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SELENIUM-CONTAINING HETEROCYCLES USING SELENOAMIDES, SELENOUREAS, SELENAZADIENES, AND ISOSELENOCYANATES

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Abstract – In recent years, considerable attention has been devoted to the synthesis of selenium-containing heterocycles because of their interesting reactivities and potential pharmaceutical applications. The significant starting materials for the selenium-containing heterocycles synthesis are selenoamides, selenoureas, selenazadienes, and isoselenocyanates. This review article introduces the developed synthetic methods mainly on our findings.

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1. INTRODUCTION

The selenium element was firstly discovered in 1817,[1] and has a form of red amorphous powder, glass-like substance, or gray metal. It was predicted to be a dangerous component causing livestock poisoning[2] until it was recognized as an essential nutrient[3] found in some selenoproteins in 1950s.[4] The chemistry of selenium-containing compounds has not been developed in comparison with that of sulfur-containing compounds because of the instability and strong toxicity of some organoselenium compounds. However, the synthetic study of selenium-containing heterocycles is becoming increasingly interesting on due to their unique reactivities[5,6] and diverse biological activities.

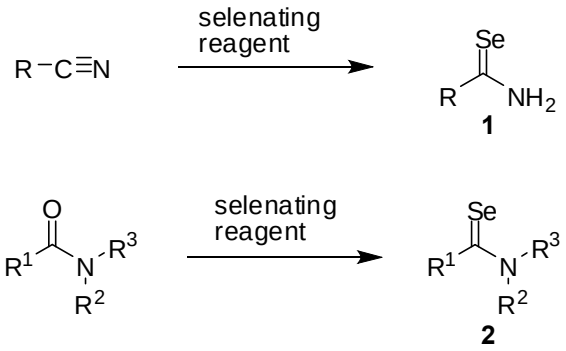
To date, it has been reported that selenium-containing heterocycles show anti-cancer,[7–10] anti-inflammatory,[11,12] anti-melanogenesis,[13,14] and neuroprotective[15] properties. For example, ebselen (2-phenyl-1,2-benzisoselenazol-3(2*H*)-one; EB) demonstrated potential as a non-steroidal anti-inflammatory agent acting like a glutathione peroxidase mimic.[16–18] Selenazolopyrimidone was prepared and showed anti-tumor activity against mouse leukemia.[19] The other examples are potent anti-viral agent selenazofurin (2-β-ribofuranosyl-1,3-selenazole-4-carboxamide),[20,21] and histamine H_2-agonist ameselamine (2-amino-5-(2-aminoethyl)-4-methyl-1,3-selenazole).[22] Besides, our investigations resulted in the preparation of selenazine derivatives with anti-bacterial and anti-tumor effects.[23,24] Hence, selenium-containing heterocycles are considered to be not merely chemically interesting, but also medicinally important[25–28] and industrially possible for development in the cosmetic and drugs potentially.

Useful key starting materials to access to a broad series of selenium-containing heterocycles in organoselenium chemistry are selenoamides, selenoureas, selenazadienes, and isoselenocyanates.[29–33] Our group has reported the synthesis of a variety of selenium-containing heterocycles using them. This review article summarizes in the recent development of such synthesis methods of selenium-containing heterocycles using the selenoamides, selenoureas, selenazadienes, and isoselenocyanates.

2. USING SELENOAMIDE

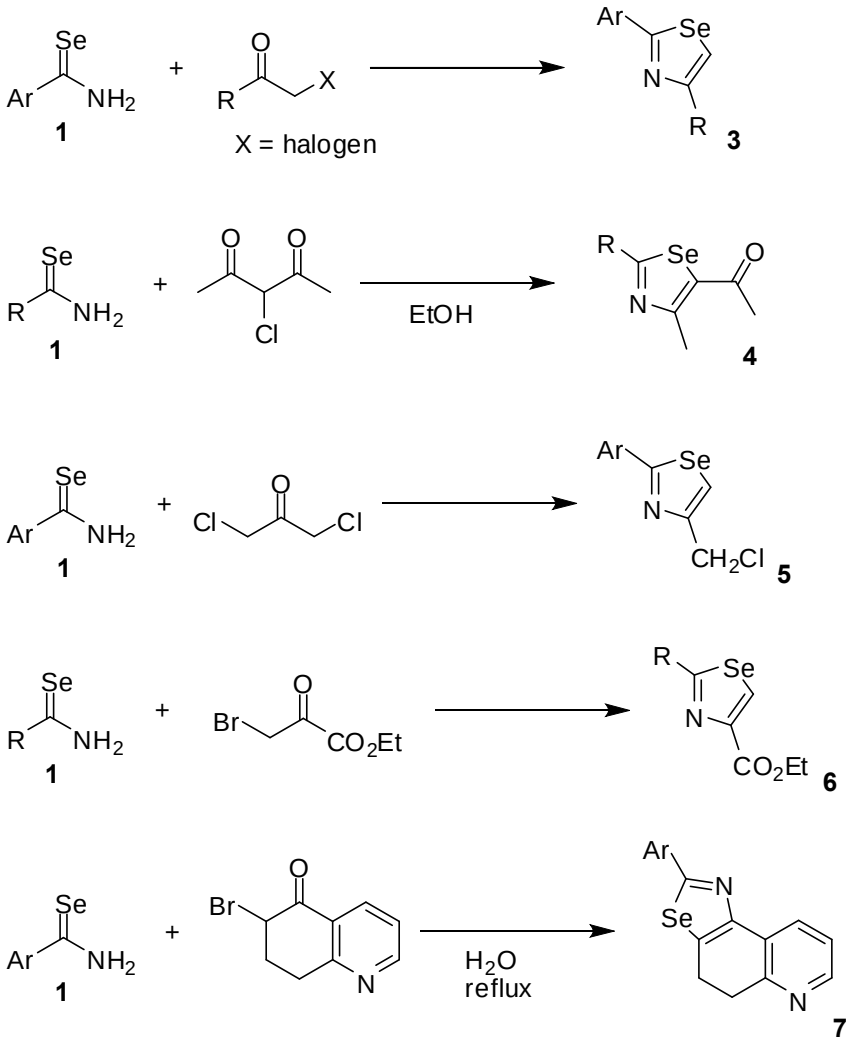
Selenoamides are widely used in the synthesis of five- and six-membered selenium-containing heterocycles. Because the selenoamides exhibit selenoamide-selenolimidate tautomerism and bear two reactive sites, their investigations are of great interest for the heterocycles synthesis.

The primary selenoamides (**1**) as starting materials for the synthesis of selenium-containing heterocycles were prepared by the reaction of nitriles with appropriate selenating reagents including phosphorus selenide (P_2Se_5),[34,35] hydrogen selenide (H_2Se), Al_2Se_3, NaSeH,[36] *tris*(trimethylsilyl)-monoselenophosphate, and potassium selenobenzoate[37] (Scheme 1).



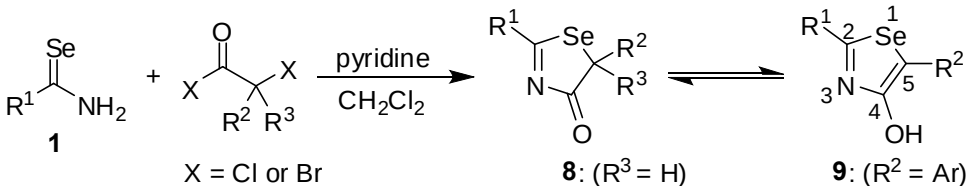
Scheme 1. Preparation of selenoamides

In addition, secondary and tertiary selenoamides (**2**) were prepared by the reaction of amides with appropriate selenating reagents such as LiAlHSeH,[38,39] a mixture of (^{i}Bu$_2$AlSe)$_2$ and (^{i}Bu$_2$Al)Se$_n$,[40,41] (MeAl)$_2$Se,[42] selenium-Lawesson's (Woollins) reagent,[43,44] and (Et$_4$N)$_2$WSe$_4$[45,46] (Scheme 1).



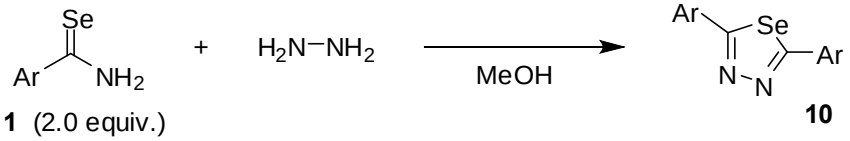
Scheme 2. Synthesis of several selenazoles

Reaction of primary selenobenzamides (**1**) with α-haloketones gave various kinds of 2,4-disubstituted 1,3-selenazoles (**3**).[33,34,47–50] Reaction with 3-chloropentane-2,4-dione afforded 5-acetyl-2-alkyl-4-methylselenazoles (**4**).[51,52] Reaction with 1,3-dichloro-2-propanone gave 2-aryl-4-(chloromethyl)-selenazoles (**5**).[53,54] Reaction with ethyl bromopyruvate yielded ethyl 2-alkyl-4-selenazolecarboxylates (**6**).[55,56] And reaction with 6-bromo-7,8-dihydro-5(6*H*)-quinolinone hydrobromide afforded 2-aryl-4,5-dihydroselenazolo[4,5-*f*]quinolines (**7**)[57] (Scheme 2).



Scheme 3. Reaction of selenoamides with α-haloacyl halides

Reaction of primary alkyl[58] and aryl[59] selenoamides (**1**) with α-haloacyl halides in pyridine afforded 1,3-selenazol-4-ones (**8**). When chloro(phenyl)acetyl chloride was used as α-haloacyl halides, the reaction gave 4-hydroxy-5-phenyl-1,3-selenazole (**9**), the tautomeric enol form of (**8**) (Scheme 3).



