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Pyridine-4-Selenenyl Bromides as New Reagents for Selenenylation of Olefins

Bogdan Boduszek and Roman Gancarz

Wrocław (Poland), Institute of Organic Chemistry, Biochemistry and Biotechnology, Technical University

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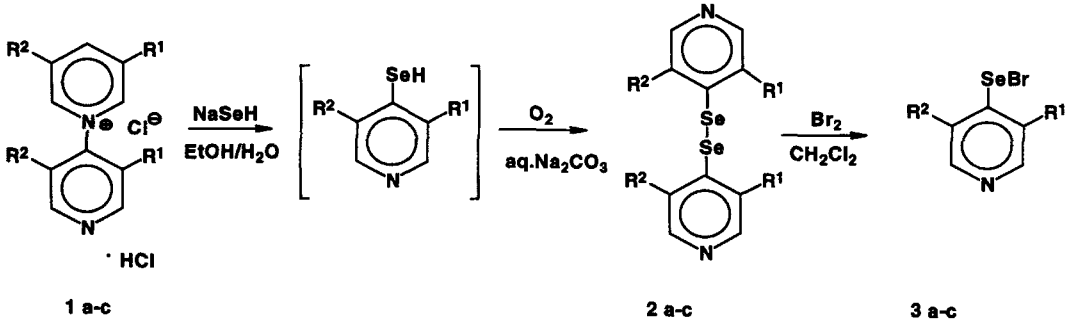
The usefulness of some organoselenium compounds for the formation a carbon-carbon double bond by selenenylation and subsequent oxidative elimination reactions is well established in organic synthesis [1–5]. The selenium compounds used widely for these reactions are mainly phenylselenenyl halides, or diphenyl diselenides combined with equimolar amount of bromine.Some years ago TOSHIMITSU and others [6] introduced a new selenylation agent; pyridine-2-selenenyl bromide, which turned out to be more effective than previously used phenylselenenyl bromide. The authors demonstrated that the pyridine-2-selenenyl group is a better leaving group than the phenylselenenyl one in the oxidative elimination reaction of the corresponding 2-methoxyalkyl selenides [7]. An additional advantage of using pyridine-2-selenenyl bromide is the lack of odor in the case of pyridine compound, therefore it is easy to handle.

Lately, in our laboratory we have synthesized three new 4,4'-dipyridyl diselenides and the corresponding selenenyl bromides. An opportunity appeared to check the reactivity of new synthesized pyridine-4-selenenyl bromides toward olefins and subsequent selenoxide elimination reactions. The 1-(4-pyridyl)-pyridinium chlorides (**1**) are very reactive toward nucleophilic agents and easily form corresponding 4-pyridyl derivatives [8,9]. For example, the pyridinium salts **1** react with thiols or thiourea to yield the corresponding 4-pyridyl sulfides [8,9], or disulfides [10]. The selenium nucleophiles being more powerful nucleophiles than the sulfur ones, react with the salts **1** even at room temperature to form di(4-pyridyl)selenides [11]. The formation of the sulfides or selenides was achieved when the molar ratio of pyridinium salt and the corresponding nucleophilic agent was 2:1 [9, 11]. When the molar ratio of the sulfur reagents was 1:1, the corresponding thiols were main products, which were oxidized *in situ* to the disulfides [10]. That observation became the basis for the synthesis of di(4-pyridyl) diselenides from pyridinium salts and sodium hydrogenselenide. When the ethanolic solution of NaHSe (prepared *in situ*) was mixed with an aqueous solution of 1-(4-pyridyl)-pyridinium salt **1**in equimolar proportions, the corresponding selenols were formed, which were oxidized *in situ* by air to the diselenides **2**. The diselenides **2** such obtained, were stable, crystalline yellow products, completely odorless at room temperature. When diselenides **2** in dichloromethane solution were treated with an equimolar amount of bromine, the corresponding pyridine-4-selenenyl bromides **3** were formed instantly, separating out from reaction mixture (scheme 1). The selenenyl bromides (**3**) were also stable, odorless, yellow crystalline compounds. The structures of diselenides **2** and selenenyl bromides **3** were confirmed by means of ^{1}H-NMR, M.S. spectra, and elemental analyses.



