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SHORT COMMUNICATION

"*On-water*" thiolysis of epoxides promoted by PhSZnBr

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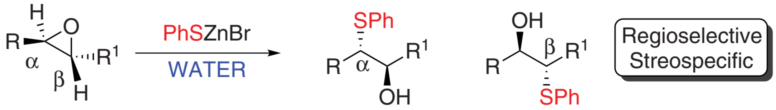
The synthesis of a new bench-stable and odorless zinc thiolate is here reported. The thiolysis of epoxides effected using this reagent showed a considerable rate acceleration of the reaction when effected in "*on-water*" conditions. In addition, the reactions evidenced a good regioselectivity combining the advantage of the procedures effected in organic solvent with those effected using Lewis acid catalysis.



Keywords: sulfur; zinc; thiolates; thiolysis; water

1. Introduction

The interest around organic sulfur compounds is continuously increasing in consideration of their importance as intermediates in organic synthesis as well as biologically active molecules. For these reasons, the development of new reagents and synthetic strategies to be able to combine efficiency with respect to the environment is currently the objective of a number of studies.

Thiolysis of 1,2-epoxides represents an efficient strategy for the preparation of β-hydroxysulfides that are generally considered useful intermediates in the synthesis of naturally occurring derivatives (*1*), pharmaceuticals (*2*), allylic alcohols (*3*, *4*), benzoxathiepines (*5*, *6*), benzotiazepines (*7*), α-thioketones (*8*) and β-hydroxysulfoxides (*9*). Moreover, β-hydroxysulfides are also widely used in asymmetric synthesis (*10*, *11*). A number of different conditions were reported for the ring-opening reaction of epoxides, using organic solvents (THF, MeOH, CH_2Cl_2, MeCN, benzene) in the presence of different catalysts or promoting agents (bases, Lewis acids, heterogeneous catalysts, microwave irradiation, silica gel, alumina, Montmorillonite, polyethylene glycol, tetrabutylammonium phenoxide). Recently some new ecofriendly protocols have been also taken into consideration (*12–20*). However, despite their synthetic utilities, most of the commonly used reaction conditions suffer from a number of drawbacks, which include the use of smelling thiols, strong and non-selective acidic catalysts, expensive and toxic solvents or

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Dedicated to the memory of Prof. Alessandro Degl'Innocenti

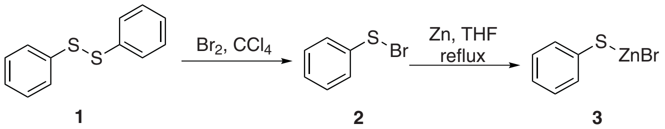
reagents, low yields, and long reaction times, sometimes associated to the formation of undesirable side products by the rearrangement of oxiranes or the oxidation of thiols. Water is rarely used in organic reactions because of the insolubility of the majority of organic compounds, their occasional decomposition as well as the incompatibility of some intermediates with this solvent. However, aqueous medium has interesting advantages with respect to organic solvents: water is inexpensive, abundant, readily available, non-toxic, and environmentally benign. Moreover, it has been demonstrated that a number of reactions occur faster in water than in organic solvents. This concept was first postulated by Sharpless and coworkers (*21*) to indicate a process in which organic insoluble reactants are stirred in aqueous suspension reacting with a considerable rate acceleration.

In continuation of our previous studies concerning the reactivity of zinc selenolates, we report here the synthesis of a bench-stable (phenylsulfenyl)zinc bromide as an excellent reagent for the thiolysis of epoxides in *on-water* conditions. During the last five years, we deeply investigated the reaction of elemental zinc with organoselenium compounds in order to prepare new nucleophilic chalcogenides. We demonstrated that, in a biphasic acidic system, it reduces diselenides affording the formation of aliphatic and aromatic selenols that can be trapped, *in situ*, by electrophiles such as epoxides, alkyl halides (*22*), and unprotected aziridines (*23*).

In a different way, elemental zinc reacts in refluxing THF with commercially available PhSeCl and PhSeBr producing, through an oxidative metal insertion, the formation of the bench-stable (phenylselenenyl)zinc halides (*24*). These reagents are characterized by extraordinary stability under ordinary conditions and showed a strong reactivity toward a number of electrophiles. Nucleophilic substitution of alkyl-, aryl-, vinyl-, and acyl- halides, ring-opening reactions (*25*) as well as Michael-type addition reactions (*26*), and thiol oxidations (*27*) were successfully realized resulting to be, in all the cases, accelerated when effected in *on-water* conditions.

2. Results and discussion

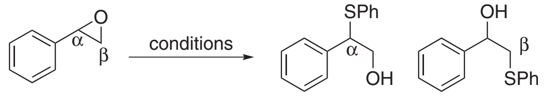
Benzenesulfenyl bromide **2** was easily prepared by bromination starting from the commercially available disulfide **1**. The product obtained after the under-vacuum evaporation of the organic solvent was immediately used for the reaction with elemental zinc in refluxing THF. After 1 h, the dissolution of the metal indicated the complete formation of the (phenylsulfenyl)zinc bromide **3** that was purified and isolated in 70% yield by crystallization from diethyl ether (Scheme 1). The zinc thiolate **3** appeared as a white amorphous solid (m.p. 238–240°C), air stable for several weeks, and was fully characterized by ^{1}H- and ^{13}C- NMR spectroscopy and elemental analysis.



