

Preparation of the First Bench-Stable Phenyl Selenolate: an Interesting “On Water” Nucleophilic Reagent

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In this communication we report the synthesis and the characterization of the first solid and air-stable selenolates, starting from commercially available phenylselenenyl halides and elemental zinc. These reagents were efficiently employed in the ring opening of epoxides as well as in other

nucleophilic substitution and addition reactions showing an unexpected rate acceleration in water suspension at room temperature.

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Introduction

Selenium-based methods have developed rapidly over the past few years, and organoselenium chemistry became a very useful tool in the hands of synthetic chemists. Various functionalities can be selectively introduced into complex molecules under very mild reaction conditions by using electrophilic as well as radical or nucleophilic selenium reagents.^[1]

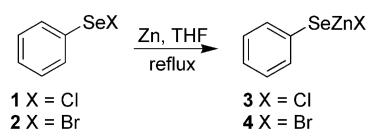
Among the methods for the introduction of a selenium moiety into organic molecules the use of selenolate anions is especially convenient and common. These are usually formed “in situ” from various precursors, for example by reductive cleavage of diselenides^[2] or by insertion of selenium into organometallic reagents.^[3] Several reducing agents, including LiAlH₄, NaBH₄, Na/NH₃, Bu₃SnH, have been reported for the preparation of the corresponding metal selenolates under basic as well as neutral conditions.^[2] A considerable interest in the clarification of the chemical properties of organoselenium derivatives possessing selenium–metal bonds stems from their potential use as precursors for M/Se materials^[4] and their relevance as models for the active sites of selenocysteine-containing metalloproteins.^[5]

Despite its well-known reducing properties zinc has been rarely employed in the preparation of selenols or selenolates.^[6] We recently reported that zinc in biphasic acidic systems reduces diselenides to afford selenols, which can be isolated or directly treated with halides or epoxides to give

selenides or β-hydroxy selenides, respectively.^[7] The S_N2 ring opening of epoxides by using selenolate ions is a common method for preparing β-hydroxy selenides. These compounds are valuable intermediates in the synthesis of allylic alcohols,^[8] olefins,^[9] bromohydrins^[10] and vinyl selenides.^[11] Recently, β-hydroxy selenides were also widely used for the synthesis of some important natural compounds.^[12–16] Several selenium anions can be used for this purpose like (phenylseleno)silanes,^[17] aluminium selenolates,^[18] selenoboranes,^[19] benzeneselenol in the presence of alumina^[20] and selenostannanes.^[21] All these reagents are relatively unstable, and they should be prepared “in situ” under controlled anhydrous conditions.

Results and Discussion

Here we report that treatment of commercially available PhSeCl (**1**) and PhSeBr (**2**) with a stoichiometric amount of zinc powder in refluxing THF leads to the corresponding zinc selenolates **3** and **4** through an oxidative insertion of zinc into the selenium–halide bond (Scheme 1).



Scheme 1. Oxidative zinc insertion.

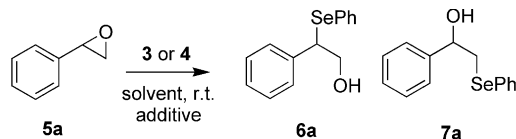
Compounds **3** and **4** can be isolated in quantitative yields by precipitation from Et₂O as white amorphous solids (m.p. > 300 °C), air-stable for several days. These selenolates were fully characterized by ¹H, ¹³C and ⁷⁷Se NMR spectroscopy, and the latter proved particularly diagnostic for the presence of an Se–Zn bond (δ = –41 ppm for **3** and δ = –28 ppm for **4**).

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Some years ago, Xu et al. hypothesized that an ArSeZnCl compound was formed from the reaction of an aromatic Grignard salt with ZnCl_2 followed by treatment with grey selenium.^[22] The authors described this “in situ” preparation of selenolates followed by the reaction with electrophiles to give, in moderate yields, the desired selenides. Nevertheless, our attempts to isolate **3** by using the above reported procedure starting from PhMgBr failed, and the ^1H NMR spectrum of the reaction mixture showed a pattern of resonances significantly different from those assigned by us to compounds **3** and **4**.