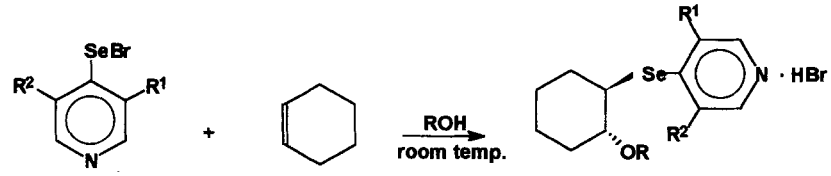
1 a-c **2 a-c** **3 a-c**

Scheme 1

The selenenylation ability of selenenyl bromides **3** to olefins was examined toward cyclohexene as a model compound. After having added cyclohexene to a suspension of pyridine-4-selenenyl bromide **3a** in methanol, the bromide **3a** disappeared, and after short time clear, a pale yellow solution was formed. The product, *trans*-2-methoxycyclohexyl-4-py-

ridyl selenide (**4a**), was isolated as crystalline hydrobromide, after adding an excess of diethyl ether and refrigeration. When the reaction was carried out in ethanol the corresponding *trans*-2-ethoxycyclohexyl-4-pyridyl selenide was formed as hydrobromide (**4'a**). The selenenyl bromides **3b** and **3c** reacted similarly, forming the products **4'b** and **4'c** in high yields.

The addition reaction of the bromides **3** to cyclohexene proceeded smoothly, likewise as in the case of previous used pyridine-2-selenenyl bromide [7]. On the other hand, the use of pyridine-4-selenyl bromides has some advantage in comparison to pyridine-2-selenenyl bromide. The major difference is, that in this case the crystalline hydrobromides of the selenides **4** can be isolated. This simplifies the isolation of the products and makes the experimental work-up much easier. Also, the facile preparation of 4,4'-dipyridyl diselenides, (as precursors of the bromides **3**) is an additional advantage in comparison to the 2-pyridyl derivative, which is not easy available [7].



3a-c

4a: R = Me
4'a: R = Et

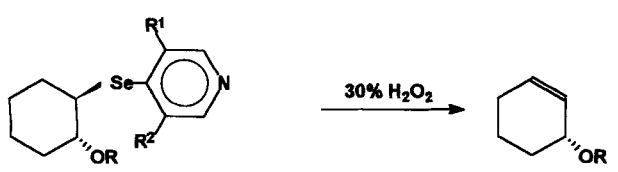
Scheme 2

The evidence for the *trans*-addition products **4** comes from the ^{1}H-NMR spectra of the obtained compounds. For the *trans* addition product one should expect that in the preferred conformation both bulky substituents (OCH_3, and SePh) are in equatorial positions whereas both protons occupy axial positions. This should be manifested by a relatively large coupling constant. Indeed, in the compound **4a** the coupling constant is 11.1 Hz, which is appropriate to the expected value.

The oxidative elimination of the selenyl group from 2-methoxycyclohexyl-4-pyridyl selenides was briefly tested with compounds **4a** (R=Me) and **4'a** (R=Et). The chloroform solution of the chosen compound was treated with two equivalents of 30% queous hydrogen peroxide, at room temperature. The oxidation process proceeded smoothly, as in the case of the pyridine-2-derivative [7], with elimination of the pyridine-4-selenoxy group, and almost exclusive formation of 3-alkoxycyclohexene . The product (3-methoxycyclohexene or 3-ethoxycyclohexene) was identified by G.C.-M.S. analysis and ^{1}H-NMR spectra. Its regioisomer (1-methoxy or 1-ethoxycyclohexene) was detected by G.C.-M.S. analysis in amounts less than 5%.

The ^{1}H-NMR spectrum of the **5a** (3-methoxycyclohexene) confirmed this structure. The proof for the elimination towards 3-methoxycyclohexene was obtained from the NMR studies. There are two olefin protons at 5.84 and 5.76 ppm, coupled together with a coupling constant 10.19 Hz (as expected for such compound). For 1-methoxycyclohexene only one olefinic proton should be observed.

In conclusion, the new obtained pyridine-4-selenenyl bromides can be applied successfully for selenenylation of cyclohexene. The usefulness of these compounds seems to be very attractive, surpassing considerably the previously used phenylseleno derivatives.



