Vistas in the domain of organoselenocyanates

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Abstract

In this review we compile and update recent developments in the synthesis, chemical properties, and biological importance of organic selenocyanates. The diverse synthetic routes to organoselenocyanates are described in the first part, including direct and indirect cyanoselenation. In the second part, the chemical reactions of organoselenocyanate are discussed. These included oxidation-reduction reactions. Further reactions included addition to the selenocyanate carbonitrile group, and reactions accompanied with cyanide group loss. These compounds exhibit anticancer, antioxidative, antileishmanial, antimutagenic and chemopreventive properties. The reported biological properties of this group of compounds are summarized in the last part.

Keywords: Organoselenocyanates, potassium selenocyanate, triselenium diselenide, selenocyanation, antileishmania

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1. Introduction

Organic compounds in which chalcogen atoms (oxygen, sulphur, selenium or tellurium) are connected on one side to a hydrocarbon substituent and on the other side to a carbonitrile group are called cyanate (OCN), thiocyanate (SCN), selenocyanate (SeCN), and tellurocyanate (TeCN), respectively. Organocyanates are relatively unstable, difficult to prepare and handle. On the other hand, organothiocyanates are being utilized as intermediates in organic chemistry because of their relative stability. The chemistry of organothiocyanates has been the subject of several outstanding monographs and reviews.[1-5] They have recently received wide attention due to their cancer chemopreventive properties.[6,7] These compounds play a leading role in organoselenium chemistry as they are stable and readily available. Indeed, they are efficiently metabolized to selenols and diselenides and therefore thought to be favorable selenide precursors.[8]

Although preparative methods as well as the chemical properties of organic selenocyanates have been reviewed before, most of these reviewed citations are three decades old.[9,10] Furthermore, several new studies providing extensive new knowledge have recently been published. Therefore, rather than dwell further on the triumphs of the past, this survey aims to compile and update recent developments in the synthesis, chemical properties and biological importance of organoselenocyanates. Our aim here is a comprehensive survey of recent literature reports on the current state of the art concerning the chemistry and biology of

these compounds. We have tried to avoid duplicating the content of previous reviews, although some work is discussed again when necessary to the discussion and to serve to illustrate a particular reaction category or strategy.

2. Synthetic Aspects of Organoselenocyanates

There are several known methods for the synthesis of organic selenocyanates. These methods can be classified into direct and indirect selenocyanation.

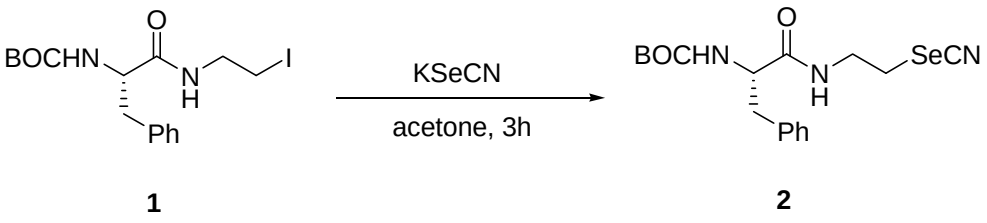
2.1. Direct cyanoselenation

This can be performed by direct reaction with a selenocyanating agent such as potassium selenocyanate, triselenium dicyanide (TSD), dicyanodiselenide or copper diselenocyanate ($Cu(SeCN)_2$) in an appropriate solvent.

2.1.1. Cyanoselenation using potassium selenocyanate. Nucleophilic cyanoselenation using potassium selenocyanate is the most common and preferred method used for the incorporation of selenocyanate group into organic compound backbones. This can be done either by the reaction with alkyl/aryl halides, sulfonyl/tosyl derivatives, diazonium salts, olefins or organosilanes.

2.1.1.1. *Reaction of potassium selenocyanate with alkyl and aryl halides.* This reaction is applicable to diverse functionalities (*e.g*. alkyl, aryl, allylic, propargylic, and natural compounds). Indeed, the reaction is usually performed under mild conditions using ethanol, acetone, dimethylformamide or acetonitrile as solvent. It is found that the reaction can also be improved under irradiation (microwave or ultraviolet), using two-phase systems or by using a suitable catalyst (*e.g.* a Lewis acid).

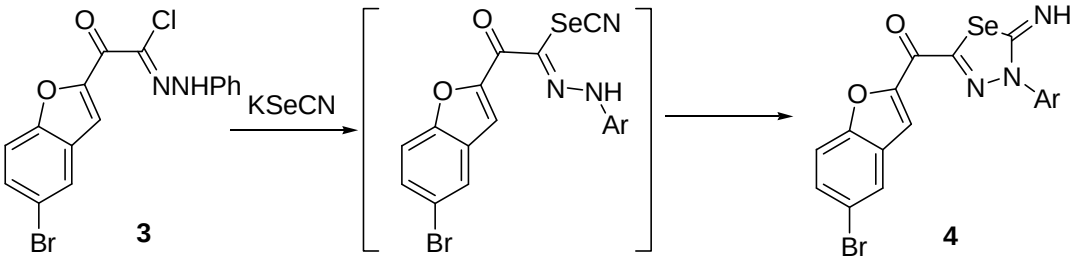
The reaction of potassium selenocyanate with the iodo derivative **1** in acetone afforded the corresponding selenocyanate **2** in 93 % yield. The reaction proceeded *via* nucleophilic substitution of the iodine by the selenocyanate anion at the selenium atom (Scheme 1).[11]



1 **2**

Scheme 1

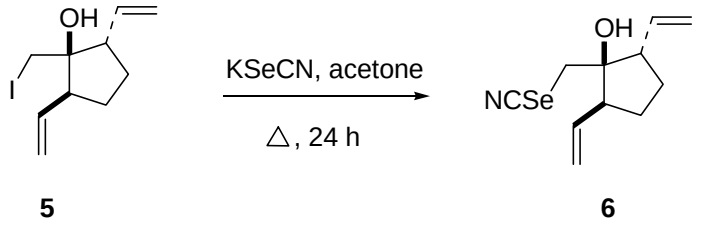
Treatment of ethanolic solutions of hydrazonoyl chloride **3** with potassium selenocyanate gave the corresponding non-isolable hydrazone selenocyanates which cyclized to give the selenadiazolimine derivatives **4** in good yields (72-78 %) (Scheme 2).[12]



[Ar= C_6H_5, 4-$CH_3C_6H_4$]

Scheme 2

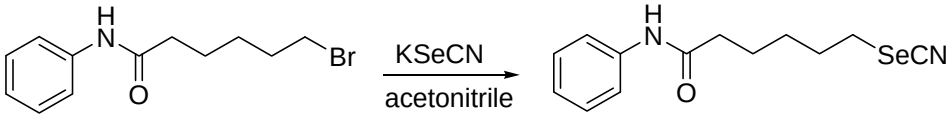
Furthermore, selenocyanate **6** was obtained in 53% yield by refluxing potassium selenocyanate with iodohydrin **5** in acetone (Scheme 3).[13]



5 **6**

Scheme 3

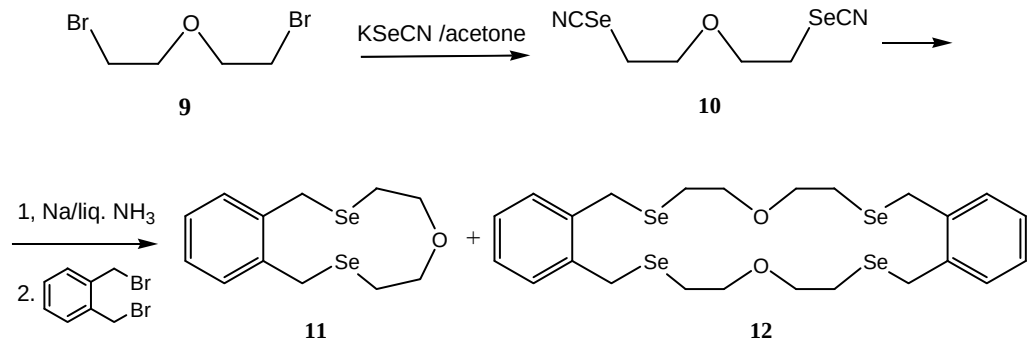
Desai *et al.*[14] reported the synthesis of *N*-phenyl-6-selenocyanatohexanamide **8**, a histone deacetylase inhibitor, in 64 % yield *via* the reaction of 6-bromo-*N*-phenylhexanamide **7** with potassium selenocyanate in acetonitrile at ambient temperature (Scheme 4).



