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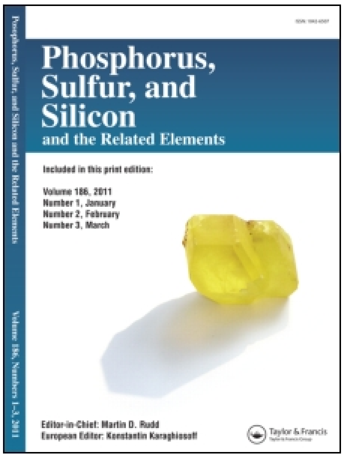

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Isoselenocyanates as Building Blocks for Selenium-Containing Heterocycles

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Isoselenocyanates as Building Blocks for Selenium-Containing Heterocycles

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Isoselenocyanates are conveniently accessible from elemental selenium in safe and efficient reactions. They can be used either as reactive intermediates or as relatively stable and storable starting materials for the preparation of selenaheterocycles or heterocyclic selones. In most cases, the reactions are initiated by a nucleophilic attack onto the isoselenocyanate, followed by a cyclization via the Se- or the N-atom. Alternatively, the intermediate adduct of the nucleophile and the isoselenocyanate can undergo a second nucleophilic addition with a third compound and subsequent cyclization.

Keywords Heterocyclic selones; isoselenocyanates; multi-component reactions (MCR); selenaheterocycles

INTRODUCTION

Within the last 25 years, the chemistry of organoselenium compounds has attracted much attention because of their importance as synthetic tools,[1] but especially as a result of their biological,[2] agricultural,[3] and medicinal activities.[4] In particular, selenium-containing heterocycles have contributed to the remarkable growth of interest in organoselenium chemistry. They have proven to be useful antioxidant,[4e] antibacterial,[4g,5] antiviral,[6] fungicidal,[7]anticancer,[4i,8]etc. compounds, as well as enzyme inhibitors.[9] Therefore, efficient and safe syntheses for Se-heterocycles are highly desirable. On the other hand, preparations of selenium-containing heterocycles often involve the use of toxic Se-reagents, which are difficult to handle and to store. For this reason,

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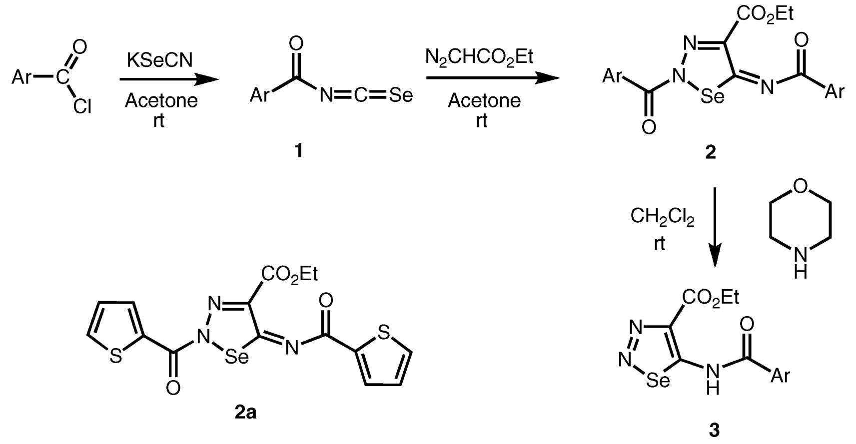
new synthetic approaches by using easily accessible, more stable, and less toxic Se-reagents are of high interest. Isoselenocyanates have less unpleasant chemical properties[10] and can easily be prepared,[11] and in most cases, safely stored and handled. Consequently, they are very useful as starting materials in heterocyclic chemistry.[12]

In this review article, our recent attempts to use isoselenocyanates as versatile synthons in the preparation of Se-heterocycles are presented.

REACTIONS WITH AROYL ISOSELENOCYANATES

The first synthesis of aroyl isoselenocyanates **1** as reactive intermediates via the reaction of aroyl chlorides and KSeCN, has been described by Douglas.[13] They can be trapped by diazomethane to give 1,2,3-selenadiazoles[14] or by diphenyldiazomethane to yield, in a multistep reaction, benzoselenophene derivatives.[15] The addition of an aroyl chloride to a mixture of KSeCN and ethyl diazoacetate yields the 2-aroyl-1,2,3-selenadiazole derivatives **2**[16] (Scheme 1), whereas in the analogous reaction with isothiocyanates, the 2-unsubstituted 5-aroylamino-1,2,3-thiadiazole-4-carboxylates are formed.[17] On treatment of **2** with morpholine, the aroyl group at N(2) can be removed to give **3**.[16] By using heterocyclic acid chlorides, analogues of **2**, which bear two heteroaroyl residues, e.g., **2a**, are formed.

