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Review

Isoselenocyanates: A Powerful Tool for the Synthesis of Selenium-Containing Heterocycles

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Abstract: Selenium-containing heterocyclic compounds have been well recognized, not only because of their remarkable reactivities and chemical properties, but also because of their diverse pharmaceutical applications. In this context, isoselenocyanates have been emerged as a powerful tool for the synthesis of selenium-containing heterocycles, since they are easy to prepare and store and are safe to handle. In this review the recent advances in the development of synthesis methods for selenium-containing heterocycles from isoselenocyanates are presented and discussed.

Keywords: Selenium; Isoselenocyanates; Heterocycle.

Contents:

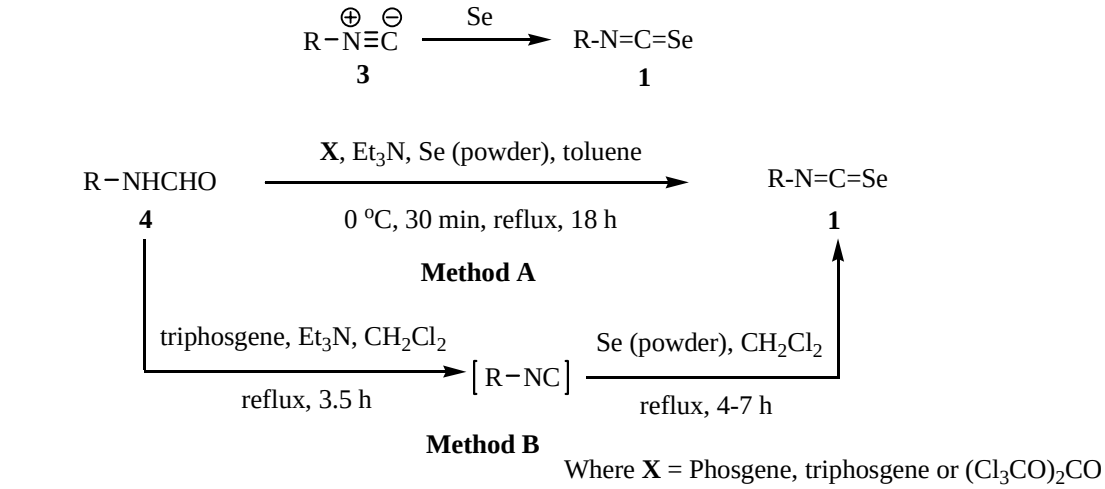
1. Introduction

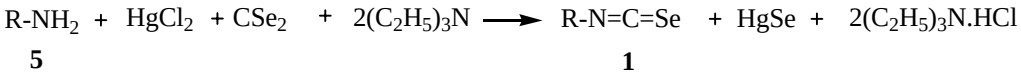
Selenium was discovered in 1817 by J.J. Berzelius [1] and the first organoselenium compound, i.e., ethylselenol, was reported by F. Wöhler and C. Siemens in 1847 [2]. Most progress in the area of the synthetic organic chemistry of Se was accomplished more than 100 years later, in contrast to the chemistry of *O*- and *S*-containing organic molecules, which is much better developed. Although the chemistry of *Se*-containing compounds is often similar to that of the corresponding *S* analogues, some significant differences are also known, and because of the toxicity and instability of many Se compounds, the synthesis of Se heterocycles is much less developed. Despite the high toxicity of many selenium compounds, organic derivatives of selenium have been synthesized as anticancer [3-5], and for other medicinal applications [6], as well as biologically active substances exhibiting antiviral [7], antibacterial [8], antihypertensive [9], and fungicidal properties [10]. As a result, selenium-containing heterocycles are of increasing interest because of their chemical properties and biological activities. Also, new approaches for the synthesis of selenium heterocycles by using more stable, less toxic, and easily accessible Se reagents are of great interest. In this context, isoselenocyanates have emerged as a powerful tool for the synthesis of selenium-containing heterocycles, since they are easy to prepare and store, less-toxic and safe to handle. In this review article, the recent progress in the development of synthesis methods of selenium-containing heterocycles from isoselenocyanates is presented and discussed in the form of their reactions with various nucleophiles.

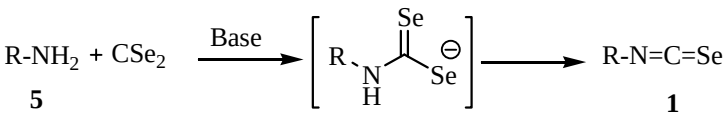
2. Synthesis of isoselenocyanates and acylisoselenocyanates

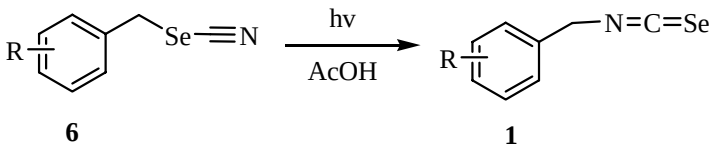
The literature to date contains few descriptions of the preparation of isoselenocyanates **1** (Scheme 1) [11-19]. The classical method of synthesis of organic isoselenocyanates involves the addition of elemental selenium to isonitriles **3** [11] or synthesis from the corresponding formamides **4** [12-14] Several other methods have also been investigated. An apparently more convenient procedure consists of treatment of a primary amine **5** with equimolar amounts of CSe_2 and $HgCl_2$ in the presence of triethylamine to give the corresponding isoselenocyanate **1** in reasonable yields [15]. The disadvantages of this method are that the presence of isoselenocyanate and the amine-mercuric chloride adduct leads to the formation of the corresponding selenourea and carbodiimide (R-N=C=N-R) as major side products, which make the purification of the desired material difficult [15]. Other methods of only limited applicability include, the alkylation of selenocyanate ion [16], the reaction of *N*-aryl-carbimidic dichlorides with sodium selenide [17], the treatment of isocyanates with phosphorous(V) selenide [17b], photochemical rearrangement of selenocyanates **6** [18] and *via* cycloaddition by the reaction of nitrile oxides **7** with primary selenoamides [19].

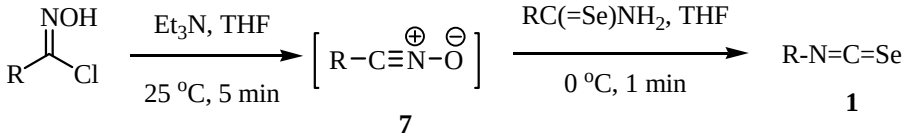
Scheme 1





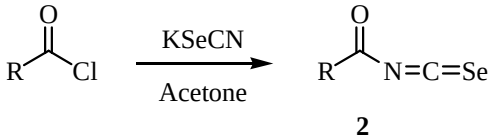




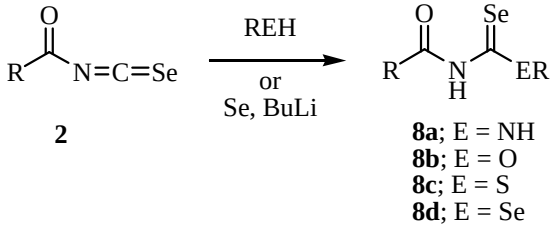


Acylisoselenocyanates **2** were prepared by a reaction of acyl chloride with potassium selenocyanate (Scheme 2), a method first investigated by Douglas [20]. The acylisoselenocyanates were never isolated. It was assumed that a polymeric form was present in equilibrium with the monomer that underwent the observed reaction. The generation of the acylisoselenocyanates was confirmed by a subsequent reaction with nucleophiles (Scheme 3) [21]. Douglas reported a reaction of the acylisoselenocyanates with amine in 1937 [20].

Scheme 2



Scheme 3



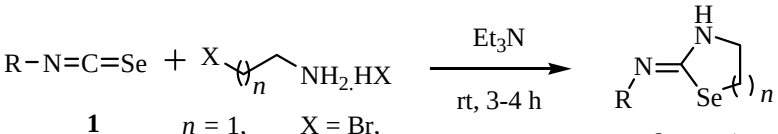
2

8a; E = NH
8b; E = O
8c; E = S
8d; E = Se

3. Reactions with amines

Treatment of ω-halo-alkylamines with aryl and alkylisoselenocyanates **1** in the presence of triethylamine (Scheme 4) gave the corresponding 1,3-selenazolidin-2-imines **9** [22], 1,3-selenazin-2-imines **10** [23], and 1,3-selenazepane-2-imines **11** [24], respectively.

Scheme 4



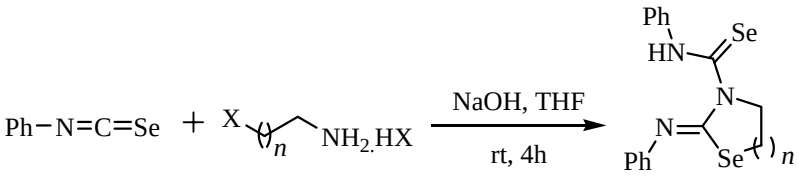
1

n = 1, X = Br,
n = 2 or 3 X = Cl

9 *n* = 1
10 *n* = 2
11 *n* = 3

On the other hand, the reaction of haloamines with two equiv. of isoselenocyanates in an organic solvent in the presence of a stronger base such as sodium hydroxide gave 2-(phenylimino)-1,3-selenazolidine-3-carboselenoic anilide **12** and 2-(phenylimino)-1,3-selenazane-3-carboselenoic anilide **13** in excellent yields (Scheme 5) [23].

Scheme 5

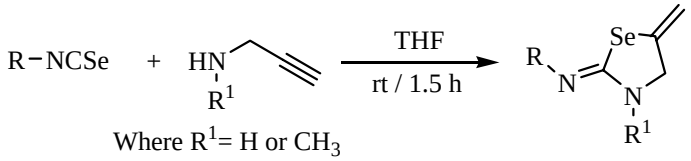


n = 1, X = Br
n = 2, X = Cl

12 *n* = 1
13 *n* = 2

A one-pot synthesis of 2-imino-5-methylene-1,3-selenazolidines in high yields has been achieved by the reaction of alkylisoselenocyanates with propargylamines [25,26]. In these reactions primary amines gave higher yields, as compared to secondary amines (Scheme 6).

