Research Article

Reaction of Acyl Chlorides with In Situ Formed Zinc Selenolates: Synthesis of Selenoesters versus Ring-Opening Reaction of Tetrahydrofuran

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Attempting to apply the in situ production of PhSeZnSePh to the synthesis of selenoesters, an unexpected reaction involving the solvent (tetrahydrofuran) was observed and studied. We reported here some evidences about the mechanism and the possibility to control the chemoselectivity of this new reaction that afforded the formation of interesting selenoderivatives in which the selenium moiety and the carboxylic one are spaced by four carbon units.

1. Introduction

Given the continuous interest around the synthesis, the reactivity, and the biological properties of organochalcogen compounds and continuing our ongoing studies on the development of new ecofriendly protocols for the selenenylation of organic substrates, we investigated a new strategy for the preparation of selenoesters [1–4].

The incorporation of selenium into organic compounds can be conveniently achieved using nucleophilic reagents such as selenols or selenolates, which can be generated in situ via a reductive cleavage of the Se-Se bond starting from a diselenide. Commonly used protocols for generating selenolates involve the use of several reducing agents, such as NaBH₄, LiAlH₄, and other expensive and often not easily handled metal sources [5–8].

We recently demonstrated that elemental zinc reduces diselenides in acidic biphasic system (aq. 10% HCl/Et₂O) affording in situ a seleno-zinc complex (in equilibrium with the corresponding selenol) that can be conveniently used to effect ring-opening reactions of aziridines [9] and epoxides, as well as nucleophilic substitution [10] and hydroselenylation of alkynes [11] (Scheme 1). The novelty of this protocol is mainly related to the simplicity of the procedure that prevents the typical drawback of using volatile selenols, which has a persistent smell. In this case, the selenol is formed in a closed vial and immediately used for the reaction with the electrophile. We also demonstrated that, in some cases, the water and the organic phase can be recovered after the first reaction and directly reused as medium for further reactions, maintaining good yields for 5–10 cycles. This aspect positively impacts the overall sustainability of the reaction [12].

Starting from diphenyl diselenide, the discoloration of the organic phase is an unequivocal indication of the complete reduction of the Se-Se bond and the formation of the zinc complex that, due to the presence of the hydrochloric acid,
is most reasonably in equilibrium with the corresponding benzeneselenol.

During the attempts to apply this methodology to the synthesis of selenol esters, starting from the corresponding acyl chlorides, in order to avoid the presence of strong hydrolytic conditions, we tested tetrahydrofuran (THF) as solvent and triflic acid as anhydrous acidic catalyst for the reduction. Serendipitously, we discovered that in these conditions the ring-opening reaction of THF was favored. Ring-opening reaction of cyclic tetrahydrofuran is an important synthetic transformation because it affords a functionalized 4-carbon building block that can be used in many synthetic applications including polymer chemistry. In addition, a reaction able to break a carbon-oxygen bond of an ether linkage during the attempts to apply this methodology to the synthesis of seleno-esters in THF was performed on silica gel 60 F254 precoated aluminum foils sheet and visualized by UV irradiation or by iodine staining. Silica gel Kieselgel 60 (70–230 mesh) was used for column chromatography. NMR experiments were conducted at 25°C with a Bruker DPX 200 spectrometer operating at 200 MHz for 1H and 50.31 MHz for 13C, or with a Bruker DRX spectrometer operating at 400 MHz for 1H and 100.62 MHz for 13C experiments.

1H and 13C chemical shifts (δ) are reported in parts per million (ppm), relative to TMS (δ = 0.0 ppm) and the residual solvent peak of CDCl3 (δ = 7.26 and 77.00 ppm in 1H and 13C NMR, resp.). Data are reported as chemical shift (multiplicity, coupling constants where applicable, number of hydrogen atoms, and assignment where possible). Abbreviations are s (singlet), d (doublet), t (triplet), q (quartet), quin (quinet), sex (sexet), dd (doublet of doublet), dt (doublet of triplet), ddt (doublet of doublet of triplet), m (multiplet), and br. s (broad signal). Coupling constant (J) is quoted in hertz (Hz) to the nearest 0.1 Hz. GC-MS analyses were carried out with a HP-6890 gas chromatograph (dimethyl silicone column, 12.5 m) equipped with an HP-5973 mass-selective detector.