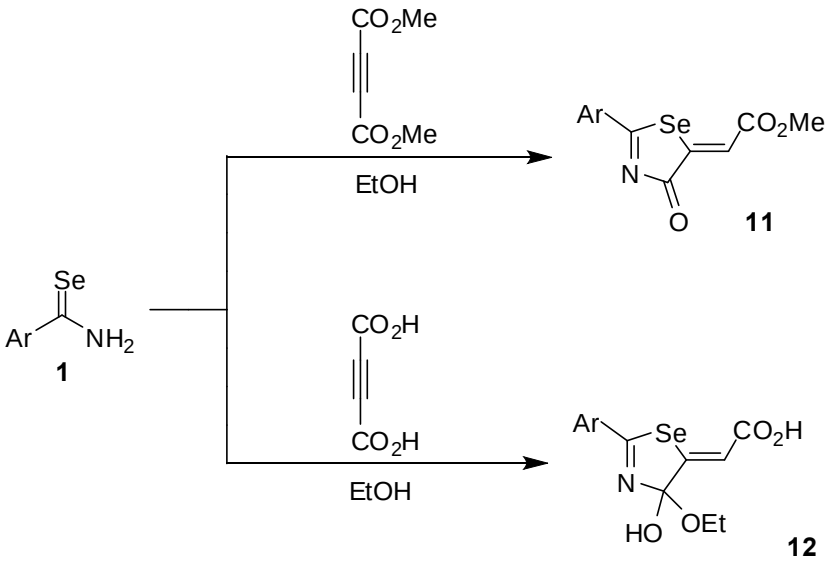
Scheme 4. Reaction of selenoamides with hydrazine

Treatment of primary selenoamides (**1**: 2.0 equiv.) with hydrazine in methanol for a few days resulted in the formation of 2,5-disubstituted 1,3,4-selenadiazoles (**10**) (Scheme 4).[60]

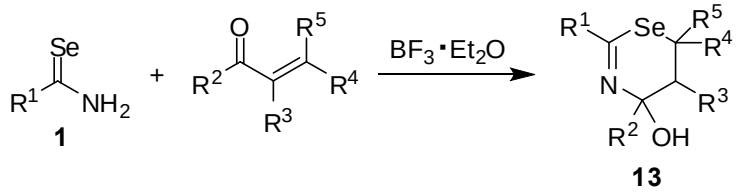
Reaction of primary selenoamides (**1**) with dimethyl acetylenedicarboxylate (DMAD) afforded 2-aryl-5-(methoxycarbonylmethylene)-4,5-dihydro-1,3-selenazol-4-ones (**11**) in moderate to high yields. Whereas, reaction of **1** with acetylenedicarboxylic acid gave 2-aryl-5-(carboxymethylene)-4-ethoxy-4,5-dihydro-1,3-selenazol-4-ols (**12**) (Scheme 5). In this case, the ethoxy group at C4 was introduced by the nucleophilic addition of oxygen of ethanol solvent.[61]

Many kinds of 4-hydroxy-4*H*-5,6-dihydro-1,3-selenazines (**13**) have been prepared in high yields by the reaction of primary selenoamides (**1**) with α,β-unsaturated ketones or aldehydes in the presence of borontrifluoride diethyl ether complex under mild conditions (Scheme 6). The products consist of diastereomers containing two or three asymmetric centers at the C4, C6, and/or C5 positions of selenazine

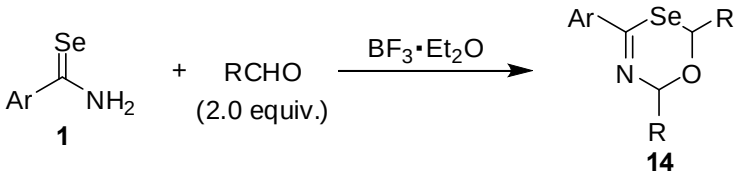
ring. The predominant diastereomer has a *cis* relationship between the hydroxy group at C4 and the substituent at C6.[62,63]



Scheme 5. Reaction of selenoamides with DMAD or acetylenedicarboxylic acid

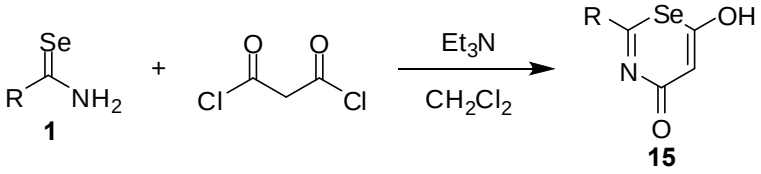


Scheme 6. Synthesis of 4-hydroxy-4*H*-5,6-dihydro-1,3-selenazines employing $BF_3 \cdot Et_2O$



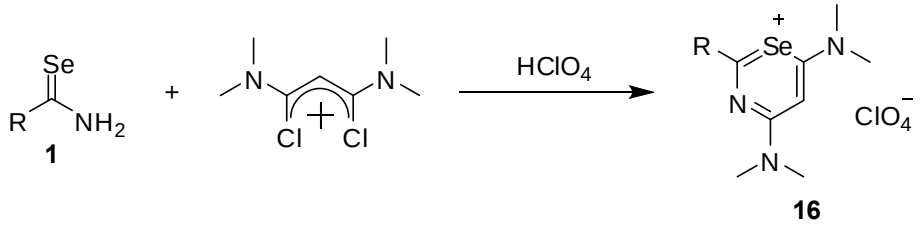
Scheme 7. Reaction of selenoamides with aldehydes employing $BF_3 \cdot Et_2O$

6*H*-1,3,5-Oxoselenazines (**14**) were prepared by the reaction of primary selenoamides (**1**) with aldehydes (2.0 equiv.) in the presence of borontrifluoride diethyl ether complex (Scheme 7).[64]



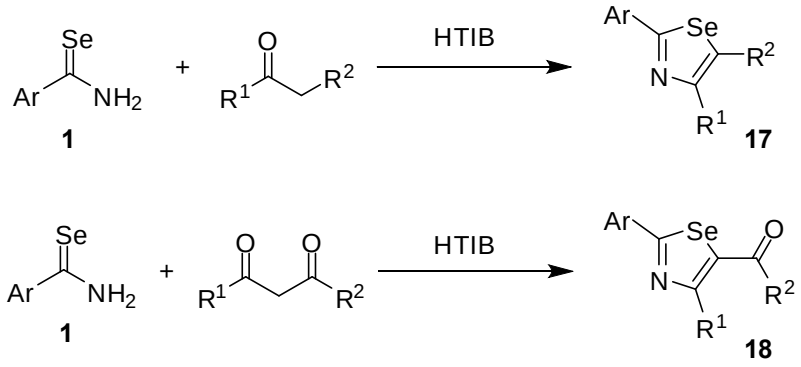
Scheme 8. Reaction of selenoamides with diacyl chloride

Reaction of primary selenoamides (**1**) with diacyl chloride in the presence of triethylamine afforded 6-hydroxy-1,3-selenazin-4-ones (**15**) (Scheme 8).[58,65]



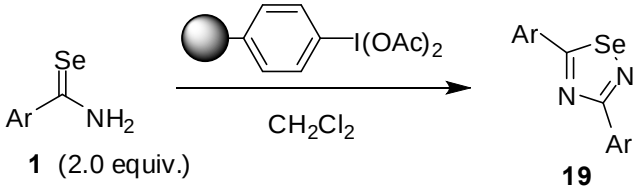
Scheme 9. Reaction of selenoamides with 1,3-bis(dimethylamino)-1,3-dichloropropenium chloride

4,6-Bis(dimethylamino)-1,3-selenazinium salts (**16**) have been prepared by the reaction of primary selenoamides (**1**) with 1,3-bis(dimethylamino)-1,3-dichloropropenium chloride (Scheme 9).[66]



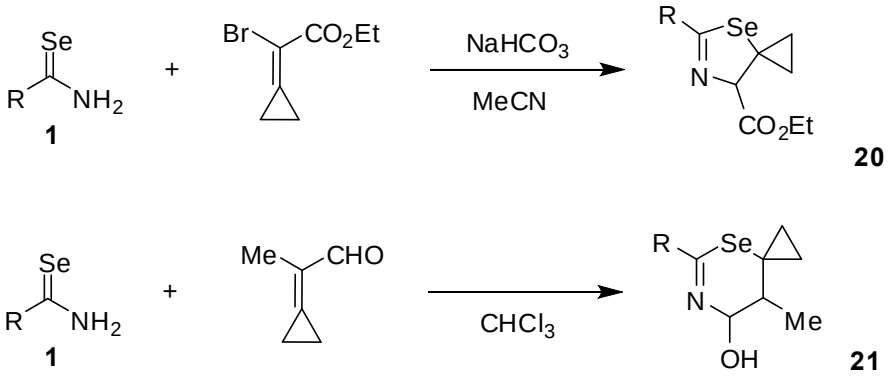
Scheme 10. Synthesis of 1,3-selenazoles employing hypervalent iodine

P-.F. Zhang *et al.*, have reported the synthesis of 1,3-selenazoles using hypervalent iodine. α-Tosyloxylation of ketones and diketones with [hydroxyl(tosyloxy)iodo]benzene (HTIB), followed by treatment with selenoamides (**1**) provided convenient methods to prepare 1,3-selenazoles (**17** and **18**) (Scheme 10).[67–69] These synthetic methods were simple, and mild and the yields were high.



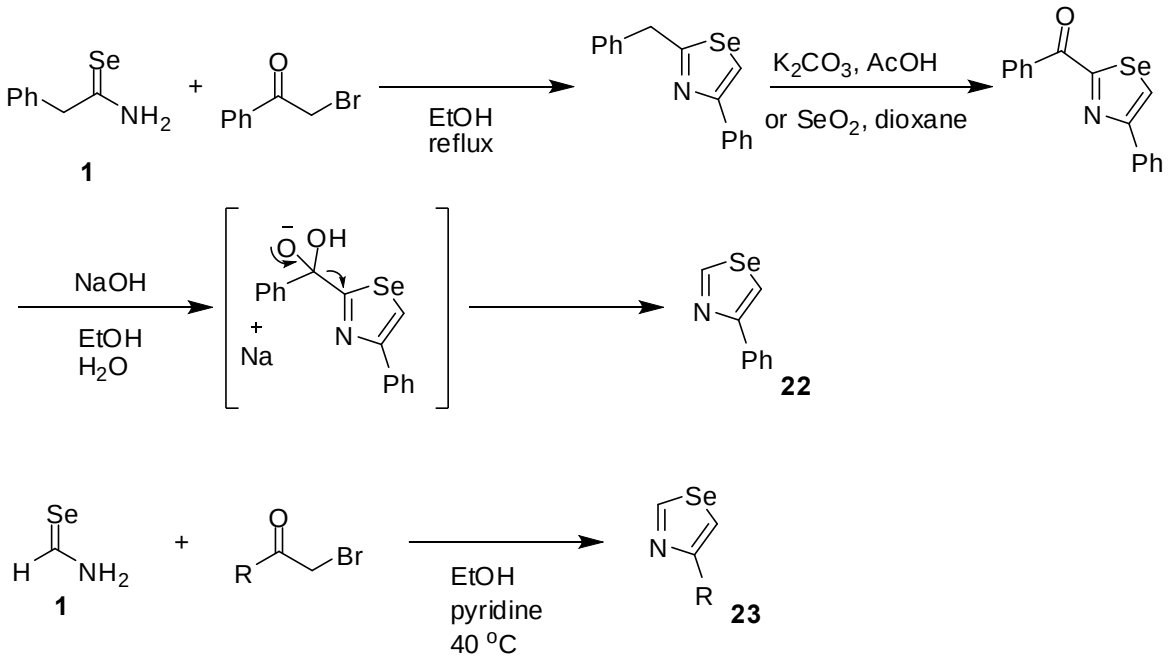
Scheme 11. Synthesis of 3,5-diaryl-1,2,4-selenadiazoles employing poly[styrene(iodosodiacetate)]

3,5-Diaryl-1,2,4-selenadiazoles (**19**) were prepared in high yields from primary selenoamides (**1**: 2.0 equiv.) using poly[styrene(iodosodiacetate)] as an oxidant with the advantages of ease of manipulation, short reaction time, high yields, and regeneration and recycling of the polymer reagent with no loss of reactivity (Scheme 11).[70]