Scheme 6

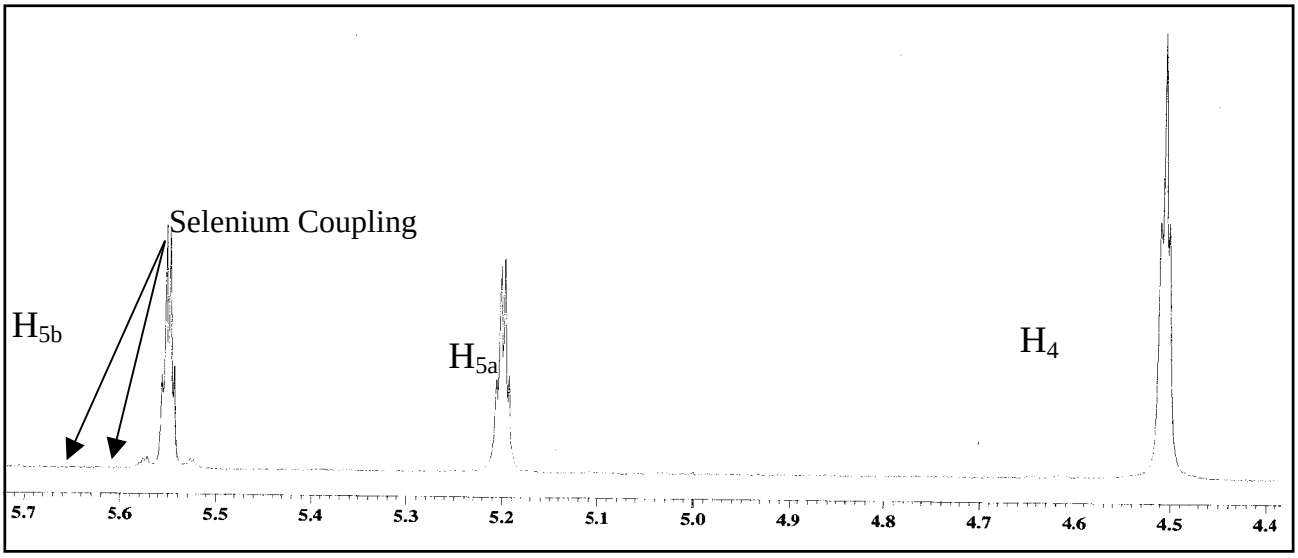


Where R^1= H or CH_3

14

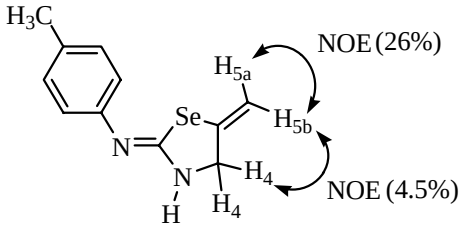
In the ^{1}H-NMR spectra of **14** in $CDCl_3$, selenium coupling with the H_{5b} proton $^{3}J(^{77}Se\text{-}^{1}H)$ = 23.9 *Hz* was observed, but the same coupling has not observed with the H_{5a} proton. The H_{5b} proton is more downfield as compared to the H_{5a} proton (Figure 1).

Figure 1



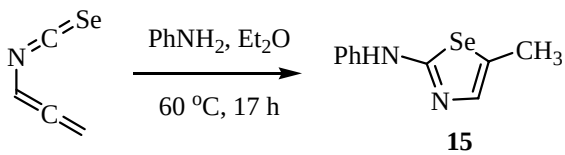
The NOE experiment of compound **14** showed a NOE of H_{5a} proton with H_{5b} (26%) and NOE of the H_{5b} proton with H_4 protons (4.5%) (Figure 2). From the above result it was confirmed that selenium shows coupling with the *trans* proton [26]. This observation is an important aid for determining structures and conformations of organoselenium compounds for which such NMR information is not available.

Figure 2



The selenazoles **15** were synthesized by the reaction of allenyl isoselenocyanate with a nitrogen-containing nucleophile (Scheme 7) [27]. Due to their pronounced tendency to polymerize, the isoselenocyanates can only be handled in solution. The synthesis of selenazoles **15** shows that allenyl isoselenocyanate reacts distinctly more slowly with nucleophiles than the unusually reactive allenyl isothiocyanate [28].

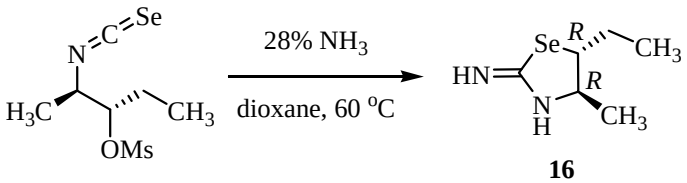
Scheme 7



15

The reaction of chirally pure isoselenocyanate with 28% ammonia aqueous solution in dioxane gave (4*R*,5*R*)-5-ethyl-2-imino-4-methylselenazolidine (**16**, Scheme 8) [29]. The order of inhibitory activity against *i*NOS of the series of **16** was (4*R*,5*R*) > (4*S*,5*S*) > (4*R*,5*S*) > (4*S*,5*R*). Inversion of the *R*-configuration at the 4-position of **16** to the *S*-configuration reduced the inhibitory activity against *i*NOS and *n*NOS and the selectivity for *i*NOS. Among the oxazolidines [30], thiazolidines [31] and selenazolidines synthesized so far, compound **16** showed the best selectivity for *i*NOS (IC_{50}*n*NOS/IC_{50}*i*NOS = 85).

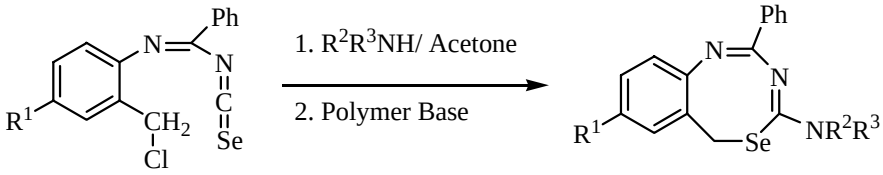
Scheme 8



16

The reaction of *N*-arylbenzimidoyl isoselenocyanates with primary and secondary amines in acetone at room temperature, followed by treatment with a base, led to 6*H*-(5,1,3)-benzoselenadiazocine derivatives of type **17** (Scheme 9) [32].

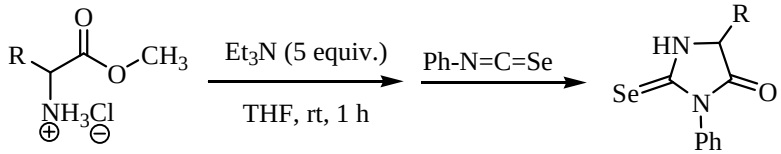
Scheme 9



17

Reaction of isoselenocyanates with methylaminoacetate hydrochloride in the presence of excess of triethylamine afforded selenohydantoins, *i.e.*, 2-selenoxoimidazolidin-4-ones **18** (Scheme 10) [33].

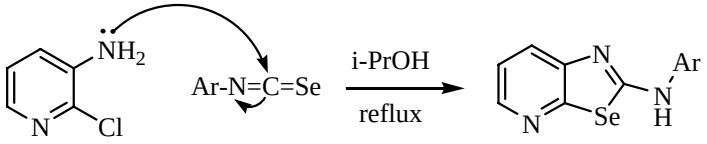
Scheme 10



18

The reaction of 3-amino-2-chloropyridine with aryl isoselenocyanates in refluxing 2-propanol gave the hydrochlorides of 2-arylaminoselenazolo[5,4-b]pyridines in good yields (Scheme 11) [34]. The free bases **19** were obtained after treatment with aqueous NaOH and recrystallization.

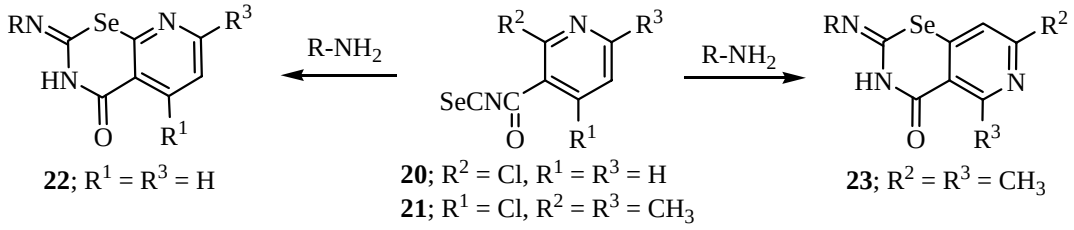
Scheme 11



19

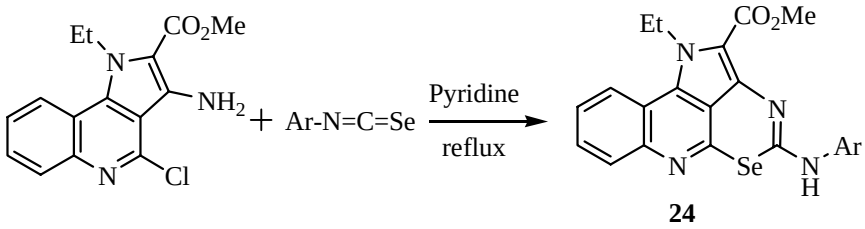
2-Chloronicotinoyl isoselenocyanate (**20**) and 2,6-dimethyl-4-chloronicotinoyl isoselenocyanate (**21**) react with arylamines to give 2-arylimino-4-oxopyrido[3,2-e]-1,3-selenazine (**22**) and 2-arylimino-5,7-dimethyl-4-oxopyrido[3,4-e]-1,3-selenazine (**23**) (Scheme 12) [35].

Scheme 12



The reaction of aryl isoselenocyanates with methyl 3-amino-4-chloro-1-ethylpyrrolo[3,2-c]quinoline-2-carboxylate in boiling pyridine leads to tetracyclic selenoheterocycles of type **24** in high yields via an intermediate selenoureido derivative and cyclization via nucleophilic substitution of Cl by Se (Scheme 13) [36].

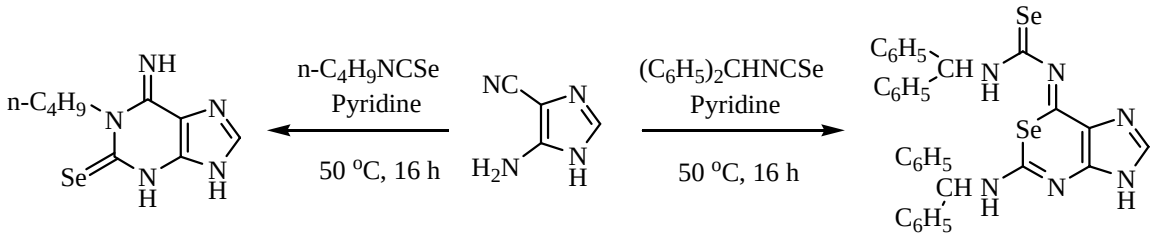
Scheme 13



24

1-Selenapurine derivatives **25** and 1-substituted 1,6-dihydro-6-imino-9H-purine-2(3H)-chalcogenone (**26**) were synthesized by the reaction in pyridine of 5(4)-aminoimidazole-4(5)-carbonitrile with various isoselenocyanates (Scheme 14). The outcome of cyclization reactions involving 5(4)-iminoimidazole-4(5)-carbonitrile and isoselenocyanates depends to a remarkable extent on the R portion of the isoselenocyanates. The predominant formation of purine-type products presumably comes from preferential nucleophilic attack on the imino group by the nitrogen atom of the selenoureido intermediate [37].

