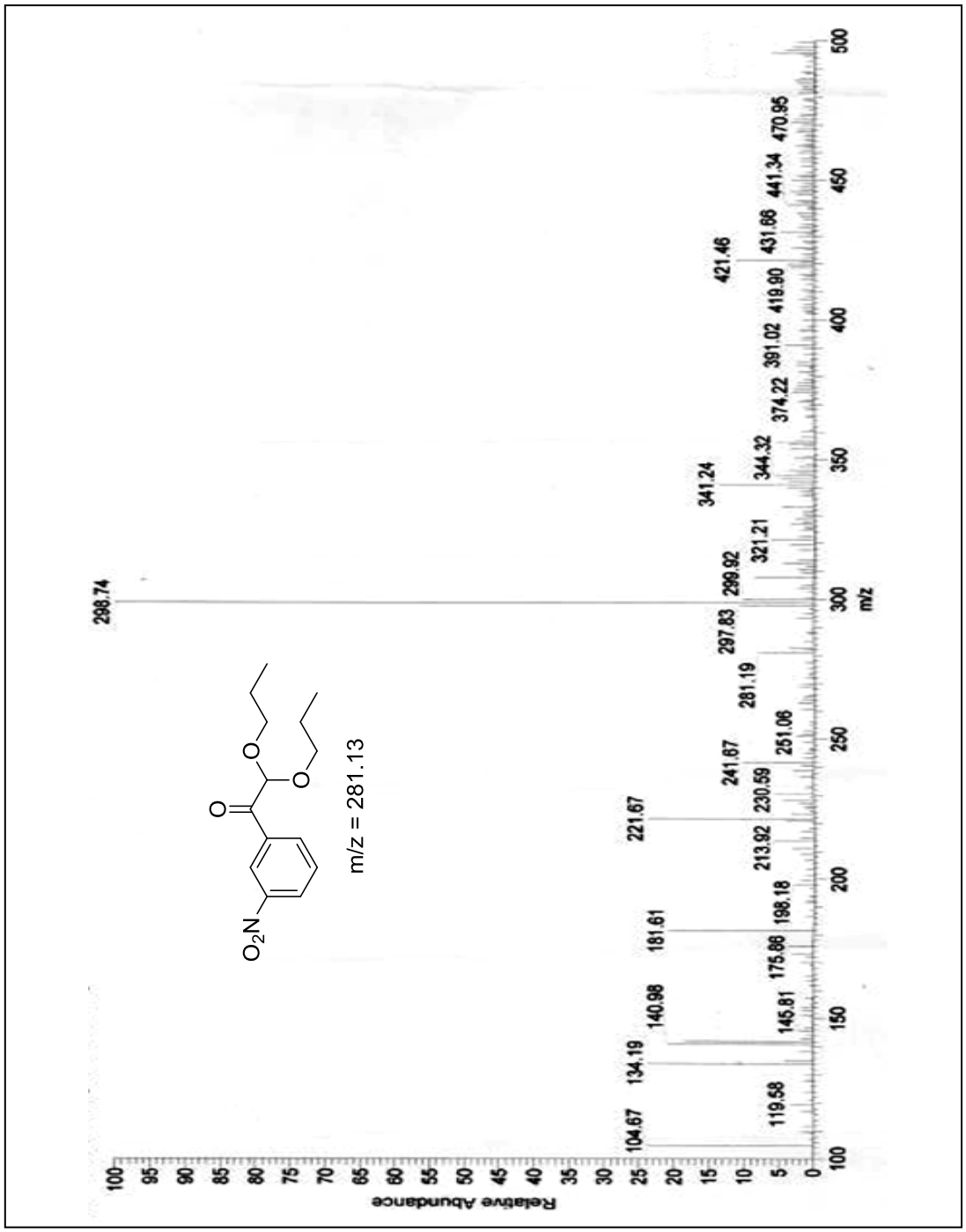


Figure 5.4 Mass spectrum of 1-(3-nitrophenyl)-2,2-dipropoxyethanone **(3l)**

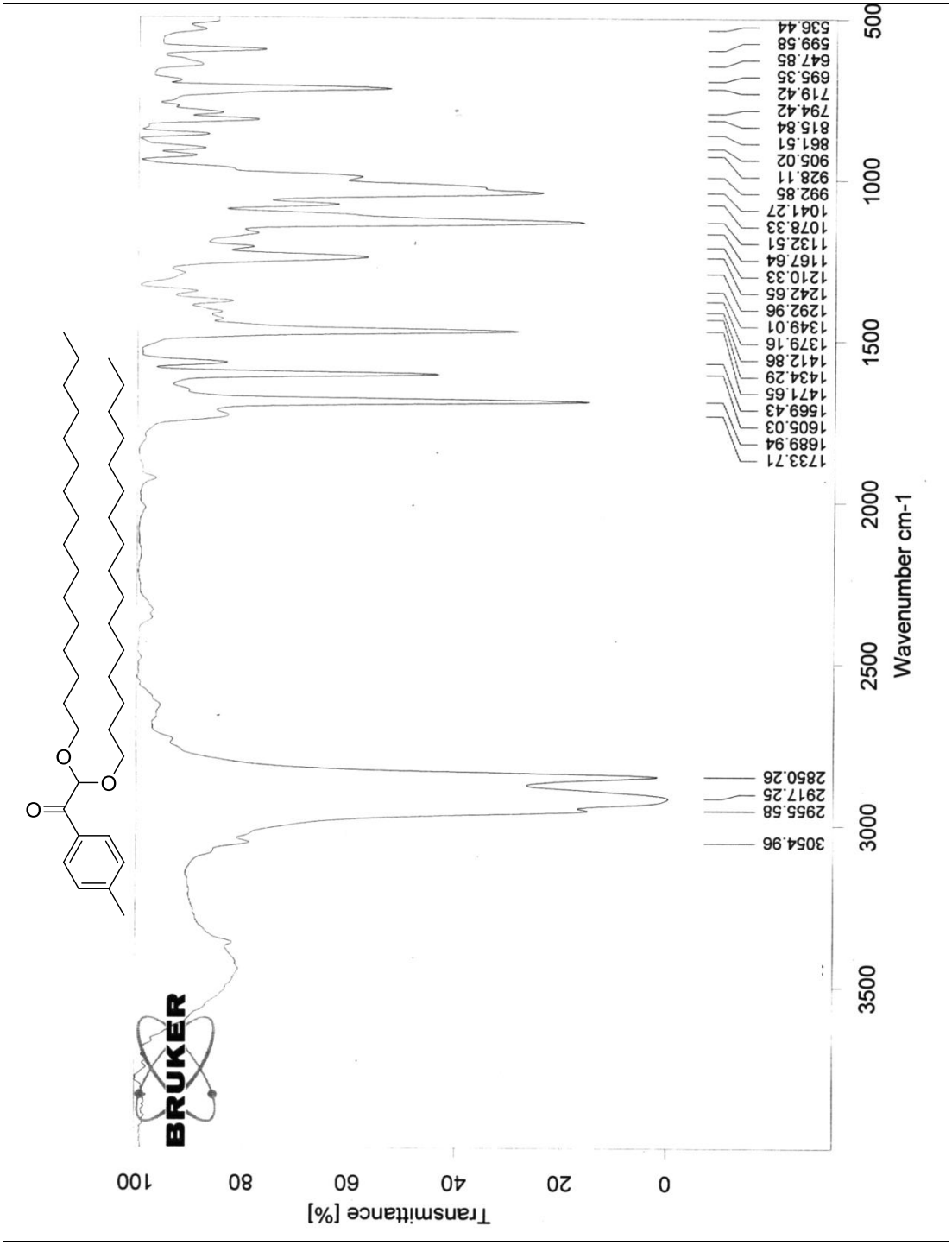


Figure 5.5 IR spectrum of 