2. Materials and Methods

Reactions were conducted in round bottom flasks and were stirred with Teflon-coated magnetic stirring bars. Solvents and reagents were used as received unless otherwise noted. Acyl chlorides 1a, 1d, and 1g were commercially available; acyl chlorides 1b, 1c, 1e, and 1f were synthesized according to the literature [16]. Analytical thin-layer chromatography (TLC) was performed on silica gel 60 F254 precoated aluminum foil sheets and visualized by UV irradiation or by iodine staining. Silica gel Kieselgel 60 (70–230 mesh) was used for column chromatography. NMR measurements were conducted at 25°C with a Bruker DPX 200 spectrometer operating at 200 MHz for 1H and 50.31 MHz for 13C, or with a Bruker DRX spectrometer operating at 400 MHz for 1H and 100.62 MHz for 13C experiments. 1H and 13C nuclear magnetic resonance (NMR) spectroscopy (CDCl3, 200 MHz): δ = 7.96–7.92 (m, 2H, H-Ar), 7.68–7.64 (m, 8H, H-Ar) ppm. 13C-NMR (CDCl3, 50 MHz): δ = 193.5, 138.8, 136.4, 133.9, 129.4, 129.1, 128.9, 127.4, 125.8 ppm. GC-MS spectral analysis.

2.1. General Procedures for the Synthesis of Selenoester in Biphasic Conditions. Diphenyl diselenide (0.637 mmol) was poured into a biphasic system composed of Et2O (2 mL) and HCl (aq. 10%, 2 mL) and zinc pellets (20 eq.) were added. The mixture was vigorously stirred (800 rpm) in a closed vial until discoloration of the organic layer (around 15 min).

Acyl chlorides 1a–g (1.274 mmol) were added and the mixture was stirred at room temperature for 4 h. The organic phase was diluted with EtOAc (2 mL), separated, dried with Na2SO4, and filtered and the solvent was removed under vacuum. The products reported in Table I were purified by flash chromatography on silica gel (PE/EtOAc) and characterized by 1H-NMR and 13C-NMR spectra. Physical and spectroscopic data of selected compounds are reported below.

Se-phenyl benzeneselenoate (2a): 1H-NMR (CDCl3, 200 MHz): δ = 7.96–7.92 (m, 2H, H-Ar), 7.68–7.64 (m, 8H, H-Ar) ppm. 13C-NMR (CDCl3, 50 MHz): δ = 193.5, 138.8, 136.4, 133.9, 129.4, 129.1, 128.9, 127.4, 125.8 ppm. GC-MS: m/z (%) = 262 (1) [M]+, 157 (5), 105 (100), 77 (50), 51 (14).

Se-phenyl 2-bromobenzeneselenoate (2b): 1H-NMR (CDCl3, 200 MHz): δ = 7.72–7.76 (m, 4H, H-Ar), 7.45–7.34 (m, 5H, H-Ar) ppm. 13C-NMR (CDCl3, 50 MHz): δ = 194.4, 140.6, 135.8, 134.3, 132.6, 129.5, 129.2, 128.8, 127.3, 126.6, 118.0 ppm. GC-MS: m/z (%) = 340 (1) [M]+, 232 (3), 183 (100), 157 (54), 76 (16), 50 (9).

Se-phenyl 4-butylbenzeneselenoate (2c): 1H-NMR (CDCl3, 200 MHz): δ = 7.85 (d, J = 8.1 Hz, 2H, H-Ar), 7.61–7.57 (m, 2H, H-Ar), 7.44–7.41 (m, 3H, H-Ar), 7.31–7.26 (m, 2H, H-Ar), 2.67 (t, J = 7.8 Hz, 2H, CH2), 1.61 (quin, J = 8.15 Hz, 2H, CH2), 1.36 (sex, J = 7.6 Hz, 2H, CH2), 0.95 (t, J = 7.2 Hz, 3H, CH3) ppm. 13C-NMR (CDCl3, 100 MHz): δ = 192.7, 149.8, 136.4, 136.2, 133.9, 129.4, 129.1, 128.9, 127.4, 125.8 ppm. GC-MS: m/z (%) = 340 (1) [M]+, 232 (3), 183 (100), 157 (54), 76 (16), 50 (9).
Table 1: Scope of the reaction (see Scheme 2).