In order to evaluate their nucleophilic properties, PhSeZnCl (**3**) and PhSeZnBr (**4**) were preliminarily employed in the ring opening of styrene oxide (**5a**), and the effects produced by the use of several additives were also screened (Scheme 2). The results summarized in Table 1 clearly show that in all the cases the selenium attacks regioselectively the benzylic carbon atom to afford mainly 2-phenyl-2-(phenylselenyl)ethanol (**6a**) with respect to the corresponding regioisomer **7a**. This is in contrast to the results obtained with other selenolates,^[4d–23] and it probably indicates that the reaction of styrene oxide with **3** or **4** proceeds via a partially stabilized carbocation (Figure 1a).



Scheme 2. $\text{S}_{\text{N}}2$ ring opening mediated by **3** and **4**.

Table 1. Preliminary investigation on the best reaction conditions.

Reagent	Solvent	Additive ^[a]	Time	6a/7a	Yield
3	THF	ZnBr_2	24 h	60:40	84%
3	THF	ZnCl_2	24 h	60:40	74%
3	THF	AlCl_3	24 h	65:35	53%
3	THF	$\text{Yb}(\text{OTf})_3$	24 h	70:30	94%
3	THF	$\text{Ti}(\text{OiPr})_4$	24 h	75:25	74%
3	THF	DMF	24 h	73:27	97%
3	THF	SnCl_2	24 h	60:40	44%
3	THF	TiCl_4	24 h	–	–
3	THF	$\text{Al}(\text{OTf})_3$	24 h	80:20	14%
3	THF	$\text{Zn}(\text{OTf})_2$	24 h	77:23	80%
3	THF	$\text{Mg}(\text{ClO}_4)_2$	24 h	78:22	53%
3	THF	$\text{Cu}(\text{OTf})_2$	24 h	–	–
3	THF	$\text{Sc}(\text{OTf})_3$	24 h	89:11	25%
3	THF	$\text{Sm}(\text{OTf})_3$	24 h	91:9	87%
3	THF	InBr_3	24 h	79:21	34%
3	THF	InCl_3	24 h	89:11	34%
3	THF	$\text{In}(\text{OTf})_3$	24 h	78:22	30%
3	THF	none	24 h	88:12	100%
4	THF	none	24 h	56:44	20%
3	H_2O	none	2 h	80:20	100%

[a] 1.1 equiv.

The best results in terms of regioselectivity and chemical yields were obtained by using PhSeZnCl (**3**) at room temperature in THF. When the reaction was carried out in water suspension a remarkable rate acceleration, similar to those recently reported by Sharpless et al., was observed.^[24] These preliminary results indicate also that the presence of

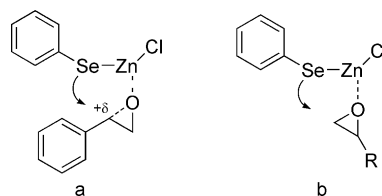


Figure 1. Competition between electronic (a) and steric (b) effects controls the regioselectivity of the ring opening reaction.

a Lewis acid as additive in THF effects negatively the yields and in some cases also the regioselectivity.

The reaction of a variety of substituted alkyl and aryl epoxides with PhSeZnCl (**3**) was then investigated. Table 2 lists the results obtained by treatment of the substrates **5a–j** with selenolate **3** in THF for 24 h and under “on water”

Table 2. $\text{S}_{\text{N}}2$ ring opening reaction of epoxides mediated by **3**.

Epoxides 5	Products 6,7	Yield [%] (6/7) ^[a]	Yield [%] (6/7) ^[b]
5a	6a 7a	100 (88:12)	100 (80:20)
5b	6b 7b	40 ^[c] (20:80)	99 (45:55)
5c	6c	20 ^[c]	99
5d	6d	0	48
5e	7e	99	100
5f	7f	74	100
5g	6g	27 ^[c]	98
5h	6h	100	100
5i	6i 7i	44 (0:100)	100 (9:91)
5j	6j 7j	0	45 (93:7)

[a] THF, 20 °C, 24 h. [b] H_2O , 20 °C, 2 h. [c] THF, 60 °C, 24 h.