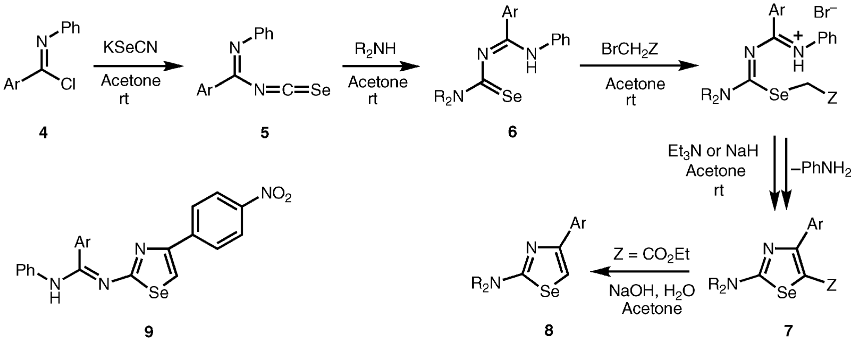


SCHEME 1

Acyl isoselenocyanates and carbodiimides react at room temperature to give formal [2+2] cycloadducts, i.e., 1,3-selenazetidines, together with 4-selenoxo-3,4-dihydro-2*H*-1,3,5-oxadiazines, the formal [4+2] cycloadducts, as minor products.[18]

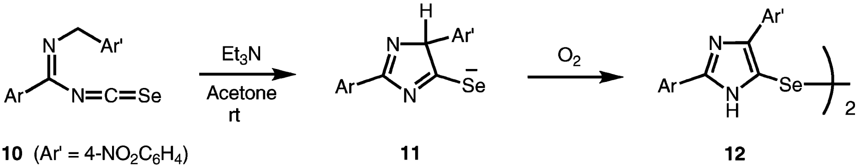
REACTIONS WITH IMIDOYL ISOSELENOCYANATES

The relatively stable *N*-phenyl and *N*-benzylimidoyl isoselenocyanates of type **5** are conveniently prepared by the reaction of imidoyl chlorides **4** with potassium selenocyanate.[19,20] The reaction with ammonia, primary or secondary amines yields selenourea derivatives **6**, which react with activated bromomethylene compounds and subsequent treatment with a base to give 1,3-selenazoles **7**[20] (Scheme 2). The cyclization occurs in the Se-alkylated selenourea intermediate, followed by elimination of aniline. In the case of ethyl bromoacetate (Z = CO_2Et), saponification and decarboxylation yields the 5-unsubstituted 2-amino-4-aryl-1,3-selenazole **8**. A different cyclization to give **9** takes place when **5** is reacted with ammonia and 4-nitrophenacyl bromide.[20]



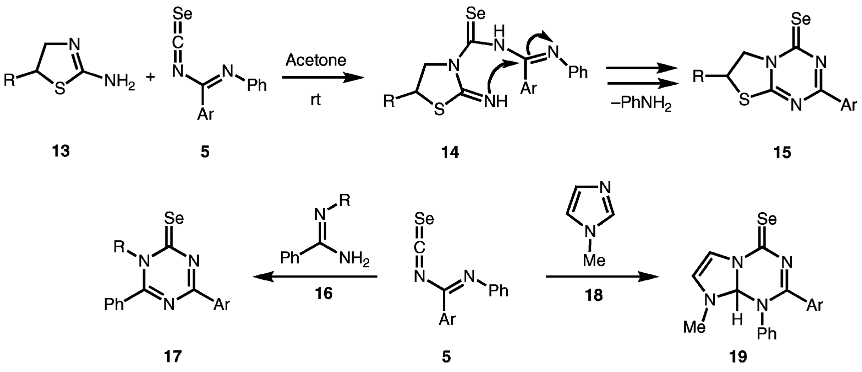
SCHEME 2

Treatment of imidoyl isoselenocyanate **10**, which bears a 4-nitrobenzyl group, with Et_3N gives bis(imidazol-5-yl) diselenides **12**[21] (Scheme 3). It is most likely that the base-catalyzed ring closure leads to an intermediate imidazole-5-selenolate **11**, followed by an aromatization and oxidative dimerization.



SCHEME 3

The reaction of **5** with molecules containing an amidine structure, e.g., 2-amino-4,5-dihydro-1,3-thiazole **13**, leads to fused 1,3,5-triazineselones of type **15**[22] (Scheme 4). A reaction mechanism via an

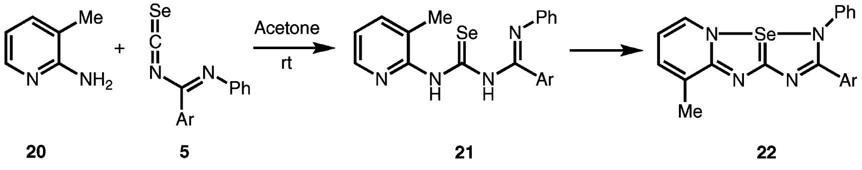


SCHEME 4

intermediate selenourea derivative **14**, which undergoes cyclization and elimination of aniline, is likely. Similarly, benzamidines **16**, react with **5** to yield 1,3,5-triazineselones **17**, which, in the case of R = H, undergo a spontaneous oxidative dimerization to yield the corresponding aromatic diselenides.[22]

N-Alkylated imidazoles **18** also react with **5**, the products being imidazo[1,2-*a*][1,3,5]triazineselones **19**[22] (Scheme 4). Obviously, a different cyclization of the intermediate selenourea takes place, including the aniline N-atom into the triazine ring.