4a: R = Me
4'a: R = Et

5a: R = Me
5'a: R = Et

Scheme 3

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Experimental

G.C.-M.S. analyses were carried out with a Helwett Packard HP5971A apparatus, equipped with HP-1, 25m capillary column. Mass spectra were recorded with a Lkb-2091 (EI, 15 eV) apparatus and with a Finnigan NAT-95 (FAB spectra) mass spectrometer. ^{1}H-NMR spectra were recorded on a Bruker Avance TM DRX 300 MHz spectrometer, and also on a Tesla BS 587A 80 MHz apparatus in $CDCl_3$ or D_2O solutions. Melting points were determined with the Digital Melting Point Apparatus Electrothermal 9200, and are uncorrected. Elemental analyses were performed in the Laboratory of Instrumental Analysis in this department.

All commercially available chemicals were used as received from the suppliers. The 1-(4-pyridyl)-pyridinium chlorides were prepared according to the literature method [8, 9]. Sodium hydrogenselenide (NaHSe) was prepared *in situ*, from elemental selenium and sodium borohydride in ethanol [12].

Preparation of 4,4'-dipyridyl diselenides (2a-c)

To a suspension of selenium powder (4.0 g, 50 mmol) in abs. ethanol (100 ml) sodium borohydride (2.3 g, 60 mmol) was added, in small portions during a 20 min. period, under ice cooling. Then 1-(4-pyridyl)-pyridinium chloride (**1a-c**) (50

mmol) dissolved in water (50 ml) was added to the resulting pale brown ethanolic solution of NaHSe. The mixture was allowed to stand for 6–7 h at room temp., and then evaporated *in vacuo* to a small volume (50 ml). The remaining mixture was made alkaline by adding an aqueous solution of sodium carbonate (15 g, 150 mmol, in 100 ml water), and extracted with toluene (100 ml). The toluene extract (containing pyridine bases, some by-products, and 4-pyridyl selenides [11]) was set aside, the remaining aqueous layer was filtered, and air was bubbled into the filtrate for several hours (usually 8 h). The diselenides (**2a-c**) separated as solids from the solution and were collected by filtration, washed with water and dried. The products **2** were obtained as yellow, crystalline solids, enough pure for next steps, but they can be additionally purified by recrystallization from a mixture of THF and toluene.

2a: m.p. 115–117 °C ([8]: 113–114 °C). Yield 48 %. – ^{1}H-NMR ($CDCl_3$ δ, ppm) 8.44 (d, 4H, J=6Hz), 7.49(d, 4H, J=6Hz). – MS [(M+ 1)$^+$] (m/e)% 316 (100, molecular ion for the ^{80}Se isotope), 314 (84.4, molecular ion for the ^{78}Se isotope).

2b: m.p. 115–118 °C. Yield 61%. – ^{1}H-NMR ($CDCl_3$, δ, ppm) 8.29 (s, 2H), 8.26 (d, 2H J=5.3Hz), 7.45 (d, 2H, J=5.3 Hz), 2.46 (s, 6H, 2×CH_3). – MS [(M+1)$^+$] m/e (%) 344 (100, molecular ion of the ^{80}Se isotope), 342 (86.4 molecular ion of the ^{78}Se sotope).

2c: m.p. 152–156 °C (dec.), Yield 36 %. – ^{1}H-NMR ($CDCl_3$, δ, ppm) 8.26 (s, 4H), 2.16 (s, 12H, 4×CH_3): – MS [(M+1)$^+$] (m/e)% 372 (81, molecular ion of the ^{80}Se isotope), 370 (71.2, molecular ion of the ^{78}Se isotope)

Preparation of pyridine-4-selenenyl bromides (3a-c)

To a solution of diselenide (**2a-c**) (10 mmol) in dichloromethane (80 ml) was added dropwise a solution of bromine (1.6 g, 10 mmol), with stirring. Immediately, a yellow precipitate was formed. The mixture was stirred additionally for 0.5 h, and the product **3a-c** was collected by filtration, washed with a small amount of dichloromethane and dried. The obtained products **3** are yellow powders, practically pure and used directly to the next step.