Scheme 14

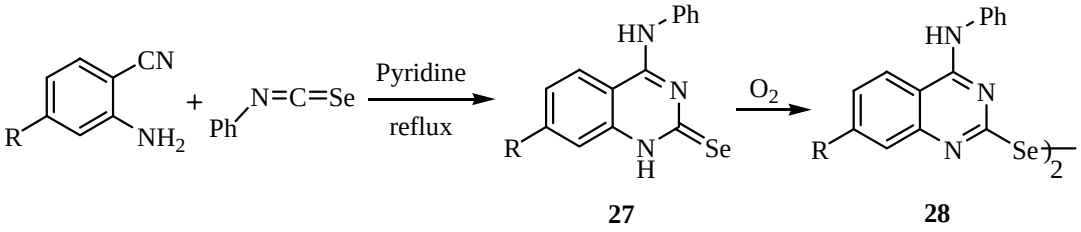


26 **25**

The reaction of anthranilonitriles with phenyl isoselenocyanate in dry pyridine under reflux gave 4-(phenylamino)quinazoline-2(1*H*)-selones **27** (Scheme 15) [38]. These compounds are easily

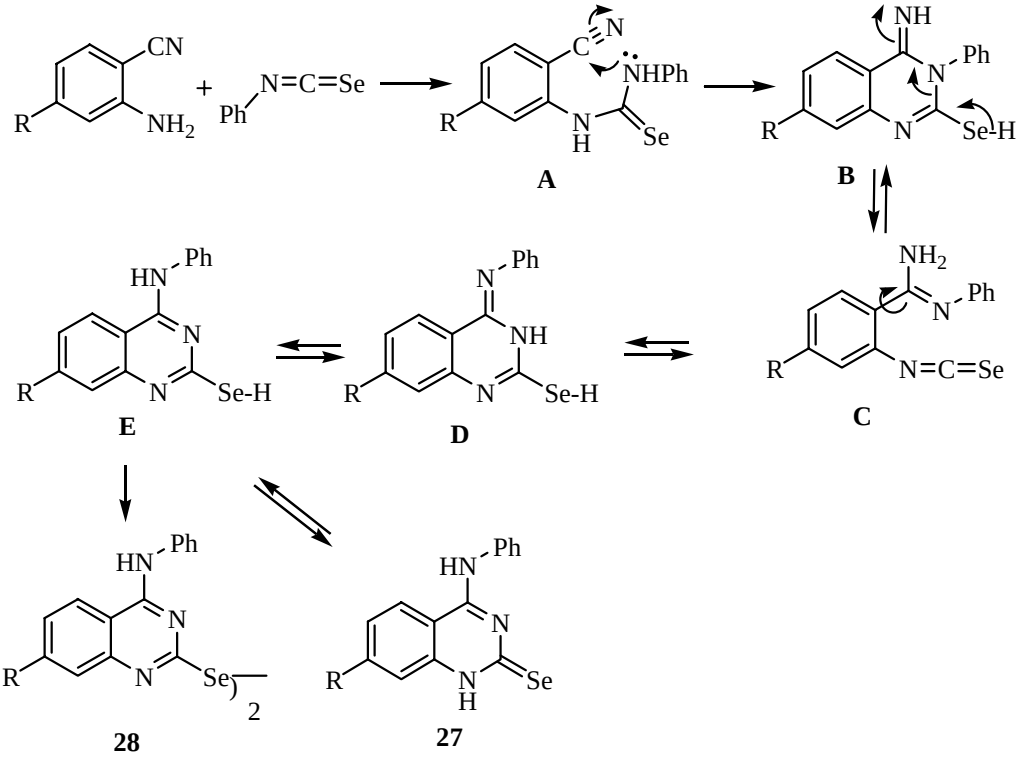
oxidized and converted to diselenides of type **28**. A possible reaction mechanism involving a Dimroth rearrangement of the primarily formed intermediate is presented in Scheme 16.

Scheme 15



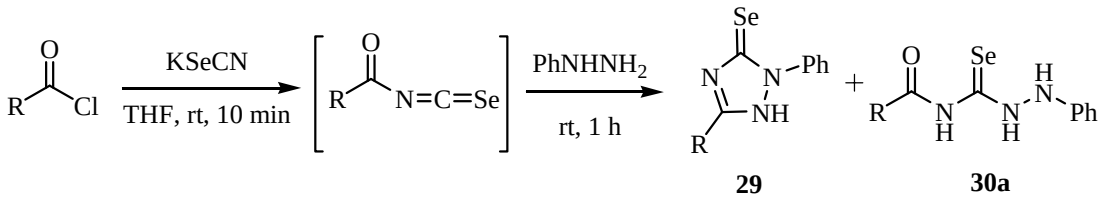
27 **28**

Scheme 16



Addition of the NH_2 group of anthranilonitriles to phenyl isoselenocyanate leads to the selenourea derivative **A**, which undergoes a ring closure to give **B** (or its tautomer). An isomerization *via* ring opening to **C** and a new ring closure leads to **D**, which tautomerizes to give **27** [36], a reaction similar to the Dimroth rearrangement [39]. An analogous isomerization has been reported by Taylor and Ravindranathan [40], who obtained the imino derivative of type **B** as a stable compound.

Scheme 17

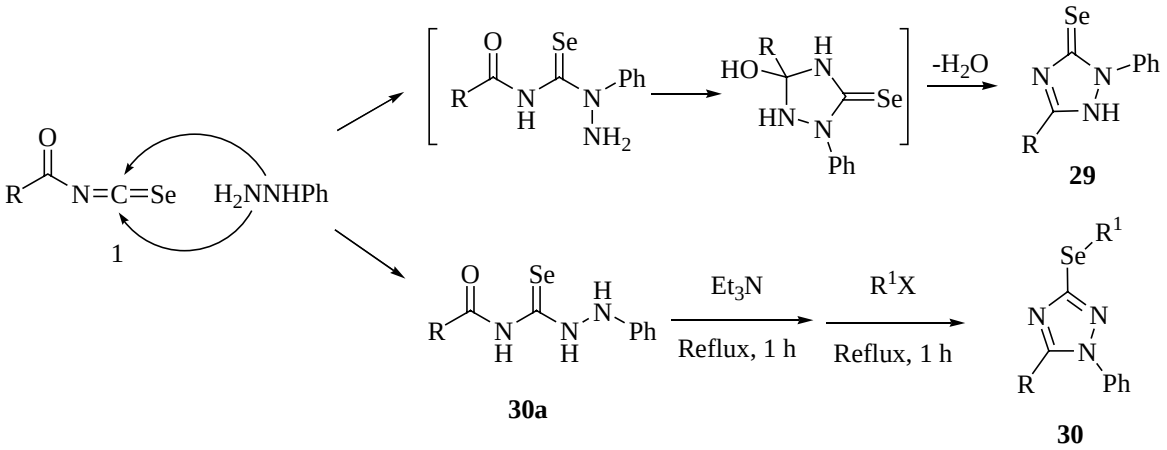


29 **30a**

Reactions of the acylisoselenocyanates with phenylhydrazine at room temperature gave 4-acyl-phenylselenosemicarbazides **30a** as the major products and 2-phenyl-1,2-dihydro-3H-1,2,4-triazole-3-selones **29** as minor ones, whereas reaction at -80°C gave selenosemicarbazides in moderate yields (Scheme 17) [41].

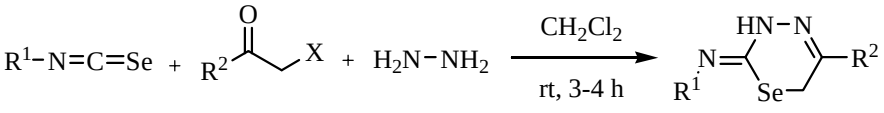
The mechanism of the reaction is as shown in Scheme 18. The formation of **29** is initiated on the nucleophilic addition of the phenylate amine of phenylhydrazine to the isoselenocyanate carbon, affording the 2-phenyl-1,2-dihydro-3*H*-1,2,4-triazole-3-selones **29**, whereas the formation of **30a** is initiated by the nucleophilic addition of terminal amine of the phenylhydrazine to the isoselenocyanate carbon, affording 1-phenylselenosemicarbazides **30a**. The cyclization of **30a** in the presence of triethylamine took place and the product was then trapped by alkyl halides at reflux to afford 3-alkylseleno-1-phenyl-5-*p*-tolyl-1*H*-1,2,4-triazoles **30.**

Scheme 18



A three component reaction of arylisoselenocyanates, phenacyl halides and hydrazine hydrate resulted in the formation of 1,3,4-selenadiazines **31** in good-to-excellent yields (Scheme 19) [42].

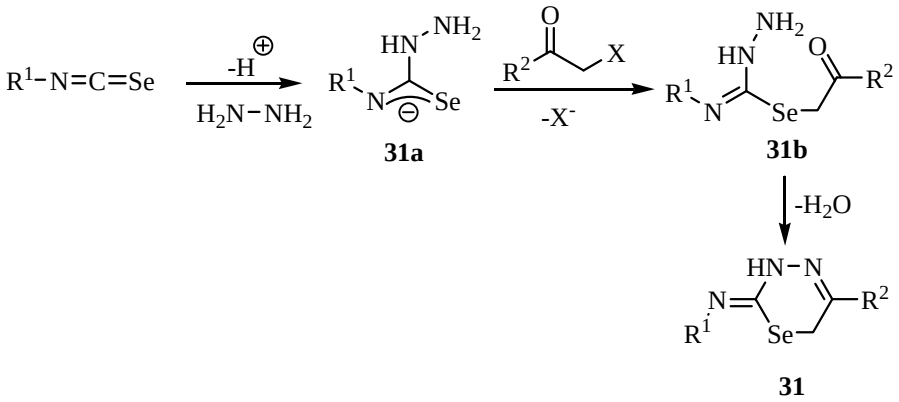
Scheme 19



31

The mechanism of the reaction is shown in Scheme 20. The addition of hydrazine to the isoselenocyanate leads to the adduct **31a**, which immediately reacts with the third component to give **31b**. Finally, an intramolecular condensation with elimination of H_2O, *i.e.*, the formation of a hydrazone, leads to the selenium-containing heterocycles **31**.