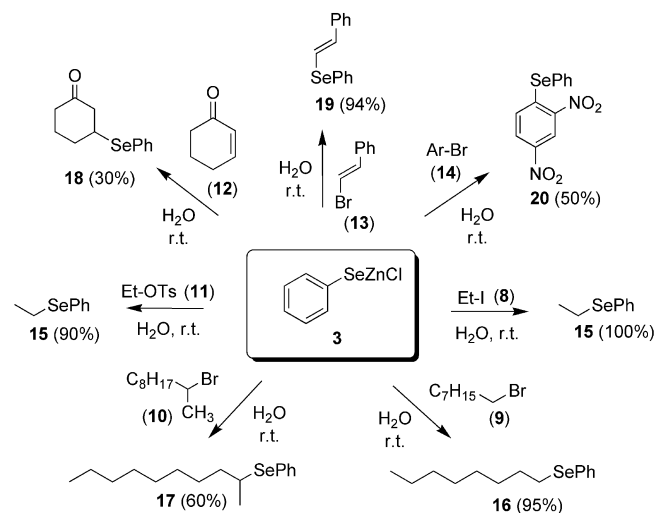
conditions for 2 h. All the reactions were carried out at room temperature with the only exception of α -methylstyrene oxide (**5b**), β -methylstyrene oxide (**5c**) and cyclopentene oxide (**5g**), which reacted in THF at 60 °C.

As can clearly be seen, the reactions under “on water” conditions are faster and in all the cases more efficient than those carried out in THF; they afford in only 2 h almost quantitative yields for all the analyzed substrates. The regioselectivity of the ring-opening reaction is dependent on the steric and electronic features of the epoxide system. In the cases of alkyl-substituted derivatives **5e**, **5f** and **5i** the nucleophilic attack occurs preferentially on the less hindered carbon atom (Figure 1b) to lead to the stereospecific formation of **7e**, **7f** and the regioisomers **6i/7i** (9:91), respectively.

On the other hand in the aryl-substituted epoxides **5a**, **5c** and **5j** the electronic effects overshadow the steric ones of the bulky aromatic group (Figure 1a), and the selenium attacks selectively the benzylic carbon atom. Only in the case of the α -methylstyrene oxide (**5b**) has a poor regioselectivity been found.

To highlight and stress the synthetic versatility of this new nucleophilic reagent, a series of substitution and nucleophilic addition reactions are presently under investigation in our laboratory.

In Scheme 3 some representative preliminary examples are summarized, which were obtained by starting from the aliphatic halides **8**, **9**, **10**, the vinyl bromide **13**, 2,4-dinitrobenzene (**14**), the tosylate **11** and 2-cyclohexenone (**18**). All the reaction were carried out in water suspension at the temperature and with the yields indicated in Scheme 3.



Scheme 3. S_N2 ring opening mediated by **3** and **4**.

Conclusions

We demonstrated that treatment of readily available and inexpensive electrophilic selenium species with zinc causes umpolung on the selenium atom to lead to a stable sele-

nolate that shows an interesting and unexpected nucleophilic reactivity under “on water” conditions.

Experimental Section

(Phenylselenenyl)zinc Chloride (3): Zinc (653.9 mg, 10.0 mmol) was added to a solution of **1** (1.915 g, 10.0 mmol) in THF (20 mL). The reaction mixture was refluxed for 30 min, and then diethyl ether (20 mL) was added. The resulting white solid was filtered, washed 3 times with diethyl ether, and the solvent was removed under reduced pressure. Yield 2.569 g (100%). M.p. >300 °C. ^1H NMR (400 MHz, $[\text{D}_8]\text{THF}$, 25 °C, TMS): δ = 7.45–7.35 (m, 2 CH, Ar), 6.78 [t, $^3J(\text{H,H})$ = 6.5 Hz, 1 CH, Ar], 6.70 [t, $^3J(\text{H,H})$ = 6.5 Hz, 2 CH, Ar] ppm. ^{13}C NMR (100.62 MHz, $[\text{D}_8]\text{THF}$, 25 °C, TMS): δ = 133.6, 126.6, 123.4 ppm. ^{77}Se NMR (76.27 MHz, $[\text{D}_8]\text{THF}$, 25 °C, Me_2Se): δ = –41.6 ppm.

Supporting Information (see footnote on the first page of this article): Experimental details and characterization data for the new compounds.

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