Zn(II)-Catalyzed Thiolysis of Oxiranes in Water under Neutral Conditions

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Abstract: Thiolysis of a variety of 1,2-epoxides in water at 30 °C and pH 7.0 is strongly accelerated by $ZnCl_2$ (10 mol %) except when amino- and carboxythiophenol are used. The aqueous medium and the catalyst were recovered and reused in various runs without affecting the efficiency of the process.

Introduction

The β-hydroxysulfide unit is present in compounds of biological and pharmacological interest[1] and is a versatile moiety for synthesizing allylic alcohols,[2] benzoxathiepines,[3] benzotiazepines,[4] α-thioketones,[5] α-substituted α,β-unsaturated enones,[6] and β-hydroxysulfoxides used in the synthesis of naturally occurring compounds.[7]

The easiest access to β-hydroxysulfides is the thiolysis of 1,2-epoxides that is usually carried out in organic solvents (THF, CH_2Cl_2, MeOH, MeCN, or PhH) by using thiols under basic conditions[8] or in the presence of promotors and/or catalysts.[9]

Thiolysis in sole water was first investigated in our laboratory.[8g,10] Under basic conditions (pH 9.0), the nucleophilic attack occurs, as expected, almost exclusively on the less substituted carbon of the oxirane-ring.[8g]

We found[10] that under acidic conditions (pH 4.0), it was possible to partially modify the regioselectivity of the reaction allowing the thiophenol attack on the more substituted α-carbon. The reactions, however, were extremely slow and led to the formation of undesired side products. At pH 4.0, $InCl_3$ (10 mol %) was a very efficient catalyst, which gave the same regioselectivity results but in very short reaction times. Our previous studies[8g,10] would seem to indicate that under neutral conditions (pH 7.0) this reaction should be slow and that a metal catalyst would therefore be necessary. While many Lewis acids have proven to be very efficient in sole water under acidic conditions, the same catalysts are generally not effective under neutral or basic conditions.[11]

Metal–thiol and metal–thiolate interactions are extremely important in biochemical processes;[12] in fact, in vivo Nature regulates the catalytic efficiency of biocatalysts such as Co(II), Ni(II), Cu(II), and Zn(II) exploiting their interactions with sulfur-containing functionalities.[13] This biological behavior would suggest that these cations could be efficient catalysts in water even under neutral conditions. Their $pK_{1,1}$ hydrolysis constants (9.65, 9.86, 7.97, and 8.96, respectively)[14] confirm this hypothesis because at pH 7.0 (below their $pK_{1,1}$) their highest efficiency is expected.[11e,f]

From a chemical perspective, Co(II), Ni(II), Cu(II), and Zn(II) salts are *classic* Lewis acids that could offer the

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(1) (a) Corey, E. J.; Clark, D. A.; Goto, G.; Marfat, A.; Mioskowski, C.; Samuelsson, B.; Hammarström, S. *J. Am. Chem. Soc.* **1980**, *102*, 1436−1439. (b) Hammarström, S.; Samuelsson, B.; Clark, D. A.; Goto, G.; Marfat, A.; Mioskowski, C.; Corey, E. J. *Biochem. Biophys. Res. Commun.* **1980**, *92*, 946−953. (c) Conchillo, A.; Camps, F.; Messeguer, A. *J. Org. Chem.* **1990**, *55*, 1728−1735. (d) Luly, J. R.; Yi, N.; Soderquist, J.; Stein, H.; Cohen, J.; Perun, T. J.; Plattner, J. J. *J. Med. Chem.* **1987**, *30*, 1609−1616.

(2) (a) Kesavan, V.; Bonnet-Delpon, D.; Bégué, J.-P. *Tetrahedron Lett.* **2000**, *41*, 2895−2898. (b) Mitra, R. B.; Muljiani, Z.; Deshmukh, S. D.; Joshi, V. S.; Gadre, S. R. *Synth. Commun.* **1984**, *14*, 101−112. (c) Adams, H.; Bell, R.; Cheung, Y.-Y.; Jones, D. N.; Tomkinson, N. C. O. *Tetrahedron: Asymmetry* **1999**, *10*, 4129−4142.