7 **8**

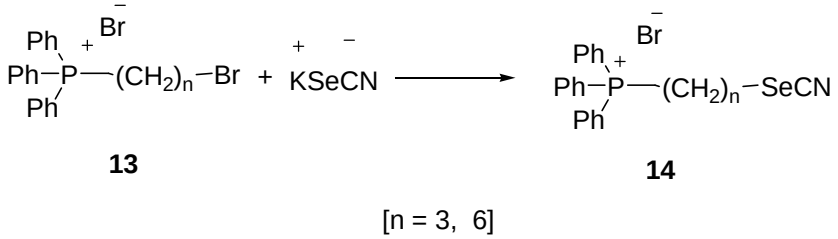
Scheme 4

This reaction was also applied to the synthesis of mixed macrocyclic selenoethers **11** and **12** *via* cyclization of the corresponding bis-selenocyanate precursor **10**. The latter was prepared in 62% yield by careful addition of bis-(2-bromoethyl)ether **9** to an acetone solution containing potassium selenocyanate (Scheme 5).[15]



Scheme 5

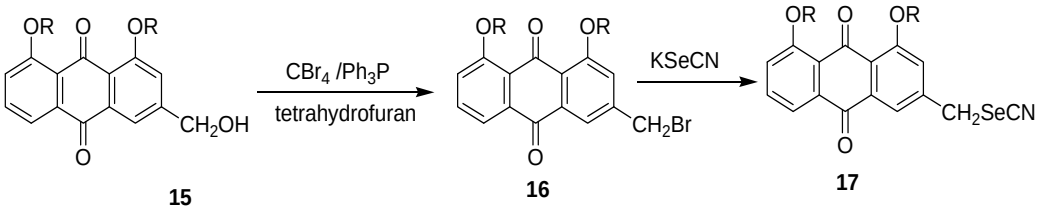
Masked phosphonioalkylselenoate ligands **14**, used for the preparation of phosphonioalkylselenoate-functionalised gold nanoparticles, were prepared by the reaction of (bromoalkyl)triphenylphosphonium bromide **13** with potassium selenocyanate in aqueous ethanol (Scheme 6).[16]



Scheme 6

15-Selenocyanochrysophanols **17** were prepared from the naturally occurring aloe-emodin **15**. The latter was brominated using carbon tetrabromide and triphenylphosphine in tetrahydrofuran to give the corresponding bromide **16** (82% yield), which in turn was used as the starting material for the introduction of selenocyanate group (65-86% yields) by the reaction with potassium selenocyanate. The cytotoxic effects of these compounds were

evaluated using HCT 116 and Hep G2 cancer cell lines and they were found to possess much more potent effects than the parent aloe-emodin **15** (Scheme 7).[17]

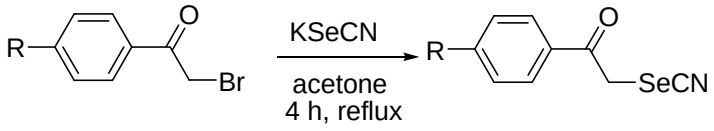


15 **16** **17**

[R = H, hexyl]

Scheme 7

1-Phenyl-2-selenocyanatoethanone (**19**), known as useful building blocks for the synthesis of selenium heterocycles, was prepared in fair yields (33%) by the reaction of phenacyl bromides (**18**) with potassium selenocyanate in acetone (Scheme 8).[18]

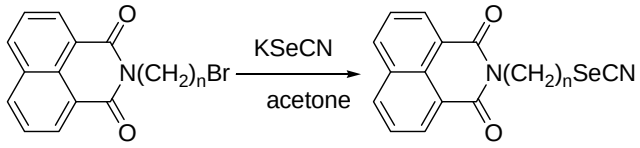


18 **19**

[R= H, Cl, Br]

Scheme 8

Sk *et al.*[19] reported the synthesis of different organoselenocyanates possessing 1,8-naphthalimide moiety **21** and evaluated their preventive potential for cadmium induced hepatic lipid peroxidation and oxidative stress. These compounds were able to prevent the oxidative stress in mice induced by cadmium and enhanced the mice ability to restore hepatic lipid peroxidation level and they showed also hepatoprotective activity. The target compounds were synthesized in good yields (68-89%) *via* nucleophilic substitution of the bromides **20** with selenocyanate using potassium selenocyanate in acetone (Scheme 9).[19]



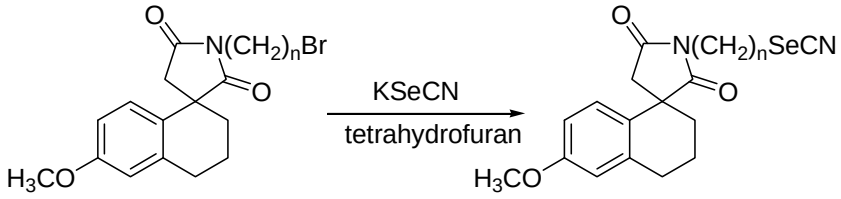
20 **21**

[n=2-5]

Scheme 9

Once more, Sk and his group[20] reported the synthesis of spiro[tetralin-1,3′-pyrrolidine] based organoselenocyanates **23** and evaluated their inhibitory activity against cadmium induced toxicity in Swiss albino mice. The preadministration of these compounds was accompanied by an improvement in the hepatotoxicity with exception that naphthalimide containing selenocyanates were more active. This was in agreement with Sk *et al.*[19] previous report where these compounds were able to retain redox homeostasis and exhibited hepatoprotective activity.[19]

The spiro selenocyanato tetralin-1,3′-pyrrolidines **23** were obtained in 75-80% yields *via* nucleophilic substitution reaction of the corresponding bromide derivatives **22** with potassium selenocyanate in anhydrous tetrahydrofuran (Scheme 10).[20]



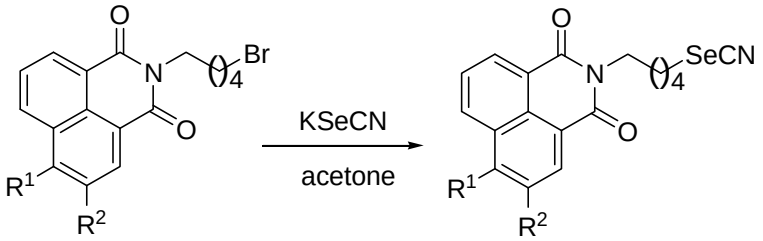
22 **23**

[n = 2,3,4 and 5]

Scheme 10

In a similar study, Roy *et al.*[21] described the synthesis of a series of substituted naphthalimide-based organoselenocyanates and investigated their corresponding hepatotoxicity, nephrotoxicity and also their ability to modulate the levels of phase II detoxifying and antioxidant enzymes such as glutathione-S-transferase (GST), superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), thioredoxin reductase (TRxR) and nonenzymatic antioxidant like reduced glutathione (GSH) levels in liver.