2,2-bis(hexadecyloxy)-1-(*p*-tolyl)ethanone **(3v)**

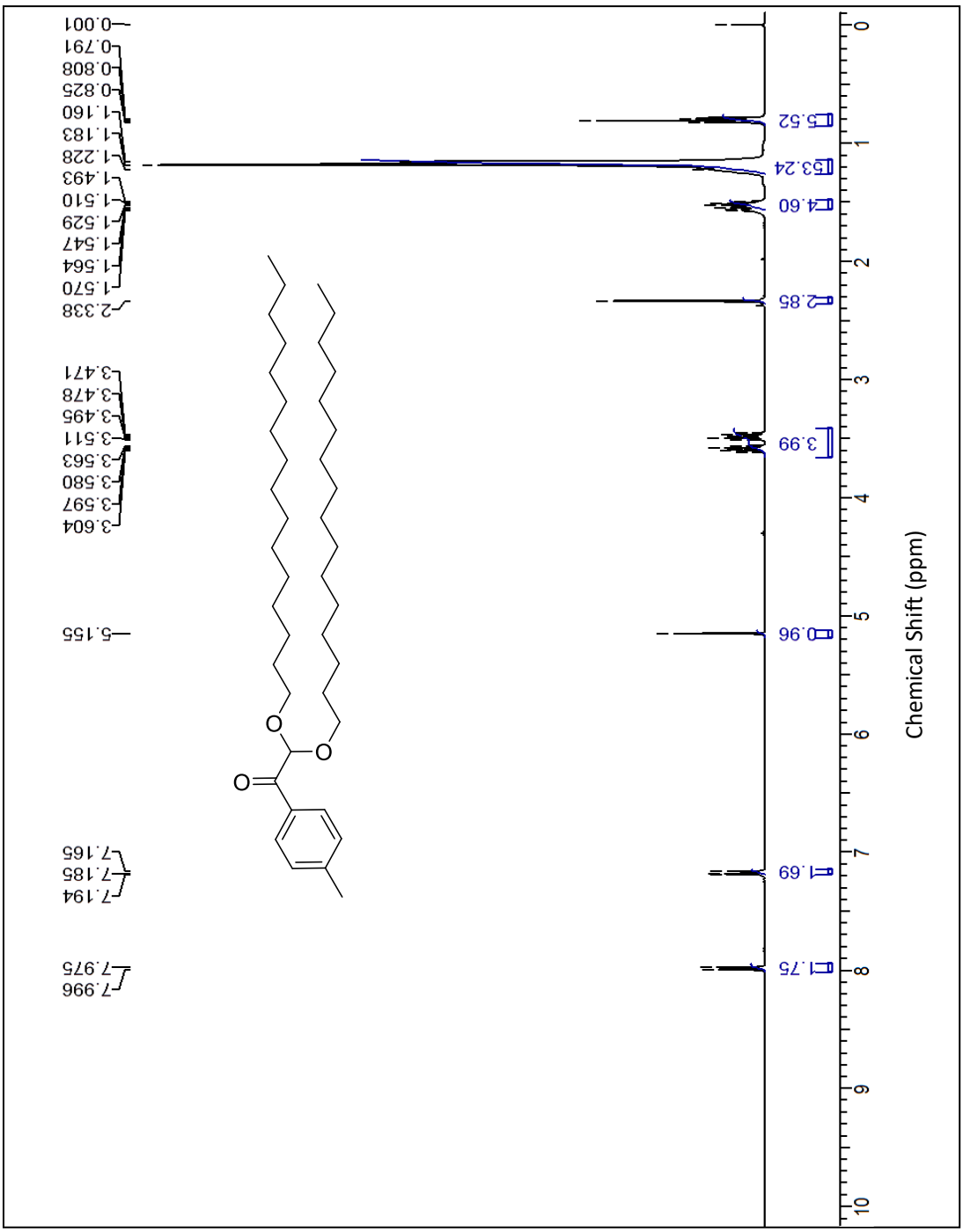


Figure 5.6 ^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of 2, 2-bis(hexadecyloxy)-1-(*p*-tolyl)ethanone **(3v)**