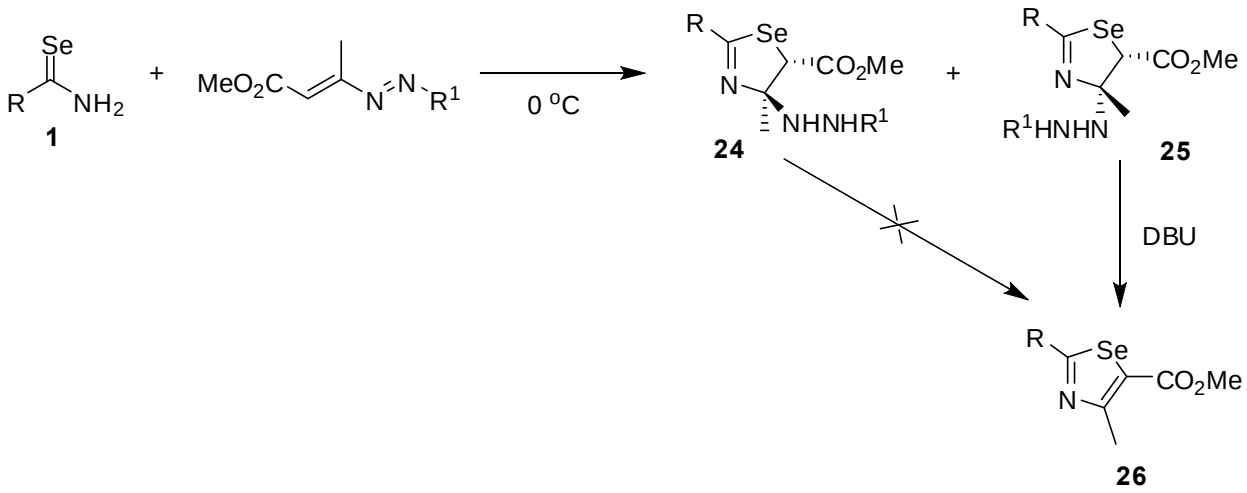
Scheme 12. Synthesis of spirocyclopropane-annulated selenoheterocycles *via* tandem Michael addition

X. Huang *et al.*, have developed a useful way to synthesize the 5-spirocyclopropane-annulated selenazoline-4-carboxylates (**20**) *via* tandem Michael addition of primary selenoamides (**1**) to bromo(cyclopropylidene)acetates followed by an intramolecular substitution under basic conditions.[71] In addition, they have reported the synthesis of 6-spirocyclopropane-annulated 4-hydroxyselenazines (**21**) by the reaction of primary selenoamides (**1**) with 2-cyclopropylidenepropionaldehyde under the mild conditions without base (Scheme 12).[72]



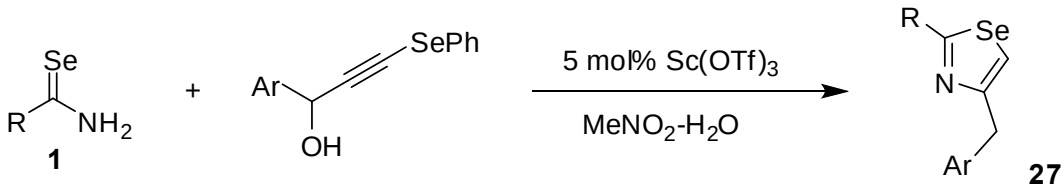
Scheme 13. Synthesis of 2-unsubstituted 1,3-selenazoles

K. Geisler *et al.*, have reported efficient methods for the synthesis of 2-unsubstituted 1,3-selenazoles (**22** and **23**). The elimination of acyl group of 2-acyl-1,3-selenazoles gave the 1,3-selenazoles (**22**) in good yields, and lower field resonances in the range of 10.13–10.23 ppm were observed for the proton at 2-position in DMSO-d_6. The cyclization of selenoformamide (**1**) with α-bromoketones provided an independent and useful approach to the 1,3-selenazoles (**23**) (Scheme 13). The advantage of this methodology lies in the fact that only two steps were required.[73–75]



Scheme 14. Reaction of selenoamides with 1,2-diaza-1,3-butadienes

1,2-Diaza-1,3-butadienes reacted easily with primary selenoamides (**1**) to afford the cyclized products (**24** and **25**). Reaction of the (4*R**,5*S**)-products (**25**) with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave 4-methyl-1,3-selenazole-5-carboxylates (**26**) (Scheme 14). In contrast, the same treatment of (4*S**,5*S**)-products (**24**) did not reveal any formation of the selenazole-5-carboxylates (**26**), suggesting that the aromatization process involved an *anti*-elimination of the hydrazine moiety.[76]

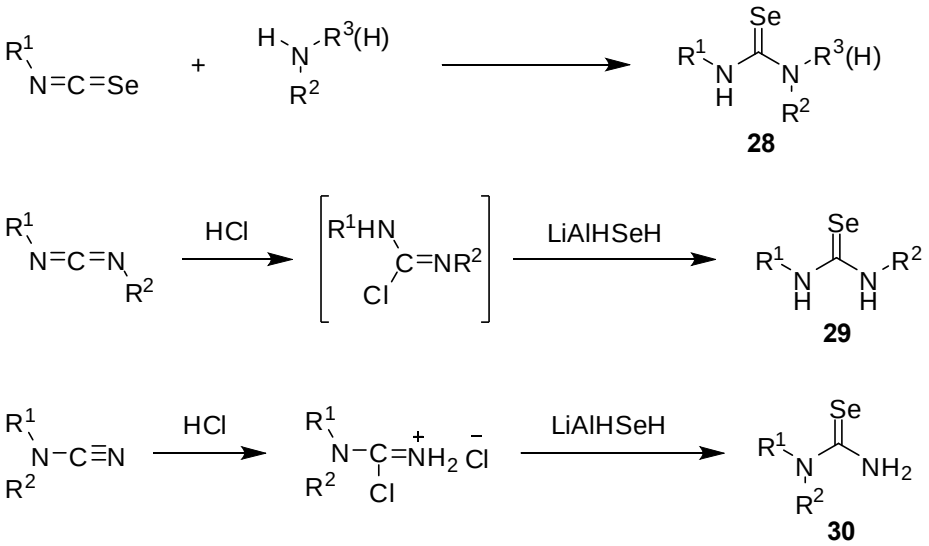


Scheme 15. Reaction of selenoamides *via* α-selanyl proradienyl cation

Cycloaddition reaction of primary selenoamides (**1**) *via* α-selanyl proradienyl cation as intermediate using scandium catalyst yielded 4-(arylmethyl)selenazoles (**27**). The reaction was completely regioselective, presumably due to nitromethane-H_2O system (Scheme 15).[77]

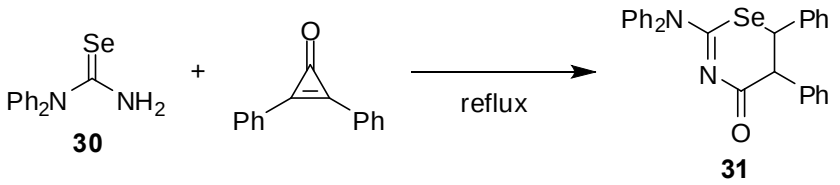
3. USING SELENOUREA

The use of selenourea as the precursor is one of the most efficient methods for the synthesis of heterocyclic compounds containing selenium atom. Therefore, their preparations and reactions are being actively investigated.



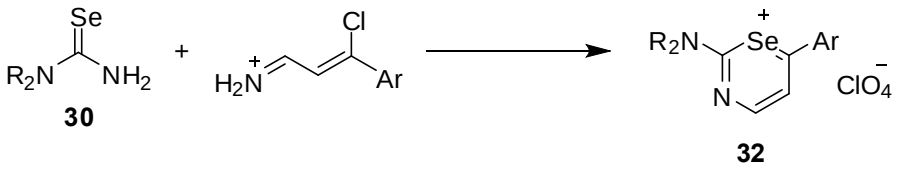
Scheme 16. Preparation of selenoureas

Selenoureas (**28**–**30**) are easily prepared by the reaction of isoselenocyanate with amines,[78–80] carbodiimides with LiAlHSeH,[81] and cyanamides with LiAlHSeH[82,83] (Scheme 16).



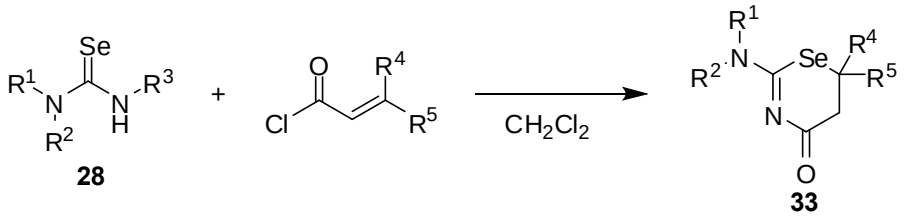
Scheme 17. Reaction of selenourea with diphenylcyclopropenone

M. Takahashi, *et al.*, have reported the synthesis of 2-(*N*,*N*-diphenylamino)-5,6-diphenyl-5,6-dihydro-4*H*-1,3-selenazin-4-one (**31**) by the reaction of *N*,*N*-diphenylselenourea (**30**) with diphenylcyclopropenone at reflux (Scheme 17).[84]



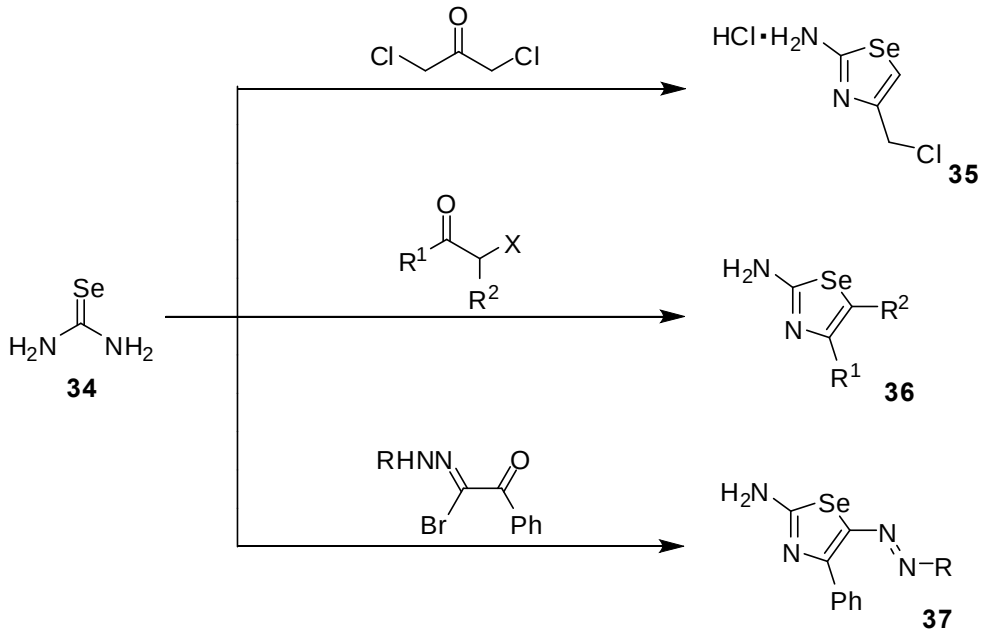
Scheme 18. Reaction of selenoureas with chloropropenylidene iminium salt

Reaction of *N*,*N*-dialkylselenoureas (**30**) with chloropropenylidene iminium salt gave 2-amino-1,3-selenazinium salts (**32**) (Scheme 18).[85]