(3) (a) Sugihara, H.; Mabuchi, H.; Hirata, M.; Iamamoto, T.; Kawamatsu, Y. *Chem. Pharm. Bull.* **1987**, *35*, 1930−1952. (b) Aifheli, C. G.; Kaye, P. T. *Synthetic Commun.* **1996**, *26*, 4459−4475. (c) Krishnamutri, R.; Nagy, S.; Smolka, T. F. U.S. Patent NO. 5621153, 1997.

(4) (a) Scwartz, A.; Madan, P. B.; Mohacsi, E.; O'Brien, J. P.; Todaro, L. J.; Coffen, D. L. *J. Org. Chem.* **1992**, *57*, 851−856. (b) Adger, M. A.; Barkley, J. B.; Bergeron, S.; Cappi, M. W.; Flowerden, B. E.; Jackson, M. P.; McCange, K.; Nugent, T. C.; Roberts, S. M. *J. Chem. Soc., Perkin Trans 1* **1997**, 3501−3507.

(5) Bégué, J.-P.; Bonnet-Delpon, D.; Kornilov, A. *Synthesis* **1996**, 529−532.

(6) (a) Apparao, S.; Schmidt, R. R. *Synthesis* **1987**, 896−899. (b) Fioroni, G.; Fringuelli, F.; Pizzo, F.; Vaccaro, L. *Green Chem.*, in press.

(7) (a) Gabbi, C.; Ghelfi, F.; Grandi, R. *Synth. Commun.* **1997**, *27*, 2857−2863. (b) Alvarez-Ibarra, C.; Cuervo-Rodrìguez, R.; Fernánedz-Monreal, M. C.; Ruiz, M. P. *J. Org. Chem.* **1994**, *59*, 7284−7291.

(8) (a) Forristal, I.; Lawson, K. R.; Rayner, C. M. *Tetrahedron Lett.* **1999**, *40*, 7015−7018. (b) Yamada, O.; Ogasawara, K. *Synlett* **1995**, 427−428. (c) Behrens, C. H.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 5696−5704. (d) Nishikubo, T.; Ilizawa, T.; Shimojo, M.; Kato, T.; Shiina, A. *J. Org. Chem.* **1990**, *55*, 2536−2542. (e) Ilizawa, T.; Goto, A.; Nishikubo, T. *Bull. Soc. Chem. Jpn.* **1989**, *62*, 597−598. (f) Behrens, C. H.; Ko, S. Y.; Sharpless, K. B.; Walker, F. J. *J. Org. Chem.* **1985**, *50*, 5687−5696. (g) Fringuelli, F.; Pizzo, F.; Tortoioli, S.; Vaccaro, L. *Green Chem.,* in press.

(9) (a) Guindon, Y.; Young, R. N.; Frenette, R. *Synth. Commun.* **1981**, *11*, 391−398 (ZnI$_2$). (b) Lay, L.; Nicotra, F.; Panza, L.; Russo, G. *Synlett* **1995**, 167−168 (ZnCl$_2$). (c) Yamashita, H. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1213−1220 (Zn and other metal(II) tartrates). (d) Yamashita, H.; Mukaiyama, T. *Chem. Lett.* **1985**, 1643−1646 (Zn(II) tartrate). (e) Gansauer, A.; Bluhm, H. *J. Chem. Soc., Chem. Commun.* **1998**, 2143−2144 (ZnCl$_2$/Zn). (f) Karikomi, M.; Ayame, K.; Toda, T. *Heterocycles* **2001**, *55*, 1451−1454 (MgClO$_4$, LiClO$_4$). (g) Chini, M.; Crotti, P.; Giovani, E.; Macchia, F.; Pineschi, M. *Synlett* **1992**, 303−305 (LiClO$_4$). (h) Sasaki, M.; Tanino, K.; Miyashita, M. *J. Org. Chem.* **2001**, *66*, 5388−5394 (R$_3$Al). (i) Choudary, B. M.; Rani, S. S.; Kantam, M. L. *Synthetic Commun.* **1990**, *20*, 2313−2317 (Pd(PPh$_3$)$_4$). (j) Onaka, M.; Sugita, K.; Takeuchi, H.; Izumi, Y. *J. Chem. Soc., Chem. Commun.* **1988**, 1173−1174 (zeolite). (k) Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557−1560 (Ti(O-*i*-Pr)$_4$).