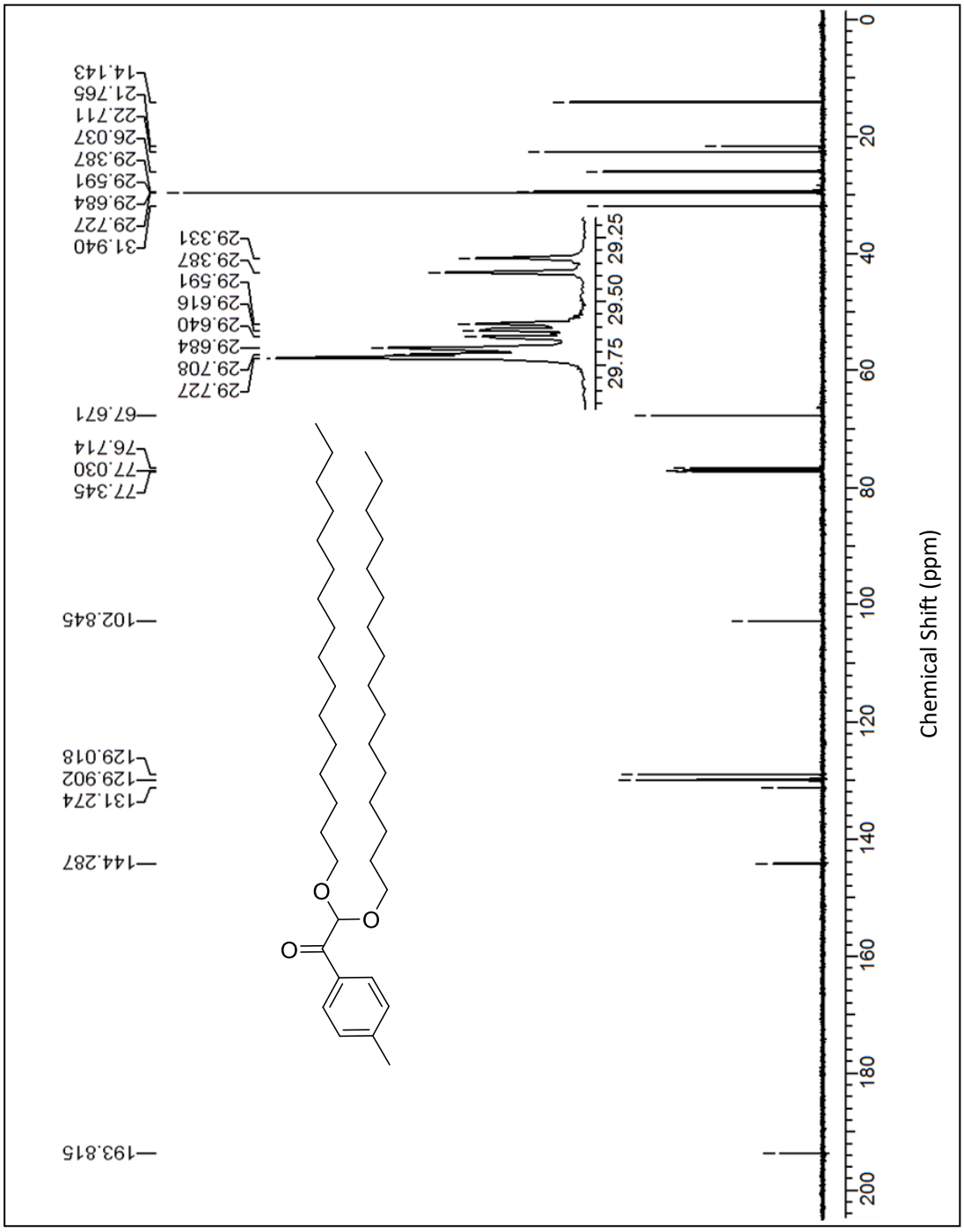


Figure 5.7 ^{13}C NMR ($CDCl_3$, 100 MHz) spectrum of 2, 2-bis(hexadecyloxy)-1-(*p*-tolyl)ethanone **(3v)**

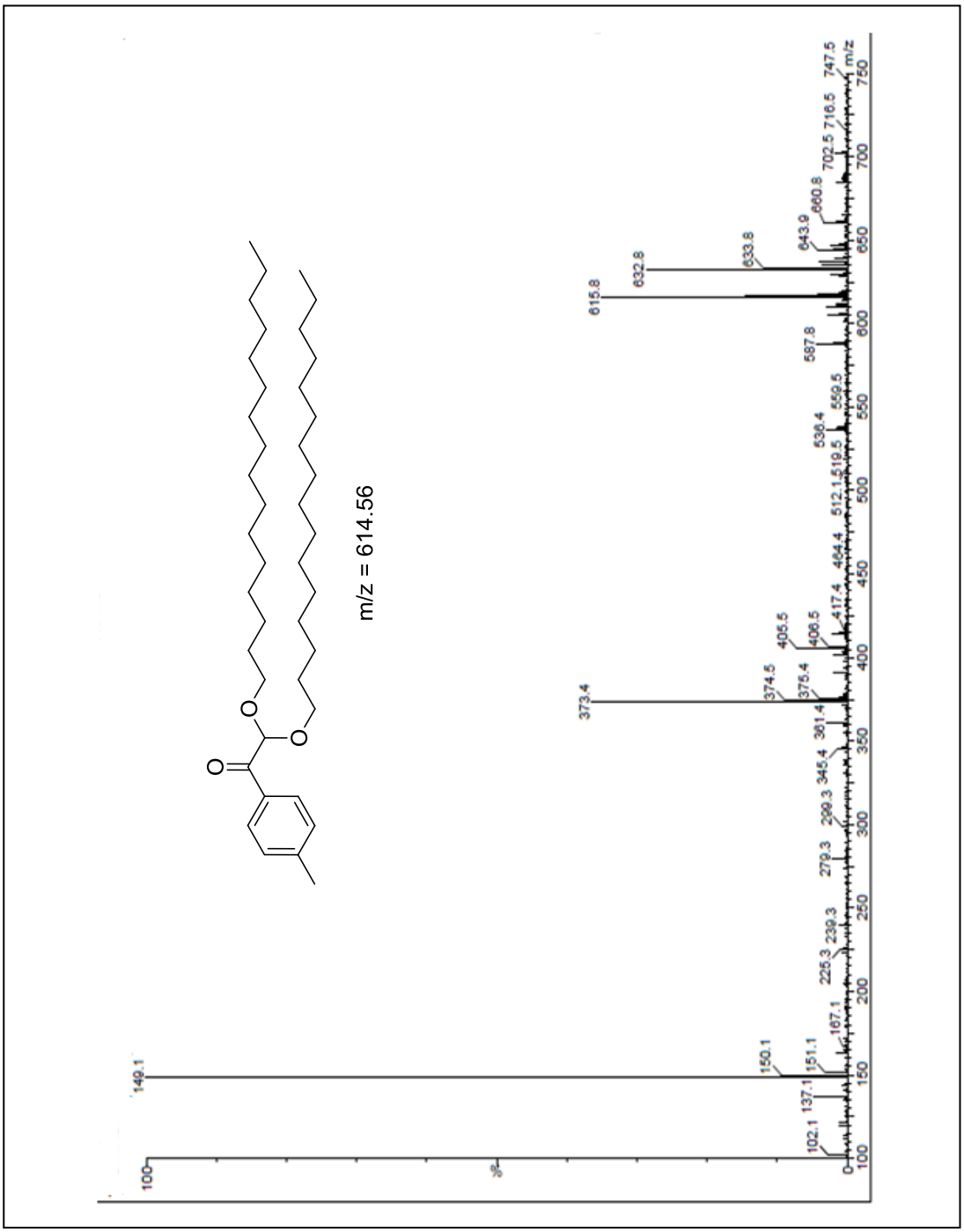


Figure 5.8 Mass spectrum of 2, 2-bis(hexadecyloxy)-1-(*p*-tolyl)ethanone **(3v)**

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Appendix

SUMMARY

In summary, we have developed a method for the synthesis of *α,α*-dicarbonyl selenides in a one-step process. This method is simple and provides an alternative for their preparation. The used of selenium dioxide as a selenium source add to the overall synthetic valuable in organic synthesis.

