Reactions of Selenium Dihalides with Vinylbenzenes

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Abstract—Alkoxyselenation of vinylbenzenes with selenium dihalides was accomplished for the first time. The reaction with selenium dibromide was the most efficient. Selenium dibromide reacted with vinylbenzene and 1-chloro-4-(prop-1-en-2-yl)benzene in chloroform or methylene chloride in the presence of methanol or ethanol to give the corresponding Markovnikov adducts, bis(2-alkoxy-2-phenylethyl) selenides and bis[2-alkoxy-2-(4-chlorophenyl)propyl] selenides in 82–95% yield with high regioselectivity. Bis(2-halo-2-phenyl-ethyl) selenides can be obtained at low temperature (–60°C).

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Functionalized organoselenium compounds exhibit high biological activity [1, 2]. Development of efficient methods for the preparation of practically important organoselenium compounds is a topical problem.

In recent years, researchers in many countries have been interested in selenium dihalides as new efficient reagents for the synthesis of organoselenium compounds [3–10]. Selenium dihalides are capable of adding in regio- and stereoselective fashion to compounds possessing double or triple bonds [3–10]. The addition of selenium dihalides to C=C double bond with an electron-donating substituent (alkyl or alkoxy group) is regioselective, and the corresponding Markovnikov adducts are formed [6, 7]. Alkenes with electron-withdrawing substituents, such as methyl vinyl ketone, acrylic acid and its esters, and acrylonitrile, react with selenium dihalides to give mainly anti-Markovnikov adducts [8, 9].

Addition of selenium dihalides to vinylbenzene has not been reported previously. According to Migalina et al. [11], reactions of selenium tetrahalides with vinylbenzene lead to the formation of double bond halogenation products, whereas no addition products were detected. Reactions of selenium dihalides with phenyl vinyl ether and vinyl benzene afforded mainly double bond halogenation products [6].

In this work we studied the addition of selenium dihalides to vinylbenzenes. The reactions of selenium dichloride and dibromide with vinylbenzene at room temperature in chloroform, methylene chloride, or carbon tetrachloride gave 1,2-dihaloethylbenzenes 1 and 2 and were accompanied by precipitation of elemental selenium from the reaction mixture (Scheme 1).



In the reactions of selenium dichloride and dibromide with vinylbenzene at reduced temperature (at -78° C in methylene chloride or at -60° C in chloroform) we succeeded in obtaining the addition products, bis(2-halo-2-phenylethyl) selenides **3** and **4** together with halogenation products **1** and **2** (Scheme 2). The yield of selenide **3** was 40%, whereas selenide **4** was the major product (75%). We failed to isolate pure compounds **3** and **4** by column chromatography on silica gel or aluminum oxide, since they slowly decomposed in solution at room temperature with formation of a poorly soluble solid.

Molecules **3** and **4** possess both electrophilic group (CHCl or CHBr) and nucleophilic center (selenium atom). It may be presumed that the halogen atom in **3** or **4** is highly reactive due to strong anchimeric effect of the selenium atom [10] and activation by the phenyl



group; therefore, compounds 3 and 4 are capable of undergoing intermolecular nucleophilic substitution where the selenium atom of another molecule acts as nucleophile. As a result, the corresponding selenonium salts are formed.

Unlike the addition reactions, alkoxyselenation of vinylbenzene and 1-chloro-4-(prop-1-en-2-yl)benzene with selenium dihalides in chloroform (or methylene chloride) in the presence of methanol or ethanol was selective (Scheme 3). Methoxyselenation was the most efficient when selenium dibromide was used, the chloroform-methanol ratio being 3:1. To achieve a high yield and chemoselectivity, it is advisable to carry out the reaction at reduced temperature $(-20^{\circ}C)$. The yields of alkoxyselenation products 5 and 6 from vinylbenzene were 82-83%; bis[2-alkoxy-2-(4-chlorophenyl)propyl] selenides 7 and 8 were formed from 1-chloro-4-(prop-1-en-2-yl)benzene in almost quantitative yield (93-95%).



7, R = Me, Ar = 4-ClC₆H₄, Alk = Me; 8, R = Me, Ar = 4-ClC₆H₄, Alk = Et; X = Cl, Br.