(10) Fringuelli, F.; Pizzo, F.; Tortoioli, S.; Vaccaro, L. *Adv. Synth. Catal.* **2002**, *344*, 379−383.

(11) For recent works: (a) Fringuelli, F.; Pizzo, F.; Vaccaro, L. *Tetrahedron Lett.* **2001**, *42*, 1131−1133. (b) Amantini, D.; Fringuelli, F.; Pizzo, F.; Vaccaro, L. *Green Chem.* **2001**, *3*, 229−232. (c) Attanasi, O.; De Crescentini, L.; Filippone, P.; Fringuelli, F.; Mantellini, F.; Matteucci, M.; Piermatti, O.; Pizzo, F. *Helv. Chim. Acta* **2001**, *84*, 513−525. (d) Fringuelli, F.; Matteucci, M.; Piermatti, O.; Pizzo, F.; Burla, M. C. *J. Org. Chem.* **2001**, *66*, 4661−4666. (e) Fringuelli, F.; Pizzo, F.; Vaccaro, L. *J. Org. Chem.* **2001**, *66*, 3554−3558. (f) Fringuelli, F.; Pizzo, F.; Vaccaro, L. *J. Org. Chem.* **2001**, *66*, 4719−4722. (g) Amantini, D.; Fringuelli, F.; Pizzo, F.; Vaccaro, L. *J. Org. Chem.* **2001**, *66*, 6734−6737. (h) Fringuelli, F.; Piermatti, O.; Pizzo, F.; Vaccaro, L. *Eur. J. Org. Chem.* **2001**, *3*, 439−455. (i) Amantini, D.; Fringuelli, F.; Pizzo, F.; Vaccaro, L. *J. Org. Chem.* **2001**, *66*, 4463−4467. (j) Amantini, D.; Fringuelli, F.; Pizzo, F.; Vaccaro, L. *J. Org. Chem.* **2002**, *67*, 7238−7243.

(12) Srogl, J.; Liu, W.; Marshall, D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1999**, *121*, 9449−9450.

(13) *Handbook of Metal−Ligand Interactions in Biological Fluids*; Berthon, G., Ed.; Marcel Dekker: New York, Basel, Hong Kong, 1995.

(14) (a) Richens, D. T. In *The Chemistry of Aqua Ions*; Wiley: New York, 1997. (b) Bases, C. F., Jr.; Mesmer, R. E. *The Hydrolysis of Cations*; Wiley: New York, 1976.

TABLE 1. Thiolysis of 1,2-Cyclohexene Oxide (1) by Thiophenol[a] with Various Catalysts in Water at 30 °C and pH 7.0
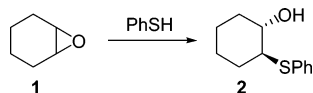
entry	metal salt (10 mol %)	time (min)	$C^{b,c}$ (%)
1		480	95
2	$Cu(NO_3)_2$	130	95
3	$Ni(NO_3)_2$	85	97
4	$CoCl_2$	10	100
5	$Zn(OTf)_2$	5	100
6	$Zn(NO_3)_2$	5	100
7	$Zn(ClO_4)_2$	5	100
8	$ZnCl_2$	5	100
9	$ZnCl_2^d$	5	97
10	$ZnCl_2^e$	15	97

[a] 1.5 mol/equiv. [b] Reaction conversion. [c] The β-hydroxy sulfide product has been isolated in 94–96% yields. [d] 5 mol %. [e] 2 mol %.

possibility of performing the thiolysis of 1,2-epoxides in aqueous medium under virtually biomimetic conditions (using water, at pH 7.0, room temperature). This opportunity is of great value in the case of acid- and base-sensitive 1,2-epoxides.