Scheme 19. Reaction of selenoureas with α,β-unsaturated acid chlorides

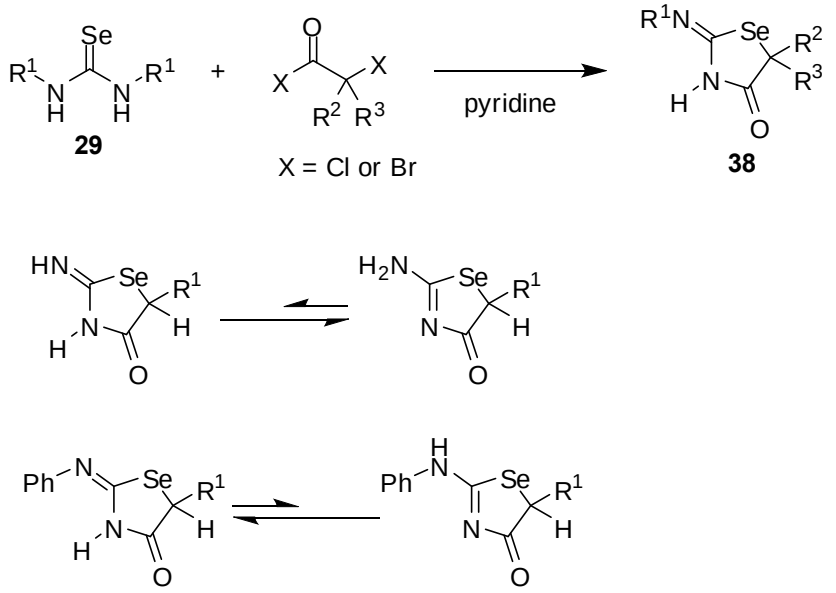
2-Amino-4*H*-5,6-dihydro-1,3-selenazin-4-ones (**33**) were obtained by the reaction of *N*,*N*'-substituted selenoureas (**28**) with α,β-unsaturated acid chlorides (Scheme 19).[86,87]



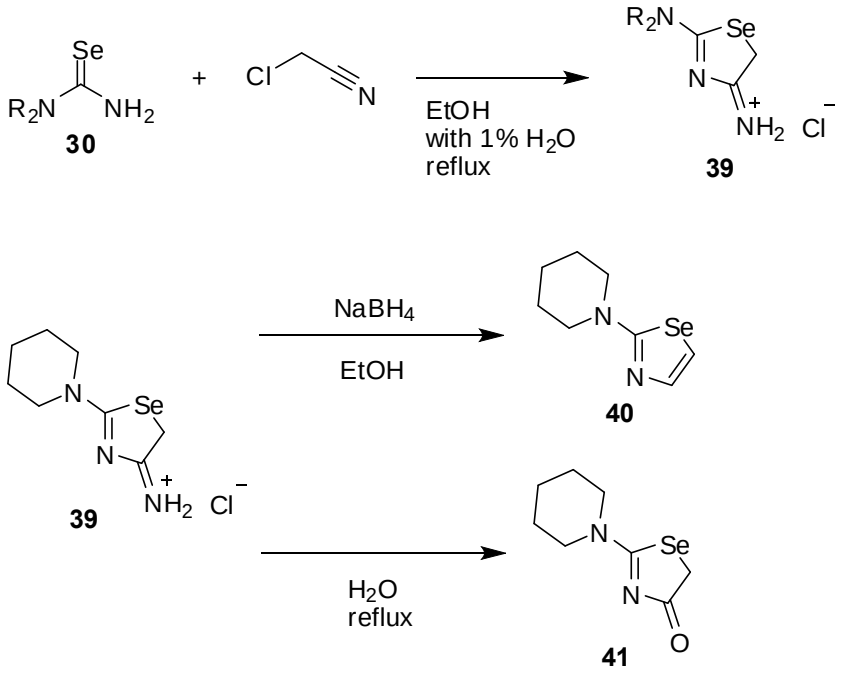
Scheme 20. Synthesis of several 2-amino-1,3-selenazoles

Condensation of unsubstituted selenourea (**34**: commercial compound) with 1,3-dichloroacetone afforded 2-amino-4-(chloromethyl)-1,3-selenazole hydrochloride (**35**).[88] Reaction with α-haloketones gave 2-amino-1,3-selenazoles (**36**).[22,32,52,89–91] Furthermore, reaction with hydrazonoyl bromides yielded 5-alkylazo-2-aminoselenazoles (**37**) (Scheme 20).[92]

Reaction of *N*,*N*'-dialkylselenoureas (**29**) with α-haloacyl halides in pyridine gave 2-imino-1,3-selenazolidin-4-ones (**38**).[93] This type of selenazoles can exist in a tautomeric equilibrium between 2-amino and 2-imino-1,3-selenazolin-4-ones (Scheme 21).

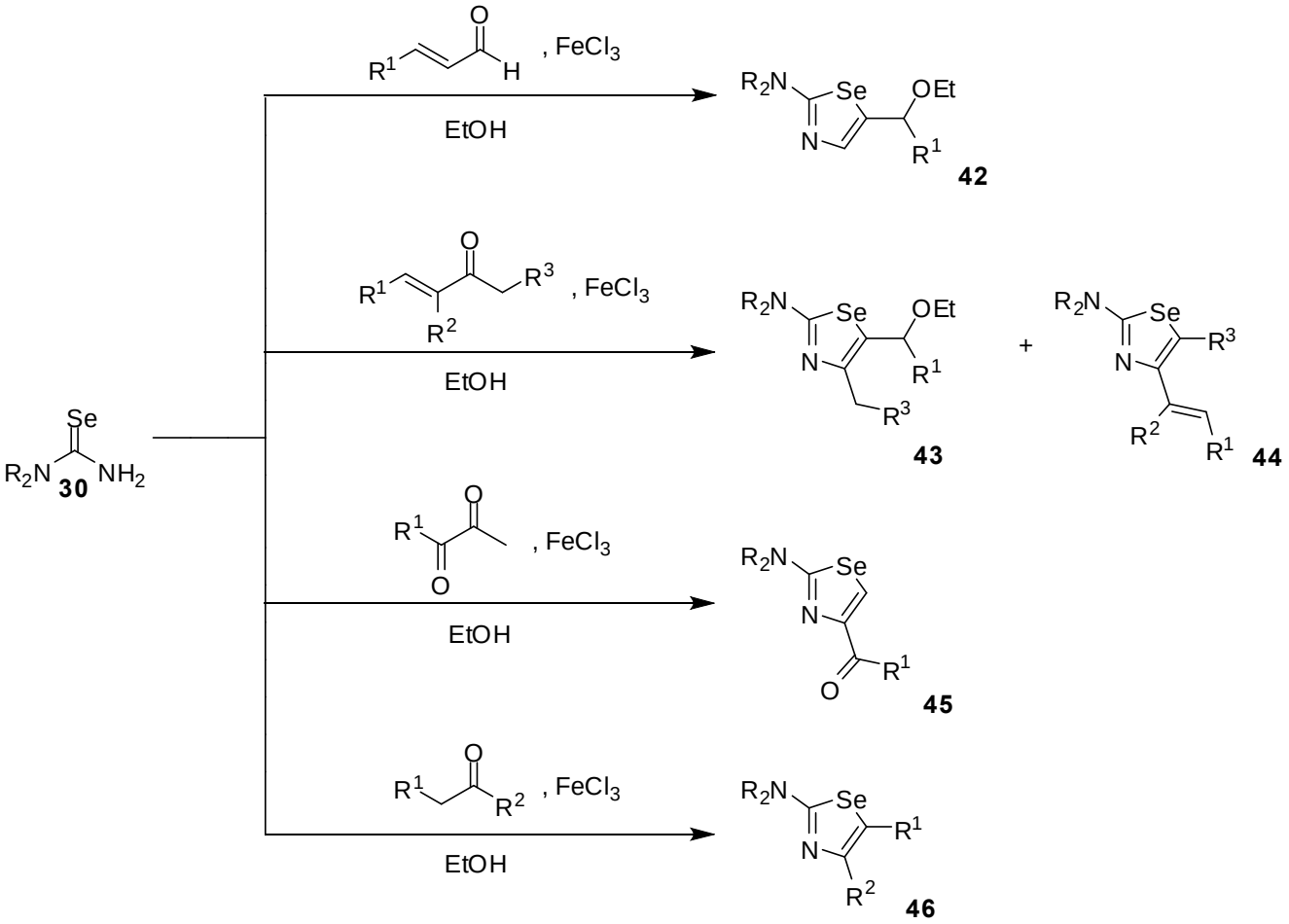


Scheme 21. Reaction of selenoureas with α-haloacyl halides



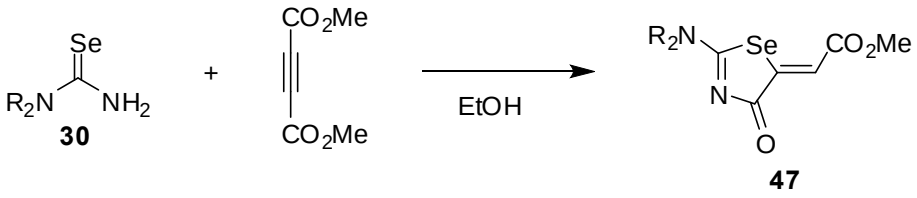
Scheme 22. Reaction of selenoureas with chloroacetonitrile

Reaction of selenoureas (**30**) with chloroacetonitrile afforded 2-amino-4,5-dihydro-1,3-selenazoles (**39**).[34,94] Furthermore, 2-piperidino-1,3-selenazole (**40**) was yielded by the reaction of 2-piperidino-4,5-dihydro-1,3-selenazol-4-iminium chloride (**39**) with sodium borohydride (2.0 equiv.). A reaction of **39** in water under reflux gave 2-piperidino-4,5-dihydro-1,3-selenazol-4-one (**41**) (Scheme 22).[94]



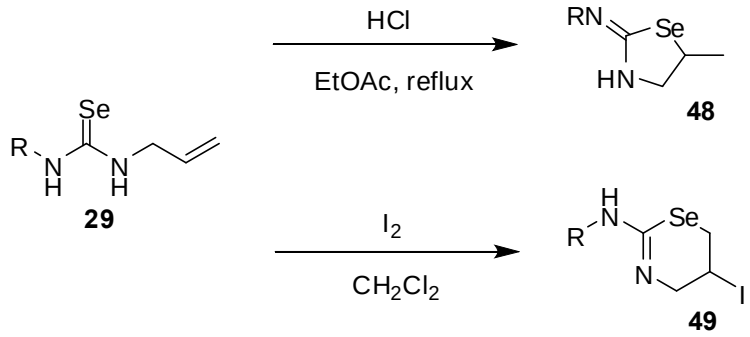
Scheme 23. Synthesis of several 2-amino-1,3-selenazoles employing ferric chloride

Several types of 2-amino-1,3-selenazoles (**42**–**46**) were prepared by the reaction of *N*,*N*-unsubstituted selenoureas (**30**) with α,β-unsaturated aldehydes,[95] ketones,[96] α-diketones,[97] and ketones[98] in the presence of ferric chloride in ethanol (Scheme 23). The formation of the products (**43** and **44**) could be explained by two pathways; the selenoureas (**30**) reacted with both β-carbonyl carbons of α,β-unsaturated ketones to give two kinds of the products (**43** and **44**).