Selenocyanato-isoquinolines **25** were prepared from bromoalkyl-naphthalimides **24** upon reaction with potassium selenocyanate in acetone (51-74% yields) (Scheme 11).[21]

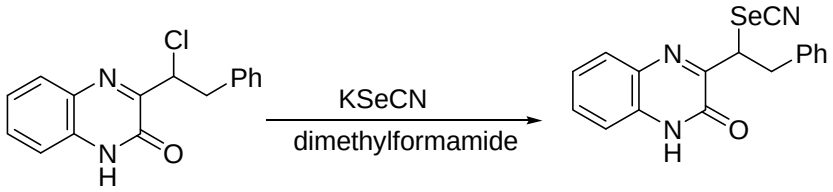


24 **25**

[R^1 = H, Cl; R^2= H, NO_2]

Scheme 11

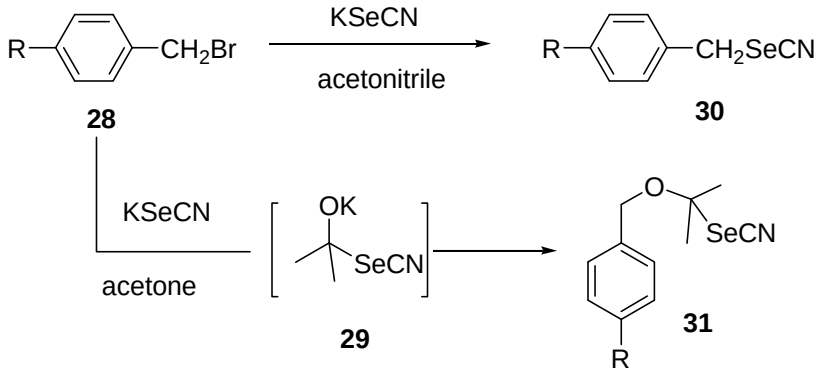
Mamedov and his colleagues[22] also reported the synthesis of 3-(3-phenyl-1-selenocyanatopropyl)quinoxalin-2(1*H*)-ones **27** by the reaction of potassium selenocyanate with chlorophenylethylquinoxalinone **26**. The reaction proceeded using excess of potassium selenocyanate in dimethylformamide at 40 °C and the yield was up to 81% (Scheme 12).[22]



26 **27**

Scheme 12

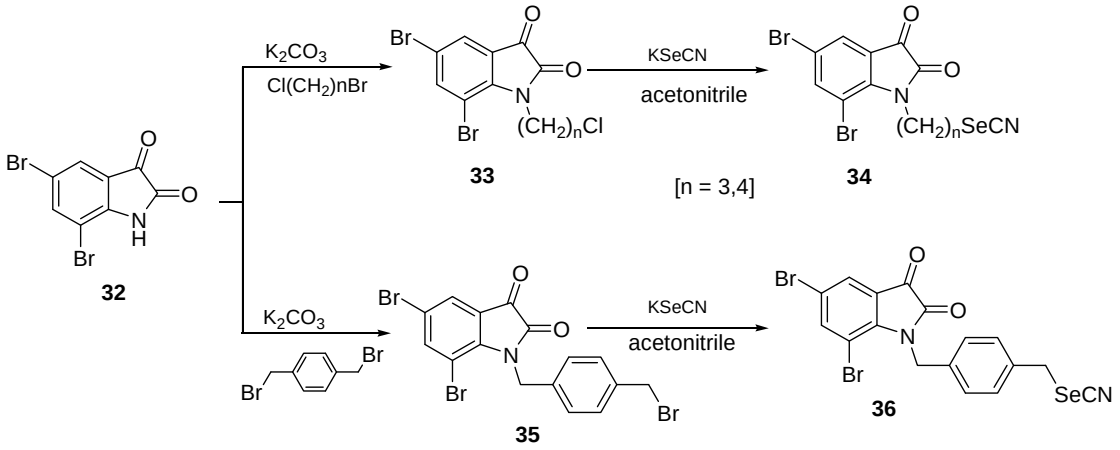
Benzyl selenocyanates **30** were obtained from the reaction of the reaction of benzylic bromides **28** with potassium selenocyanate in acetonitrile.[23] The products were pure enough and obtained in satisfactory yields (up to 70%). When acetone was used as the solvent, **31** were obtained. This was interpreted as the formation of a second nucleophile **29** which further reacted with benzylic halides leading to the formation of **31**. It was also postulated that long reaction time was the cause of this side reaction (Scheme 13).[23]



[R = H, F, CH_3, OCH_3, t-Bu]

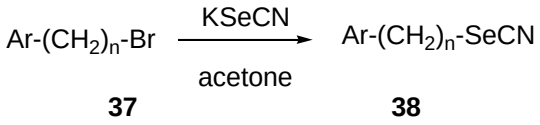
Scheme 13

Very recently, Krishnegowda *et al.*[24] described the synthesis of 5,7-dibromoisatin containing selenocyanate groups **34** and **36**. The later were obtained in a good yield (67 and 76 %, respectively) *via* the nucleophilic substitution of potassium selenocyanate with 5,7-dibromo-*N*-chloroalkylisatin **33** and -*N*-(4-bromomethyl)benzylisatin **35**, respectively (Scheme 14). These compounds were evaluated for their cytotoxicity against colon, breast, lung and melanoma cancer cells and were reported to display good *in vitro* activity against breast cancer cells (MCF-7) compared to their thiocyanate analogs. Furthermore, the compounds were found to inhibit tubulin polymerization as vinblastine sulfate (antimicrotubule drug used to treat certain kinds of cancer). This further support the hypothesis that a combination of indoles and selenocyanates might lead to a novel dual targeted inhibitors which may further developed as future drugs.[24]



Scheme 14

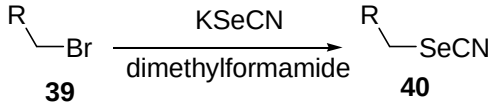
Different aromatic selenocyanates **38** were obtained (15-81% yields) by refluxing haloarenes or haloalkylarenes **37** with potassium selenocyanate in acetone (Scheme 15).[25] It is noteworthy that the substrate nature played an important role in determining the reaction progress and rate. Within this context, electron-withdrawing substituents facilitate the nucleophilic selenocyanate anion attack by stabilizing the formed negative charge via mesomeric and inductive effect.[25]



[Ar = 4-aminophenyl, 4-bromophenyl, 4-nitrophenyl, 4-methoxyphenyl; n = 0, 1, 2]

Scheme 15

Allylic and propargylic selenocyanates (**40**) were also obtained in good yields (up to 80 %) by the reactions of allylic and propargylic bromides **39** with potassium selenocyanate in acetonitrile and at room temperature.[26-31] It is worth noting that the replacement of dimethylformamide by acetonitrile led to byproduct minimization (Scheme 16). Indeed, the rate of the reaction may be increased either by irradiation (ultraviolet) or by using Lewis acids (e.g. copper(I) iodide dissolved in warm hexamethylphosphoric triamide).[32-35] On the other hand, alkenyl and alkynyl halides were basically unreactive toward cyanoselenation under these conditions.[33] This may be attributed to the induced repulsion between the electrons of the double/triple bond and the selenocyanate anion.[33]

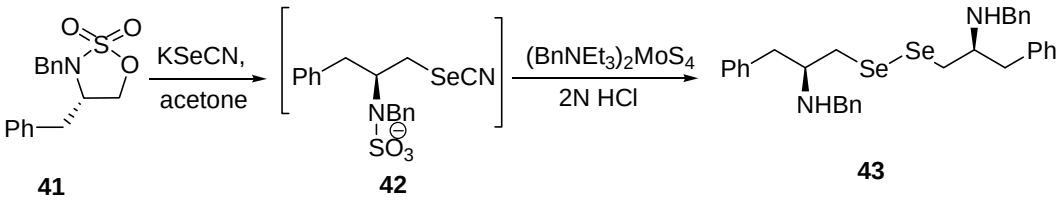


[R= CH_2=CH, HC≡C]

Scheme 16

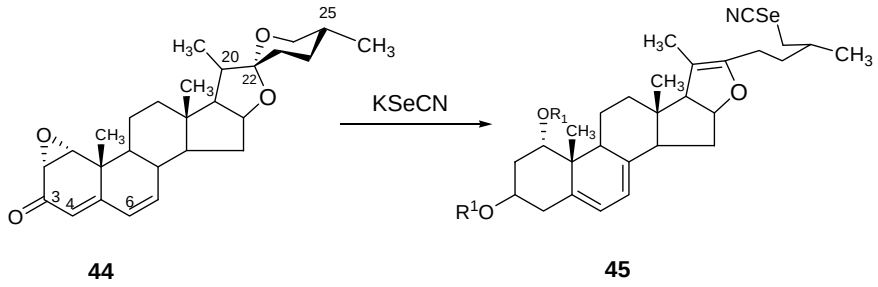
Besides, *N*-benzyl-ß-amino diselenides **43** were also synthesized from sulfamidates in a multistep one-pot reaction using potassium selenocyanate and benzyltriethylammonium tetrathiomolybdate in acetone. The non isolable selenocyanate key intermediate **42** was *in situ* formed *via* regioselective ring opening of sulfamidate **41** using potassium selenocyanate. The

corresponding *N*-benzyl-β-aminodiselenide derivative **43** was obtained upon reductive dimerization followed by hydrolysis by treatment with tetrathiomolybdate and hydrochloric acid in quantitative yield (up to 99 %) (Scheme 17).[36]