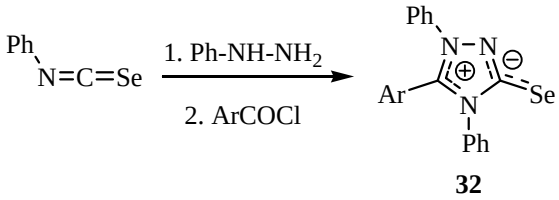
Scheme 20



31a **31b** **31**

1,3,4-Triazolium-2-selenolates **32** were prepared by the reaction of isoselenocyanates and phenyl hydrazine and then treatment with an aroyl chloride (Scheme 21) [43]. The structures were interpreted according to the comparative method used by Stefaniak *et al*. [44,45], Bartels-Keith *et al*. [46] and by Miller and Montanari [47].

Scheme 21

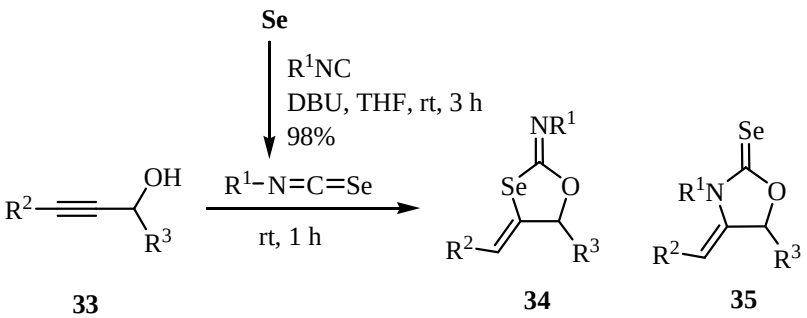


32

4. Reactions with alcohols and thiols

The reaction of isocyanides with selenium in the presence of DBU gave isoselenocyanates, which then were allowed to react with alk-2-yn-1-ols **33** to give, without purification, the selenium-containing heterocycles 2-imino-4-alkylidene-1,3-oxaselenolanes **34** and 2-selenoxo-1,3-oxolidine **35** (Scheme 22) [48].

Scheme 22

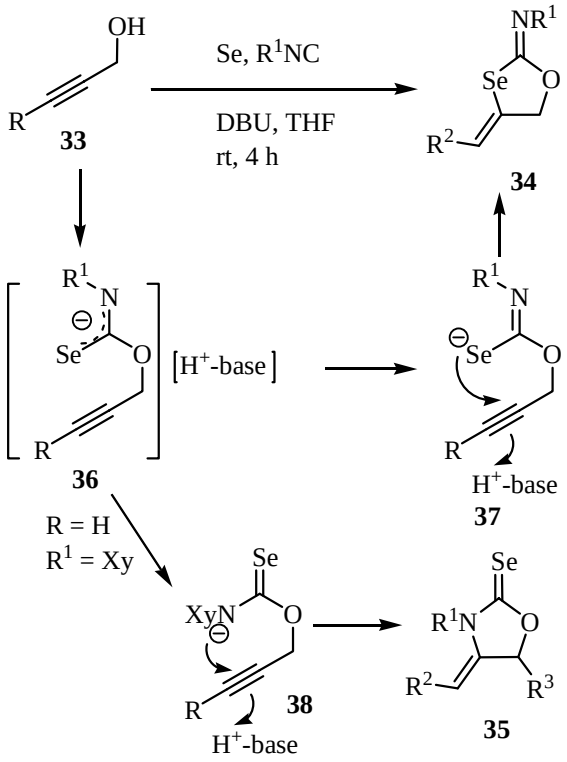


33 **34** **35**

A plausible reaction mechanism for this transformation is shown in Scheme 23. First, alk-2-yn-1-ol **33** undergoes selenoimidoylation by the reaction with selenium and isocyanide to yield oxyimidoylselenoate **36**, which underwent intramolecular cycloaddition affording new selenium-

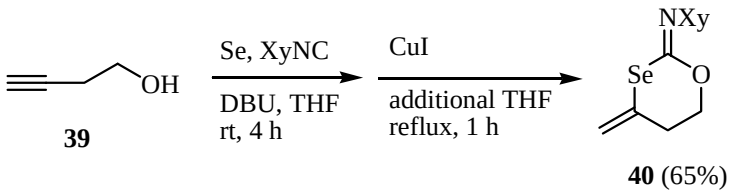
containing heterocycles **34**. The stereoselectivity of the C=C double bonds of the products can be explained by a *trans* addition mechanism (**36** => **37** => **34**), where proton coordination to the carbon-carbon triple bond facilitates nucleophilic addition of selenium to this triple bond from the opposite side. 2-Selenoxo-1,3-oxolidine **35** is formed by the nucleophilic addition of nitrogen to the carbon-carbon triple bond of **36**. The product selectivity observed is due to the higher nucleophilicity of the selenium atom. In fact, the product ratio was almost the same when the reaction time was shortened to 1 h. Isolated **34** and **35** were not interconverted under similar reaction conditions.

Scheme 23



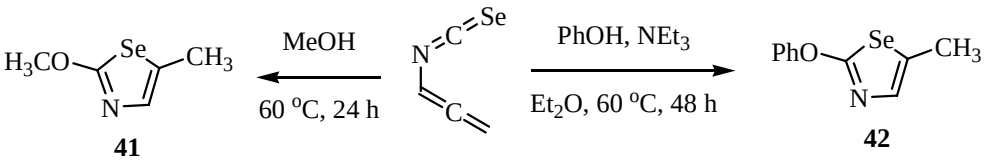
The reaction of but-3-yn-1-ol **39** under similar conditions did not result in the formation of the expected six-membered heterocycle, 4-methylidene-1,3-selenane **40**, at all. Since it is known that CuI promotes the intramolecular cyclization of *N*-propargyl selenocarbamates [49] and *O*-propargyl thiocarbonates [50] the addition of CuI and subsequent heating of the reaction mixture at reflux afforded **40** in 65% yield (Scheme 24) [48].

Scheme 24



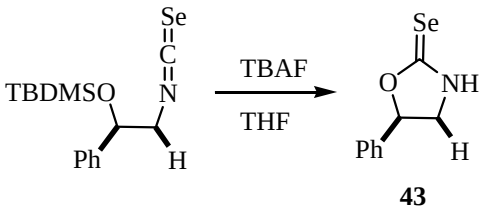
The selenazoles **41**, **42** were synthesized by the reaction of allenyl isoselenocyanate with oxygen-containing necleophiles (Scheme 25) [27].

Scheme 25



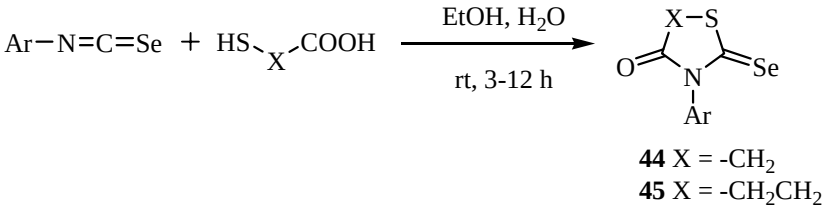
Cleavage of the silyl ether with tetrabutylammonium fluoride (TBAF) in tetrahydrofuran was followed by ring closure to give the (4*S*, 5*R*)-(-)-4-methyl-5-phenyloxazolidine-2-selone (**43**, Scheme 26) [51].

Scheme 26



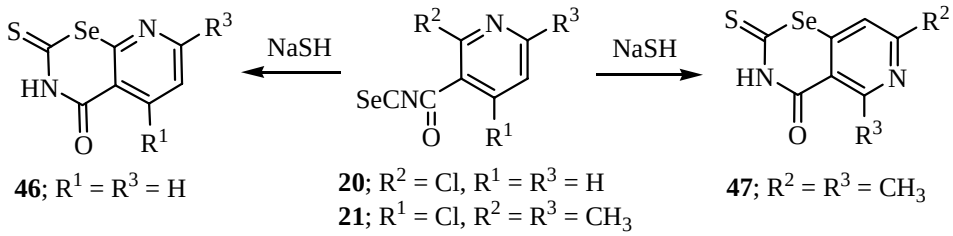
2-Selenoxo-1,3-thiazolidin-4-ones (selenorhodanines) **44** and 2-selenoxo-1,3-thiazinanes **45** were synthesized in a one pot reaction in 60-96% yields from arylisoselenocyanates and α- and β-mercapto carboxylic acids (Scheme 27). No additional base is needed to catalyse the reaction [52].

Scheme 27



2-Chloronicotinoyl isoselenocyanate **20** and 2,6-dimethyl-4-chloronicotinoyl isoselenocyanate (**21**) react with sodium hydrogen sulfide to afford the respective 2-thioxo-4-oxopyrido-1,3-selenazines **46** and **47** (Scheme 28) [35].

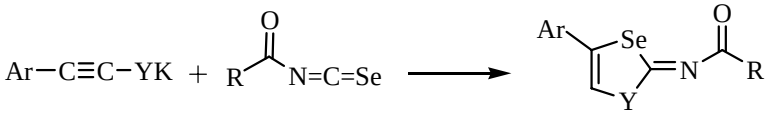
Scheme 28



5. Reactions with selenolates

A reaction of potassium 2-arylethynethiolates **48** with acyl isoselenocyanates, which were prepared *in situ* from the reaction of acetyl or aroyl chloride with potassium selenocyanate in THF, yielded *N*-(4-aryl-1,3-thiaselenol-2-ylidene)-amides **50** (Y = S) and the reaction of compound **49** (Y = Se) with acylisoselenocyanates gave *N*-(4-aryl-1,3-diselenol-2-ylidene)-amides **51** (Y = Se) in high yields (Scheme 29) [53].

Scheme 29

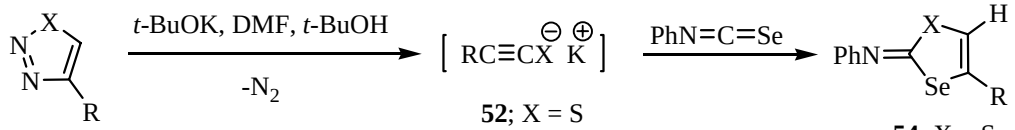


48; Y = S
49; Y = Se

50; Y = S
51; Y = Se

Potassium 2-aryl- and 2-alkylethyneselenolates **53**, obtained by the decomposition of 4-substituted-1,2,3-selenadiazoles, participate in a cyclization reaction with isoselenocyanates to afford 2-aryl alkylimino-1,3-diselenoles **55** [54,55], whereas the reaction of potassium 2-aryl- and 2-alkylethynethiolates **52** with isoselenocyanates yielded 2-arylimino-1,3-thiaselenole, **54** (Scheme 30) [55].

Scheme 30

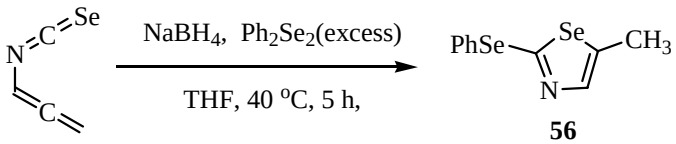


52; X = S
53; X = Se

54; X = S
55; X = Se

The reaction of allenyl isoselenocyanate with seleno-containing nucleophiles gave selenazoles **56** (Scheme 31) [27].