Scheme 1. Synthesis of **3**.

The nucleophilic properties of the zinc thiolate **3** were preliminarily investigated in the ring-opening reaction of styrene oxide **4a**. The reaction was performed in THF solution as well as in water suspension and neat conditions, in order to verify the *on-water* rate acceleration previously observed for the analogs of zinc selenolates (*25*). The results, summarized in Table 1 (Entries 9 and 11), clearly indicated that when water is the medium the reaction afforded in 15 min quantitative yield of the β-hydroxysulfides **5a** and **6a**, whereas in THF solution, after 5 h, the yield

Table 1. Comparison of different reaction conditions for the thiolysis of styrene oxide (**4a**).



4a **5a** **6a**

Entry	Conditions	t(min)	Yield (%)	**5a/6a**	Reference
1	PhSH, H_2O, 20°C	43200	41	80/20	(*12*, *13*)
2	PhSH, DABCO (1%), H_2O, 25°C	43200	98	85/15	(*12*)
3	PhSH, [Emim] BF_4, 50°C	10	90	72/28	(*15*)
4	PhSH, $LiClO_4$ (12.5 mol), 25°C	20	98	83/17	(*16*)
5	PhSH, Borax (10%), H_2O, 25°C	180	98	80/20	(*17*)
6	PhSH, $Ga(OTf)_3$ (1%), 25°C	40	86	97/3	(*18*)
7	PhSH, $InCl_3$ (10%), H_2O, 30°C	5	91	97/3	(*19*)
8	PhSH, $ZnCl_2$ (10%), H_2O, 30°C	20	100	84/16	(*20*)
9	PhSZnBr, H_2O, 20°C	15	100	89/11	
10	PhSZnBr, THF, 20°C	300	41	89/11	
11	PhSZnBr, neat, 20°C	60	0		

was only moderate. The nucleophilic attack was driven predominantly at the benzylic α-carbon by electronic effects with a good regioselectivity (89:11) for both the applied conditions.

In Table 1, the results obtained from the thiolysis of **4a** mediated by (phenylsulfenyl)zinc bromide **3** are compared with those reported in the literature for the same reaction effected using benzenethiol as the nucleophile in different reaction conditions: using alternative solvents (water, ionic liquids), in solvent-free conditions, and in the presence or absence of catalysts.

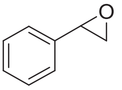
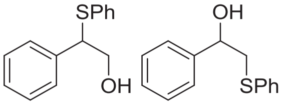
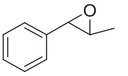
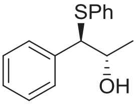
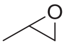
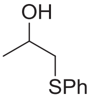
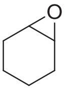
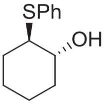
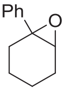
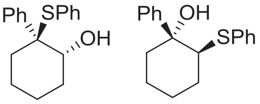
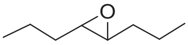
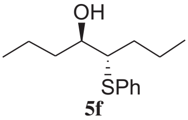
The reaction of PhSH with **4a** at room temperature in water and in the absence of catalysts is particularly slow (Entry 1) (*12*, *13*) and afforded the couple of β-hydroxysulfides **5a** and **6a** in moderate yield and regioselectivity (*14*).[1] Slightly better yields can be obtained with additives such as DABCO (Entry 2) (*12*) and borax (Entry 5) (*17*), whereas the use of ionic liquids (Entry 3) (*15*) or solvent-free conditions (Entry 4) (*16*) are much more effective in reducing the reaction time increasing the yields. Better results were reported for the process catalyzed by Lewis acids (Entries 6–8) (*18–20*). In these cases, good yields were associated with very short reaction times and also the regioselectivity was usually enhanced, probably as a consequence of the acidic activation of the oxirane. In this context, the use of PhSZnBr **3** appears to be superior to all the reactions effected in water showing most of the advantages of the Lewis-acid-catalyzed reactions (rate acceleration, high yields, and high regioselectivity). In addition, zinc thiolate is a completely odorless compound offering a valuable advantage with respect to the use of the smelling benzenethiol.

In order to investigate the scope of the reaction, the conditions described in Table 1 (Entries 9 and 10), were applied to the thiolysis of a number of variously substituted epoxides. The results are summarized in Table 2 and indicate that, in all the cases, the process is accelerated when carried out in water suspension. For the epoxides **4e** and **4f**, in THF, it was not possible to isolate the desired β-hydroxysulfides and a mixture of non-identified products and the starting material was recovered.