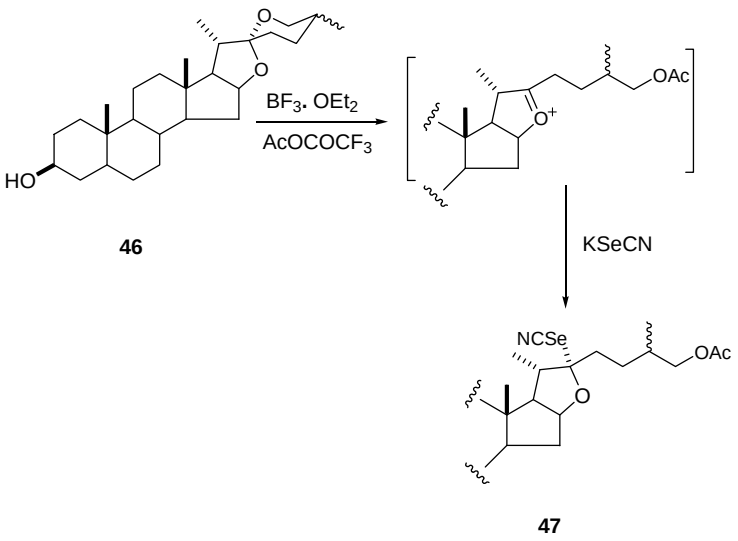
Scheme 17

Naturally occurring furostanol derivatives **45** modified by the incorporation of a selenocyanate group at position 26 were synthesized in a multistep reaction of **43** and potassium selenocyanate in fair yield (24 %) (Scheme 18).[37,38] The cytotoxic activity of this compound was evaluated against HCT 116 and Hep G2 cancer cells. Interestingly, **45**showed higher effects than the parent natural compound on both HCT 116 and Hep G2 cells.[37,38]



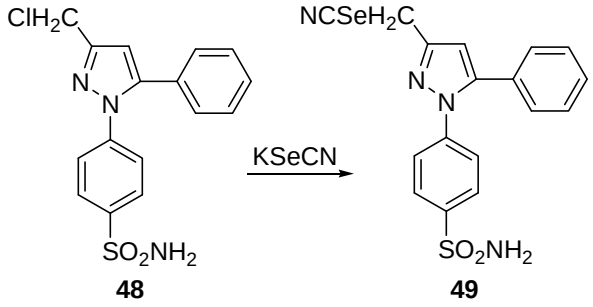
Scheme 18

Viñas-Bravo *et al.*[39] reported the synthesis of selenocyanatofurostan **47** in high yields (90 %) *via* treatment of sapogenins **46** with a mixture of acetic/trifluoroacetic mixed anhydride, borontrifloride ether and potassium selenocyanate at room temperature (Scheme 19).[39]



Scheme 19

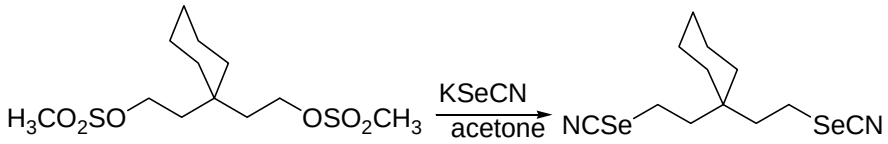
Another report by Desai *et al.*[40] described the synthesis of Selenocoxib-1 (**49**), a selenocyanate analogue of the sulfonamide nonsteroidal anti-inflammatory drug Celecoxib (Scheme 20). The reaction of chloro-derivative **48** with potassium selenocyanate in acetone afforded the corresponding selenocyanate **49** in 57 % yields. Interestingly, Selenocoxib-1 was more efficient than Celecoxib itself in controlling the tumor growth in the short-term PAIII transplantable LW model and provided greater inhibition of invasive prostate cancer growth at lower dose.[40]



Scheme 20

2.1.1.2. *Reaction of potassium selenocyanate with sulfonate/tosylates sulfonyl/tosyl derivatives*. 1,1′-Di-(2-selenocyanatoethyl)cyclohexane (**51**) was obtained in 87% yield from

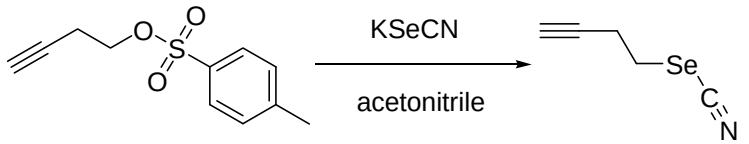
the reaction of (1,1′-di-(2-methane-sulfonyloxyethyl)cyclohexane) (**50**) with excess potassium selenocyanate in anhydrous acetone and at 56 °C (Scheme 21).[41]



50 **51**

Scheme 21

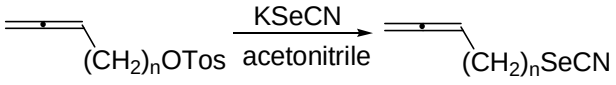
Similarly, heating equimolar amounts of 3-butyn-1-yl-*p*-toluenesulfonate (**52**) and potassium selenocyanate in acetonitrile for 3 h afforded **53** in 83% yields (Scheme 22).[42]



52 **53**

Scheme 22

Tosylates could also be used instead of sulfonates for the preparation selenocyanates. In this context, allenyl selenocyanates **55** were synthesized (in 60-80 % yields) by the reaction of their corresponding tosylates **54** with potassium selenocyanate in acetonitrile (Scheme 23).[43]

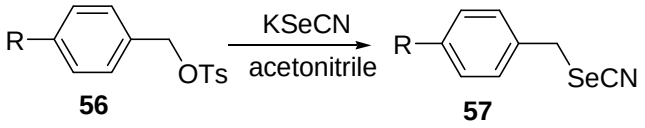


54 **55**

[n =1, 2]

Scheme 23

Furthermore, Jacob *et al.* also reported the synthesis of benzyl selenocyanates **57** from benzyl tosylates **56** using the same reaction conditions. Nevertheless, the yield was low and accompanied by formation of colloidal red selenium (Scheme 24).[23]

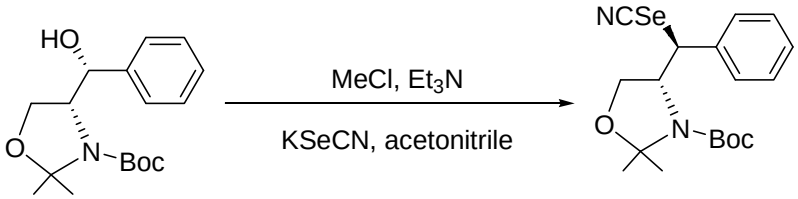


56 **57**

[R = H, F, Me, MeO, t-Bu]

Scheme 24

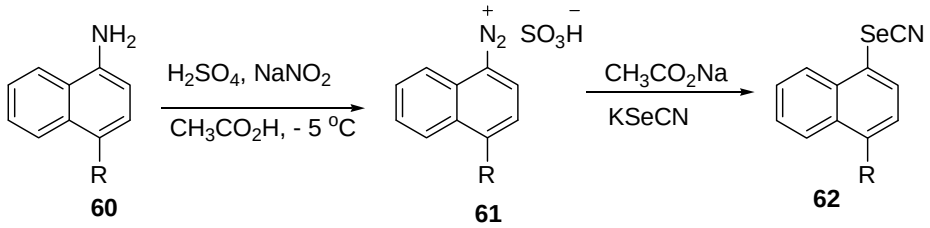
Mesylation of **58** followed by introduction of the crucial selenocyanate moiety *via* SN2, afforded the corresponding selenocyanate **59** in fair yield (29%) (Scheme 25).[44]