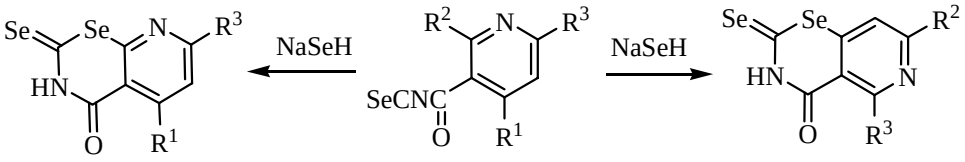
Scheme 31



56

The reaction of **20** and **21** with sodium hydroselenide afforded the respective 2-selenoxo-4-oxopyrido-1,3-selenazines **57** and **58** (Scheme 32) [35].

Scheme 32



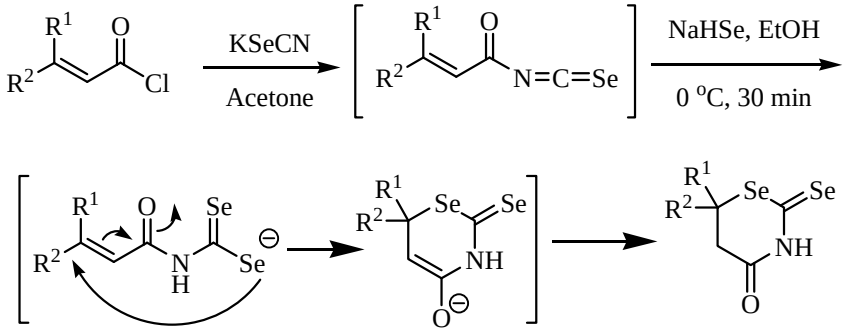
57; $R^1 = R^3 = H$

20; $R^2 = Cl$, $R^1 = R^3 = H$
21; $R^1 = Cl$, $R^2 = R^3 = CH_3$

58; $R^2 = R^3 = CH_3$

1,3-Selenazines and 1,3-selenzoles have been prepared from isoselenocyanates *via* diselenocarbamate intermediates [56]. The acryloyl isoselenocyanates were generated *in situ* by reaction of an α,β-unsaturated acyl chloride with potassium selenocyanate. The treatment of substituted acryloyl isoselenocyanate with sodium hydroselenide gave 2-selenoxoperhydro-1,3-selenazin-4-ones **59** (Scheme 33) [56].

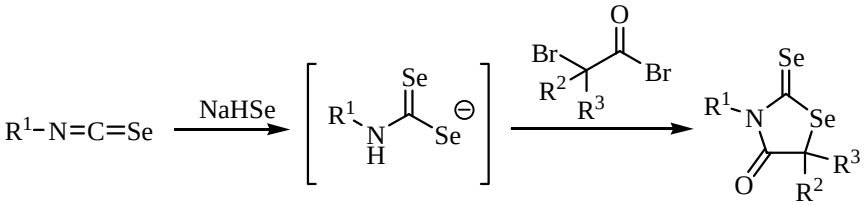
Scheme 33



59

Selenium-nitrogen-containing five membered heterocycles were similarly synthesized. An intermediate *N*-alkyl diselenocarbamate reacted with bromoacetyl bromides to afford 3-alkyl- or 3-aryl-2-selenoxo-1,3-selenazolidine-4-ones **60** in 10-37% yields. The corresponding diselenides were also obtained (Scheme 34) [56].

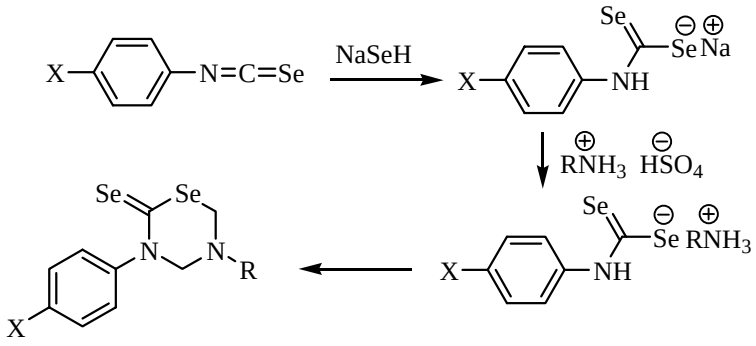
Scheme 34



60

Phenyl isoselenocyanates undergo nucleophilic addition of sodium hydrogen selenide in the presence of a salt of a primary amine and formaldehyde to form 3,5-disubstituted tetrahydro-1,3,5-selenodiazine-2-selenones **61** (Scheme 35) [57]. The best yields were obtained in the case when phenyl isoselenocyanates containing an electron-accepting substituent were used for the addition-cyclization reaction.

Scheme 35

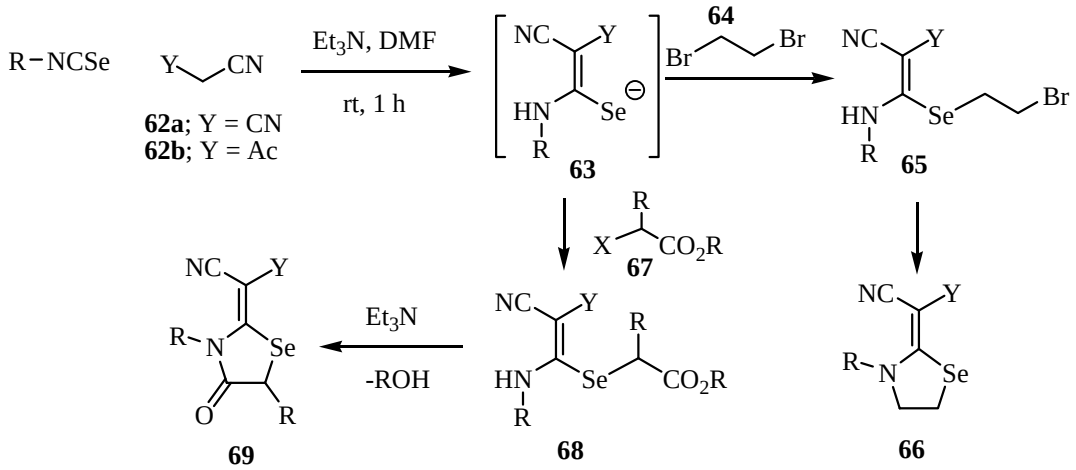


61; X = Cl, H, CH_3, C_2H_5, CH_3O, or $(CH_3)_2N$
R = Bn

6. Reactions with carbanions

The carbanion obtained from malononitrile (**62a**) and triethylamine was reacted in DMF with isoselenocyanates to give an intermediate of type **63**. The latter reacted with 1,2-dibromoethane (**64**) to give another intermediate **65**, which cyclized to yield 1,3-selenazolidine derivatives of type **66**. Similar reactions were performed starting with ethyl cyanoacetate (**62b**). Only one isomer was obtained in the case of the cyanoacetates (Scheme 36) [58].

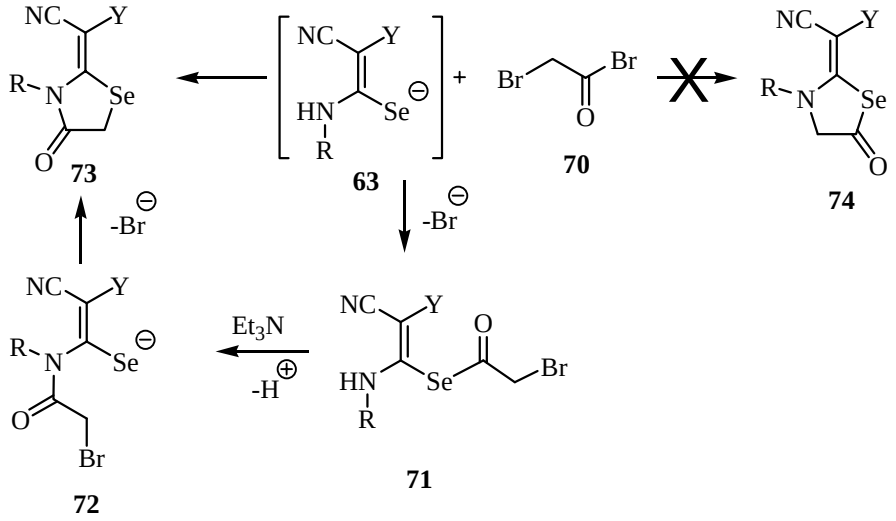
Scheme 36



The analogous reaction of isoselenocyanates, **62a**, and methyl 2-chloroacetate (**67**) gave the intermediate **68**, which on subsequent condensation by elimination of alcohol yields 2-(4-oxo-1,3-selenazolidin-2-ylidene)malononitriles **69**.

Treatment of the intermediates **63** with bromoacetyl bromide (**70**) led to the formation of a single product, 4-oxo-1,3-selenazolidine (**73**). As the reaction between thioureas and acyl halides is known to give *S*-acylated isothioureas [59], the formation of the 4-oxo-1,3-selenazolidine derivatives **73** in the reactions with 2-bromoacetyl bromide **70** can be explained by the reaction mechanism shown in Scheme **37**.

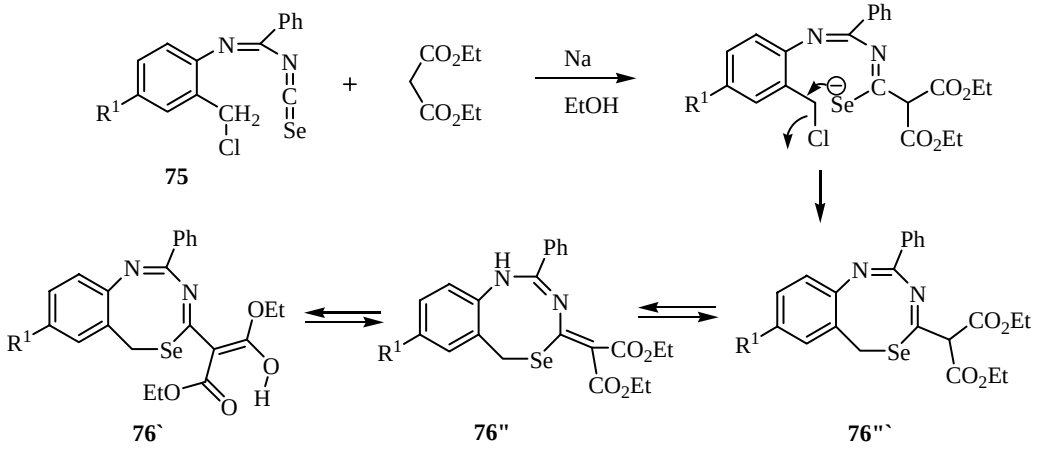
Scheme 37



The intermediate **71**, which is formed by the nucleophilic substitution of the acyl bromide of **70** by the Se-atom of **63** undergoes a base catalyzed 1,3-acyl shift to give the rearranged intermediate **72**. Similar S/N migrations of the acetyl group are known and have been studied in depth kinetically [60] and were described recently by Pihlaja and coworkers [61]. Finally, the Se-atom attacks the α-carbon atom of the amide group and forms the 1,3-selenazolidinone ring by displacing the bromide ion to give **73**.