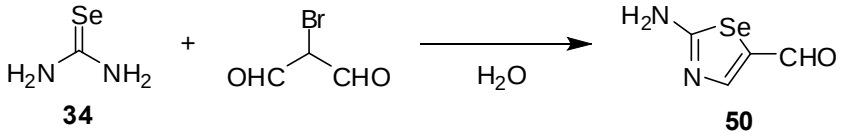
Scheme 24. Reaction of selenoureas with DMAD

Reaction of *N*,*N*-unsubstituted selenoureas (**30**) with DMAD without any catalyst yielded 2-amino-4,5-dihydro-1,3-selenazol-4-ones (**47**) (Scheme 24).[99]



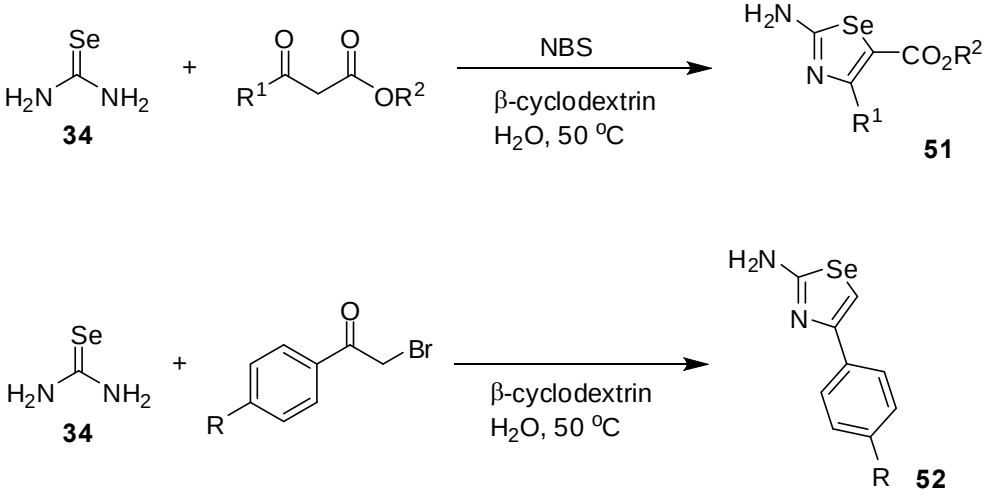
Scheme 25. Synthesis of 1,3-selenozolidines and 1,3-selenazines *via* intramolecular cyclization of *N*-allylselenoureas

The intramolecular cyclization of *N*-allylselenoureas (**29**) afforded five-membered ring 1,3-selenazolidines (**48**) through 5-*exo* closure or six-membered ring 1,3-selenazines (**49**) through 6-*endo* closure by the treatment of hydrogen chloride or iodine, respectively (Scheme 25).[100]



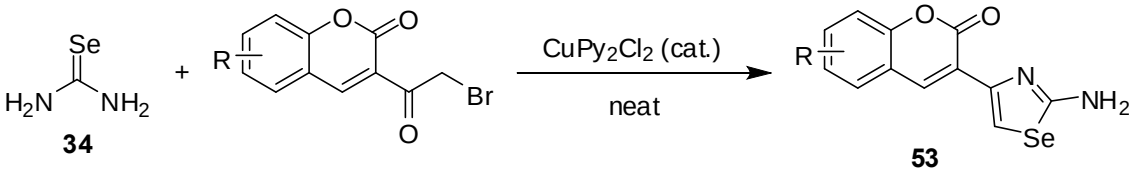
Scheme 26. Reaction of selenourea with bromomalonaldehyde

Reaction of selenourea (**34**) with bromomalonaldehyde in water gave 2-amino-1,3-selenazole-5-carbaldehyde (**50**) (Scheme 26).[101]



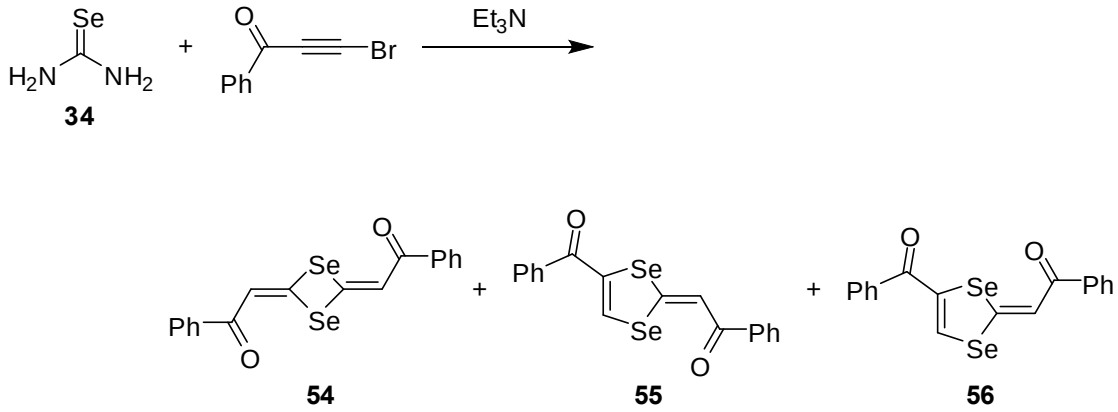
Scheme 27. Synthesis of several 2-amino-1,3-selenazoles employing β-cyclodextrin

M. Narender *et al.*, have demonstrated the novel and efficient biomimetic conversion of β-keto esters into 2-amino-1,3-selenazoles (**51**) using easily accessible *N*-bromosuccinimide and the appropriate selenourea (**34**) with β-cyclodextrin as a promoter in water.[102] 2-Amino-4-aryl-1,3-selenazoles (**52**) were synthesized from α-bromo ketones and unsubstituted selenourea (**34**) in the presence of β-cyclodextrin in water (Scheme 27).[103]



Scheme 28. Reaction of selenourea with 3-bromoacetylcoumarins employing $CuPy_2Cl_2$

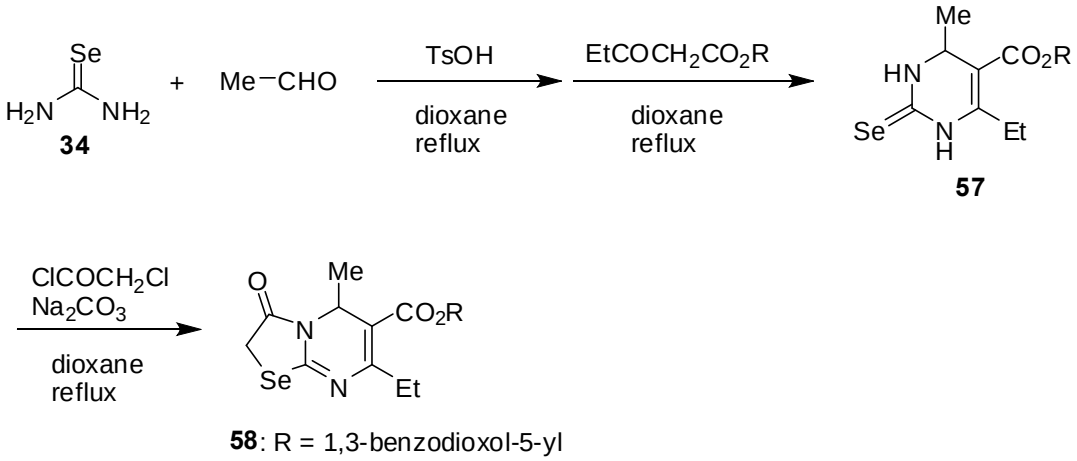
3-(2-Amino-1,3-selenazol-4-yl)-2*H*-chromen-2-ones (**53**) were prepared by the reaction of selenourea (**34**) with 3-bromoacetylcoumarins in the presence of $CuPy_2Cl_2$ as an efficient Lewis acid catalyst under solvent-free conditions (Scheme 28).[104]



Scheme 29. Synthesis of 1,3-diselenetanes and 1,4-diselenafulvenes

S. V. Amosova *et al.*, have reported a novel reaction of unsubstituted selenourea (**34**) with benzoylbromoacetylene proceeded in the presence of triethylamine to afford (*E*)-2,4-bis(benzoylmethylene)-1,3-diselenetanes (**54**), (*E*)-3,5-dibenzoyl-1,4-diselenafulvenes (**55**), and (*Z*)-3,5-dibenzoyl-1,4-diselenafulvenes (**56**), respectively (Scheme 29).[105]

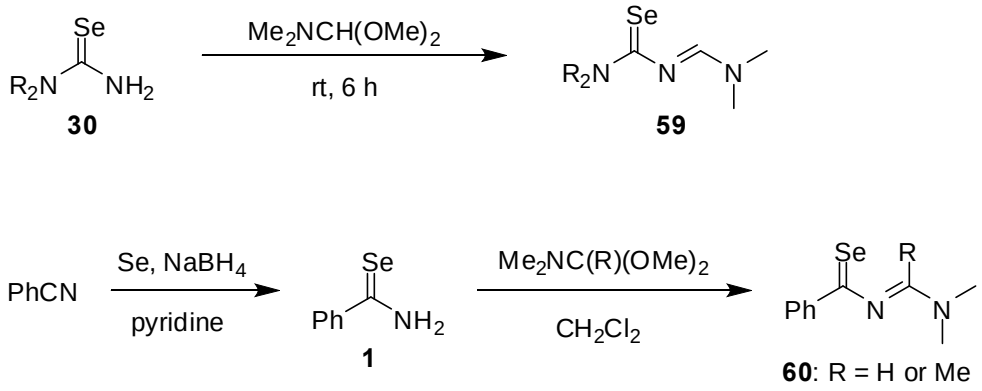
S. Kolb *et al.*, have prepared selenazolopyrimidine (**58**). The first stage led to the formation of 3,4-dihydropyrimidine-2-(1*H*)-selenone derivative (**57**) by using Biginelli condensation. Cyclocondensation of the derivative with chloroacetyl chloride gave the corresponding product (**58**) (Scheme 30).[106]



Scheme 30. Synthesis of selenazolopyrimidine

4. USING SELENAZADIENE

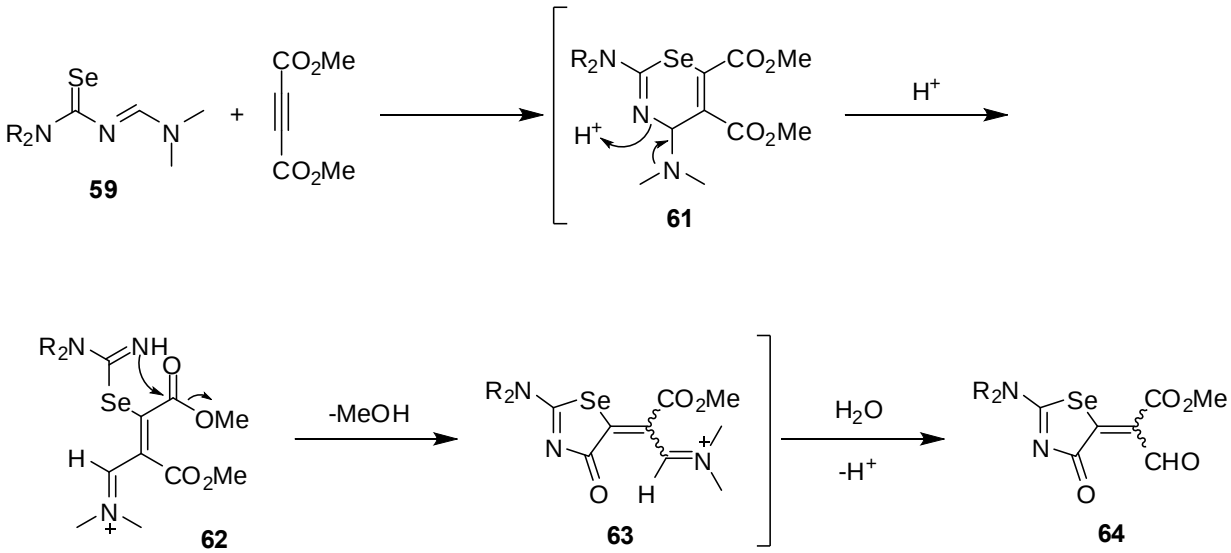
Though selenazadienes are superior starting materials to obtain selenium-containing heterocycles, only a few examples on the synthesis using selenazadienes have been reported in literature.