58 **59**

Scheme 25

2.1.1.3. *Reaction of potassium selenocyanate with diazonium salts*. Primary aromatic amines are convenient starting building blocks for the synthesis of organoselenocyanates.[45,46] For instance, diazotized anilines **61** reacted with potassium selenocyanate to give the corresponding aromatic selenocyanates **62**. These compounds were mostly obtained in low yields due to the decomposition of potassium selenocyanate by the acid traces remaining from the diazotization step. The reaction was accordingly performed in a buffered solution (sodium acetate; pH = 5.5) and the yield was moderately improved (38-46%) (Scheme 26).[45, 46]

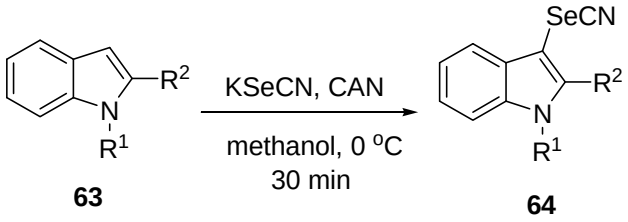


60 **61** **62**

[R = H, Cl, Br, NO_2]

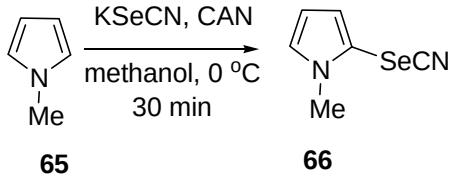
Scheme 26

2.1.1.4. *Reaction of potassium selenocyanate with indoles and olefins*. Nair *et al.*[47] reported that indoles **63** may undergo cyanoselenation in a good yield (72 %) using cerium(IV) ammonium nitrate (CAN) and potassium selenocyanate in methanol (Scheme 27).



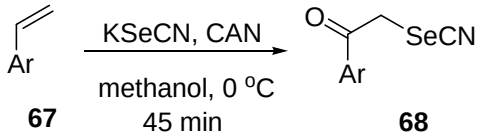
Scheme 27

The same result was obtained with 1-methylpyrrole (**65**); however, the yield was lower (25 % yield) (Scheme 28).[47]



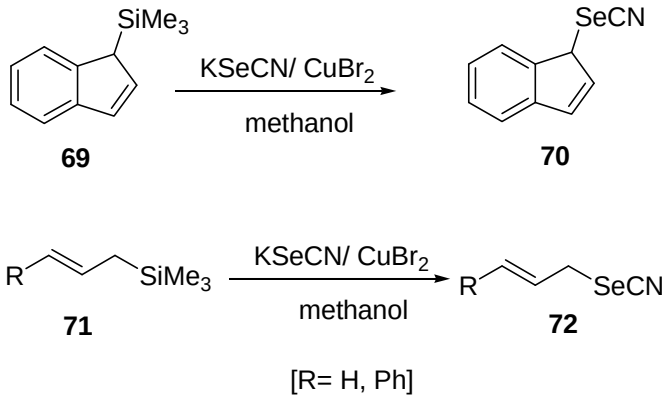
Scheme 28

Selenocyanation of styrenes and vinyl naphthalenes **67** in the presence of CAN using potassium selenocyanates afforded the corresponding selenocyanates **68** in a moderate yields (46-67 %) (Scheme 29).[47]



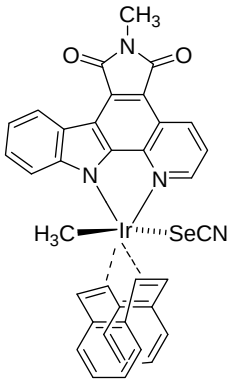
Scheme 29

2.1.1.5. *Reaction of potassium selenocyanate with organosilanes.* Regioselective α-substitution of allylic silanes **69** and **71** with a selenocyanate group using potassium selenocyanate took place in methanol to give the corresponding allylic selenocyanates **70** and **72** in moderate yields (up to 72%) (Scheme 30).[48] It is worth noting that readily available allylic halides are favorably preferred than allylic silanes as the selenocyanates are obtained from allylic halides in higher yields.[26-31]



Scheme 30

2.1.1.6. *Reaction of potassium selenocyanate with metal-based complexes*. The Meggers, Murray and Klingele goups[49-55] exploited the substitutionally inert metal complexes as sophisticated scaffolds for the design of enzyme, protein and lipid kinase inhibitors *via* targeting their active sites. They demonstrated that octahedral metal coordination geometries provide novel scope to implement specific molecular scaffolds that can fit into protein pockets. Furthermore, linear gold complex **78** was used as a model for theoretical studies and for determining the electronic characteristics of metal–ligand bonding through structural studies. The selenocyanate group was introduced in order to increase the inhibition activity. This was performed by heating the metal based complex with potassium selenocyanate in dimethylformamide, acetonitrile or methanol at 95 ºC for 12 h (Scheme 31).[49-57]



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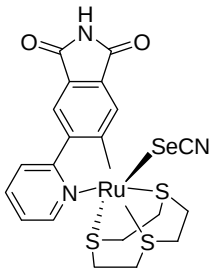

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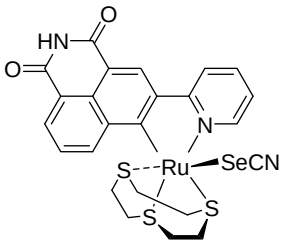

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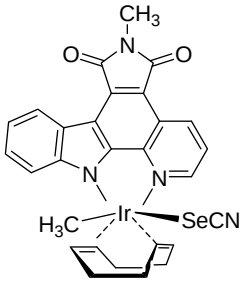

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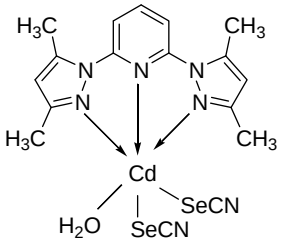

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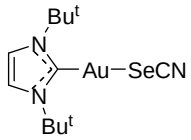
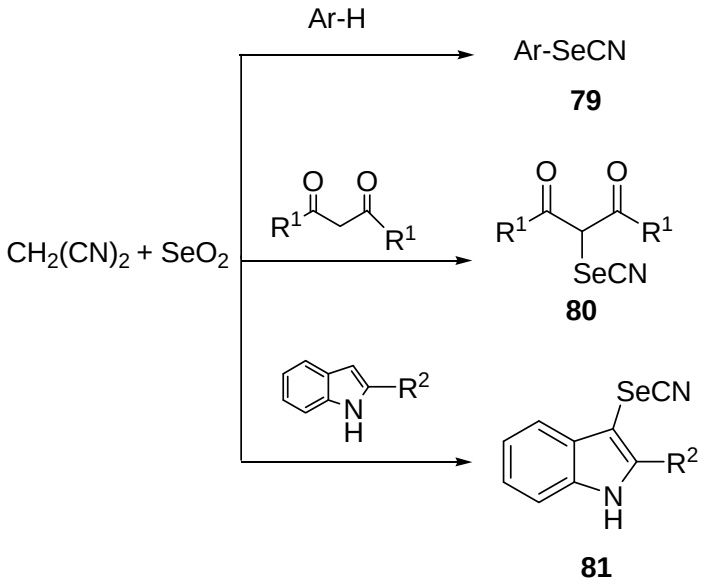


78

Scheme 31

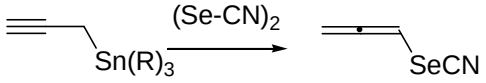
2.1.2. Cyanoselenation using triselenium dicyanide. The TSD reagent ($Se(SeCN)_2$) was used to insert the selenocyanate group directly into the scaffold of some active methylene compounds, arenes with free *para* positions and indoles with a free 3-position and dimedone to give the corresponding selenocyanates **79-81** (Scheme 32).[58] The most convenient method for the preparation of TSD is by oxidative coupling of malononitrile with selenium dioxide. Dimethylsulfoxide or dimethylformamide is the usual solvent used.[25,59] TSD could also be prepared *via* the oxidation of potassium selenocyanates using suitable oxidizing agents (e.g. dinitrogen tetroxide, iodine pentafluoride, chlorine, bromine or iodine).[60]



[Ar = 4-aminophenyl, dimethylaminophenyl, 4-amino-3-methylphenyl, 4-amino-3-carboxyphenyl; R^1, R^2 = H, Me, COOEt]

Scheme 32

2.1.3. Cyanoselenation using dicyanodiselenide. Selenocyanogen, $(SeCN)_2$, prepared from the reaction of silver selenocyanate with iodine,[61] was used for the synthesis of various selenocyanates which could not be prepared by any of the previously mentioned approaches. Thus, allenyl selenocyanate **83** was prepared by the reaction of selenocyanogen with propargyl tri-n-butylstannane **82** *via* a propargyl-allenyl rearrangement in a 55 % yield (Scheme 33).[43]

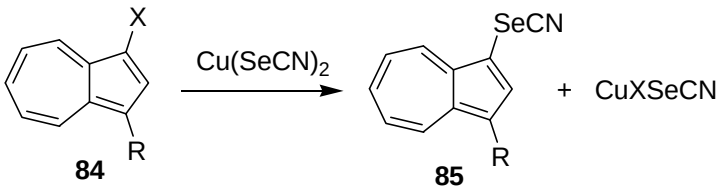


82 **83**

[R= Ph, Bu]

Scheme 33

2.1.4. Cyanoselenation using copper diselenocyanate. Disubstituted azulenes **84** reacted with copper diselenocyanate to furnish the corresponding selenocyanate **85.**[62] It was found that the second substituent plays a determining role in the rate of the reaction (Scheme 34).