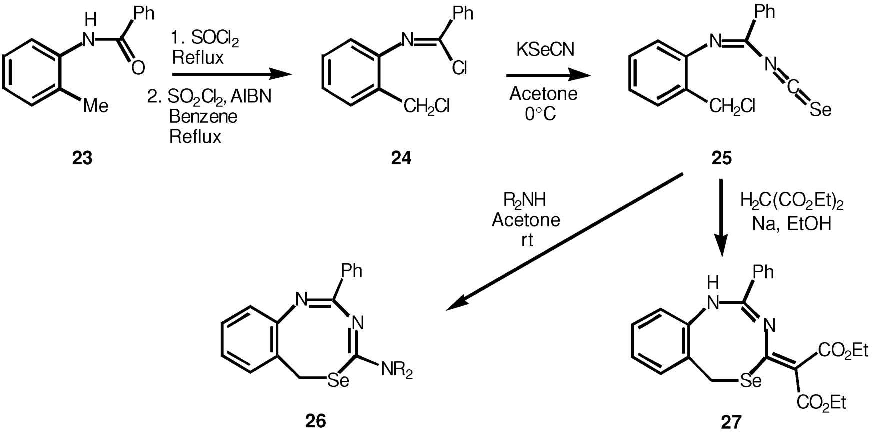
Again, a different type of product is formed in the reaction of **5** and 2-aminoaniline **20**. The isolated product has the heteropentalene structure **22**[22] (Scheme 5); its formation can be explained via the intermediate selenourea **21**. As a result of the more pronounced aromaticity of **20** compared with that of **18**, the N-atom of the exocyclic amino group is the most nucleophilic center. The oxidative dehydrogenation then yields **22** with a hypervalent Se-atom.



SCHEME 5

An analogous reaction pathway has been described recently for the transformation of a thiocarbamoyl isoselenocyanate with the carbanion of α-diketones to a 1-thia-6-oxa-6aλ^4-selena-3-azapentalene.[23] On the other hand, 5-imino-2,5-dihydro-1,2,4-thiadiazoles react with isopropyl isoselenocyanates to give 2,3-dihydro-6aλ^4-thia-1,3,4,6-tetraazapentalene-2-selones.[24]

Imidoyl isoselenocyanates **25**, which can be prepared from benzanilides **23** by successive treatment with $SOCl_2$ and SO_2Cl_2, followed by the usual reaction with KSeCN, react with secondary amines to yield 6*H*-5,1,3-benzoselenadiazocines **26**[25] (Scheme 6). The analogous reaction of **25** with the anion of diethyl malonate gives **27**. The proposed mechanism involves the attack of the nucleophile at the isoselenocyanate, followed by a nucleophilic substitution of the benzylic Cl-atom by the Se-atom.



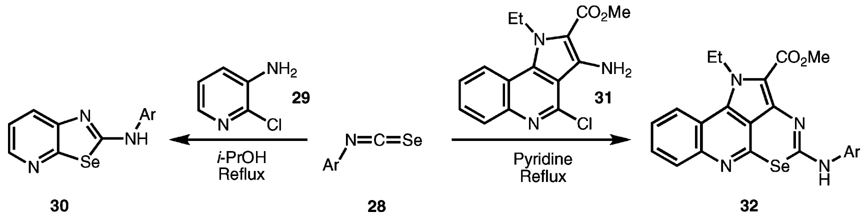
SCHEME 6

REACTIONS WITH ARYL ISOSELENOCYANATES

Two-Component Reactions

Reactions of aryl isoselenocyanates **28**, which are conveniently prepared from isocyanides and elemental Se,[11,26] with bifunctional nucleophiles can lead to Se-containing heterocycles. For example, the reaction with α-lithiated isocyanides give 1,3-selenazoles and 2-imidazole-5(4*H*)-selones in good yield.[12b] Therefore, the reactive intermediate, which is formed by addition of the carbanion to the isoselenocyanate, can undergo ring closure via the Se or the N-atom.