Scheme 31. Preparation of selenazadienes

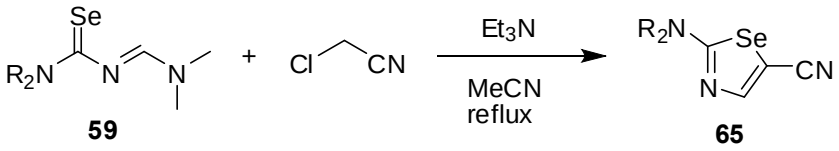
Our group prepared selenazadienes (**59**) by condensation of *N*,*N*-unsubstituted selenoureas (**30**) with *N*,*N*-dimethylformamide dimethylacetal (1.5 equiv.) at room temperature and shown its utility in the synthesis of selenium-containing heterocycles.[107,108] F. Purseigle *et. al.*, have prepared selenazadienes (**60**) starting from benzonitrile in two steps. Sodium hydrogen selenide was heated in the presence of benzonitrile at 80 ^{o}C in pyridine to give selenobenzamide (**1**). The condensation of the selenobenzamide (**1**) with *N*,*N*-dimethylformamide dimethylacetal resulted in the preparation selenazadienes (**60**) (Scheme 31).[109]

Hetero Diels-Alder reaction of selenazadienes (**59**) with DMAD gave 1,3-selenazol-4-ones (**64**) in good yields. Six-membered intermediates (**61**) were converted into five-membered intermediates (**63**) during



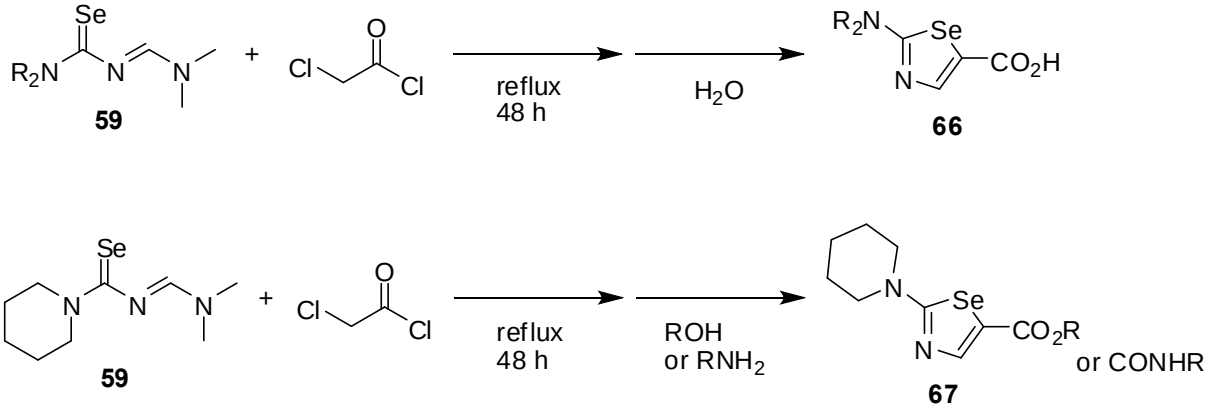
Scheme 32. Reaction of selenazadienes with DMAD

the process of purification using silica gel. Protonation of cycloaddition adducts (**61**) afforded selenoamidines (**62**). The amidines (**62**) were converted into the intermediates (**63**) by a nucleophilic recyclization (Scheme 32).[108]



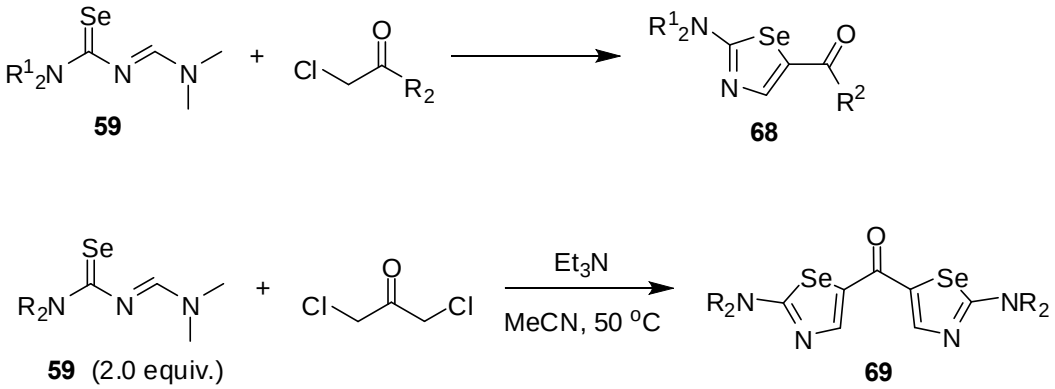
Scheme 33. Reaction of selenazadienes with chloroacetonitrile

Reaction of selenazadienes (**59**) with chloroacetonitrile yielded 1,3-selenazol-5-carbonitriles (**65**) in moderate to high yields (Scheme 33).[107]



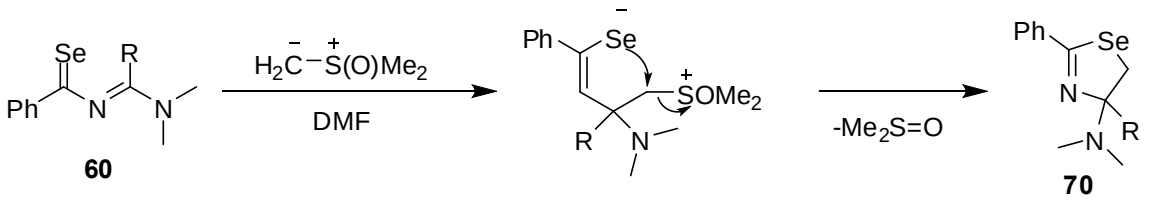
Scheme 34. Reaction of selenazadienes with chloroacetyl chloride

Reaction of selenazadienes (**59**) with chloroacetyl chloride gave 1,3-selenazol-5-carboxylic acids (**66**) in good yields. Next, trapping of the intermediate, generated from the reaction of *N*,*N*-dimethyl-*N*'-(piperidinoselenocarbonyl)formamide with chloroacetyl chloride, with various alcohols and amines was investigated. The reactions afforded the corresponding carboxylates and carboxyamides (**67**) (Scheme 34).[108,110]



Scheme 35. Reaction of selenazadienes with α-haloketones or 1,3-dichloro-2-propanone

Reaction of selenazadienes (**59**) with α-haloketones afforded 5-acyl-2-amino-1,3-selenazoles (**68**). Furthermore, reaction of selenazadienes (**59**: 2.0equiv.) with 1,3-dichloro-2-propanone in the presence of triethylamine gave the corresponding bis(2-amino-5-selenazoyl) ketones (**69**) in high yields (Scheme 35).[111]

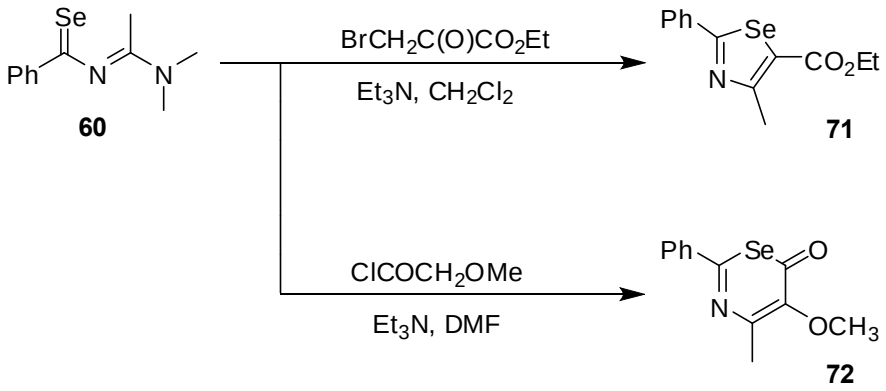


Scheme 36. Reaction of selenazadienes with sulfoxonium ylide

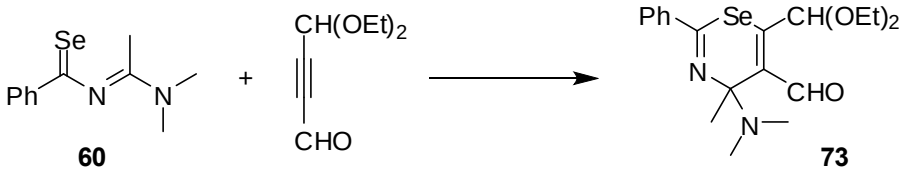
The sulfoxonium ylide, prepared *in situ* by treatment of the trimethylsulfoxonium iodide with sodium hydride in DMF, reacted with the selenazadienes (**60**) to give the 1,3-selenazol-2-ines (**70**) (Scheme 36).[109]

Reaction of selenazadiene (**60**) with electrophiles such as ethyl bromopyruvate and methoxylacetyl chloride in the presence of triethylamine afforded selenazole (**71**) and 6*H*-selenazin-6-one (**72**) (Scheme 37).[109]

K. Heuzè *et. al.*, have reported Diels-Alder reaction of selenazadiene and 4,4-diethoxy-2-butyn-1-al which led to the corresponding 4*H*-1,3-selenazine (**73**) (Scheme 38).[112]



Scheme 37. Reaction of selenazadiene with ethyl bromopyruvate or methoxylacetyl chloride



