International Journal of Chemical Science
www.chemicaljournals.com
Online ISSN: 2523-2843, Print ISSN: 2523-6075
Received: 12-04-2021, Accepted: 28-04-2021, Published: 13-05-2021
Volume 5, Issue 3, 2021, Page No. 43-47

On the Chemistry of Pyridylselenides

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Abstract
Selenium, an ubiquitous metalloid and a third member of the chalcogen group, is currently being considered as a unique essential micronutrient and a fundamental element in biological systems. It replaces sulfur in cysteine and forms the 21st amino acid called selenocysteine. Interesting potential biological properties, namely, antioxidant, antihypertensive, and anticancer exhibited by selenium containing compounds in living beings have been proved to be highly valuable in organic chemistry over the past four decades. Organoselenium compounds, especially those containing nitrogen atoms, are attractive molecules because of their key role in organic synthesis. Consequently, the development of efficient methodologies for the synthesis of nitrogen functionalized organochalcogen compounds is of vital significance in the field of chemical research. Pyridine constitutes an important motif in heterocyclic compounds in the context of nitrogen-functionalized compounds as pyridine derivatives have numerous applications in the realm of bioactive molecules. Consequently, a galaxy of methods for the preparation of dipyridyl selenides/ dipyridyl diselenide has been well documented.

Keywords: Selenide, pyridyl, chalcogen, organodiselenide

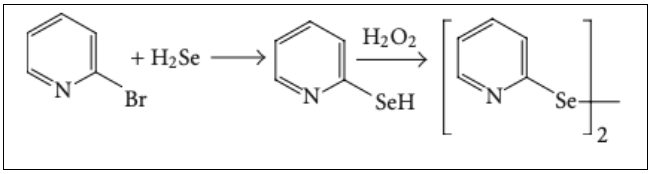
Introduction

Pyridylselenium compounds, apart from their usefulness in organic synthesis [1, 2], find wide applications in biochemistry [3, 7]. Recently, it has been shown that 2,2'-dipyridyldiselenide is a potential immuno-stimulant and inducer of gamma interferon and other cytokines in human peripheral blood leukocytes. It has also been suggested that organoselenium compounds containing Se–N non-bonded interaction exhibit strong GPx antioxidant activity[5]. However, the major breakthrough in this field came with the observation that 5-ethyl-6-pyridylthio/seleno acyclouracils are active against HIV-1 [1, 5].

Pyridylselenium compounds serve as important ligands that contain a set of nitrogen/selenium donor atoms and, therefore, can provide insight into the competitive coordination behavior between hard and soft Lewis bases towards the same metal center [8, 14]. It is also conceivable that complexes of this type with platinum centers could be used as cytostatic drugs and as a single-source precursor for metal organic chemical vapour deposition [15, 17].

In continuation of our studies [18, 19], this review article summarises advancements in synthesizing pyridylselenides by various methods.

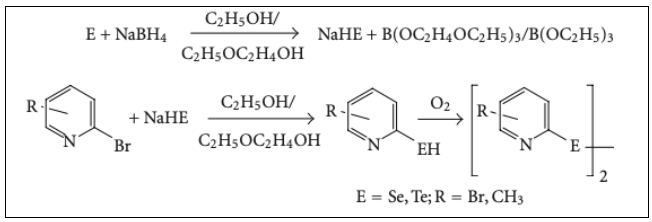
Mautner[20] *et al* were the first to prepare *bis*(2-pyridyl) diselenide by reacting 2-bromo pyridine with toxic hydrogen selenide (Scheme 1).