Treatment of 3-amino-2-chloropyridine (**29**) with aryl isoselenocyanate **28** in boiling 2-propanol, followed by treatment with NaOH, leads to 2-(arylamino)selenazolo[5,4-*b*]pyridines **30**[27] (Scheme 7). Similarly, the reaction of **28** with the

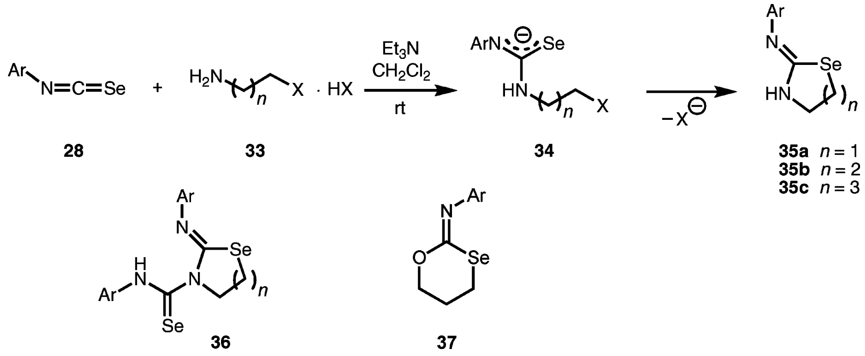


SCHEME 7

3-amino-4-chloropyrrolo[3,2-*c*]quinoline-2-carboxylate **31** in boiling pyridine yields 1*H*-5-selena-1,3,6-triazaacenaphthylene derivative **32**[28] (Scheme 7). In both cases, the cyclization of the intermediate zwitterion, which is formed by the nucleophilic attack of the amino group onto **28**, occurs via nucleophilic substitution of chloride by the Se-atom.

A related cyclization to give isomeric 4-oxopyrido[3,2-*e*]- or [3,4-*e*]-1,3-selenazin-2-amines has been achieved by treatment of the corresponding 2-chloro- or 4-chloronicotinoyl isoselenocyanate with arylamines.[29]

The same concept has been used for the preparation of 1,3-selenazolidin-2-imines,[30] 1,3-selenazinan-2-imines,[30] and 1,3-selenazepan-2-imines.[31] The reaction of **28** with ω-haloalkylamine hydrohalides **33** in the presence of triethylamine yields the corresponding selenaheterocycles **35** (Scheme 8). A reaction mechanism via the initially formed adduct of type **34** and subsequent ring closure via the Se-atom, is most likely.

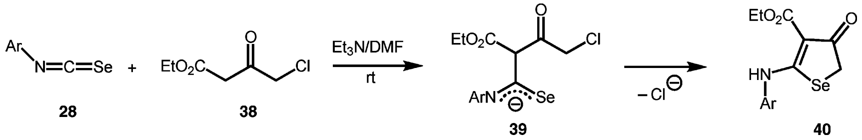


SCHEME 8

The analogous reaction with two equivalents of **28** and NaOH in THF gives the 2:1 products **36** in excellent yields.[30] By using 3-bromopropanol, the one-pot reaction with **28** and NaH in DMF at room temperature leads to 1,3-oxaselenan-2-imines **37**.[32] Unfortunately, the generalization of this reaction for the synthesis of the corresponding 5- and 7-membered products failed.

A slightly different approach for the preparation of all stereoisomers of 5-ethyl-4-methyl-1,3-selenazolidin-2-imine has been developed by Ueda et al.[33] In this case, the starting material is the corresponding optically active, mesylated 2-hydroxy-1-methylbutyl isoselenocyanate, which by treatment with ammonia in dioxane at 60°C yields the selenazolidine in a stereoselective manner.

Furthermore, aryl isoselenocyanates **28** are prone to react with carbanionic species, and in the presence of a leaving group, a subsequent cyclization is possible. For example, treatment of a mixture of **28** and γ-chloroacetoacetate (**38**) in DMF with triethylamine at room temperature gives 4-oxo-2-amino-4,5-dihydroselenophene-3-carboxylates **40** in fair yields[34] (Scheme 9). The initially generated intermediate **39** again undergoes a cyclization via a S_N2-reaction by the Se-atom.

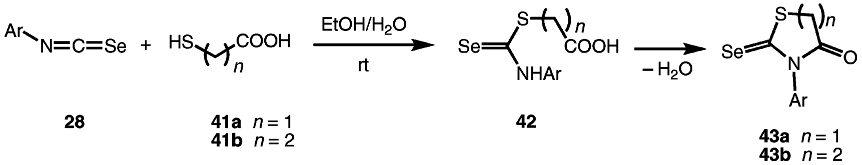


SCHEME 9

Ring closure of the intermediate adduct, which is formed by the addition of an amine to **28**, i.e., a selenourea derivative, is also possible via the attack of ArN or Se at a sp^2- or sp-hybridized C-atom. This methodology has been used for the synthesis of 5-methylidene-1,3-selenazolidin-2-imines from propargylamine and alkyl isoselenocyanates.[35] The preparation of 2-arylamino-5-methyl-1,3-selenazoles can be achieved by treatment of allenyl isoselenocyanate with aniline, whereby a similar selenourea intermediate undergoes the ring closure.[36] The analogous reaction path leads to the formation of the corresponding 2-methoxy- and 2-phenoxy-1,3-selenazoles when methanol and phenol, respectively, are used as nucleophiles. The competitive formation of 4-alkylidene-1,3-oxaselenolan-2-imines and 4-alkylidene-1,3-oxazolidine-2-selones has been observed by treatment of a mixture of 2-alkyn-1-ols and isoselenocyanates with DBU in THF.[37]