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<td>6</td>
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(E)-Se-phenyl 3-phenylprop-2-eneselenoate (2f): $^1$H-NMR (CDCl$_3$, 200 MHz): $\delta$ = 7.58–7.54 (m, 5H, H-Ar), 7.43–7.40 (m, 6H, H-Ar), 6.78 (d, $J = 15$ Hz, 1H, CH) ppm. $^{13}$C-NMR (CDCl$_3$, 50 MHz): $\delta$ = 190.8, 141.1, 135.9, 133.9, 130.9, 129.4, 129.1, 129.0, 128.6, 128.1, 126.3 ppm. GC-MS: m/z (%) = 288 (1) [M$^+$], 157 (14), 131 (100), 103 (55), 77 (36).

Se-phenyl 2-phenylethaneselenoate (2g): $^1$H-NMR (CDCl$_3$, 200 MHz): $\delta$ = 7.45–7.35 (m, 2H, H-Ar), 7.34–7.26 (m, 8H, H-Ar), 3.88 (s, 2H, CH$_2$) ppm. $^{13}$C-NMR (CDCl$_3$, 50 MHz): $\delta$ = 198.9, 135.8, 132.6, 130.1, 129.3, 128.8, 127.8, 126.6, 53.6 ppm. GC-MS: m/z (%) = 276 (10) [M$^+$], 157 (22), 119 (26), 91 (100), 65 (26).

4-(Phenylselenyl)butyl benzoate (5a): pale oil; $^1$H-NMR (CDCl$_3$, 200 MHz): $\delta$ = 7.99–7.94 (m, 2H, H-Ar), 7.48–7.35 (m, 5H, H-Ar), 7.21–7.18 (m, 3H, H-Ar), 4.27 (t, $J = 5.5$ Hz, 2H, CH$_2$O), 2.92 (t, $J = 6.3$ Hz, 2H, CH$_2$-Se), 1.90–1.78 (m, 4H, CH$_2$) ppm. $^{13}$C-NMR (CDCl$_3$, 50 MHz): $\delta$ = 166.5, 132.8, 132.6, 130.2, 129.9, 129.5, 128.9, 128.3, 64.2, 28.7, 27.3, 26.6 ppm.

4-(Phenylselenyl)butyl 2-bromobenzoate (5b): pale oil; $^1$H-NMR (CDCl$_3$, 200 MHz): $\delta$ = 7.69 (m, 2H, H-Ar), 7.49 (m, 2H, H-Ar), 7.35–7.22 (m, 5H, H-Ar), 4.33 (t, $J = 5.7$ Hz, 2H, CH$_2$O), 2.96 (t, $J = 6.7$ Hz, 2H, CH$_2$-Se), 1.9–1.87 (m, 4H, CH$_2$) ppm. $^{13}$C-NMR (CDCl$_3$, 100 MHz): $\delta$ = 166.2, 134.3, 132.7, 132.5, 132.4, 131.2, 130.0, 129.1, 127.1, 126.9, 64.9, 28.6, 27.3, 26.7 ppm.

4-(Phenylselenyl)butyl 4-butylbenzoate (5c): pale oil; $^1$H-NMR (CDCl$_3$, 200 MHz): $\delta$ = 7.9 (d, $J = 8.0$ Hz, 2H, H-Ar), 7.5–7.47 (m, 2H, H-Ar), 7.25–7.22 (m, 3H, H-Ar), 4.3 (t, 2H, CH$_2$O), 2.96 (t, 2H, CH$_2$Se), 2.66 (t, $J = 8$ Hz, 2H, CH$_2$), 1.94–1.87 (m, 4H, CH$_2$), 1.61–1.35 (m, 2H, CH$_2$), 1.37–1.30 (m, 2H, CH$_2$), 0.93 (t, $J = 7.1$ Hz, 3H, CH$_3$) ppm. $^{13}$C-NMR (CDCl$_3$, 100 MHz): $\delta$ = 166.6, 148.5, 132.7, 130.1, 129.6, 129.0, 128.5, 127.7, 126.8, 64.06, 35.7, 33.3, 28.8, 27.4, 26.2, 22.3, 13.9 ppm.