In continuation of our work on the synthetic utility of selenium dioxide, we have reported a direct method for the selenoamidation of aryl methyl ketones. The method described here employed easily available selenium dioxide as a selenylating agent. The attractiveness of this method is that the reaction proceeds without using any catalyst, acid or base and under mild reaction condition. To the best of our knowledge, this is the first method for the synthesis of so far unreported *α*-oxo-*N*-alkyl selenoamides. The present method and the properties of the unreported compounds will be further explored and investigated in the near future.

During our studies on the development of new methodologies, we have devised a protocol for the synthesis of new selenium-containing heterocycles *viz* 1, 4-selenazine. The method displays a series of 1, 4-selenazine and its derivatives. The reaction is superior in terms of minimization of steps and the used of readily available, inexpensive reagents.

Finally, we have reported an efficient method for the synthesis of *α*-keto acetals with a wide substrates scope. Various substrate was well tolerated in this reaction. The simplicity of the reaction procedure coupled with the easy availability of the reactants used will certainly make this methodology a more attractive and viable alternative.

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Qualification	Board/ University	Result	Remark
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NET (June 2017) (December 2017)	**Joint UGC-CSIR**	**NET-LS NET-JRF**	**-**
GATE Chemistry (CY) 2016	**IISC**	**GATE**	**-**
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2. Participated in "*National Symposium on Radiation and Photochemistry (NSRP-2013)*", Department of Chemistry, North-Eastern Hill University, Shillong, **20th -22nd March, 2013**.

3. Participated and presented a poster in "*National Seminar on Recent Advances in Chemical Research (RACR-14)",* Department of Chemistry, Raiv Gandhi University, Arunachal Pradesh, **20th and 21th March, 2014**.

4. Participated and presented a poster in "*National Symposium on Sustainable Chemistry: Frontiers and Challenges (SCFC-2014)*", Department of Chemistry, North-Eastern Hill University, Shillong, **27th -1st March, 2014**.

5. Participated in "*North East Regional Seminar on Trend in Colloid and Interface Science (NERSTCIS-2014)*", Department of Chemistry, North-Eastern Hill University, Shillong, **27th -28th November, 2014**.

6. Participated and presented a poster in "*National Seminar on Newer Trends in Chemistry and Environment*", Department of Chemistry, Don Bosco College,Tura, **10th -11th December, 2014**.

7. Participated and presented a poster in "*An International Symposium on Recent Advances in Chemistry (REACH-2015)*", UGC-Centre for Advanced Studies in Chemistry, Department of Chemistry, North-Eastern Hill University, Shillong, **3rd-5th March, 2015**.

8. Participated and presented a poster in *"National Seminar on Exploring Recent Advances in Chemistry in Service for Mankind -2015*", Department of Chemistry, Shillong College, Shillong, **30th-31st July, 2015**.

9. Participated and presented a poster in *"National Conference on Contemporary Developments in Chemical Sciences -2015"*, Department of Chemical Sciences, Tezpur University, Napaam, Assam, **23rd-24th November, 2015**.

10. Participated and presented a poster in "*18th CRSI National Symposium in Chemistry -2016*", Panjab University, Chandigarh, **5th-7th February, 2016**.

11. Participated in the National Symposium on "*Emerging Trends in Chemistry (ETC-2016)*", Department of Chemistry, North-Eastern Hill University, Shillong, **28th-29th March, 2016.**

12. Participated and presented a poster in *"International Conference on Chemistry and its Diversities-2016"*, Department of Chemistry, St.Anthony's College, Shillong, **24th-25th November, 2016**.

13. Participated and presented a poster in *"23rd ISCB International Conference (ISCBC-2017)*", SRM University, Tamil Nadu, ***8th-10th February, 2017***.

14. Presented a Poster in the "*14th International Conference on the Chemistry of Selenium and Tellurium (ICCST-14)"*, Flamingo Hotel Resort, Santa Margherita di Pula (CA), Sardinia, Italy, ***3rd – 7th June, 2019***.

Research Publications

1. PTSA-Catalyzed reaction of alkyl/aryl methyl ketones with aliphatic alcohols in the presence of selenium dioxide: a protocol for the generation of an *α*-ketoacetals.

   O. Risuklang Shangpliang, Kmendashisha Wanniang, Baskhemlang Kshiar, Ibakyntiew D Marpna, Tyrchain Mitre Lipon, Pushpak Mizar, Bekington Myrboh.

   ACS Omega **2019**, *4*, 6035−6043.

2. Selenium dioxide as an alternative reagent for the direct *α*-selenoamidation of aryl methyl ketones.

   O. Risuklang Shangpliang, Baskhemlang Kshiar, Kmendashisha Wanniang, Ibakyntiew D Marpna, Tyrchain Mitre Lipon, Badaker M Laloo, Bekington Myrboh.

   Journal of Organic Chemistry **2018**, *83*, 5829−5835.

3. A three component one-pot synthesis of *N*-amino-2-pyridone derivatives catalyzed by KF-Al_2O_3.

   Baskhemlang Kshiar, **O. Risuklang Shangpliang**, Bekington Myrboh.