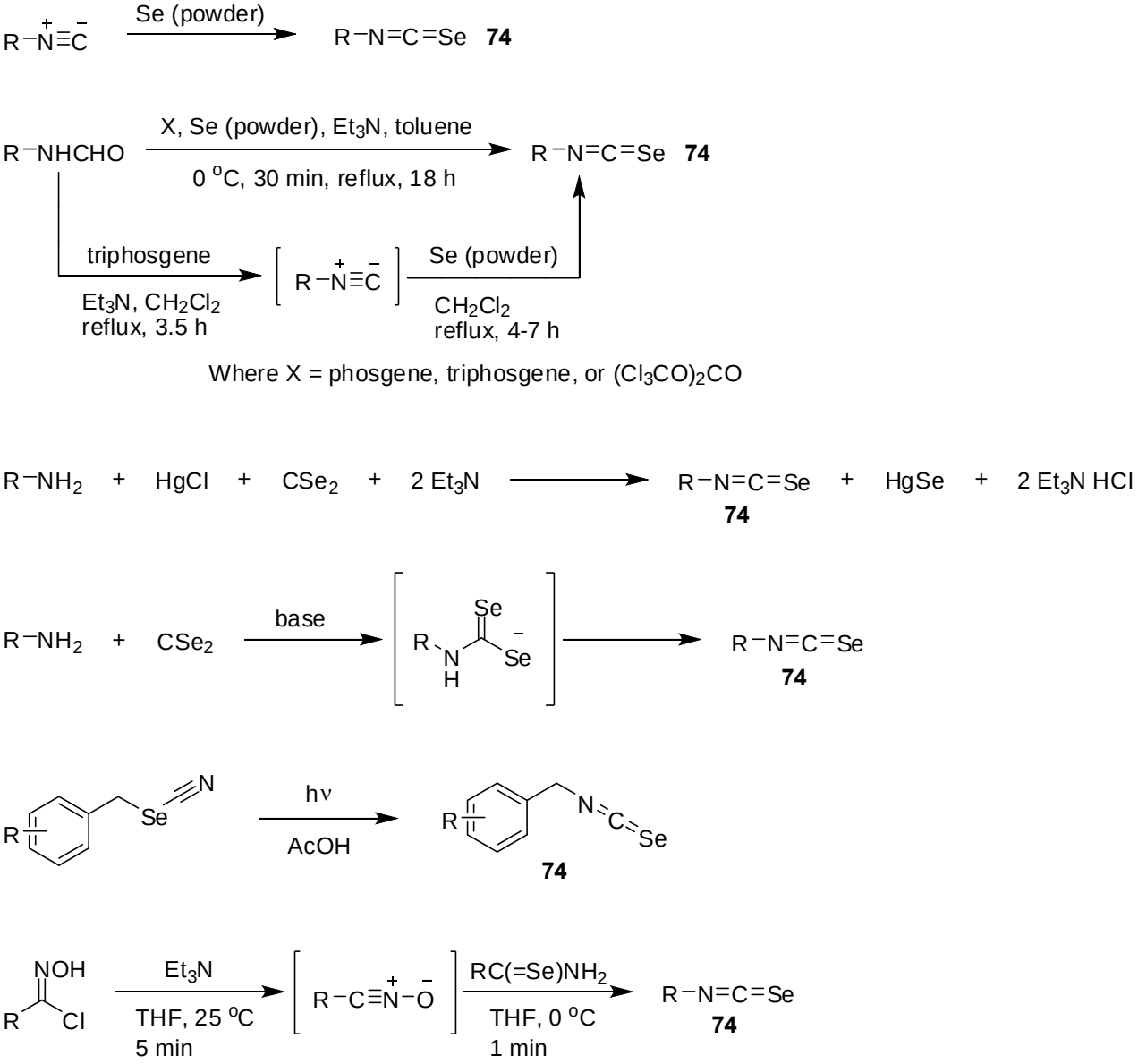
Scheme 38. Reaction of selenazadiene with 4,4-diethoxy-2-butyn-1-al

5. USING ISOSELENOCYANATE

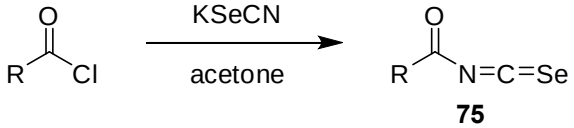
Isoselenocyanates are included in one of the heterocumulenes, have been emerged as a powerful tool for the synthesis of selenium-containing heterocycles because they are easy to prepare and store, less-toxic, and safe to handle.[113] Some years ago, we started a research program concerning the synthetic potential of isoselenocyanates as building blocks for selenoheterocycles. In 2007, our group showed a review of the utility of isoselenocyanates in the synthesis of a variety of four-, five-, and six-membered selenium-containing heterocycles.[31] Herein, we introduce the recent progress of the heterocycles using isoselenocyanates by recent articles.

The classical method of synthesis of isoselenocyanates (**74**) involved the addition of elemental selenium to isonitriles[79,114,115] or synthesis from the corresponding formamides.[83] More convenient procedure consisted of the treatment of primary amines with CSe_2 and $HgCl_2$ in the presence of triethylamine,[116] photochemical rearrangement of selecocyanates,[117] and *via* cycloaddition by the reaction of nitrile oxides with primary selenoamides to give the corresponding isoselenocyanates (**74**) (Scheme 39).

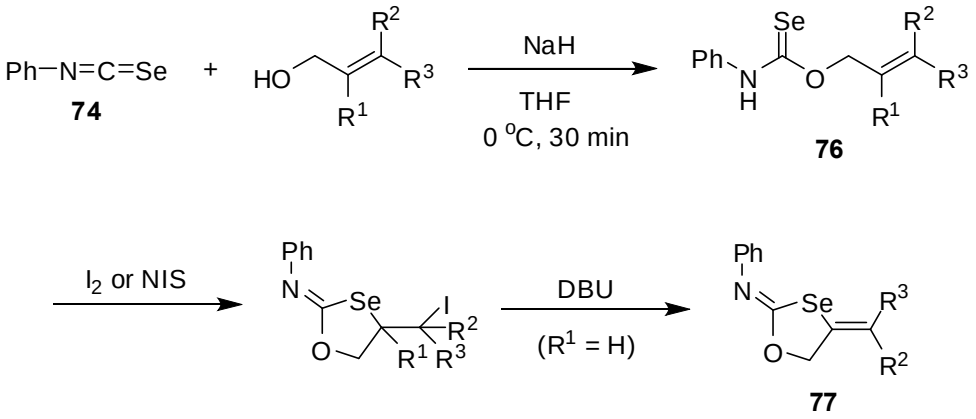
Acyl isoselenocyanates (**75**) were prepared by the reaction of acyl chlorides with potassium selenocyanate (Scheme 40).[118,119]



Scheme 39. Preparation of isoselenocyanates

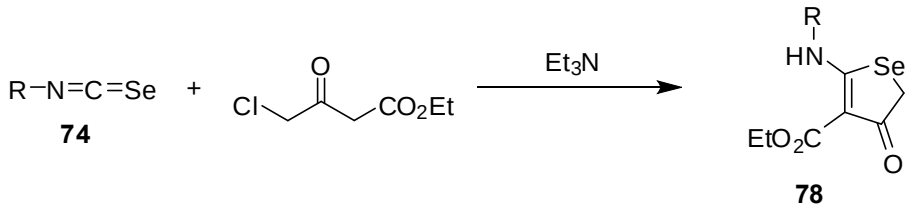


Scheme 40. Preparation of acyl isoselenocyanates



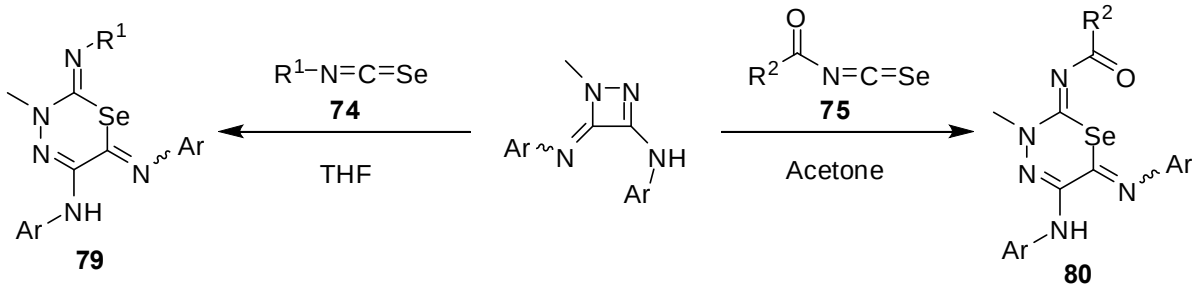
Scheme 41. Synthesis of (*Z*)- or (*E*)-4-alkylidene-2-imino-1,3-oxaselenolanes

We described the iodocyclization of *O*-allyl selenocarbamates (**76**), prepared from isoselenocyanates (**74**), using I_2 or NIS as the electrophile; this led to 4-alkyl-2-imino-1,3-oxaselenolanes, which on the treatment with DBU resulted in the formation (*Z*)- or (*E*)-4-alkylidene-2-imino-1,3-oxaselenolanes (**77**) (Scheme 41).[120]



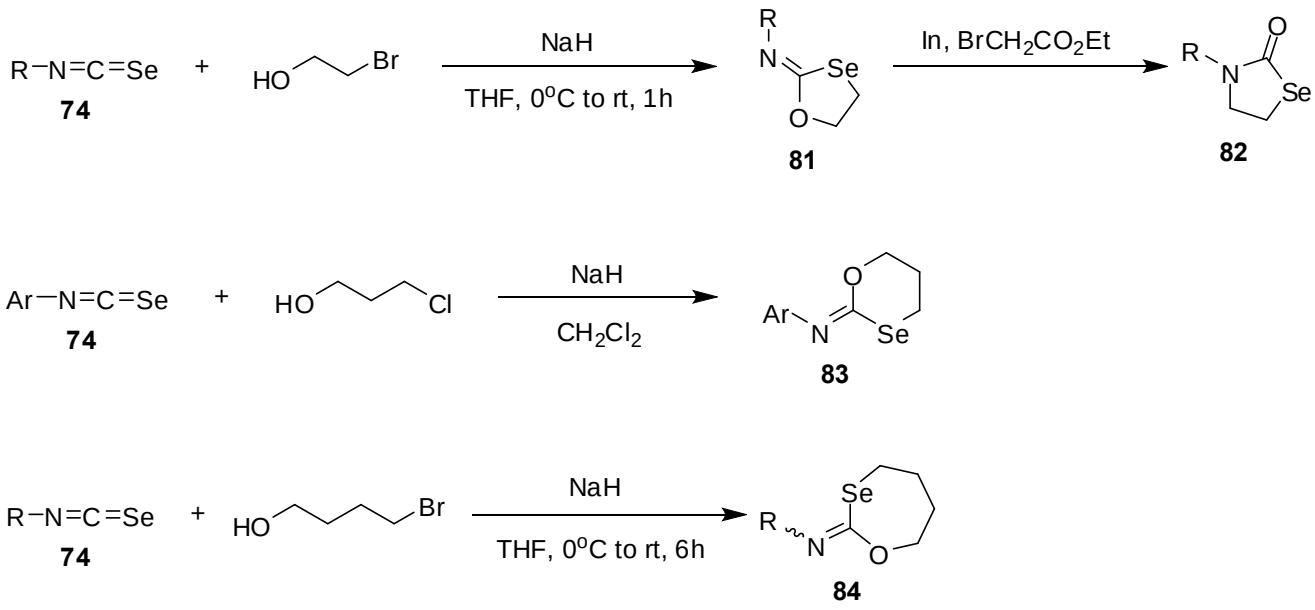
Scheme 42. Reaction of isoselenocyanates with ethyl γ-chloroacetoacetate

Isoselenocyanates (**74**) reacted with ethyl γ-chloroacetoacetate in the presence of triethylamine to yield 4-oxo-2-amino-4,5-dihydroselenophene-3-carboxylates (**78**) (Scheme 42).[121]



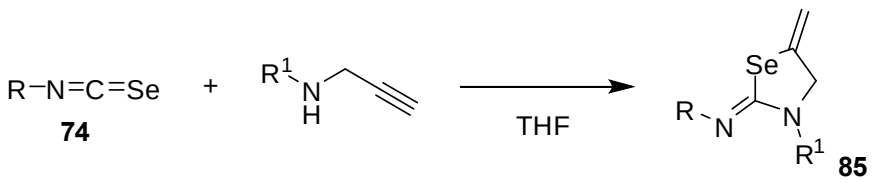
Scheme 43. Synthesis of 1,3,4-selenadiazines