The alkoxyselenation with selenium dichloride was less selective, and the yield of compounds 5-8 was lower (53-72%) than in the reactions with selenium dibromide. Unlike compounds 5-7, selenide 8 turned out to be unstable, and it slowly decomposed on storage at room temperature with formation of an insoluble solid.

The structure of compounds 3-8 was confirmed by ¹H and ¹³C NMR spectra and elemental analyses (for **5–7**). Compounds **4–6** were also characterized by 77 Se NMR spectra, and the 77 Se $-^{13}$ C coupling constant with

the CH₂ carbon atom was measured in the ¹³C NMR spectra; the value 66-70 Hz corresponded to direct coupling $({}^{1}J_{Se-C})$. Thus, the selenium atom adds to the terminal carbon atom of vinylbenzenes, i.e., Markovnikov adducts are formed in all cases.

Each compound 3-8 was a mixture of two diastereoisomers (*dl* and *meso*) at a ratio of 1:(1-1.2)which were characterized by different signals in the ¹H, ¹³C, and ⁷⁷Se NMR spectra. The CH₂Se and CHX (X = OAlk, Cl) signals in the ¹³C NMR spectra of **3–8** were generally doublets, and each signal belonged to a single diastereoisomer; however, in some cases, signals of two diastereoisomers coincided and appeared as one signal. One diastereoisomer of 5-7 predominated (ratio 1:1.2), and it was possible to reliably assign signals to each diastereoisomer.

In summary, products of addition of selenium dihalides to vinylbenzene have been isolated. Alkoxyselenation of vinylbenzenes with selenium dihalides in the presence of methanol and ethanol has been accomplished for the first time, and previously unknown Markovnikov adducts have been synthesized. On the basis of this reaction, an efficient procedure has been developed for the regioselective synthesis of bis(2-alkoxy-2-phenylethyl) selenides and bis[2-alkoxy-2-(4chlorophenyl)propyl] selenides as promising intermediate products for organic synthesis and potential biologically active compounds.

EXPERIMENTAL

The NMR spectra were recorded on a Bruker DPX-400 spectrometer in CDCl₃ at 400.13 (¹H, HMDS), 100.61 (¹³C, HMDS), and 76.30 MHz (⁷⁷Se, Me₂Se). The elemental analyses were obtained with a Thermo Flash EA1112 analyzer. The solvents used were preliminarily dried and distilled. Selenium dichloride and dibromide were prepared by reactions of elemental selenium with sulfuryl chloride and bromine, respectively [4–10]. Dihaloethylbenzenes 1 and 2 were described previously [11].

Bis(2-chloro-2-phenylethyl) selenide (3). A solution of 0.52 g (5 mmol) of vinylbenzene in 30 mL of

methylene chloride was cooled to -78°C, and a solution of 2.5 mmol of SeCl₂ in 20 mL of methylene chloride, cooled to -78°C, was added dropwise. The mixture was stirred for 30 min and allowed to warm up to room temperature with stirring (2 h). The mixture was filtered, washed with water, and dried over CaCl₂, the solvent was distilled off on a rotary evaporator, and the residue was dried under reduced pressure. Yield of mixture 1/3 0.592 g (48% of 1 and 40% of 3, according to the ¹H NMR data). We failed to isolate compound 3 by silica gel chromatography using hexanecarbon tetrachloride (1:6) as eluent. ¹H NMR spectrum, δ, ppm: 2.74-2.79 m (4H, SeCH₂), 4.49-4.55 m (2H, CHCl), 7.09-7.21 m (10H, Ph). ¹³C NMR spectrum, δ_{C} , ppm: 33.10 and 33.44 (SeCH₂), 61.97 and 62.26 (CHCl), 127.11 (Carom), 127.50 (Carom), 128.29 (Carom), 137.20 (Carom).