3a: m.p. 135-138 °C (dec.).Yield 95% (calculated on the basis of the corresponding diselenide **2**). – ^{1}H-NMR (in D_2O, δ, ppm) 8.40 (d, 2H J=6.6 Hz) 8.19 (d, 2H J=6.6 Hz).

C_5H_4NSeBr (236.97) Calcd.: C 25.3 H 1.70 N 5.91 Br 33.7; Found: C 25.1 H 2.09 N 5.58 Br 33.5.

3b: m.p. >160 °C (dec.).Yield 84% (calculated on the basis of corresponding diselenide **2**). – ^{1}H-NMR (in D_2O, δ, ppm) 8.3–8.00 (m, 3H), 2.57 (s, 3H, CH_3).

C_6H_6NSeBr (250.99) Calcd.: C 28.7 H 2.41 N 5.58 Br 31.8
Found: C 29.0 H 2.89 N 5.48 Br 31.3

3c m.p. >140 °C (dec.), Yield 82% (calculated on the basis of corresponding diselenide **2**). – ^{1}H-NMR (in D_2O, d, ppm) 8.40 (b s, 2H), 2.38s,H, 2×CH_3).

C_7H_8NSeBr (266.92) Calcd.: C 31.7 H 3.04 N 5.29 Br 30.2
Found: C 31.7 H 3.50 N 5.26 Br 29.8

Preparation of trans-2-alkoxycyclohexyl-4-pyridyl selenides (4a) and (4'a-c)

To a stirred suspension of selenenyl bromide (**3a-c**) (1.0 mmol) in methanol (or ethanol) (10 ml) pure cyclohexene (0.10 g, 1.2 mmol) was added. The precipitate disappeared gradually, and after short time a clear, pale yellow solution was formed. The solution was stirred for 3-4 h at room temp. and the solvent evaporated *in vacuo* to a small volume (about 1 ml), and diluted with diethyl ether (10 ml).After refrigeration, a yellow crystalline product precipitated, which was collected by filtration, washed with ether and dried.

Trans-2-methoxycyclohexyl-4-pyridyl selenide, hydrobromide (**4a**)

Yield: 61%, m.p. 210-215 °C (dec.)
^{1}H-NMR (D_2O, δ, ppm): 8,20 (d,1H, 2-py, J=6.8 Hz), 8.19 (d, 1H, 2-py, J=7.0 Hz), 7.93 (d, 1H, 3-py, J=6.8 Hz), 7.91(d, 1H, 3-py, J=7.0 Hz), 3.68 (ddd, 1H, J=11.1, 7.6 and 3.7 Hz), 3.59 (ddd, 1H, J=11.1, 10.0 and 4.1 Hz), 3.20 (s, 3H, CH_3), 2.15–1.15 (m, 8H, cyclohexyl protons).
$C_{12}H_{18}NOSeBr$ (351.15) Calcd.: C 41.0, H 5.17, N 3.99. Found: C 40.8, H 5.54, N 3.82.

The free base **4a** was obtained by treatment of the hydrobromide (0.175 g., 0.5 mmol) with 10% aqueous sodium carbonate solution (10 ml), and extraction of the selenide with chloroform (20 ml). The extract was dried ($MgSO_4$), filtered and evaporated *in vacuo* to leave a yellow oil (0.13 g). The product was additionally purified by preparative on TLC plates (silicagel, chloroform-acetone 9:1 as eluant).
^{1}H-NMR ($CDCl_3$, δ, ppm): 8.34 (d, 2H, J=4.5 Hz), 7.40 (d, 2 H, J=4.5 Hz), 3.33 (s,3 H, CH_3), 3.46–3.16 (m, 2 H), 2.17—1.23 (m, 8H, cyclohexyl protons).
M.S. m/e (%): 271 (M+1)$^+$ (13.2), 269 (6.3), 160 (1.5), 159 (1.5), 158 (4.4), 157 (1.7), 156 (2.5), 131 (4.1), 113 (13.5), 81(56.3),79 (10.8), 71(11.6), 51(9.5).