Concerning the regiochemistry, it is interesting to observe that the ring-opening reaction of the epoxide **4b** is completely selective on the α-position (**5b**), whereas in the case of the methyloxirane **4c**, the steric effects in the absence of a stabilizing aromatic ring lead exclusively to the product deriving from an S_N2 attack occurring on the less hindered β-carbon (**6c**). Only in the case of the phenylcyclohexene oxide **4e** the thiolysis proceeded with poor regioselectivity affording **5e** and **6e** in a ratio of 65:35.

The attempt to effect the thiolysis of the functionalized epoxide **7** with PhSZnBr (**3**) in water suspension failed leading to the corresponding hydroxylactone **8** (Scheme 2). This result suggested

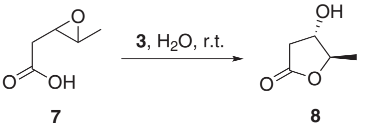
Table 2. Scope of the reaction.

Epoxide	Products (**5**/**6**)	Solvent	*t* (min)	Yield^a(%)	**5**/ **6**^{b}
 **4a**	 **5a/6a**	H_2O, THF	15, 300	99, 41	89/11, 89/11
 **4b**	 **5b**	H_2O, THF	15, 60	82, 51	
 **4c**	 **6c**	H_2O, THF	15, 240	70, 44	
 **4d**	 **5d**	H_2O, THF	15, 120	73, 46	
 **4e**	 **5e/6e**	H_2O, THF	30, 600	49, –	65/35, –
 **4f**	 **5f**	H_2O, THF	60, 600	52, –	

Notes: ^{a}The yields are referred to the amount of product obtained after purification.
^{b}The regioisomeric ratios were calculated by the ^{1}H-NMR of the crude.

that zinc reasonably acts as a Lewis acid activating the oxirane ring that is preferentially trapped by the internal nucleophile. However, it is interesting to underline that a similar competition has never been observed for the water.

In conclusion, a new zinc thiolate for the nucleophilic ring opening of epoxide is reported here. The reaction, using *on-water* conditions, is very fast and proceeds in good yield and good regioselectivity affording the corresponding β-hydroxysulfides. Further investigation devoted to the synthesis of other zinc thiolates is currently ongoing.



Scheme 2. Reaction of PhSZnBr with epoxide **7**.

3. Experimental

Epoxides **4a–d** are commercial compounds (Aldrich). Epoxides **4e** and **4f** and **7** have been prepared from the corresponding commercial olefins by oxidation with *m*-CPBA according to the procedure described in the literature (*28*). Intermediates have been purified by flash chromatography on silica gel column (eluant dichloromethane). **5a**, **5b**, **5d**, **5e**, **5f** and **6a**, **6c** and **6e** have spectral properties identical to those previously described (*29–34*), and the diasteroisomeric couples **5a**/**6a** and **5e**/**6e** were not separated and analyzed as mixture.

All the new compounds were fully characterized by NMR and elemental analysis. ^{1}H- and ^{13}C-NMR spectra were recorded at 400 and 100.62 MHz, respectively, on a Bruker Avance-DRX 400 instrument. Elemental analyses were carried out on a Carlo Erba 1106 elemental analyzer.

3.1. *Preparation of PhSZnBr 3*

Three hundred milligrams of diphenyl disulfide (1.37 mmol) was dissolved in diethyl ether (8 ml) and a solution of bromine (1.0 M in CCl_4, 1.37 mmol) was added at 0°C. After 30 min, the organic solvent was removed under reduced pressure affording a red solid (PhSBr, 380 mg). The solid was dissolved in fresh distilled THF and the resulting solution heated at reflux. After that the elemental zinc (65.4 mg, 2.21 mmol) was added and the reaction mixture was vigorously stirred at reflux until complete discoloration. The colorless solution was filtered in order to remove the unreacted elemental zinc and zinc thiolate **3** was purified by crystallization from diethyl ether.

3.2. *Phenylthiozinc(II) bromide (3)*

White solid, m.p. 238–240°C. ^{1}H-NMR (DMSO-d_6): δg.32–7.25 ppm (m, 2H), 7.02–6.95 (m, 2H), 6.9–6.8 (m, 1H). ^{13}C-NMR δg33.2, 128.6, 122.8, 102.6. Anal. Calcd for C_6H_5BrSZn: C, 28.32; H, 1.98. Found: C, 28.08; H, 1.87.

3.3. *Thiolysis in on water conditions: general procedure*

To a suspension of 50 mg of PhSZnBr (0.2 mmol) in 2 ml of water, 0.2 mmol of epoxides **4a–f** was added at room temperature and the mixture was maintained under vigorous stirring for the time reported in Table 2. After that the reaction mixture was extracted with ethyl acetate (3 × 3 ml), the organic layer dried over sodium sulfate and the crude purified by flash chromatography on a silica gel column (eluant diethyl ether 30%–petroleum ether 70%).

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Note

1. Our attempts to reproduce the yields and the regioselectivity reported for the synthesis of **5a** and **6a** failed, confirming, in all the cases, the results reported in references (*12*) and (*13*).

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