Bis(2-bromo-2-phenylethyl) selenide (4). A solution of 0.52 g (5 mmol) of vinylbenzene in 30 mL of methylene chloride was cooled to -78°C, and a solution of 2.5 mmol of SeBr₂ in 40 mL of methylene chloride, cooled to -78°C, was added dropwise. The mixture was stirred for 30 min and allowed to warm up to room temperature with stirring (2 h). The mixture was filtered, washed with water, and dried over CaCl₂, the solvent was distilled off on a rotary evaporator, and the residue was dried under reduced pressure. Yield of mixture 2/4 0.982 g (12% of 2 and 75% of 4, according to the ¹H NMR data). We failed to isolate compound 4 by silica gel chromatography using hexanecarbon tetrachloride (1:6) as eluent. ¹H NMR spectrum, δ, ppm: 3.44–3.54 m (4H, SeCH₂), 4.59–4.63 m (2H, CHBr), 6.78-6.87 m (10H, Ph). ¹³C NMR spectrum, $\delta_{\rm C}$, ppm: 34.89 (SeCH₂, $J_{\rm C-Se}$ = 70 Hz), 50.72 (CHBr), 126.05 (Carom), 127.47 (Carom), 128.51 (Carom), 138.26 (C_{arom}).

Bis(2-methoxy-2-phenylethyl) selenide (5). A solution of 0.52 g (5 mmol) of vinylbenzene in a mixture of 7 mL of methanol and 8 mL of chloroform was cooled to -20° C, 0.42 g (5 mmol) of sodium hydrogen carbonate was added, and a solution of 2.5 mmol of selenium dibromide in 15 mL of chloroform, cooled to -20° C, was added dropwise over a period of 5 min. The mixture was stirred for 2 h at -20° C and for 1 h at room temperature and filtered, the solvent was distilled off on a rotary evaporator, and the residue was dried under reduced pressure. Yield 0.72 g (83%), light yellow oily material. Found, %: C 61.75; H 6.17; Se 22.35. C₁₈H₂₂O₂Se. Calculated, %: C 61.89; H 6.35; Se 22.60.

Major diastereoisomer. ¹H NMR spectrum, δ, ppm: 2.74 d.d and 2.99 d.d (4H, CH₂Se, ${}^{2}J = 12.5$, ${}^{3}J = 7.8$, 5.3 Hz), 3.26 s (6H, OCH₃), 4.32 d.d (2H, CHO, ${}^{3}J = 7.8$, 5.3 Hz), 7.28–7.45 m (10H, H_{arom}). ¹³C NMR spectrum, δ_C, ppm: 31.67 (CH₂Se, ${}^{1}J_{C-Se} = 67.5$ Hz), 56.60 (CH₃O), 84.26 (CHO), 126.50 (C_{arom}), 127.71 (C_{arom}), 128.22 (C_{arom}), 141.05 (C_{arom}). ⁷⁷Se NMR spectrum: δ_{Se} 146.3 ppm.

Minor diastereoisomer. ¹H NMR spectrum, δ , ppm: 2.75 d.d and 2.97 d.d (4H, CH₂Se, ²*J* = 12.5, ³*J* = 8.0, 5.3 Hz), 3.28 s (6H, OCH₃), 4.36 d.d (2H, CHO, ³*J* = 8.0, 5.3 Hz), 7.28–7.45 m (10H, Ph). ¹³C NMR spectrum, $\delta_{\rm C}$, ppm: 31.84 (CH₂Se, ¹*J*_{C-Se} = 66.7 Hz), 56.63 (CH₃O), 84.25 (CHO), 126.44 (C_{arom}), 127.71 (C_{arom}), 128.23 (C_{arom}), 141.07 (C_{arom}). ⁷⁷Se NMR spectrum: $\delta_{\rm Se}$ 146.9 ppm.

Bis(2-ethoxy-2-phenylethyl) selenide (6). Yield 82%, light yellow oily material. Found, %: C 63.37; H 6.89; Se 20.67. $C_{20}H_{26}O_2Se$. Calculated, %: C 63.65; H 6.94; Se 20.92.