Scheme 1: Preparation of dipyridyldiselenide

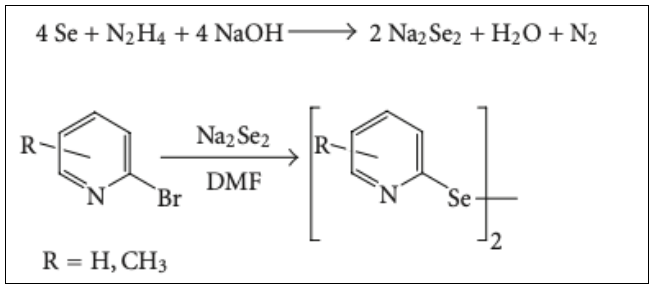
Toshimitsu [21, 2] *et al* modified this synthesis circumventing the use of toxic hydrogen selenide by using sodium hydrogen selenide obtained by the reacting elemental selenium with sodium borohydride in 2-ethoxyethanol.

Bhasin [18] *et al* have optimized the use of this reagent for the synthesis of various substituted methyl and bromopyridyl selenium compounds (Scheme 2).



Scheme 2: Preparation of substituted dipyridyldiselenide

Various methyl substituted 2-pyridyl diselenides were synthesized [23] using a mild and easily available reducing agent, hydrazine hydrate (Scheme 3).

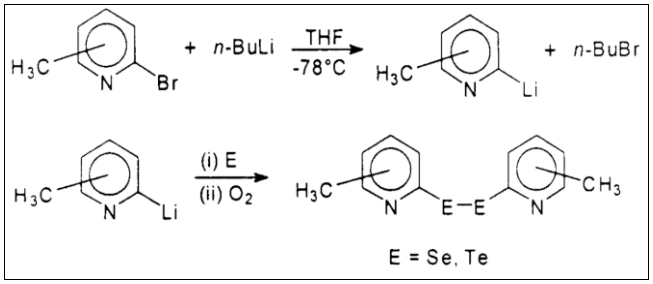


Scheme 3: Preparation of methyl substituted dipyridyldiselenide

These reactions when carried out in the presence of phase-transfer catalyst *viz*. polyethleneglycol-400 and tetrabutylammonium bromide, in an effort to improve the efficiency of the reaction, marginally increases the yields of the reactions. It, therefore, appears that the phase-transfer catalyst may not be involved in the production of the selenolate anion and only catalyzes the substitution reaction with various halomethanes. As part of studies, the solvent effect on the efficiencies of these reactions employing

treaction in various solvents was in the following order: benzene/THF/ pentane/hexane.

Engman and Cava [24] prepared *bis*(2-pyridyl) ditelluride through lithium bromine exchange of 2-bromo- pyridine using sterically hindered and highly reactive *t*-butyl lithium at -78◦C in THF. The preparation of methyl substituted *bis*(2-pyridyl) diselenides and ditellurides were extended by Bhasin [25] *et al* using metal-halogen exchange of methyl-substituted bromopyridines using *n*-butyl lithium (Scheme 4).

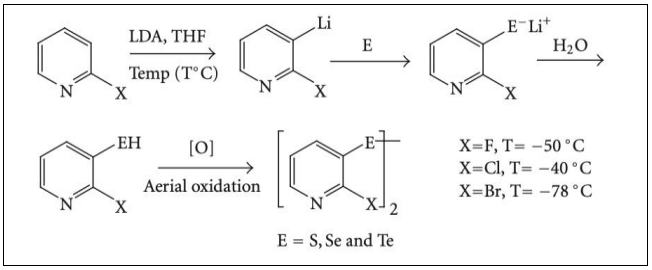


Scheme 4: Synthesis of methyl substituted dipyridyl dichalcogenides

Heteroatom-directed aromatic lithiation is a versatile route towards the synthesis of π-deficient heterocycles [26]. The presence of C−X bond in 2-halopyridines, apart from allowing easy and selective metalation at *ortho*-position, makes it potentially reactive towards nucleophiles, allowing the introduction of other functional groups. Metalation at *ortho*- position is facilitated owing to the *ortho*-directing ability of halogen substituent, particularly fluorine and chlorine. Such an intermediate is potentially reactive towards electrophilic selenium and tellurium metals. Therefore, design of new methods allowing metalation of 2-halopyridine for chalco- gen incorporation with the retention of C-X bond could be of great synthetic value.