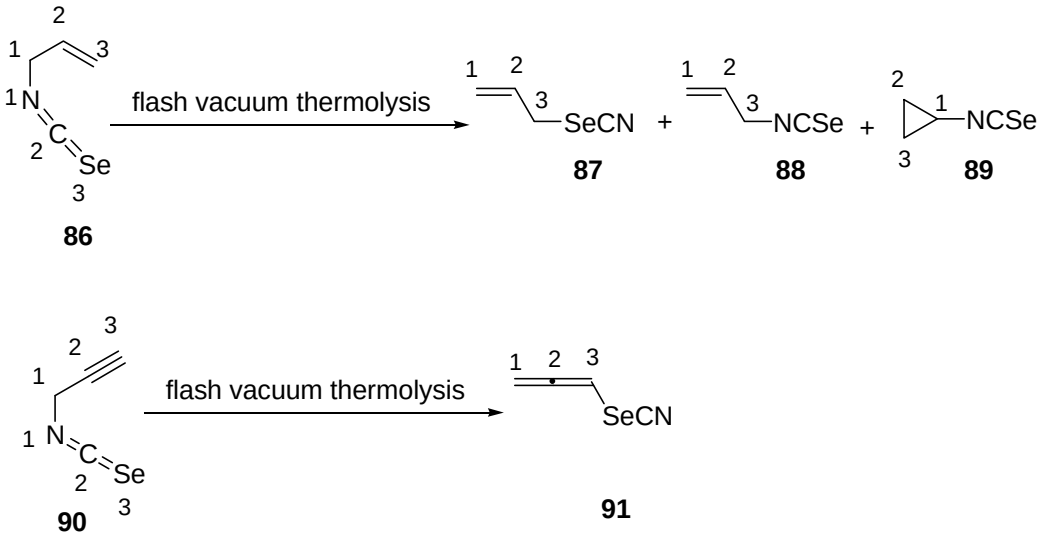
[R= MeO, Ph, COPh, SO_2Ph, NO_2; X = Cl, Br, I]

Scheme 34

2.2. Indirect cyanoselenation

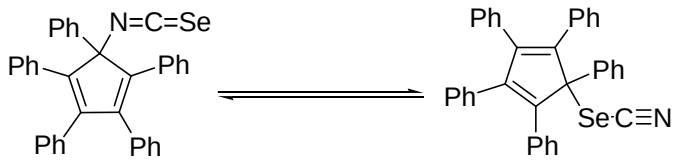
Selenocyanates could also be prepared *in situ,* without the use of a selenocyanating agent. This includes rearrangement of isoselenocyanates and reaction of alkyl magnesium halides with selenium powder and cyanogen bromide. Selenocyanates could also synthesized by other methods (e.g. electrolysis of selenocyanic acid salts, reaction of diselenides with mercury(II) cyanide and reaction of phenylselenenyl chloride with trimethylsilyl cyanide). [63-67] These methods are quite old, were seldom used in the past (more than thirty years ago) and will not be discussed here. Their relevant references are cited in case the reader needs more details.

2.2.1. Cyanoselenation *via* rearrangement of isoselenocyanates. Reversible hetero-Cope rearrangements ([3,3]-sigmatropic shifts) of isoselenocyanate to isomeric selenocyanate usually take place thermally *e.g.* on flash vacuum thermolysis.[68,69] For example, [3,3]-sigmatropic rearrangements of allylic (**86**) and propargylic (**90**) isoselenocyanates occurred upon heating to give the corresponding allylic (**87**, **88**), cyclopropyl (**89**) and allenyl (**91**) selenocyanates (Scheme 35).[31,70-72]



Scheme 35

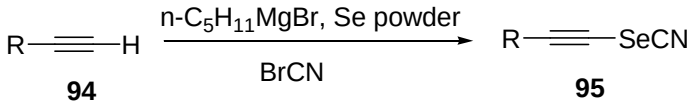
Pentaphenylcyclopentadienyl isoselenocyanate (**92**) underwent isomerization to give the corresponding selenocyanate (**93**) *via* 1,5-sigmatropic rearrangement of the selenocyanate group around the cyclopentadiene ring (Scheme 36).[68,73,74]



92 **93**

Scheme 36

2.2.2. Cyanoselenation *via* the reaction of alkyl magnesium halides, selenium powder and cyanogen bromide. Guillemin *et al.*[43] reported the synthesis of 1-propynylselenocyanate **95** from reaction of the corresponding alkyl magnesium salt with selenium powder followed by the addition of cyanogen bromide (Scheme 37).[43]



94 **95**

[R= H, Me]

Scheme 37

3. Reactions of Organic Selenocyanates

Organoselenocyanates are characterized by their distasteful odors. They are colorless stable compounds and in most cases present as oil at room temperature. The spectrophotometric properties (e.g. infrared, NMR, photoelectron and microwave studies) were described in previous reports.[9,10]

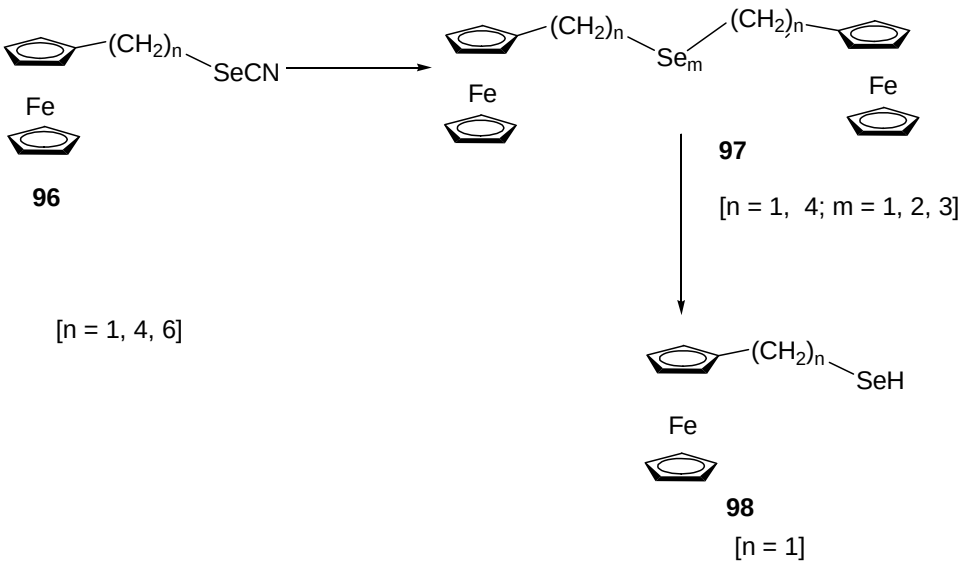
Recently, numerous organoselenium compounds have been synthesized employing organoselenocyanates. The latter can also be transformed into various selenoorganic derivatives including selenols, functionalized selenides (both symmetric and asymmetric) and diselenides.[75,76] Indeed, alkenes, alkynes, alcohols, aldehydes and carboxylic acids could be

also synthesized from organic selenocyanates.[77-80] Nevertheless, some of these reactions were reported decades ago and are no longer used. These include the reaction with halogens, thiols, acids or selenols.[81-84] Other obsolete reactions include the addition reaction of organoselenocyanates to alkenes, alkyne or enamines.[85-89] These reactions will not be discussed here and the reader is directed to other reviews or monographs.[9,10]

In the interest of clarity, recent organoselenocyanate reactions presented here have been subdivided into four sections: (i) reduction reactions; (ii) oxidation reactions; (iii) addition reactions to the carbonitrile group; and (iv) reactions accompanied with cyanide group loss.