An analogous cyclization was observed when **75** were reacted with the Na salt of diethyl malonate in EtOH at room temperature to yield the eight-membered selenaheterocycles **76** (Scheme 38). The crystal structure of the **76** revealed the presence of a co-crystal comprising two compounds [32].

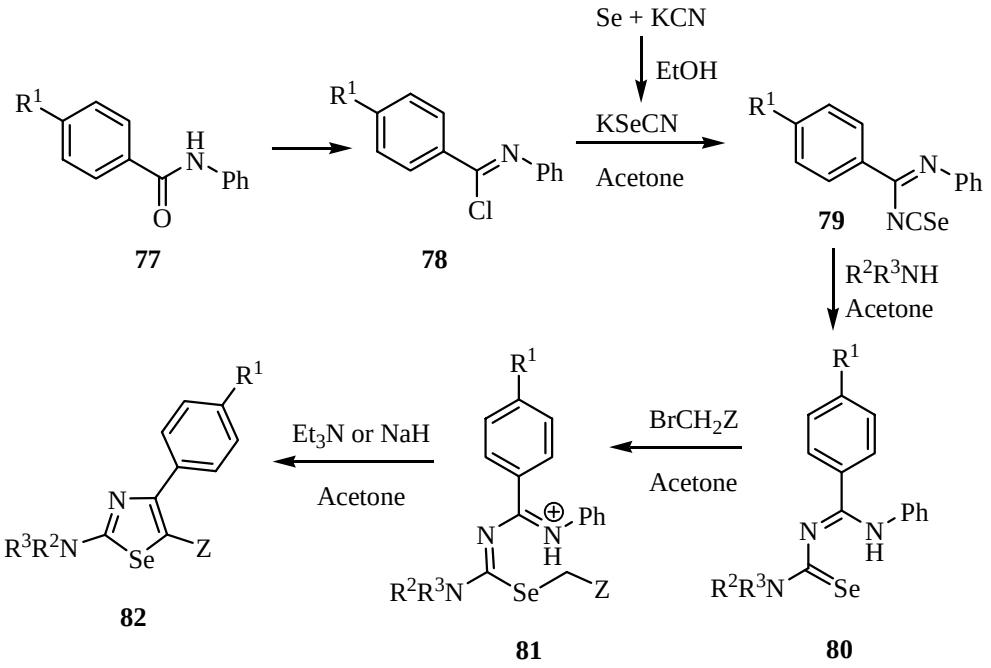
Scheme 38



The reaction of *N*-phenylbenzamides **77** with excess $SOCl_2$ under reflux gave *N*-phenylbenimidoyl chlorides **78**, which on treatment with KeSeCN in acetone yielded imidoyl isoselenocyanates of type **79**. These were transformed into selenourea derivatives **80** by the reaction with NH_3, primary or secondary amines. In acetone at room temperature, **80** reacted with activated bromomethylene compounds such as 2-bromoacetates, acetamides, and acetonitriles, as well as phenacyl bromides and 4-cyanobenzyl bromides, to give 1,3-selenazol-2-amines of type **82** (Scheme 39) [62]. A reaction

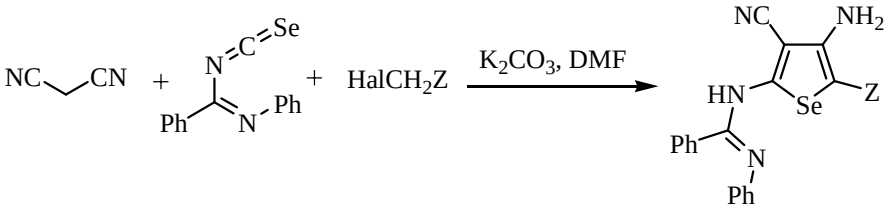
mechanism via alkylation of Se-atom of **80**, followed by ring closure and elimination of anilines, is most likely [63].

Scheme 39



The condensation of benzoyliminoisoselenocyanate in basic media with malononitrile and halides allowed the preparation of aminoselenophenes **83** (Scheme 40) [64].

Scheme 40

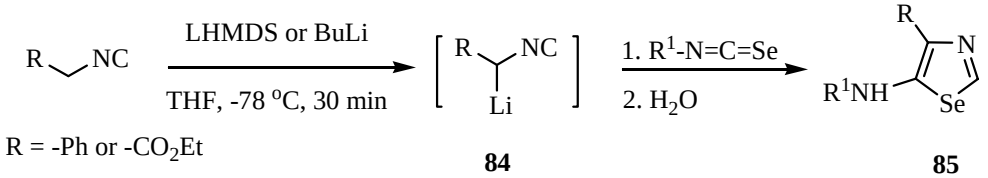


83

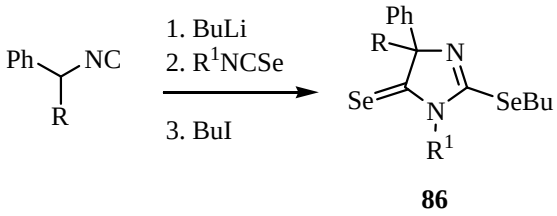
Z = COPh 79%
Z = CO_2Et 92%
Z = Ac 65%

1,3-Selenazoles and 2-imidazolin-5-selones were synthesized by the reaction of isoselenocyanates with α-lithiated isocyanides **84** [65]. Isocyanides having only one substituent on the α-carbon, such as ethyl isocyanoacetate and benzyl isocyanide, gave 1,3-selenazoles **85** in good yields (Scheme 41). On the other hand, α,α-disubstituted isocyanides such as α-methylbenzyl isocyanide and diphenylmethyl isocyanide afforded 2-butylseleno-2-imidazolin-5-selones **86** after trapping with butyl iodide. The latter products were formed from one molecule of isocyanide and two molecules of isoselenocyanate (Scheme 42) [65].

Scheme 41

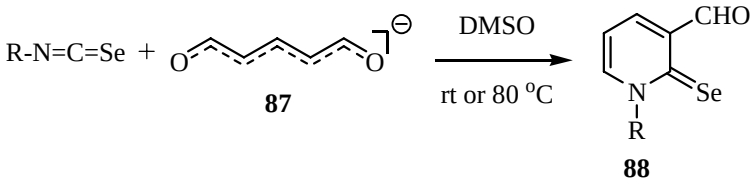


Scheme 42



Isoselenocyanates reacts with glutacondialdehyde anion (**87**) to give 1-substituted-3-formyl-2(1*H*)-pyridineselones **88**. The aryl isoselenocyanates reacted readily with **87** at room temperature, whereas the reaction with alkyl isoselenocyanates required an elevated temperature (80 °C) (Scheme 43) [66].

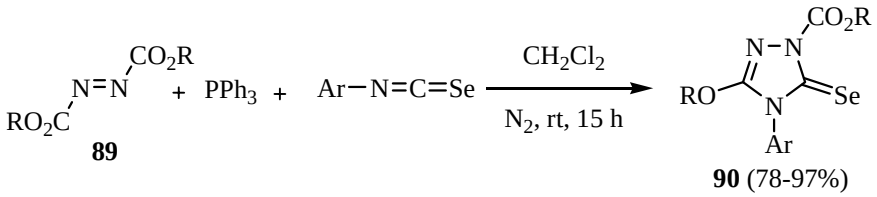
Scheme 43



7. Reactions with azodicaboxylates and diazomethanes

The reaction of isoselenocyanates with diethyl azodicarboxylate (**89**) and triphenylphosphine under *Mitsunobu* conditions was reported by Heimgartner *et al*. [67]. A mixture of an azodicarboxylate and triphenylphosphine in dichloromethane reacted with arylisoselenocyanates at room temperature to give 4,5-dihydro-5-selenoxo-1*H*-1,2,4-triazole-1-carboxylates **90** in a one-pot reaction in good to excellent yields (Scheme 44) [67].

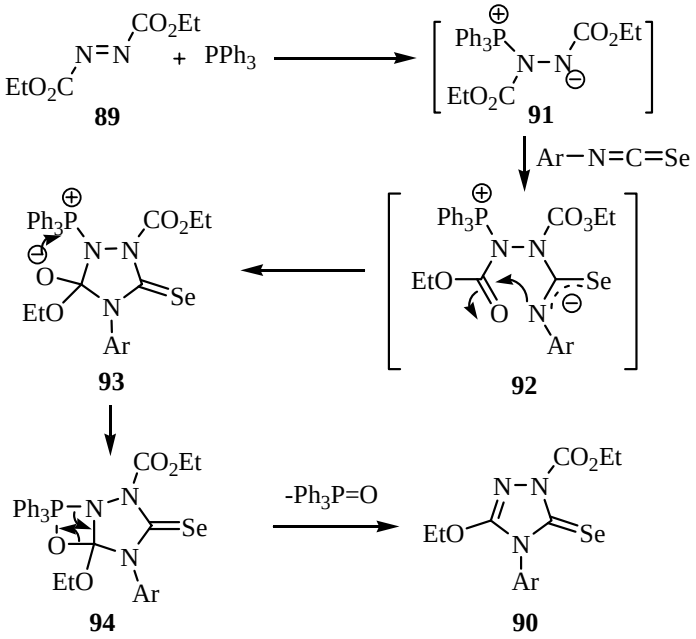
Scheme 44



The reaction mechanism for the formation of **90** is shown in Scheme 45. The addition of Ph_3P to the azodicarboxylate **89** generates the zwitterion **91**, which, as a nucleophile, attacks the isoselenocyanate to give **92**. Ring closure by nucleophilic addition of the *N*-atom at the ester group leads to **93**,

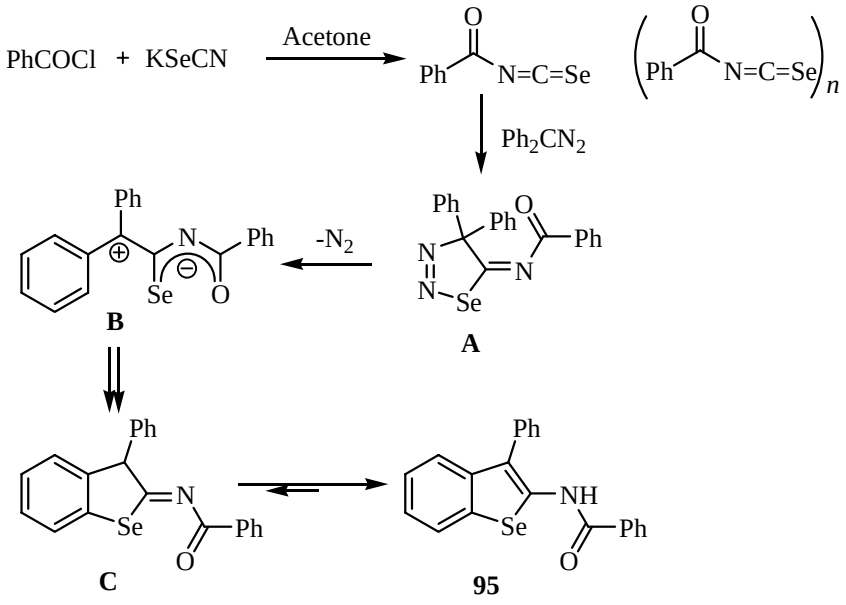
and elimination of Ph_3PO *via* the intermediate **94** yields the product **90**. The use of the diethyl azodicarboxylate (oxidant)/Ph_3P (reducing agent) system is well established [68] and is known as the *Mitsunobu* reaction [69] when the reactant is an alcohol. The betaine **91** is the initially formed intermediate in all cases and it reacts with the alcohol. In the present case, this intermediate reacts as a nucleophile with the strongly electrophilic isoselenocyanate.