4-(Phenylselenyl)butyl thiophene-2-carboxylate (5e): pale oil; $^1$H-NMR (CDCl$_3$, 200 MHz): $\delta$ = 7.76 (dd, $J = 1.1$, 3.72 Hz, 1H, H-Ar), 7.56–7.47 (m, 3H, H-Ar), 7.25–7.22 (m, 3H, H-Ar), 7.09 (dd, $J = 3.7$, 4.96 Hz, 1H, H-Ar), 4.29 (t, $J = 6$ Hz, 2H, CH$_2$), 2.96 (t, $J = 6.7$ Hz, 2H, CH$_2$), 1.92–1.80 (m, 4H, CH$_2$) ppm. $^{13}$C-NMR (CDCl$_3$, 100 MHz): $\delta$ = 162.2, 138.3, 133.3, 132.7, 132.3, 130.0, 129.05, 127.7, 126.8, 64.5, 28.7, 27.3, 26.6 ppm.

4-(Phenylselenyl)butyl 2-phenylacetate (5g): pale oil; $^1$H-NMR (CDCl$_3$, 200 MHz): $\delta$ = 7.5–7.45 (m, 2H, H-Ar), 7.37–7.23 (m, 8H, H-Ar), 4.09 (t, $J = 6.1$ Hz, 2H, CH$_2$O), 3.6 (s, 2H, CH$_2$), 2.89 (t, $J = 6.9$ Hz, 2H, CH$_2$Se), 1.8–1.7 (m, 4H, CH$_2$) ppm. $^{13}$C-NMR (CDCl$_3$, 100 MHz): $\delta$ = 171.6, 134.03, 132.7, 130.1, 129.25, 129.1, 128.6, 127.1, 126.9, 64.25, 41.4, 28.6, 27.3, 26.5 ppm.

4-(Phenylselenyl)butyloxybutyl benzoate (6a): pale oil; $^1$H-NMR (CDCl$_3$, 200 MHz): $\delta$ = 8.07–8.02 (m, 2H, H-Ar), 7.56–7.4 (m, 5H, H-Ar), 7.26–7.22 (m, 3H, H-Ar), 4.33 (t, $J = 6.3$ Hz, 2H, CH$_2$O), 3.93 (dt, $J_1 = 6.0$ Hz, $J_2 = 6.2$ Hz, 2H, CH$_2$), 2.93 (t, $J = 7.1$ Hz, 2H, CH$_2$Se), 1.86–1.67 (m, 8H, CH$_2$) ppm. $^{13}$C-NMR (CDCl$_3$, 50 MHz): $\delta$ = 166.6, 132.9, 132.45, 130.45, 130.4, 129.5, 129.0, 128.3, 126.7, 70.2, 64.8, 29.8, 27.7, 26.9, 26.4, 25.6 ppm.

4-(Phenylselenyl)butyloxybutyl 2-bromobenzoate (6b): pale oil; $^1$H-NMR (CDCl$_3$, 200 MHz): $\delta$ = 7.8–7.63 (m, 2H, H-Ar), 7.5–7.22 (m, 7H, H-Ar), 4.35 (t, $J = 6.2$ Hz, 2H, CH$_2$O),
3.42 (dt, \( J_d = 5.7 \) Hz, \( J_t = 6.18 \) Hz, 4H, \( \text{CH}_2 \)), 2.92 (t, \( J = 7.2 \) Hz, 2H, \( \text{CH}_2 \)Se), 1.84–1.67...1f confirmed as a carboxylic reactivity affording only in 20% yield associated with the chlorinated derivative 7f (Scheme 5).