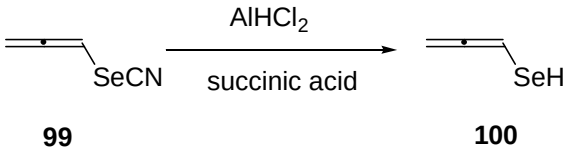
3.1 Reduction of organic selenocyanates

Alkali metal hydrides such as sodium borohydride, lithium aluminum hydride, lithium hydride, dichloroaluminum hydride and sodium hydride have been used for the reduction of organoselenocyanates. The corresponding diselenides were obtained in quantitative yields, in case if insufficient reductant was used. The former could be further reduced in the presence of excess reductant to yield the corresponding selenol in acidic medium as shown in the case of ferrocenylalkyl-selenols (Scheme 38).[43, 75, 76, 90]



Scheme 38

The chemoselective reduction of unsaturated the allenylselenocyanate **99** was performed by dichloroaluminum hydride ($AlHCl_2$). This allowed the synthesis of allenylselenol **100** (Scheme 39).[42]

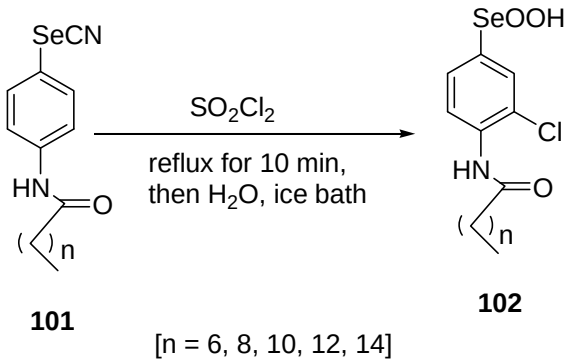


Scheme 39

3.2. Oxidation of organic selenocyanates

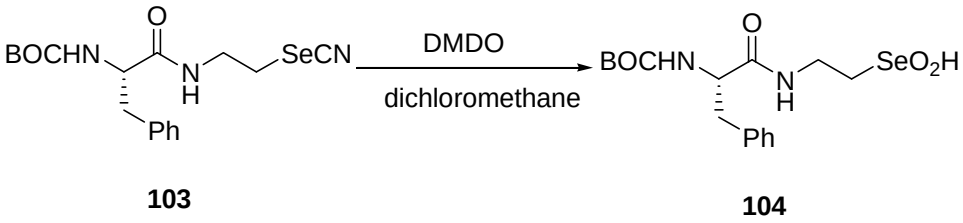
On the other hand, oxidation of selenocyanates gives the corresponding seleninic acid which in turn is very reactive and unstable. Classical hydrogen peroxide (H_2O_2) oxidation synthetic method has been used for the synthesis of seleninic acid; however, this method is not always applicable for simple seleninic acids.

In 2014, Du *et al.*[93] reported the oxidation of phenyl selenocyanates **101** to the corresponding amphiphilic seleninic acids **102** with in overall yields of 55% (Scheme 40). [93]



Scheme 40

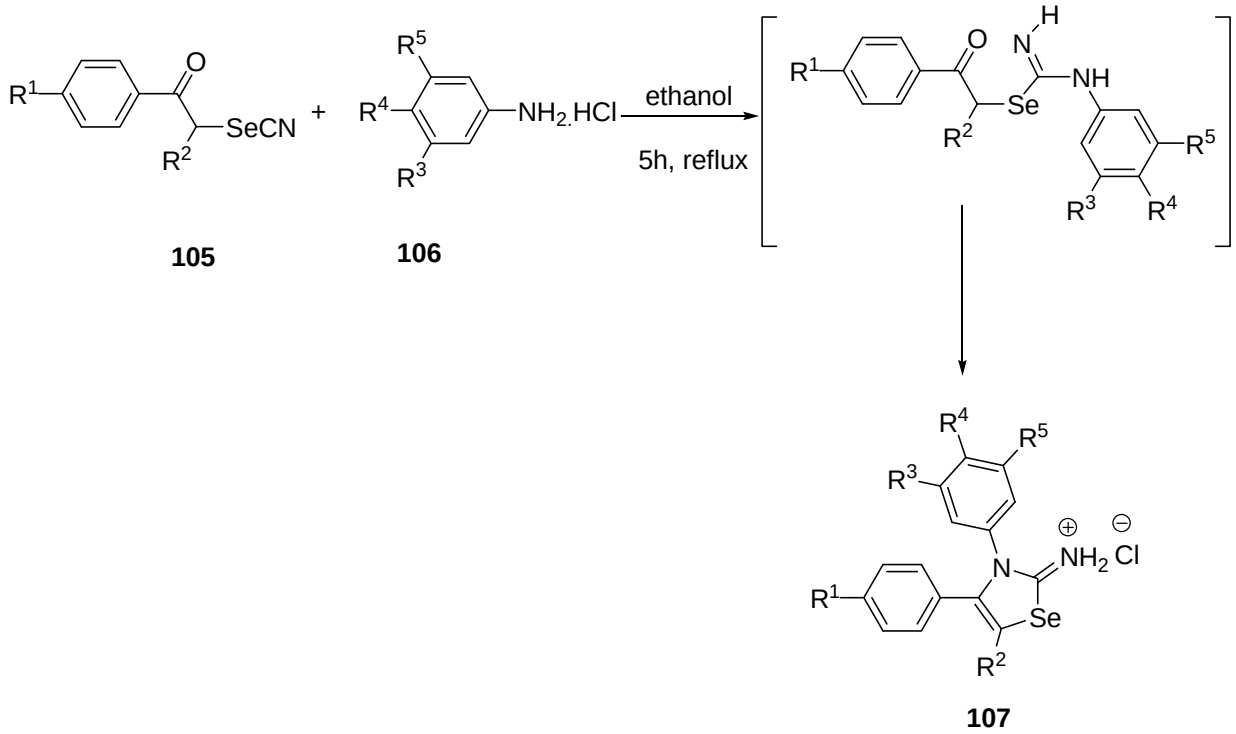
Dimethyldioxirane (DMDO) was also used for the synthesis of seleninic acid **104** in 70 % yields *via* oxidation of the corresponding selenocyanates **103** in dichloromethane (Scheme 41).[11]



Scheme 41

3.3. Addition reactions to the carbonitrile group

The reaction of aniline hydrochloride salts **106** with α-(selenocyanato)acetophenones **105** under acidic conditions afforded selenazolimine **107** in fair yields (up to 27%). This was explained *via* the acid-catalyzed addition of the aniline amino group to the selenocyanate group and further cyclization with subsequent elimination of water (Scheme 42).[18]

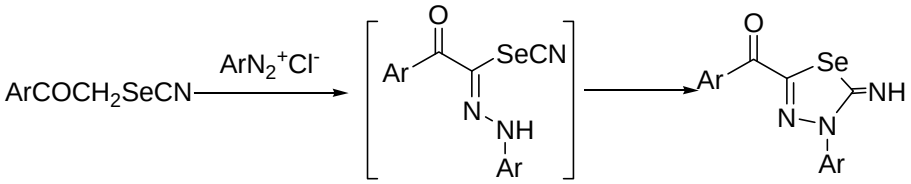


105 **106** **107**

[R^1=H, Cl, Br; R^2= H, Ph; R^3=H, Cl; R^4= H, Cl]

Scheme 42

Interestingly, the reaction of α-(selenocyanato)acetophenones **108** with diazonium salts afforded (4,5-dihydro-5-imino-4-aryl-1,3,4-selenadiazol-2-yl)(aryl)methanones **109**. This was explained by the addition of the hydrazone anilino residue onto the selenocyanate group (Scheme 43).[12]