Among the various organolithium reagents, LDA has been known to bring about selective deprotonation as it is a nonnucleophilic base and does not lead to metal-halogen exchange reactions in halogenopyridines, which occur with *n*-butyl lithium.

In an effort to achieve the synthesis of target compounds, the deprotonation of 2-halopyridines [27] (X= F, Cl, Br) was carried out under cryogenic conditions in THF using LDA as base. The intermediate, 3-lithio-2-haolpyridine, generated *in situ* was reacted with elemental chalcogen (S, Se, and Te) at low temperature. The insertion of chalcogen atom into C-Li bond took place readily resulting in the formation of 2-halo-3-pyridylchalcogenolate (Scheme 5). It was found that sulfur and selenium undergo smooth insertion into the C-Li bond while tellurium takes time to undergo insertion. This is possibly due to the metallic character and passive nature of this element. The resulting solution of 2-halo-3-pyridylchalcogenolate was subsequently subjected to hydrolysis. The oxidative coupling of resulting selenols affords the desired *bis*(2-halo-3-pyridyl) diselenide in good yield.

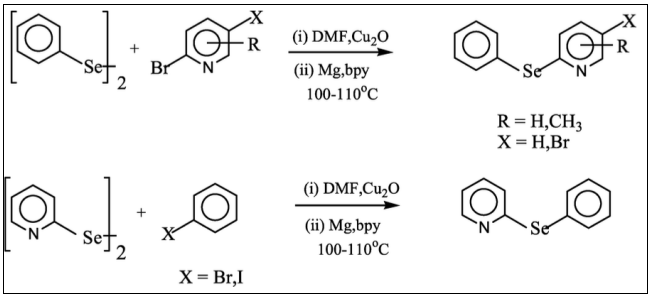


Scheme 5: Regioselective synthesis of bis(2-halo-3-pyridyl) dichalcogenides

Simple aerial oxidation was sufficient to obtain diselenides. In order to ascertain the applicability of this protocol for the synthesis of various 2-halo-3-pyridyl chalcogenides, a series of reactions was set up. The results obtained revealed that the methodology was best applicable to chloro and fluoro derivatives. The yield was lowered to less than half in case of bromoderivatives.

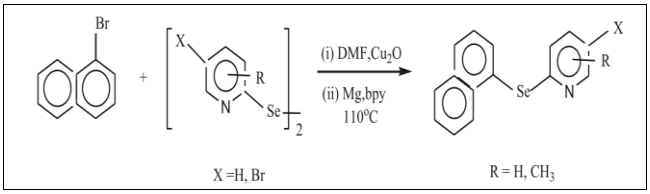
Pyridyl monoselenides display a unique competitive coordination behavior [28, 29] owing to the mixed donor characteristics of Se (soft donor) and N (hard donor) of the pyridine ring towards the same metal atom, in addition to their usefulness in biological systems [30].

In pursuance of this work on the synthesis of dipyridyl diselenides, a convenient, operationally simple, and facile synthetic route for the synthesis of hitherto unknown substituted and unsubstituted pyridyl phenyl selenides is being reported [31]. The method involves the reductive cleavage of dipyridyl/diphenyl diselenides in DMF at 110◦-120◦C using the catalyzed system Cu_2O/Mg/bpy. The intermediate selenolate anion generated in situ by the slow addition of dipyridyl/diphenyl diselenides to the heterogenous system was followed by quenching with different electrophiles as depicted in Scheme 6.