4-(4-(Phenylselenyl)butoxy)butyl thiophene-2-carboxylate (6f): pale oil; \(^1H\)-NMR (CDCl\(_3\), 200 MHz): \( \delta = 7.79 \) (dd, \( J = 1.2, 3.7 \) Hz, IH, H-Ar), 7.55 (m, 3H, H-Ar), 7.26 (m, 3H, H-Ar), 7.09 (dd, \( J = 3.74, 4.98 \) Hz, IH, H-Ar), 4.3 (t, \( J = 6.25, 2H, \text{CH}_2 \)O), 3.42 (dt, \( J_d = 5.29 \) Hz, \( J_t = 6.9 \) Hz, 4H, \( \text{CH}_2 \)), 2.92 (t, \( J = 7.1 \) Hz, 2H, \( \text{CH}_2 \)Se), 1.83–1.65 (m, 8H, 8H, \( \text{CH}_2 \)) ppm. \(^13\)C-NMR (CDCl\(_3\), 100 MHz): \( \delta = 162.3, 133.9, 133.3, 132.5, 132.2, 130.4, 129.1, 128.9, 127.7, 126.7, 70.2, 64.9, 29.8, 29.7, 27.7, 26.9, 26.3, 25.6 ppm.

4-(4-(Phenylselenyl)butoxy)butyl 2-phenylacetate (6g): pale oil; \(^1H\)-NMR (CDCl\(_3\), 200 MHz): \( \delta = 7.51–7.47 \) (m, 2H, H-Ar), 7.33–7.24 (m, 8H, H-Ar), 4.1 (t, \( J = 6.05 \) Hz, 2H, \( \text{CH}_2 \)O), 3.62 (s, 2H, \( \text{CH}_2 \)), 3.38 (dt, \( J_d = 2.3 \) Hz, \( J_t = 6.1 \) Hz, 4H, \( \text{CH}_2 \)O), 2.93 (t, \( J = 6.8 \) Hz, 2H, \( \text{CH}_2 \)Se), 1.8–1.55 (m, 8H, \( \text{CH}_2 \)) ppm. \(^13\)C-NMR (CDCl\(_3\), 100 MHz): \( \delta = 172.0, 134.1, 132.5, 130.5, 129.25, 129, 128.5, 127.05, 126.7, 70.2, 64.9, 41.5, 28.8, 27.7, 26.9, 26.2, 25.5 ppm.

3. Results and Discussion

After the zinc mediated reduction of diphenyl diselenide in the biphasic system composed by a 1:1 mixture of 10% aq. HCl and diethyl ether (2 mL), 1 equivalent of the acyl chloride 1a–g was added and the mixture was stirred in a closed vial for 4 h. The results reported in Table 1 evidenced that the nucleophilic acyl substitution proceeded in moderated to good yields only in the case of aryl carboxylic derivatives 1a–c and 1e and not in the case of vinyl (1f) or alkyl (1g) analogues. Starting from substrates bearing functional group susceptible to reductive conditions (1d), a complex mixture of unidentified compounds was obtained.

The proposed mechanism for the reaction is reported in Scheme 3. The zinc-selenolate 3, originated by reduction of diphenyl diselenide, attacks the carbonyl group promoting the nucleophilic substitution of the chloro atom. From this reaction, the formation of a molecule of PhSeZnCl 4 can be speculated. This reagent has been proven to be an effective nucleophile for the synthesis of selenoesters in “on water conditions” [17].

With the only exception of 1d, in all the cases the only side product observed was the carboxylic acid, indicating that the hydrolysis strongly competes with the desired reaction. With the aim to improve the yield of selenoesters 3 using in the reaction model benzoyl chloride 1a, we changed the conditions generating the selenium-zinc complex in THF under the catalysis of trifluoromethanesulfonic acid (TfOH) as anhydrous acid (Table 2, entry 1). After the formation of the selenolate, which occurs during time \( t_1 \), benzoyl chloride 1a was added and stirred for the additional time \( t_2 \). The entire reaction was performed at the same temperature indicated in Table 2.