Scheme 45



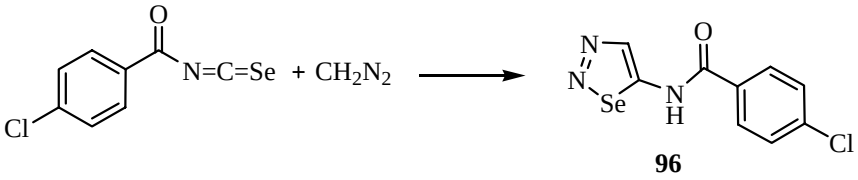
On treatment of the crude acylisoselenocyanates **2a**, prepared *in situ* by the reaction of benzoyl chloride (**1a**) and KSeCN, with diphenyldiazomethane, L´Abbé *et al*. obtained benzoselenophene **95** in 27% yield [70]. A mechanism for its formation via cycloadduct **A**, elimination of N_2 to give zwitterion **B** (or the corresponding biradical), ring closure and aromatization to **C**, and tautomerization to yield **95** is shown in Scheme 46.

Scheme 46



A second example of a reaction between an isoselenocyanate and a diazo compound is shown in Scheme 47 [71]. In this case, the primarily formed cycloadduct **96** has been isolated. It should be noted that the 1,3-dipolar cycloaddition occurs regioselectively to give the 1,2,3-selenadiazole derivative **96**.

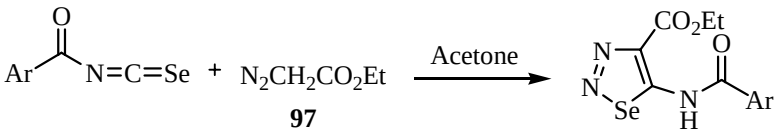
Scheme 47



96

The reaction of aroyl chlorides with KSeCN and ethyl diazoacetate (**97**) in acetone at room temperature yields ethyl 2-aroyl-5-(aroylimino)-2,5-dihydro-1,2,3-selenadiazole-4-carboxylates **98** by a 1,3-dipolar cycloaddition (Scheme 48) [72].

Scheme 48

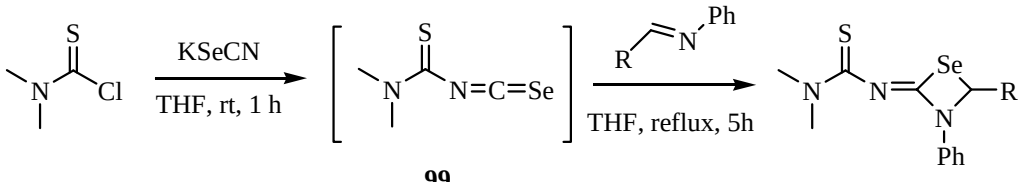


97 **98**

8. Cycloaddition reactions

Thiocarbamoyl isoselenocyanates **99** were prepared by reactions of thiocarbamoyl chloride with KSeCN. Reaction of thiocarbamoyl isoselenocyanates **99** with imines at reflux in THF for 5 h gave 1,3-selenzetidines **100**, formal [2+2] cycloadducts (Scheme 49) [73].

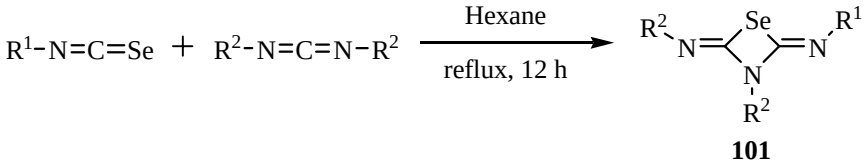
Scheme 49



99 **100**

The reaction of isoselenocyanate with cabodiimides in refluxing hexane afforded 1,3-selenazetidine-2,4-diimides **101** in moderate to good yields by a [2+2] cycloaddition (Scheme 50) [74]. Both the imino groups of **101** are (*Z*) configured and were confirmed by its X-ray crystal structure [74].

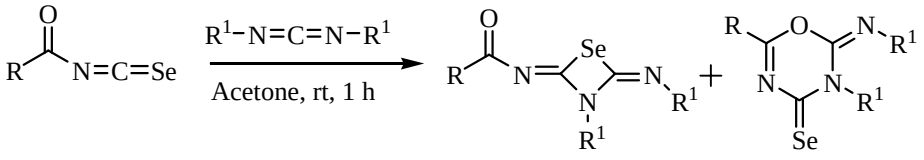
Scheme 50



101

The reaction of acylisoselenocyanates with carbodiimides at room temperature gave formal [2+2] cycloadduct 1,3-selenazetidines **102**, as the major products, and 4-selenoxo-3,4-dihydro-2*H*-1,3,5-oxadiazines **103**, formal [4+2] cycloadducts, as minor products, respectively (Scheme 51) [75].

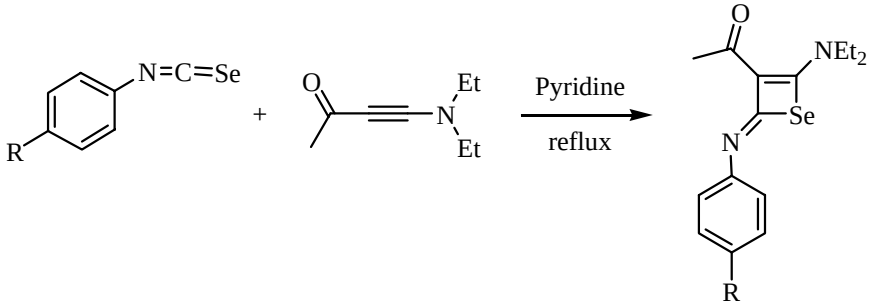
Scheme 51



102 **103**

A formal [2+2] cycloaddition of arylisoselenocyanates with 4-diethylamino-3-butyn-2-one in refluxing tetrahydrofuran afforded *N*-arylselenet-2(2*H*)-imines **104** [76] in moderate yields (Scheme 52), in analogy to the reaction involving isothiocyanates, which leads to the corresponding thiet-2(2*H*)-imines [77].

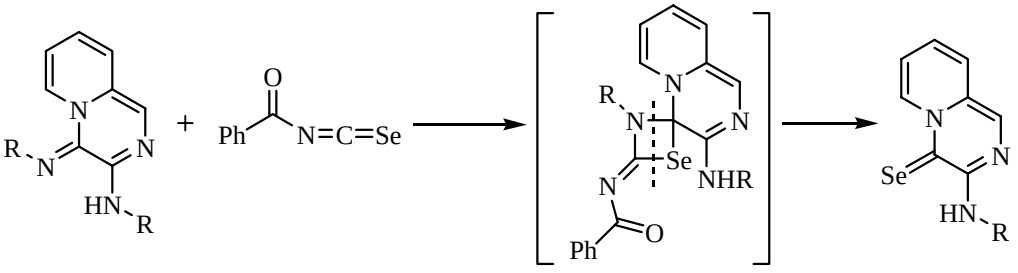
Scheme 52



104

In the course of a hetero-metathesis the new aryl-(4-selono-4*H*-pyrido[1,2-*a*] pyrazin-3-yl)amines **106** were formed by the reaction of acylisoselenocyanates with exocyclic imino functions (Scheme 53) [78]. In this reaction the exocyclic imino function was attacked exclusively by the acyl isoselenocyanate to form intermediate **105**, whose further reaction resulted in the formation of compound **106**.

Scheme 53

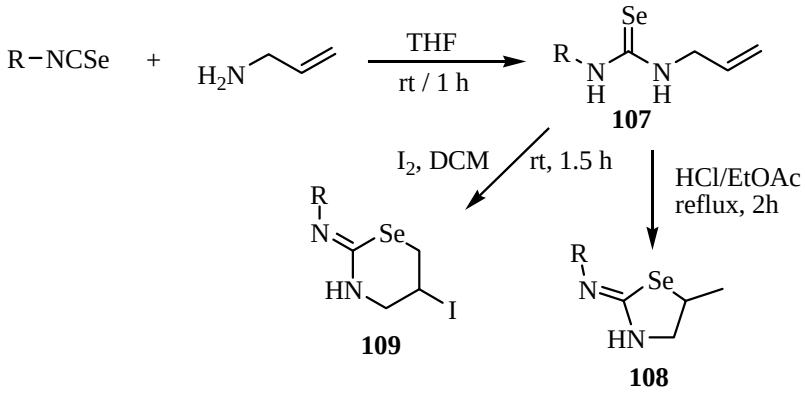


105 **106**

9. Iodo- and acid-catalyzed cyclization reactions

The regiochemistry of intramolecular addition of *N*-allylselenoureas **107** leading to 2-imino-5-methyl-1,3-selenazolidines **108** or 2-amino-5-iodo-4*H*-5,6-dihydro-1,3-selenazines **109** depends on the treatment of hydrogen chloride or iodine (Scheme 54) [79]. *N*-Allylselenoureas **107** were prepared by reactions of isoselenocyanates with allylamine. Treatment of *N*-allyl-selenoureas with hydrogen chloride affords 2-imino-5-methyl-1,3-selenazolidines **108** preferentially, through 5-*endo* closure. The driving force, in this case, is the formation of the more stable carbonium ion [79]. This behavior is in agreement with the cyclization of imidates, amides, and carbonates, which afford five-membered heterocyclic rings exclusively [80].