   Synthetic Communications **2018**, *48*, 1816-1827.

4. Synthesis of *α, α'*-symmetrical dicarbonyl selenides from aryl methyl ketones in presence of selenium dioxide and *p*-toluenesulphonic acid monohydrate.

   O. Risuklang Shangpliang, Bekington Myrboh.

   Exploring Chemistry Interface with Human Welfare **2017**, 223-226.

   ISBN: 978-93-83252-65-7.

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Article

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PTSA-Catalyzed Reaction of Alkyl/Aryl Methyl Ketones with Aliphatic Alcohols in the Presence of Selenium Dioxide: A Protocol for the Generation of an α-Ketoacetals Library

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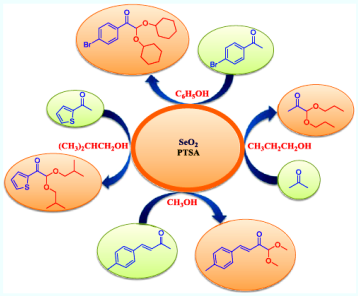
Supporting Information

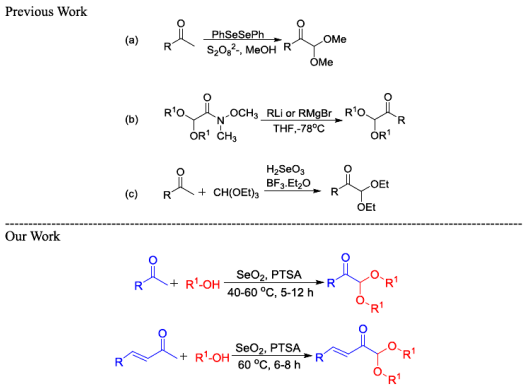
ABSTRACT: A novel approach has been developed for the synthesis of a wide range of α-ketoacetals by the reaction of alkyl/aryl methyl ketones and aliphatic alcohols in the presence of selenium dioxide catalyzed by *p*-toluenesufonic acid. This method represents a general route to obtain a wide variety of α-ketoacetals in a simple, rapid, and practical manner. This approach is particularly attractive because of the easy availability of the starting materials, mild reaction temperature, and good yields of the products. The resulting α-ketoacetals are of much synthetic value as organic intermediates.



INTRODUCTION

The α-ketoacetals are important functional moieties and are useful building blocks in organic synthesis. They are useful intermediates in that they provide an array of functional groups that are extremely valuable in organic syntheses. For instance the α-ketoacetals are a key intermediate in the synthesis of various biological active compounds such as chiral α-hydroxy acetals,[1] chiral α-amino acetals,[2] chiral auxiliaries,[3] and cyanosilylation[4] and also for the construction of important heterocycles.[5] Several methods have been described for the preparation of α-ketoacetals.[5−9] Goswami et al., reported the synthesis of aliphatic α-ketoacetals starting from ketones via a two step procedure using SeO_2.[5a,b] Tiecco and co-workers reported the synthesis of α-ketoacetals catalyzed by diphenyldiselenide and an excess of ammonium peroxydisulfate under reflux conditions (Scheme 1a).[7] Ayala-Mata and group employed Weinreb amides as a starting material for the synthesis of α-ketoacetals (Scheme 1b).[8] More recently, we have reported the synthesis of phenylglyoxal diethylacetals via the reaction of aromatic ketones with triethylorthoformate in the presence of H_2SeO_3 catalyzed by $BF_3{\cdot}Et_2O$ (Scheme 1c).[9] This method, though simple is limited by the use of triethylorthoformate as the sole source of alkoxide nucleophile. Generally, most of the other reported methods involved multistep reactions. Besides, the high cost of the reagents coupled with sensitive reaction conditions limit their scope of applications. Development of an alternative method for the synthesis of α-ketoacetals with wide substrate scope starting from simple and easily available starting materials would therefore be a welcome addition to synthetic organic chemists.

Scheme 1. Synthesis of α-Ketoacetals



The reactive behavior of SeO_2 toward organic substrates in the presence of a Lewis acid or a strong organic acid, however, has found few or no mention at all in the literature. Earlier we

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Selenium Dioxide As an Alternative Reagent for the Direct α-Selenoamidation of Aryl Methyl Ketones

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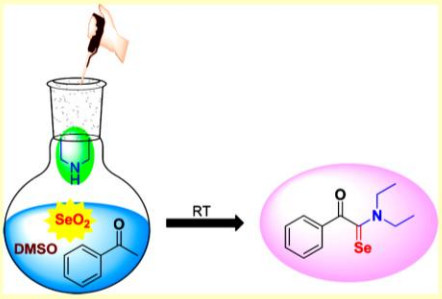
Supporting Information

ABSTRACT: A general strategy for the preparation of *N*,*N*-dialkyl-2-oxo-2-arylethaneselenoamides is described. The single step method involves direct coupling of aryl methyl ketones with secondary amines and selenium dioxide in DMSO. The reactions proceeded smoothly at room temperature to provide a number of the α-oxo-selenoamides in good to excellent yields.