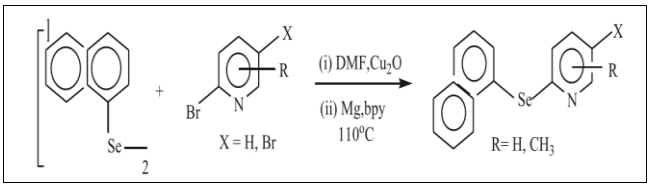


Scheme 6: Synthesis of unsymmetric pyridyl phenyl selenides

Dinaphthyl diselenides were reported to possess antioxidant activity in different *in vitro* and *in vivo* models, showed inhabitance toward Fe (II) - induced lipid peroxidation, catalytically decomposed hydrogen peroxide and oxidized thiols, such as dithiothreitol, cysteine, dimercaptopropionic acid, and thiophenol [32]. Thus, due to their recognized biological activities, there is a continued interest in the synthesis of functionalized pyridines and their derivatives and it is likely that the pyridyl naphthyl selenides might be of high potential and interest. In the light of our previous results on the synthetic studies for organoselenium compounds [31], we reported a mild, more convenient, and efficient protocol for the synthesis of unsymmetrical 2-pyridyl/4-aryl 1-naphthyl selenides (Scheme 7) [33].

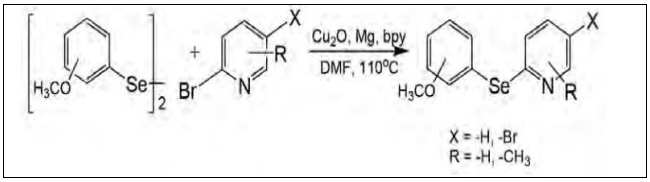


Scheme 7: Synthesis of unsymmetric pyridyl naphthyl selenides (Route 1)

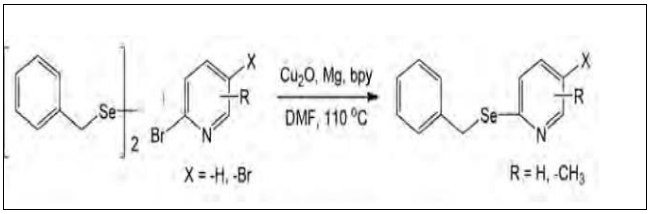


Scheme 8: Synthesis of unsymmetric pyridyl naphthyl selenides (Route 2)

In addition to this, selenation of 2-pyridyl halide with substituted and unsubstituted dianisyl diselenides under similar conditions afforded 2-pyridyl anisyl selenides [34] in good yields [scheme 9].

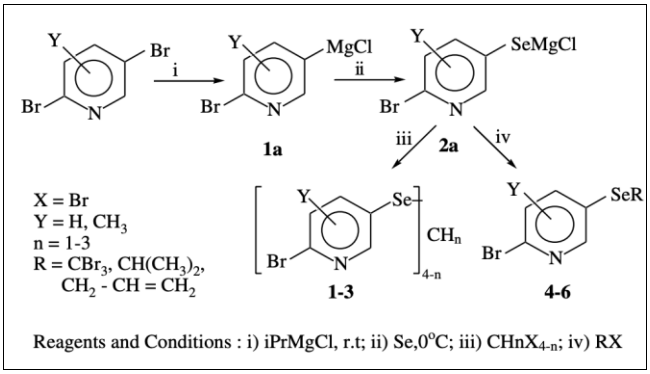


Scheme 9: Synthesis of substituted and unsubstituted pyridyl anisyl selenides



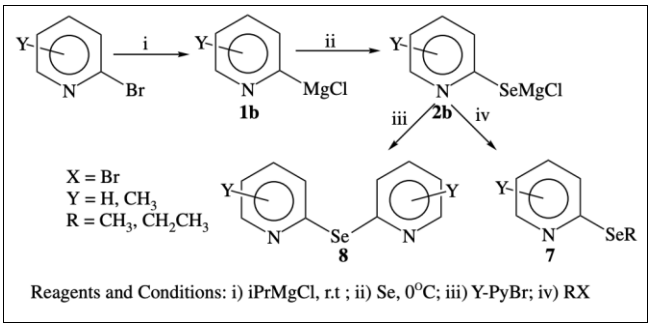
Scheme 10: Synthesis of substituted and unsubstituted pyridyl benzyl selenides

One-pot synthesis of various unsymmetrical 2-bromo-5-pyridylselenium compounds has been carried out under non-cryogenic conditions by selective single bromine-magnesium exchange of 2,5-dibromopyridine using isopropylmagnesium chloride [35]. This exchange gives 2-bromo-5- pyridylmagnesium chloride, which upon the insertion of elemental selenium followed by the treatment with alkyl halide gives the title compounds in good yield. This exchange has also been extended towards bromine–magnesium exchange of 2-bromopyridine for the improved synthesis of 2-pyridylselenium compounds.