Surprisingly, beside the desired product, we observed the formation of side compounds in which the carboxylic moiety and the selenium are spaced by one (5a) or two (6a) 4-carbon units deriving from the ring opening of THF (Scheme 4). Changes on the acid amount, the units deriving from the ring opening of THF (Scheme 4). Changes on the acid amount, the units deriving from the ring opening of THF (Scheme 4). Changes on the acid amount, the units deriving from the ring opening of THF (Scheme 4). Changes on the acid amount, the units deriving from the ring opening of THF (Scheme 4). Changes on the acid amount, the units deriving from the ring opening of THF (Scheme 4). Changes on the acid amount, the units deriving from the ring opening of THF (Scheme 4). Changes on the acid amount, the units deriving from the ring opening of THF (Scheme 4).

Interestingly, also a strong increment of \( t_1 \) (from 1 h to 6 h) did not produce evident effect on the ratios between selenoester 2a and the side products 5a and 6a (Table 2, entries 1–4).

Using the best reaction conditions reported in Table 2, entry 4, we explored the reactivity of acyl chlorides 1a–g and the results are summarized in Table 3.

In all the cases, the ratios were calculated by \(^1H\)-NMR of the crude. Yields are referred to the overall isolated products after purification by flash chromatography. All the structures were assigned based on \(^1H\)-NMR and \(^13\)C-NMR analysis.

In some cases, (Table 3, entries 1, 3, 5, and 7), both side products (5 and 6) were observed in a comparable amount with respect to the selenol ester 2. In the case of the electron rich acyl chloride 1c, the yield of selenol ester 2c was lower (34%) and only 5c was formed as side product. Interestingly, the reaction from the strongly electrophilic 1d afforded quantitatively the target compound 2d. The chloride of the cinnamic acid 1f confirmed a scarce reactivity affording 2f only in 20% yield associated with the chlorine derivative 7f (Scheme 5).
In order to verify if chloride intermediate 7 is involved in the formation of 5 and 6 or if it is formed through a parallel mechanism based on the nucleophilicity of the chloride anion, 7a was prepared according to the procedure reported by Enthaler and Weidauer [18] reacting benzoyl chloride 1a and ZnCl₂ in THF (Scheme 6).

After isolation of 7a, it was reacted with a preformed suspension of 3, following the condition reported in Table 2, entry 4, for the second part of the reaction (time \( t_2 \)). The NMR analysis of the crude evidenced the formation of 5a only in traces, confirming that, in the principal mechanism, chloride 7 is not the precursor of products 5 and 6.

### Table 3: Scope of the reaction in THF (see Scheme 5).

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All these evidences suggested a concerted mechanism in which three parallel reactions can be envisioned. Zinc-selenolate complexes 3 or 4 can attack directly acyl chloride affording the selenoesters 2 (black path in Scheme 7). Alternatively, the same complexes, which reasonably in THF solution coordinate one or two molecules of solvent, attack the carbon of THF and the nucleophilic oxygen can be immediately quenched by the electrophile 1, affording 5 (red path in Scheme 7), or open a second molecule of THF and then react with acyl chloride 1 to afford 6 (green path in Scheme 7). From the PhSeZnCl 4, a similar mechanism can be activated by the chloride, producing the ester 7 (blue path in Scheme 7).

4. Conclusions

In conclusion, we demonstrated that aqueous or anhydrous acidic conditions can be used to activate the zinc mediated reduction of diphenyl diselenide. The corresponding zinc-selenolate complex has been studied toward the reaction with a series of acyl chloride affording the corresponding selenol esters in moderate to good yields depending on the substrate and the reaction conditions. The presence of zinc and the strong hydrolytic conditions limit the scope of the reaction. Performing the reaction in refluxing THF, the ring-opening reaction of the solvent competes with the acyl substitution and it was not possible to find conditions to improve the selectivity of the process. Nevertheless, the reaction in THF resulted in being effective for some substrates that failed in the biphasic system (1d, 1f, and 1g). In addition, the possibility of using this process to depolymerize polyether based materials is an attracting and promising prospective that is currently under investigation exploring the possibility of transforming wastes in highly functionalized selenium containing chemicals.

Competing Interests

The authors declare that there is no conflict of interests.

Authors’ Contributions

Gemma Bellino and Marialaura Scisciani contributed equally to this work.
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References