During the past decade, organoselenium compounds have attracted much attention in the field of synthetic chemistry because of their interesting biological activities[1,2] and also as important reaction intermediates.[3] Selenoamides[4] constitute a class of organoselenium compounds, which have been considered to be important precursors for the synthesis of various selenium containing heterocycles[5] and as pharmaceutical agents.[6] The α-oxo-selenoamides having C═Se bond formation attached directly to the α-carbon of the C═O group are not very common, and as per our literature survey, only a few methods are available for their synthesis.[7−9] The reported methods employed selenylating agents such as ω-selenocyanatoacetophenones (Scheme 1a),[7] dihaloalkanes−selenium combination (Scheme 1b),[8] and, more recently, Murai et al. reported the synthesis of α-oxo-selenoamides from the reaction of carbonyl compounds with selenocarbamoyllithiums (Scheme 1c).[9] In all of the above methods, the selenylating agents are themselves multistep synthetic intermediates. Although these methods are quite effective, the use of a strong base, harsh reaction conditions, and multiple step procedure severely limits their scope of application. Hence, a new methodology for an efficient synthesis of selenoamides starting from easily available starting materials and under mild reaction conditions is highly desirable.

Recently, we have demonstrated the versatility of selenium dioxide in organic syntheses where the reagent participated in the reactions as an oxidizing agent in the presence of Lewis or Bronsted acids, while getting itself reduced to elemental selenium.[10] Thus, driven by our continued interest in the synthetic utility of selenium dioxide, we now demonstrate a new reaction where selenium is incorporated in the product, thereby providing an alternative method for the synthesis of α-oxo-selenoamides in a simple one step synthesis. In this paper, we wish to report the coupling of aryl methyl ketones with secondary amines and selenium dioxide in one step leading to an efficient synthetic procedure for α-oxo-selenoamides at room temperature.

Initially, when acetophenone (**1a**, 1 equiv) was treated with selenium dioxide (**2**, 1 equiv) and diethylamine (**3a**, 1 equiv) at room temperature for 8 h, the reaction product **4a** was formed in 30% yield (Table 1, entry 1). Our efforts to optimize the reaction by varying the stoichiometries of the amine showed no improvement in the product yield (Table 1, entries 2 and 3). The optimized condition was achieved when the reaction was carried out using dimethyl sulfoxide as the solvent, which resulted in the formation of **4a** in 65% yield in 2 h (Table 1, entry 4). Further attempts to improve the efficiency of the reaction by varying the amount of amine and using different solvents provided no significant result (Table 1, entries 5−11).

Under the optimized reaction conditions, the scope of the reaction of aryl methyl ketones and amines was investigated. First, we carried out the reaction of aromatic ketones with different amines. Secondary amines such as diethylamine (**3a**), pyrrolidine (**3b**), piperidine (**3c**), and morpholine (**3d**) reacted favorably to give their corresponding products (**4a**, 62%; **4b**, 57%; **4c**, 73%; **4d**, 52%) in moderate to good yields (Scheme 2). It was observed that reactions with diethylamine (**3a**) and piperidine (**3c**) were more effective than with pyrrolidine (**3b**) and morpholine (**3d**), which is probably due to the weaker nucleophilicity of the latter. Second, substituted aromatic ketones having electron donating groups, such as **1b** (*p*-Me),

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A three component one-pot synthesis of N-amino-2-pyridone derivatives catalyzed by KF-Al_2O_3

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ABSTRACT

Synthesis of 1,6-diamino-4-phenyl-3,5-dicyano-2-pyridone derivatives *via* a one-pot, three-component reaction of aryl aldehydes, malononitrile, and cyanoacetic hydrazide at room temperature using KF-Al_2O_3 as a recyclable catalyst have been developed. The reaction proceeds through the initial Knoevenagel condensation between aldehyde and malononitrile in the presence of KF-Al_2O_3 to form the benzylidene derivative which then undergoes Michael addition with cyanoacetic hydrazide followed by intramolecular cyclization of the resulting intermediate to produce the N-amino-2-pyridones in good to excellent yields. The structure of the synthesized compounds were characterized and established on the basis of their spectral data analysis and single-crystal XRD analysis.

GRAPHICAL ABSTRACT

ARTICLE HISTORY
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KEYWORDS
KF-Al_2O_3; multi-component reactions; N-amino-2-pyridones

Introduction

Multi-component reactions (MCRs) have become a powerful synthetic strategy in synthetic organic chemistry due to their flexibility, atomic economy, and convergence. They are usually favoured for development of environmentally benign synthetic methods in organic syntheses.[1] MCRs have also been successfully employed for the synthesis of diverse range of heterocyclic compounds having wide application in pharmaceutical industry and material science.[2,3] In recent years, MCRs have been used for the synthesis of N-heterocycles having structural diversity. The synthesis of 2-pyridone derivatives has attracted much attention as they are valuable building blocks in natural products synthesis. They are also known to possess pharmacological, antibacterial,[4] antifungal,[5] anti-inflammatory,[6] and anti-tumour[7,8] properties. Furthermore, 3,5-dicyanopyridine