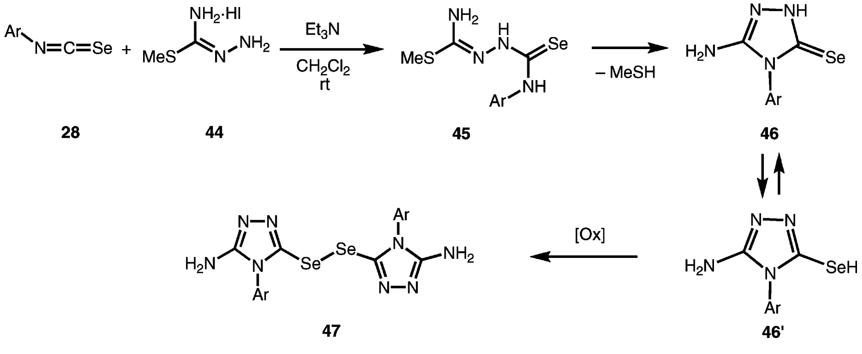
With the aim of preparing 1,3-selenathiolanes and 1,3-selenathianes, the reaction of **28** with α- and β-mercapto carboxylic acids **41** has been investigated. In an ethanol/water solution, the mixture of **28** and **41a** or **41b** reacts at room temperature to give 2-selenoxo-1,3-thiazolidin-4-ones (selenorhodanines, **43a**) and

2-selenoxo-1,3-thiazinan-4-ones (**43b**), respectively[38] (Scheme 10). It is believed that (seleno)(thio)carbamates **42** are the intermediates, which undergo the cyclization via an intramolecular condensation reaction involving the N- and not the Se-atom.



SCHEME 10

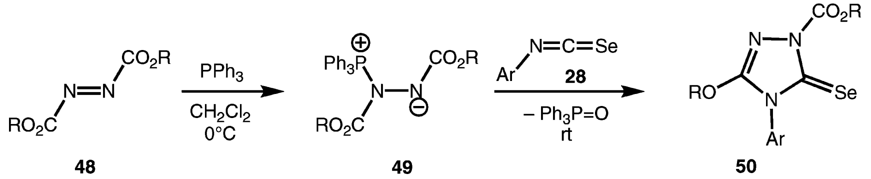
A smooth formation of 5-amino-2,4-dihydro-3*H*-1,2,4,triazole-3-selones **46** occurs when a mixture of **28** and *S*-methylisothiosemicarbazide hydroiodide (**44**) in dichloromethane is treated with triethylamine. After stirring at room temperature for 12 h, the products **46** are obtained in very good yield[39] (Scheme 11). The nucleophilic addition of the free base of **44** leads to the intermediate **45**, which spontaneously cyclize and eliminate methylmercaptane to give **46**. Crystallization in the presence of air leads to the diselenides **47** via oxidative dimerization.



SCHEME 11

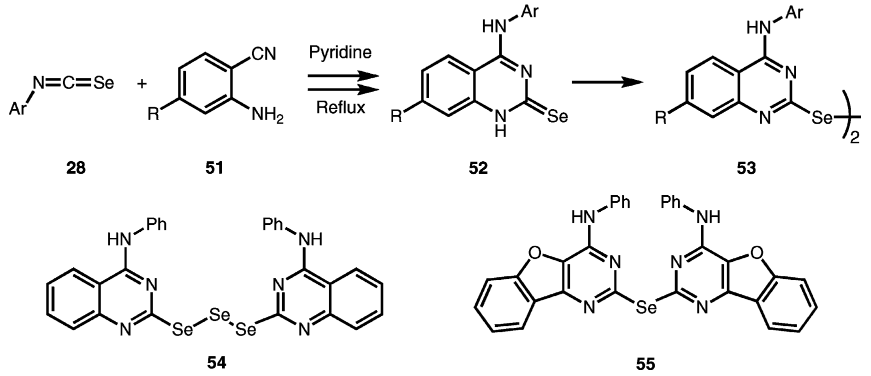
A comparable synthesis of 5-substituted 2-phenyl-1,2-dihydro-3*H*-1,2,4-triazole-3-selones has been elaborated by Koketsu et al.[40] Acyl isoselenocyanates prepared in situ react with phenylhydrazine to give mixtures of the selenaheterocycles and 4-acyl-1-phenylselenosemicarbazides. The latter can be cyclized to give the isomeric 1-phenyl-1,2-dihydro-3*H*-1,2,4-triazole-3-selones, indicating that it is not the intermediate in the formation of the first isomer.