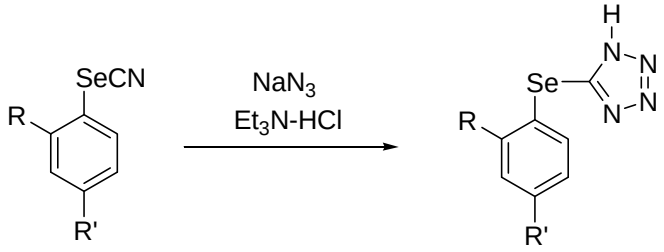


108 **109**

[Ar = C_6H_5 , 4-$CH_3C_6H_4$]

Scheme 43

Compounds containing both selenium and tetrazole ring were synthesized in high yields (75–92%) *via* the reactions of selenocyanates **110** with sodium azide under conditions of phase transfer catalysis in the presence of triethylammonium chloride in toluene (Scheme 44).[46]



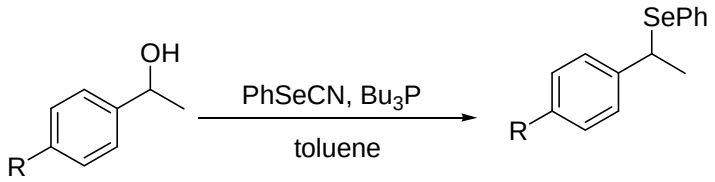
110 **111**

[R=H, Cl, CH_3; R'=H, Cl, NO_2, COOH, OCH_3]

Scheme 44

3.4. Reactions accompanied with cyanide group loss

In 2012, Brondani *et al.*[94] reported the reaction of phenyl selenocyanate with phenylethanol derivatives **115** and tributylphosphine in toluene. In this case, reaction proceeds with the loss of the cyanide group and phenylseleno derivatives 116 were obtained in good yields (79 %-87 %) (Scheme 45).[94]

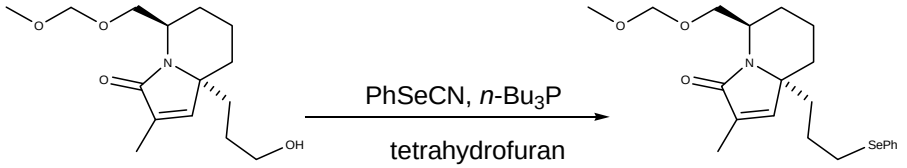


112 **113**

[R=H, F, CH_3]

Scheme 45

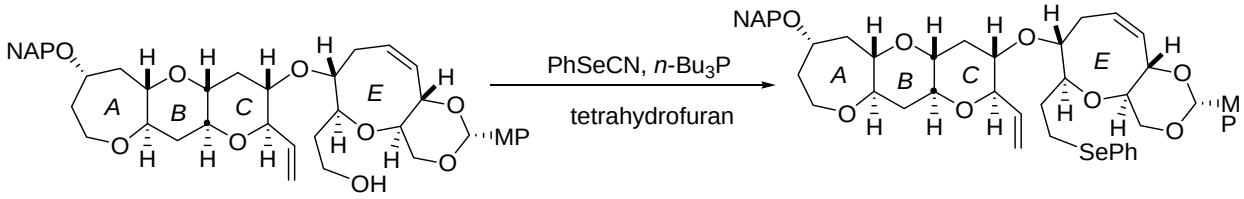
Similarly, phenyl selenocyanate reacted with primary alcohol **117** and tributylphosphine in tetrahydrofuran to give the corresponding phenylselane **118** in 97 % yields (Scheme 46). [95]



117 **118**

Scheme 46

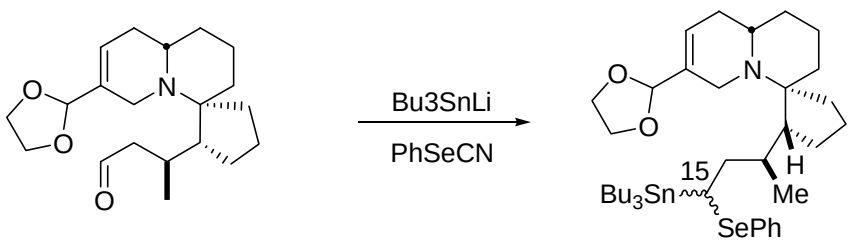
Yamashita *et al.* reported that the cyanide group could be also removed from phenyl selenocyanate when reacted with primary alcohols in the presence of tributylphosphine in tetrahydrofuran (Scheme 47).[96]



119 **120**

Scheme 47

Treatment of aldehyde **121** with Bu_3SnLi and phenyl selenocyanate afforded the corresponding selenides **122** in modest yield (61%) (Scheme 48).[95]



121 **122**

Scheme 48

4. Biological Activities

Organoselenium compounds exhibited diverse biological properties and have been used as antihypertensive, anti-bacterial, or chemopreventive anticancer agents.[6-8] Among the synthetic selenium derivatives, organoselenocyanates have received wide attention for their better cancer chemopreventive properties as well as antioxidative and antimutagenic properties.[97-99] In view of this, organic selenocyanates have recently been used in synthetic organic and metal complexes chemistry, metal extraction and in pharmaceutical and biomedical industry.[50-57] Indeed, they have also shown antiparasitic (*e.g*. antileishmanial) and antiviral activity by improving the immune response of hosts against the parasite and the viral species.[25,77]

The biological activities of organoselenocyanates depend on their structural backbone and the nature of substituents on it. Extensive studies have shown that selenocyanate incorporation into the scaffold of organic compounds has enhanced the pharmacological potentials of these drugs by supplying them with new inhibitory properties.[99] Furthermore, exchange of selenium by sulphur (i.e. selenocyanate to thiocyanate) in some compounds diminished the therapeutic potential of the compounds. These compounds showed multiple mode(s) of protection against cancer. These include inhibition of the Akt signaling pathway, reducing the levels of ALT and AST, upregulation of reduced glutathione levels and antioxidant enzymes, modulation of serum aspartate transaminase, alanine transaminase levels and also normalizing the hematological parameters.[7,19-21,98] Organoselenocyanates are known to be metabolized to the corresponding selenols. The later are very active and can further for example bind with different metals and thus ameliorating the metal-induced hepatotoxicity.[76-78, 98] In this context, organoselenocyanates were considered as an efficient therapy to protect human health from metal toxicity and hazards of environmental toxicants. On the other hand, several reports have attributed the anticancer activity of these compounds to apoptosis induction *via* generation of reactive oxygen species induction in a prooxidant fashion.[93]

Besides their antitumor properties, organoselenocyanates have latterly shown an *in vitro* antiparasitic activity against *Leishmania infantum*.[25,77] Interestingly, some of them possess a

better activity more than the prescribed oral drugs Impavido and edelfosine.[77] Their mode of action is attributed to their ability to interfere the parasites redox system.[25,77]

Among the most studied selenocyanates used in cancer chemotherapy, selenocoxib-1, 1,4-phenylenebis(methylene)selenocyanate, diphenylmethyl selenocyanate and diphenylmethyl selenocyanate have shown to be the most efficient compounds.

1,4-Phenylenebis(methylene)selenocyanate was found to be less toxic and more effective than selenomethionin.[103,104] It was found that this compound reduces the expression of cyclooxygenase-2, phospholipase A, and cyclin D1 regulated by NF-KB such as in non–small cell lung cancer cells.[102-105] Furthermore, Selenocoxib-1 provides the advantage in inhibition and controlling prostate cancer growth.[99-101] As another example, oral administration of diphenylmethyl selenocyanate lead to reduction of the reactive oxygen species levels which in turn reduced the chemically induced skin papilloma without causing any toxic effects.[101,105-109] Moreover, diphenylmethyl selenocyanate was reported to prevent chemically induced oxidative stress and to enhance serum ALT and AST level in mice.[107-109]

Conclusions

We have summarized the recent progress in the synthesis, chemical properties, and biological importance of organoselenocyanates. The synthetic preparation methods of organoselenocyanates and their corresponding chemical properties and reactions were also described. The biological properties of this group of compounds were also issued. This knowledge will be useful in developing novel organoselenocyanates that might be of enhanced biological properties that may be developed as future drugs.

Acknowledgements

The authors thank the Egyptian Ministry of Higher Education and Mansoura University for their support.

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