J. Fleischhauer *et al.*, have demonstrated the reaction of Δ^2-1,2-diazetines with various isoselenocyanates (**74** and **75**) yielded highly substituted 1,3,4-selenadiazines (**79** and **80**) (Scheme 43).[122]



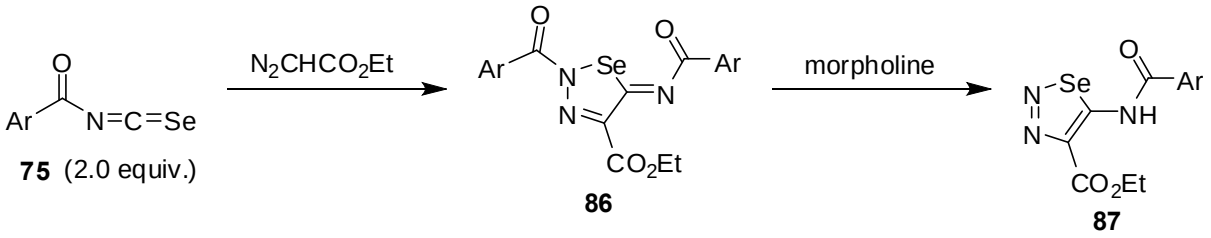
Scheme 44. Reaction of isoselenocyanates with haloalcohols

Selenium-oxygen-containing five-, six-, and seven-membered heterocycles were prepared using the corresponding haloalcohols (Scheme 44). One-pot synthesis of 2-imino-1,3-oxaselenolanes (**81**) has been achieved by the reaction of isoselenocyanates (**74**) with 2-bromoethanol in good to excellent yields. The thermal rearrangement of 2-imino-1,3-oxaselenolanes (**81**) to 1,3-selenazolidin-2-ones (**82**) employing indium and ethyl bromoacetate was observed.[123] Reaction with 3-chloropropanol in the presence of sodium hydride afforded 1,3-oxaselenan-2-imines (**83**). The reaction mechanism *via* nucleophilic attack of the alcoholate at the isoselenocyanate, followed by an 6-*exo*-*tet* cyclization, was most likely.[124] The first synthesis of 1,3-oxaselenepanes (**84**) by the reaction with 4-bromobutanol in the presence of sodium hydride as a one-pot reaction was described. The *Z*/*E* isomerism for the exocyclic carbon-nitrogen double bond in the selenium-containing heterocycles was observed.[125]



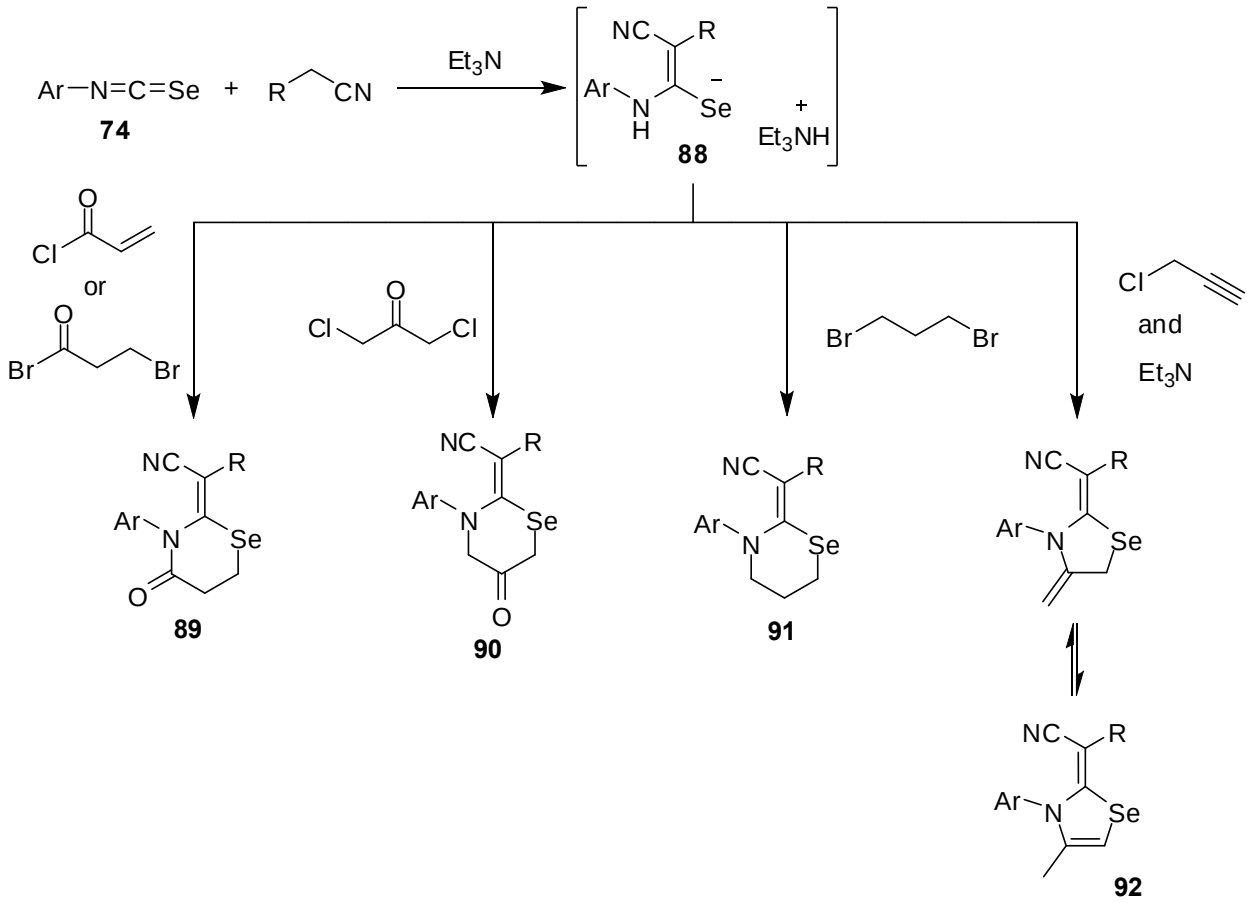
Scheme 45. Reaction of isoselenocyanates with propargylamines

One-pot synthesis of 2-imino-5-methylene-1,3-selenazolidines has been achieved by the reaction of isoselenocyanates (**74**) with propargylamines in high yields (Scheme 45).[126]



Scheme 46. Synthesis of 5-acylamino-1,2,3-selenadiazole-4-carboxylates

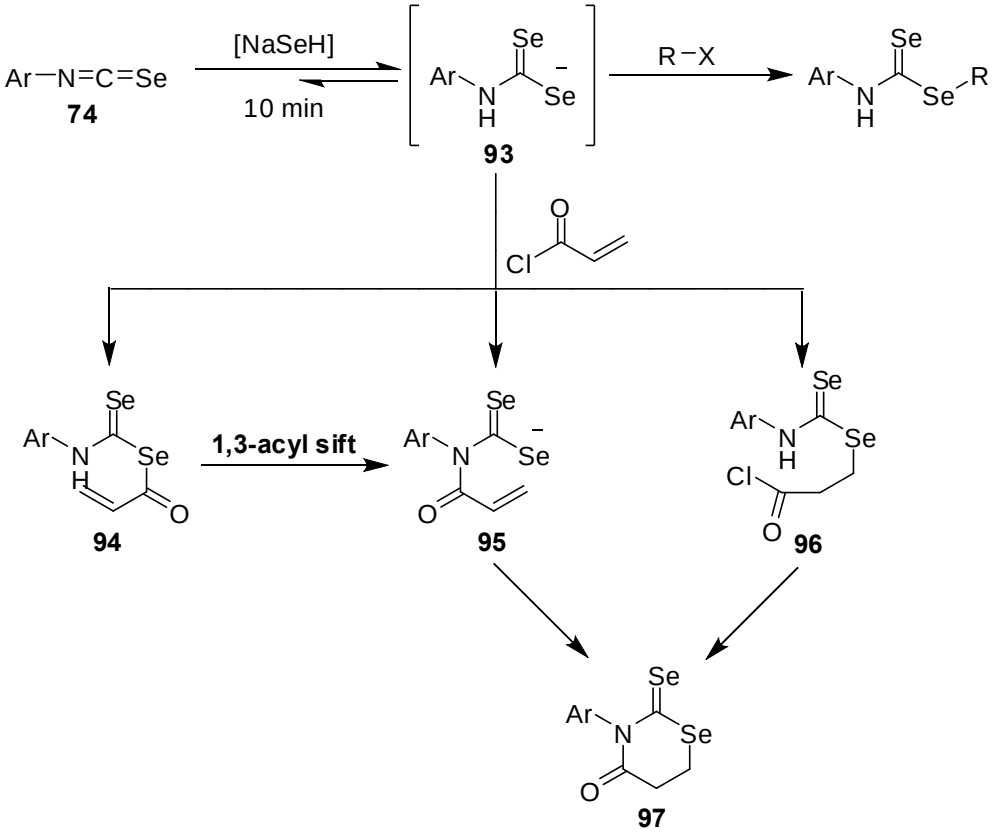
Reaction of acyl isoselenocyanates (**75**: 2.0 equiv.) with ethyl diazoacetate gave 2-acyl-1,2,3-selenadiazole derivatives (**86**). On treatment of the products with morpholine, the acyl group at N2 was removed to yield 5-acylamino-1,2,3-selenadiazole-4-carboxylates (**87**) as 2-unsubstituted forms (Scheme 46).[127]



Scheme 47. Reaction of the intermediate ketene *N*,*Se*-hemiacatal

G. L. Sommen *et al.*, have reported the reaction of the intermediate ketene *N*,*Se*-hemiacatals (**88**), prepared from cyanomethylene derivatives by treatment with aryl isoselenocyanates (**74**) and triethylamine, with bis-electrophiles afforded 1,3-selenazinane derivatives (**89**–**91**).[128,129] Reaction of

N,*Se*-hemiacatals with propargyl chloride in the presence of triethylamine gave 1,3-selenazole derivatives (**92**) (Scheme 47).[130]



Scheme 48. Synthesis of 2-selenoperhydro-1,3-selenazin-4-ones *via* diselenocarbamates

Reaction of diselenocarbamates (**93**), generated from isoselenocyanates (**74**) and sodium hydrogen selenide, with acryloyl chlorides afforded 2-selenoperhydro-1,3-selenazin-4-ones (**97**).[131] The structure of 1,3-selenazin-4-one was confirmed by X-ray analysis. The reaction proceeded *via* intermediate (**94**) or (**96**). The intermediate (**94**), which was formed by the necleophilic substitution of the acryloyl chloride by the selenium atom of the diselenocarbamate (**93**), underwent a base catalyzed 1,3-acyl shift to give the rearranged intermediate (**95**). Finally, The selenium atom attacked the β-carbon of the acrylamide group and the 1,3-selenazines (**97**) were formed by intramolecular Michael addition (Scheme 48).

6. CONCLUSIONS

In summary, this review provides recent advances in the synthesis of selenium-containing heterocycles using selenoamides, selenoureas, selenazadienes, and isoselenocyanates. A clearer understanding of the reaction details of selenoamides, selenoureas, selenazadienes, and isoselenocyanates will provide chemists with yet further tools for their synthetic endeavors in synthesis of selenium-containing biological active heterocycles.

7. ACKNOWLEDGEMENTS

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