Scheme 54

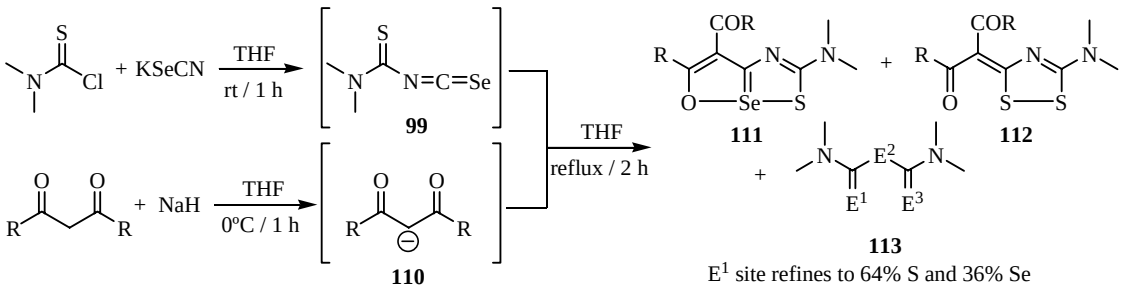


On the other hand, treatment of *N*-allylselenoureas with iodine at room temperature affords preferentially 2-amino-5-iodo-4*H*-5,6-dihydro-1,3-selenazines **109** through 6-*exo* closure. Reaction at -40ºC also resulted in the formation of only six-membered rings [79].

10. Synthesis of pentalenes

The one pot reactions of thiocarbamoyl isoselenocyanates **99**, obtained from thiocabamoyl chloride and potassium selenocyanate, with the carbanions of *β*-diketones **110** afford the corresponding 1-thia-6-oxa-6aλ^4-seleno-3-azapentalene skeletons containing a hypervalent coordinate selenium atom **111** as the major product. This is the first example of a heterocyclic compound containing a C-O-Se-S-C=N moiety in this order. 3-Diacylmethylidene-5-dimethylamino-3*H*-1,2,4-dithiazole **112** and thio-carbamate thioanhydride **113** were obtained as by-products (Scheme 55) [81].

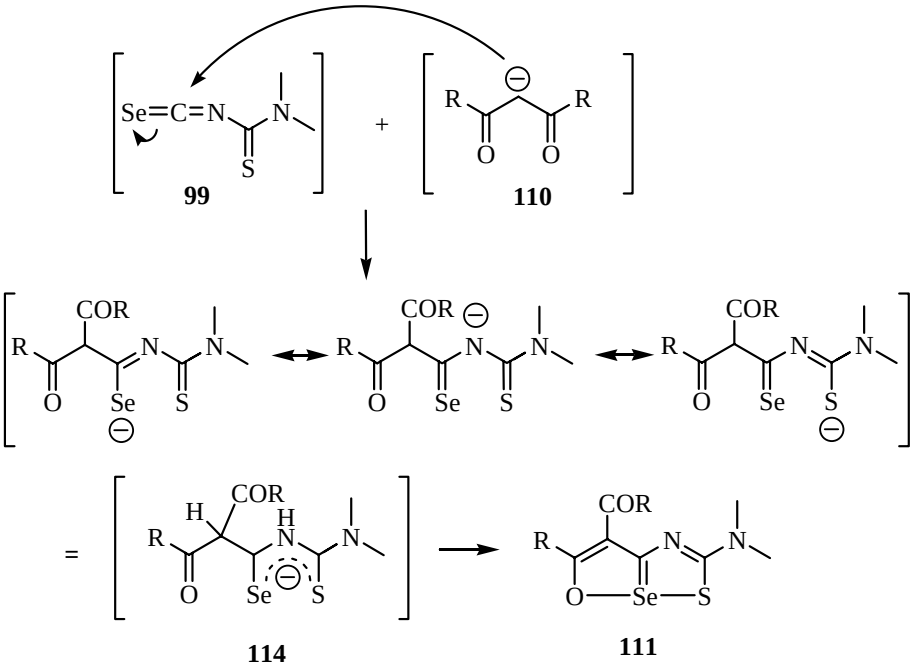
Scheme 55



E^1 site refines to 64% S and 36% Se
E^2 site refines to 73% S and 27% Se
E^3 site refines to 81% S and 19% Se

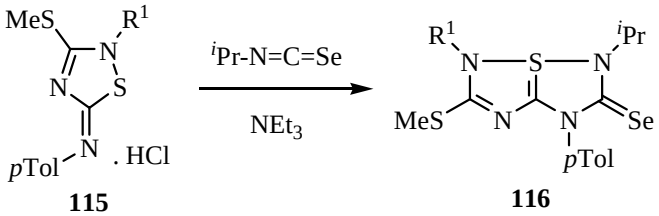
The mechanism for the formation of **111** involves initiation by nucleophilic addition of the carbon of the carbanion **110** to the central carbon of the isoselenocyanate **99**, yielding **111** *via* intermediate **114** (Scheme **56**). Intermolecular exchange of Se for S in intermediate **114** under reflux conditions would yield compound **112**. All the products (**111**, **112** and **113**) were confirmed by X-ray.

Scheme 56



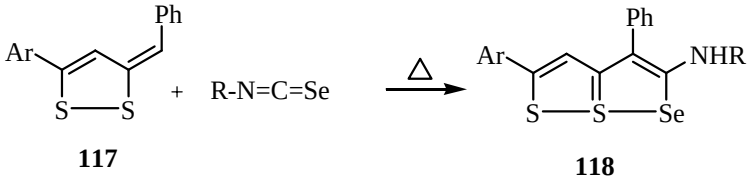
The 5-imino-2,5-dihydro-1,2,4-thiadiazole hydrochlorides **115** were converted into a variety of 2,3-dihydro-6aλ^4-thiapolyheterapentalenes **116** in nearly quantitative yields by the reaction with isoselenocyanates using triethylamine as a base, using addition of heterocumulenes (Scheme 57) [82]. Structures **116** were supported by the ^{13}C−NMR data, in agreement with values for related polyheterapentalenes [83,84].

Scheme 57



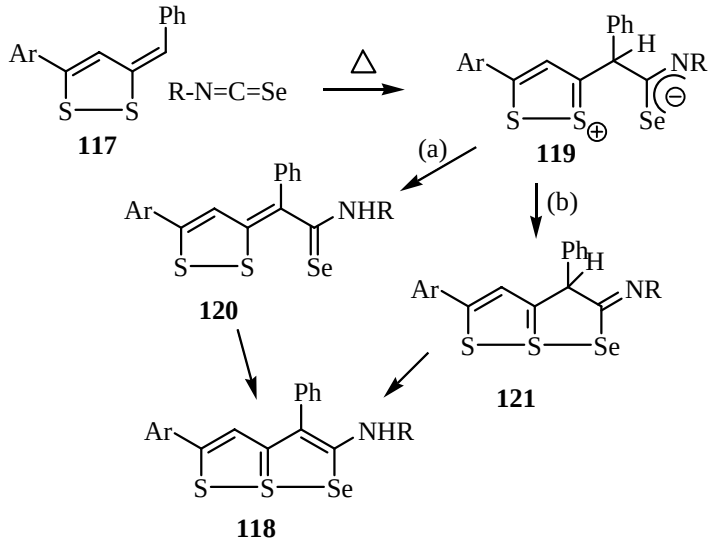
The dithioles **117** underwent thermal [2+3] cycloaddition reaction with isoselenocyanates to give 2-(substituted amino)-5-aryl-3-phenyl-6,6aλ^4-dithia-1-selena- pentalenes **118** (Scheme 58) [85].

Scheme 58



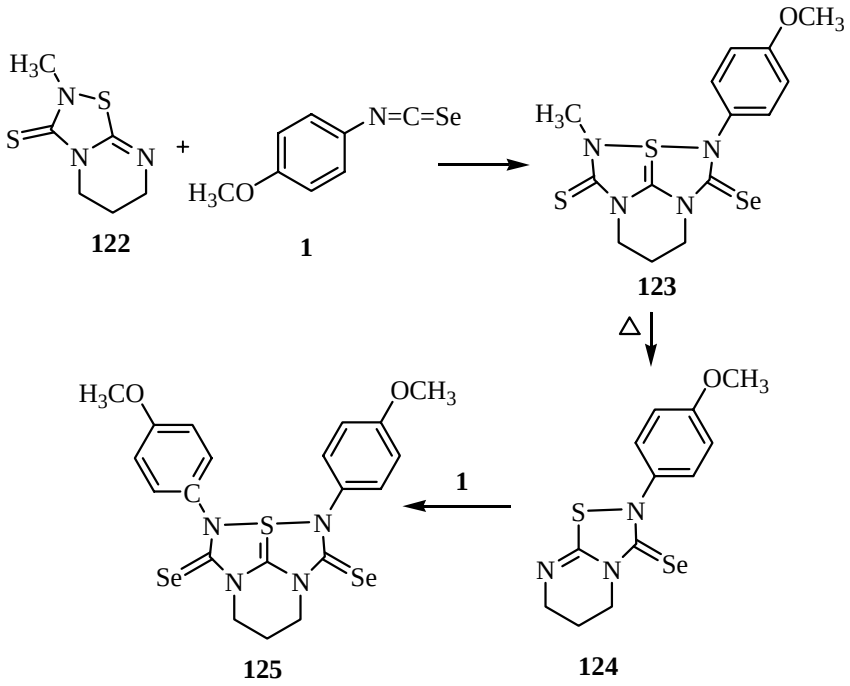
The cycloaddition reaction takes place as shown in Scheme 59, in which a zwitterionic addition product **119** is first formed. Conversion of **119** into the triheterapentalene **118** takes place by path (a) by a successive proton-transfer and ring closure sequence **119** → **120** → **118**, or by path (b) involving a 2,3-dihydrotriheterapentalene intermediate **121** that tautomerizes to give **118**.

Scheme 59



The tetraazathiapentalene derivative **123** was prepared by the reaction of **122** with isoselenocyanates **1**. The removal of the methylisothiocyanate was observed when the tetraazathiapentalene derivative **123** was subjected to heating. Furthermore, thiadiazole derivative **124** undergoes a 1,3-dipolar cycloaddition with isoselenocyanates **1** to give tetraazathiapentalene **125** in good yield. The tetraazathiapentalene derivative **125** is stable in air in the solid state, but decomposes slowly in solution (Scheme 60) [86].

Scheme 60



11. Conclusions

In summary, isoselenocyanates have been emerged as a powerful tool for the synthesis of selenium-containing heterocycles. This review provides a comprehensive survey of the progress in the various reactions of isoselenocyanates, their application in the preparation of various types of selenium-containing heterocycles.

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