Major diastereoisomer. ¹H NMR spectrum, δ, ppm: 1.14 t (6H, CH₃, ${}^{3}J$ = 7.0 Hz), 2.66 d.d and 2.92 d.d (4H, CH₂Se, ${}^{2}J$ = 12.5, ${}^{3}J$ = 8.1, 5.5 Hz), 3.34 q (4H, OCH₂), 4.35 d.d (2H, CHO, ${}^{3}J$ = 8.1, 5.5 Hz), 7.21– 7.33 m (10H, Ph). ¹³C NMR spectrum, δ_C, ppm: 15.22 (CH₃), 31.93 (CH₂Se, ¹J_{C-Se} = 66.5 Hz), 64.36 (CH₂O), 82.60 (CHO), 126.55 (C_{arom}), 127.684 (C_{arom}), 128.28 (C_{arom}), 141.91 (C_{arom}). ⁷⁷Se NMR spectrum: δ_{Se} 148.7 ppm.

Minor diastereoisomer. ¹H NMR spectrum, δ, ppm: 1.16 t (6H, CH₃, ${}^{3}J$ = 6.9 Hz), 2.69 d.d and 2.92 d.d (4H, CH₂Se, ${}^{2}J$ = 12.5, ${}^{3}J$ = 8.1, 5.4 Hz), 3.34 q (4H, OCH₂), 4.39 d.d (2H, CHO, ${}^{3}J$ = 8.1, 5.4 Hz), 7.21–7.33 m (10H, Ph). ¹³C NMR spectrum, δ_C, ppm: 15.24 (CH₃), 32.06 (CH₂Se, ${}^{1}J_{C-Se}$ = 66.5 Hz), 64.38 (CH₂O), 82.52 (CHO), 126.49 (C_{arom}), 127.67 (C_{arom}), 128.30 (C_{arom}), 141.92 (C_{arom}). ⁷⁷Se NMR spectrum: δ_{Se} 148.1 ppm.

Bis[2-(4-chlorophenyl)-2-methoxypropyl] selenide (7). Yield 95%, light yellow oily material. Found, %: C 53.79; H 5.40; Cl 16.86; Se 17.67. $C_{20}H_{24}Cl_2O_2Se$. Calculated, %: C 53.83; H 5.42; Cl 15.89; Se 17.69.

Major diastereoisomer. ¹H NMR spectrum, δ , ppm: 1.57 s (6H, CH₃), 2.60, 2.76 d (4H, CH₂Se, ²*J* = 12.2 Hz), 3.04 s (6H, OCH₃), 7.24 m and 7.29 m (8H, H_{arom}). ¹³C NMR spectrum, δ_{C} , ppm: 22.52 (CH₃), 39.08 (CH₂Se), 50.80 (CH₃O), 78.95 (CO), 127.81 (C_{arom}), 128.25 (C_{arom}), 133.07 (C_{arom}), 142.36 (C_{arom}). ⁷⁷Se NMR spectrum: δ_{Se} 101.6 ppm.

Minor diastereoisomer. ¹H NMR spectrum, δ, ppm: 1.58 s (6H, CH₃), 2.64 d and 2.73 d (4H, CH₂Se, ²*J* = 12.2 Hz), 3.04 s (6H, OCH₃), 7.24 m and 7.29 m (8H, H_{arom}). ¹³C NMR spectrum, $\delta_{\rm C}$, ppm: 22.60 (CH₃), 39.08 (CH₂Se), 50.80 (CH₃O), 78.89 (CO), 127.81 (C_{arom}), 128.25 (C_{arom}), 133.07 (C_{arom}), 142.36 (C_{arom}). ⁷⁷Se NMR spectrum: $\delta_{\rm Se}$ 101.0 ppm.

Bis[2-(4-chlorophenyl)-2-ethoxypropyl] selenide (8). Yield 93%, light yellow oily material. ¹H NMR spectrum, δ , ppm: 1.21 t (6H, CH₃, ³*J* = 7.0 Hz), 1.62 m (6H, CH₃), 3.05, 3.27 d.d (4H, CH₂Se, ²*J* = 12.5, ³*J* = 8.1, 5.5 Hz), 3.63 q (4H, OCH₂), 7.35– 7.52 m (8H, H_{arom}). ¹³C NMR spectrum, $\delta_{\rm C}$, ppm: 18.73 (CH₃), 23.49 (CH₃), 39.61 (CH₂Se), 58.31 (CH₂O), 78.48 (CO), 127.43 (C_{arom}), 128.14 (C_{arom}), 133.26 (C_{arom}), 142.15 (C_{arom}).

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