Again a different approach to 1,2,4-triazole-2-selone derivatives has been realized via the Mitsunobu strategy. In this case, the nucleophile is generated by the addition of triphenylphosphane to an azodicarboxylate **48** in dichloromethane at 0°C. Subsequent addition of isoselenocyanate **28** and stirring at room temperature gives 3-alkoxy-4,5-dihydro-5-selenoxo-1*H*-1,2,4-triazole-1-carboxylates **50** in excellent yield[41] (Scheme 12). When *tert*-butyl azodicarboxylate (**48**, R = *t*-Bu) is used, a smooth decarboxylation of the corresponding product **50** by treatment with trifluoroacetic acid leads quantitatively to 3-*tert*-butoxy-4-aryl-4,5-dihydro-1*H*-1,2,4-triazole-5-selone.



SCHEME 12

In boiling pyridine, aryl isoselenocyanates **28** react with 2-aminobenzonitriles (anthranilonitriles, **51**) to give 4-(arylamino)quinazoline-2(1*H*)-selones **52** in good yield[42](Scheme 13). These products undergo easily the oxidative dimerization to yield the disulfides of type **53**. The reaction mechanism of the formation of **52** involves the cyclization of an intermediate selenourea with the cyano group followed by a Dimroth rearrangement. In one of the reactions, with phenyl isoselenocyanate (**28**, Ar = Ph) and **51** (R = H), the triselenide **54** has been isolated as a minor product.



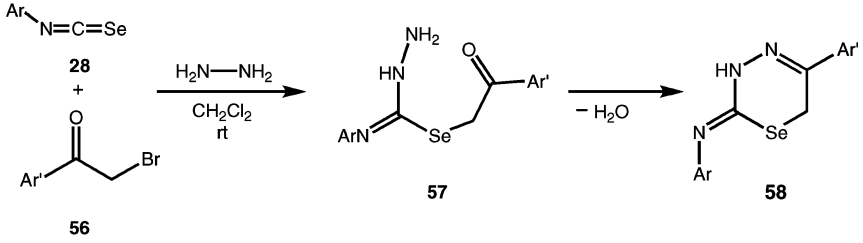
SCHEME 13

The analogous reaction of **51** with aryl isothiocyanates, has been published by two other groups.[43a] Whereas Taylor and Ravindranathan reported the isolation of the quinazoline-2(1*H*)-thiones of type **52**, Pazdera et al.[43b] claimed that they obtained the initial cyclization product, i.e., the 3-aryl-4-imino derivative. The analogous difference in the structure of the products is observed in the reactions with 3-aminobenzo[*b*]furane-2-carbonitrile: with phenyl isothiocyanate, 4-imino-1,3-dihydro-3-phenylbenzofuro[3,2-*d*]pyrimidine-2-thione has been isolated,[44] but the reaction with **28** (Ar = Ph) yields the selenide **55** with a rearranged skeleton as the only isolable product.[42] (Scheme 13).

The reaction of alkyl isoselenocyanates with 5-aminoimidazole-4-carbonitrile has been reported to yield 2-alkylamino-6-imino-1-selenapurine derivatives or 1-alkyl-6-iminopurin-2-selones, depending on the nature of the alkyl residue of the isoselenocyanate.[45] In this case, the intermediate selenourea cyclizes via the competitive Se- and RN-attack onto the nitrile group.

Three-Component Reactions

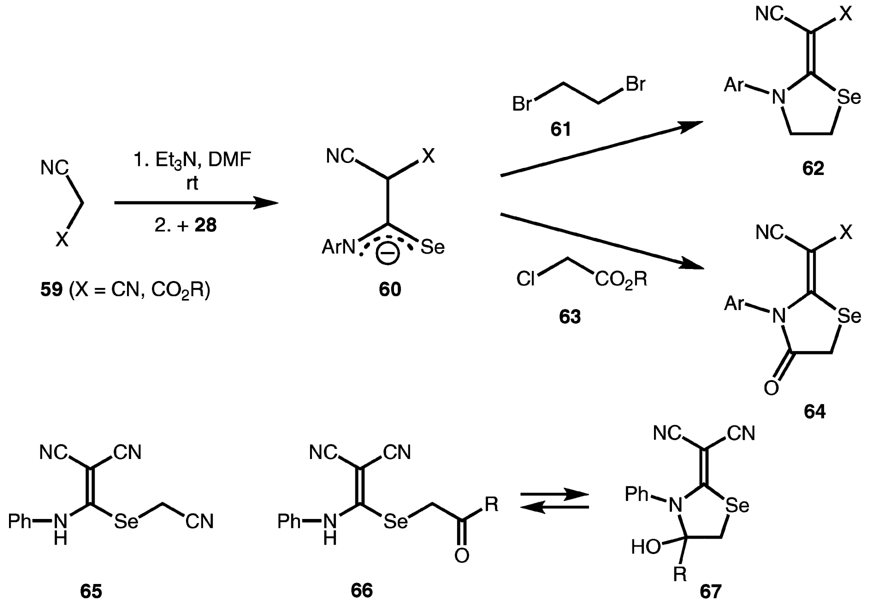
Whereas in the examples described above the nucleophilic reagent contained also an electrophilic center, reactions of aryl isoselenocyanates **28** with a nucleophile and a bis-electrophile could also be realized. For example, addition of hydrazine hydrate to a mixture of **28** and a phenacyl bromide **56** in dichloromethane at room temperature, leads to 3,6-dihydro-2*H*-[1,3,4]selenadiazin-2-imines **58** in good yield[46] (Scheme 14). The formation of these products can be explained by the nucleophilic addition of hydrazine to **28**, followed by an S_N2 substitution of bromide in **56** by the Se-atom to give the intermediate **57**. The latter undergoes an intramolecular condensation yielding the selenaheterocycle **58**.