Scheme 11: Preparation of 2-bromo-5 selenopyridylmethanes/alkanes

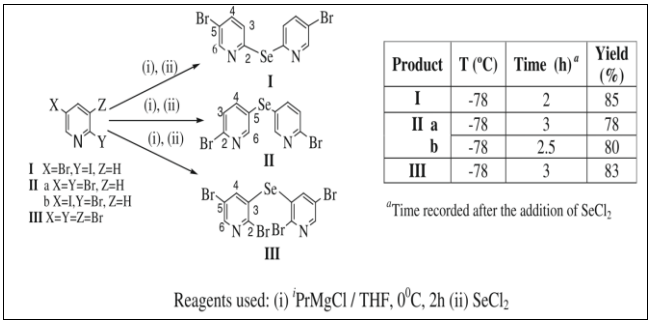
Various methyl-substituted 2-bromopyridines undergo bromine–magnesium exchange upon reaction with an equimolar quantity of isopropylmagnesium chloride to give a wine-red solution containing species 1b, as shown in Scheme 11. This species is fairly stable at room temperature under nitrogen for a long time. In situ addition of elemental selenium to this species changes the color of the solution to yellow due to the presence of species 2b. When all selenium has dissolved, equimolar quantities of alkylhalide or bromopyridine are added to obtain alkylpyridylselenide or dipyridylselenide respectively, in excellent yields at room temperature. This reaction of bromine-magnesium exchange is sensitive to high temperature and moisture. As the temperature exceeds room temperature the yield of these compounds reduces drastically due to the formation of coupled products.



Scheme 12: Preparation of unsymmetrical 2-pyridylselenium compounds

Metal-halogen exchange route has been used to introduce electrophilic selenium into phenyl systems[36] that affords the symmetrical diphenyl monoselenides in good yields. Curiously, this methodology remained untouched for the pyridyl systems to synthesize the symmetrical pyridyl monoselenides.

Bhasin [35] *et al* reported direct selenylation of the pyridine ring using selenyl chloride, $SeCl_2$ as compared to the existing procedures that employ multiple steps involving the preparation of diselenide, its cleavage to selenolate ion followed by arylation[37-40].

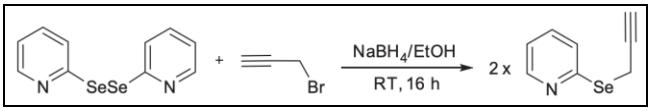


Product	T (°C)	Time (h)[a]	Yield (%)
I	-78	2	85
II a	-78	3	78
b	-78	2.5	80
III	-78	3	83

[a]Time recorded after the addition of $SeCl_2$

Scheme 13: Preparation of monoselenides I, II and III

Regio- and stereoselective syntheses of novel unsaturated chalcogen-containing pyridine derivatives have been developed using the previously unknown electrophilic and nucleophilic reactions of 2-pyridinechalcogenolate anions by Bhasin *et al* [41]. The selective formation of product indicates that the reaction proceeded as a 1,3-nucleophilic substitution rather than a 1,1-nucleophilic substitution (Scheme 14).



Scheme 14: Preparation of propargyl 2-pyridinyl selenide[41]

Conclusion: During the past decade significant progress has been made in the development of novel methods for the synthesis of pyridyl selenides. A number of hitherto unknown structures of pyridylselenides with unique biological properties and low toxicity were reported. On the basis of these findings, this review gives ample and updated information on the different methodologies for the synthesis of pyridyl selenides.

Acknowledgement: Thanks to my Ph.D. mentor KK Bhasin and SK Mehta at Panjab University Chandigarh for introducing me to this frontier area of Organochalcogen Chemistry

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