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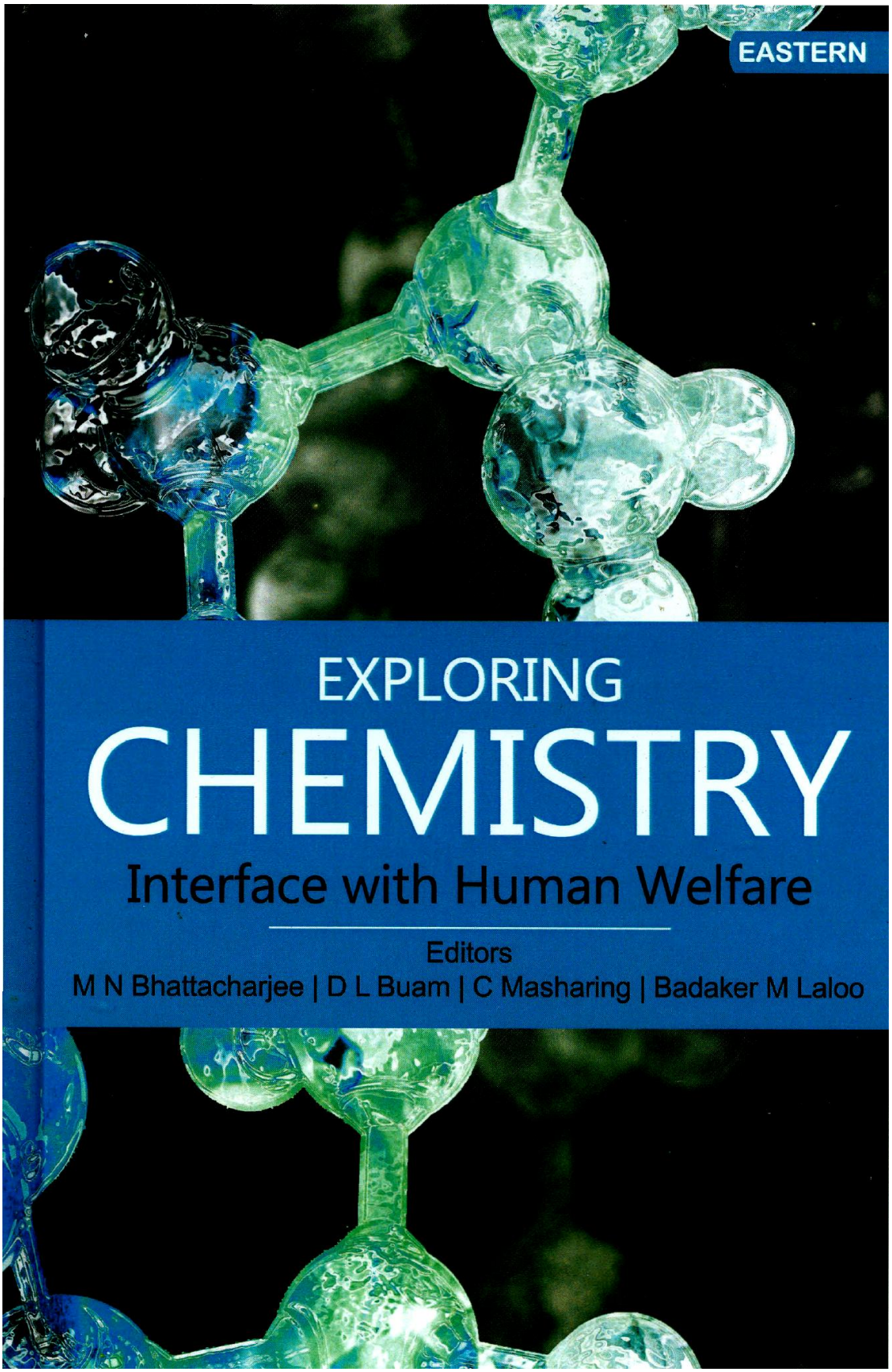
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Synthesis of Symmetrical α, α'-Dicarbonyl Selenides from Aryl Methyl Ketones in presence of Selenium Dioxide and *p*-Toluenesulfonic Acid Monohydrate

O. Risuklang Shangpliang
Bekington Myrboh

Abstract

A simple route to α, α'-dicarbonyl selenides has been developed. A coupling reaction between aryl methyl ketones and selenium dioxide takes place in the presence of *p*-TsOH.H_2O, leading to C–Se bond formation.

Keywords: *Selenium Dioxide/C-Se coupling/ p-TsOH.H_2O*

Introduction

Selenium is an important trace element involved in different physiological functions of the human body. Organoselenium compounds have substantially greater bioavailability than that of inorganic selenium [1]. More importantly, organic selenium is usually found to be less toxic than inorganic forms 2-5]. Lowig, in 1836 prepared the first organoselenium compound, diethyl selenide [6]. Organoselenium compounds have attracted much attention in recent decades due to their important biological effects [7] and their application as chiral catalysts [8], anticancer, antitumor, antiviral, antimicrobial, and antioxidant properties [9].

Traditional methods require the use of strong reducing agents such as Na or NaH, and harsh reaction conditions, such as high reaction temperatures, UV

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