SCHEME 14

Another three-component reaction with **28**, phenylhydrazine, and aroyl chlorides, which leads to mesoionic 1,2,4-triazolium-3-selenoates, has been published recently.[47] In this case, the initially formed adduct of **28** and phenylhydrazine reacts via the N-atom with the aroyl chloride.

In an additional series of three-component reactions, **28**, a carbanion of a CH-acidic methylene compound, and a bis-electrophile have been used as reaction partners. For example, treatment of malononitrile or 2-cyanoacetate **59** with triethylamine and subsequent addition of **28** and dibromoethane (**61**) gives 2-(1,3-selenazolidin-2-ylidene)malononitriles or 2-cyano-2-(1,3-selenazolidin-2-ylidene)acetates **62**[48] (Scheme 15). Similarly, the reaction with 2-chloroacetate (**63**), instead of **61**, leads to the 4-oxo derivatives **64**. With the aim of preparing the 5-oxo analogues, the reaction has also been carried out with 2-bromoacetyl bromide. Surprisingly, the product is again the 2-methylidene-1,3-selenazolidin-4-one **64**.

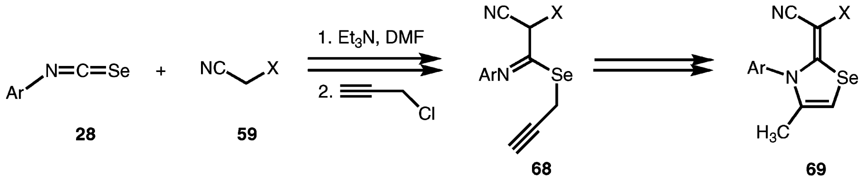


SCHEME 15

A plausible explanation of the formation of **64** in the reaction with 2-bromoacetyl bromide is its reaction with the intermediate **60** to give a selenoester, which rearranges via a subsequent 1,3-acyl shift to give an N-acylated intermediate. The latter undergoes a cyclization to yield the final product via a S_N2 reaction.

The analogous reaction of malononitrile (**59**, X = CN), **28**, and 2-bromoacetonitrile yields the selenide **65** (Scheme 15) and not the expected selenazole derivative.[49] All attempts to cyclize compound **65** failed. Trapping of the intermediate of type **60** with α-bromoketones leads to the selenide **66**, which is in equilibrium with the cyclic hemiacetal **67** (Scheme 15). It has been shown by spectroscopic methods that structure **66** exists in solution, whereas the X-ray crystal-structure determination proves that **67** is the structure in the solid state. Again, all attempts to eliminate water to give the corresponding 2-(3*H*-selenazol-2-ylidene)malononitrile **69** failed.

The desired 1,3-selenazole derivative **69** can be prepared by the base-catalyzed reaction of malononitrile (**59**, X = CN), **28**, and propargyl chloride[50] (Scheme 16). Some of the reactions with triethylamine lead to a mixture of **69** and the propargyl selenide **68**. Most likely, **68** is an intermediate in the formation of **69**, as by using a stronger base such as sodium hydride, only the selenazole **69** is formed. Whether the cyclization occurs in **68** or in its allenyl isomer cannot be decided.