Trans-2-ethoxycyclohexyl-4-pyridyl selenide, hydrobromide (**4'a**)

Yield: 79%, m.p. > 110 °C.(dec.).
^{1}H-NMR (D_2O, δ, ppm) 8.25 (d, 2H, 2-py), 7.99 (d, 2H, 3-py), 3.9–3.1 (m, 4H, CH_2O, CHO, CHSe), 2.3–1.0 (m, 8H, cyclohexyl protons), 0.87 (t, 3H, CH_3).
The free base **4'a** was obtained from the hydrobromide as described above. The selenide **4'a** was a yellow oil.
^{1}H-NMR ($CDCl_3$, δ, ppm): 8.35 (d,2H, 2-py), 7.48 (d, 2 H, 3-py), 3.66–3.26(m, 4H, CH_2O, CHO, CHSe), 2.14–1.19 (m,8H, cyclohexyl protons).
M.S m/e (%): 285(M+1)$^+$ (3.6), 283 (1.8), 159 (1.2), 127 (4.3), 99 (2.9), 81(26.4), 79 (4.2), 57 (3.9).

Trans-*2-ethoxycyclohexyl-4[(3-methyl)-pyridyl]sel- enide hydrobromide* (**4'b**)

Yield: 56%, m.p. 185–190 °C.(dec).
^{1}H-NMR (D_2O) δ, ppm): 8.50–7.94 (m, 3H, 2-py and 3-py), 3.80–3.10 (m, 4H, CH_2O, CHO, CHSe), 2.61 (s,3H, CH_3), 2.4–1.0 (m, 8H, cyclohex. protons), 0.91(t, 3H, CH_3).
M.S (FAB) m/e (%): 300(M+1–Br)$^+$ (100).

Trans-2-ethoxycyclohexyl-4-[(3,5-dimethyl)-pyridyl] selenide hydrobromide (**4'c**)

Yield: 86%,. m.p. 162-166 °C. (dec.)
^{1}H-NMR (D_2O, δ, ppm): 8.31(s, 2H, 2-py), 3.80–3.00 (m,

4H, CH_2O, CHO, CHSe), 2.52(s, 6H, 2×CH_3), 2.4–0.9 (m, 8H, cyclohexyl protons), 0.84 (t,3H, CH_3).
M.S. (FAB): m/e (%): 314 $(M+1-Br)^+$ (100%).

Oxidative eliminations of selenides (4a) or (4'a)
3-Methoxycyclohexene (**5a**) *or 3-Ethoxycyclohexene* (**5'a**):

To a solution of selenide **4a** (R =Me) (free base), or **4'a** (R = Et) (free base) (1.0 mmol) in deuterated chloroform (5 ml), was added 30% aqueous hydrogen peroxide (0.225 g, 2.0 mmol), and the mixture was stirred at room temp. for 2 h.Then aqueous 10% sodium carbonate (5 ml) was added and the mixture was stirred for an additional 1 h. The organic layer was separated, dried over $MgSO_4$, filtered and analysed by means of G.C.-M.S. and ^{1}H-NMR spectra.
5a:
^{1}H-NMR ($CDCl_3$, δ, ppm): Two olefinic protons were found: 5.84 (dtd, 1H, J= 10.19, 3.42 and 1.81 Hz) and 5.76 (ddt, 1H, J= 10.19, 2.67 and 1.10 Hz). Additional protons: 3.41(m, 1H), 3.35 (s, 3H, CH_3), 2.4–1.1(m, 6H, cyclohexyl).
The G.C.-M.S. analysis of the chloroform extract showed the presence of *3-methoxycyclohexene* (92%) (M. wt.=112) and also some 1-methoxycyclohexene (4.5%) (M.wt.=112).
5'a:
The G.C.-M.S. analysis of the chloroform extract showed the presence of *3-ethoxycyclohexene* (91%) (M.wt. =126).
^{1}H-NMR ($CDCl_3$, δ, ppm): 5.79 (m, 2H, olefin.), 3.67–3.40 (m, 3H,), 2.2–1.2 (m, 6H) 1.09 (t, 3H, CH_3).

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Address for correspondence:
Dr. B. Boduszek
Technical University of Wrocław
Institute of Organic Chemistry, Biochemistry and Biotechnology
Wyb. Wyspianskiego 27
50-370 Wrocław, Poland