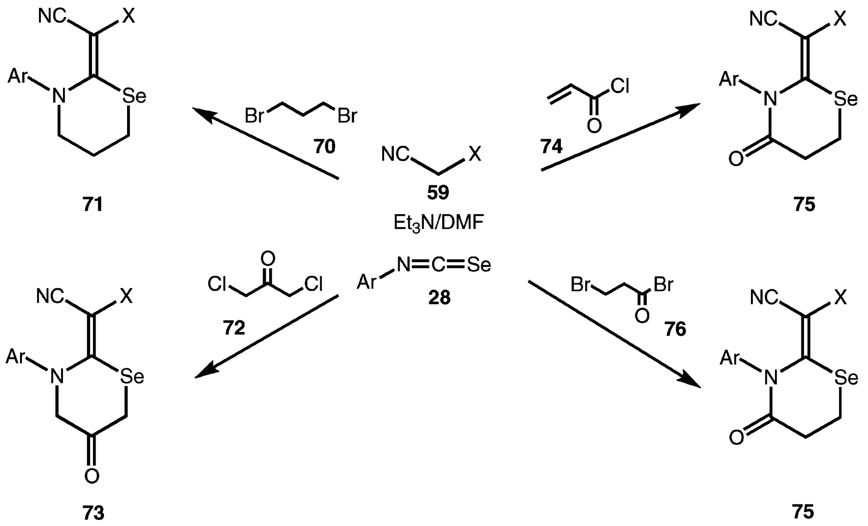
SCHEME 16

The reaction of **28**, malonic acid derivatives **59**, and bis-electrophiles is also suitable for the preparation of 1,3-selenazinanes (Scheme 17). In DMF with triethylamine, the reaction with malononitrile and 1,3-dibromopropane (**70**) gives 2-(1,3-selenazinan-2-ylidene)malononitrile **71**, whereas the corresponding 4-oxo- and 5-oxo derivatives **73** and **75** are formed in the reactions with 1,3-dichloroacetone (**72**) and acryloyl chloride (**74**), respectively.[51] Instead of **74**, 3-bromopropanoyl bromide (**76**) can also be used for the preparation of **75**.

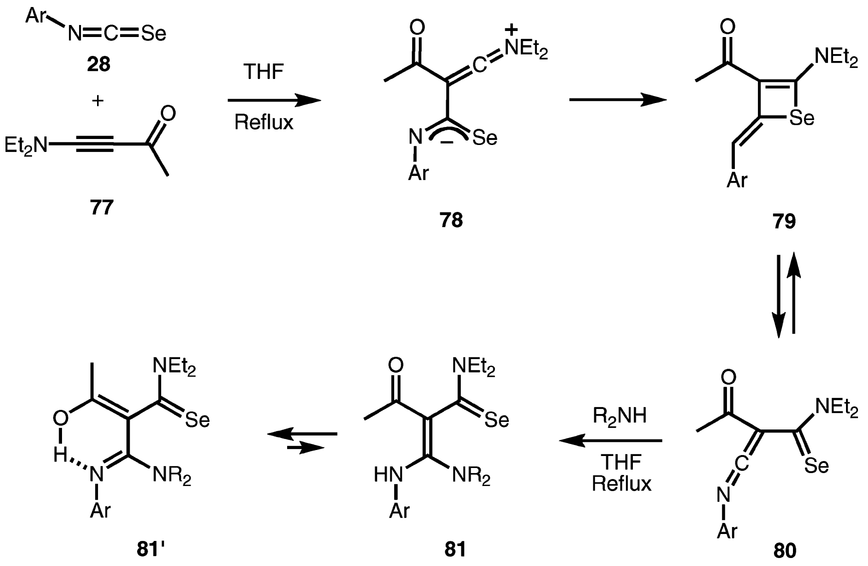
Formal [2+2] Cycloadditions

Aryl isoselenocyanates **28** react with the push-pull substituted acetylene **77** in refluxing THF to give the selenet-2(2*H*)-imines **79** in fair yields[52] (Scheme 18). A two-step mechanism via the zwitterionic intermediate **78** is likely.

Treatment of **79** with primary and secondary amines in boiling THF gives adducts of type **81/81'**. Similar reactions take place with other nucleophiles, such as alcohols and thiols. The proposed reaction mechanism involves an electrocyclic ring opening to give a ketenimine **80**, followed by the addition of the nucleophile.

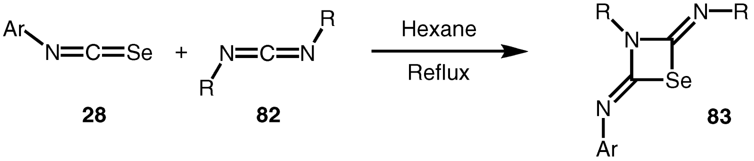


SCHEME 17



SCHEME 18

Formal [2+2] cycloadditions also occur when a mixture of an isoselenocyanate **28** and a carbodiimide **82** is heated in hexane. The corresponding 1,3-selenazetidin-2,4-diimines **83** are obtained in excellent yields[53] (Scheme 19).



SCHEME 19

Analogous reactions of acyl isoselenocyanates and **82** have been reported by Koketsu et al.[18] In this case, the products of the competitive [4+2] cycloaddition are also formed. Furthermore, in situ generated thiocarbamoyl isoselenocyanates react with imines in refluxing THF to give *N*-(1,3-selenazetidin-2-ylidene)thiourea derivatives.[54]

CONCLUSIONS

The presented reactions of isoselenocyanates proved that they are versatile building blocks for the synthesis of selenaheterocycles and heterocyclic selones, i.e., compounds of significant biological and pharmaceutical interest. As isoselenocyanates can be prepared conveniently and safe from inexpensive, stable, and less toxic starting materials, they are outstanding reagents for the synthesis of selenium-containing heterocycles.

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