In any case, an attempt to find a good catalyst for a reaction carried out in neutral water, as sole reaction medium, is an intriguing challenge.

Results and Discussion

As a part of our research on organic synthesis in aqueous medium,[6b,8g,10,11] in this paper we report the results of catalyzed and uncatalyzed thiolysis of 1,2-epoxides carried out in sole water under neutral conditions (pH 7.0).

Initially, we investigated the thiolysis of 1,2-cyclohexene oxide (**1**) by thiophenol (Table 1). Co(II), Ni (II), Cu(II), and Zn(II) salts were screened as catalysts.

The catalytic efficiency of Ni(II) and Cu(II) was very poor (Table 1, entries 2 and 3), while Zn(II) and Co(II) gave a very high catalytic efficiency (Table 1, entries 4 and 5). The results showed that Zn(II) salts were excellent catalysts for the reaction at 30 °C independent of the counterion used (Table 1, entries 5–8 vs 1). Only the *trans*-β-hydroxysulfide **2** was found, and the nucleophilic addition of water was never observed. Zn(II) salts have rarely been used to catalyze the thiolysis of 1,2-epoxides and always in organic solvents,[9a–e] despite the fact that Zn(II) has been recognized as the most important Lewis acid in metallo-enzyme-catalyzed reactions in biological systems.[15]

$ZnCl_2$ was chosen as the Zn(II) salt as the research was extended to other 1,2-epoxides and other thiols because it is the cheapest Zn(II) salt and is efficient even at 5 and 2 mol % (Table 1, entries 9,10).

Table 2 illustrates the results of the thiolyses of a variety of α- and β-substituted 1,2-epoxides, 2,3-epoxy alcohols, and their OTMS, OTs, and OPh derivatives by thiophenol in water at 30 °C under neutral conditions. Thiolyses carried out under the same reaction conditions, but in the absence of catalyst, are included for comparison.

(15) Suh, J. *Acc. Chem. Res.* **1992**, *25*, 273–278.

TABLE 2. $ZnCl_2$-Catalyzed Thiolysis of 1,2-Epoxides by Thiophenol[a] in Water at 30 °C and pH 7.0

Entry	Epoxide	$ZnCl_2$ (10 mol%)	t (min)	$C (\%)^{b,c}$	Regio-selectivity
1	Ph α β **3**	-	510	100	α/β: 78/22
2		$ZnCl_2$	20	100	α/β: 84/16
3	C_6H_{13} α β **4**	-	6120	83	α/β: 1/99
4		$ZnCl_2$	10	100	α/β: 1/99
5	C_5H_{11} α β **5**	-	2220	100	α/β: 10/90
6		$ZnCl_2$	60	95	α/β: 17/83
7	α β C_4H_9 **6**	-	1080	100	α/β: 60/40
8		$ZnCl_2$	60	100	α/β: 65/35
9	**7**	-	1200	100	α/β: 20/80
10		$ZnCl_2$	5	100	α/β: 51/49
11	**8**	-	180	88	α/β: 1/99
12		$ZnCl_2$	15	91	α/β: 2/98
13	HO α β **9**	-	30	99	α/β: 1/99
14		$ZnCl_2$	5	99	α/β: 1/99
15	PhO 2 3 **10**	-	120	96	C_3/C_2: 99/1
16		$ZnCl_2$	5	100	C_3/C_2: 99/1
17	TMSO 2 3 **11**	-	5	99	C_3/C_2: 99/1
18		$ZnCl_2$	3	99	C_3/C_2: 99/1
19	HO 2 3 *n*-Pr **12**	-	1440	99	C_3/C_2: 81/19^d
20		$ZnCl_2$	300	99	C_3/C_2: 87/13^d
21	TMSO 2 3 *n*-Pr **13**	-	720	10^e	C_3/C_2: 87/13^{d,f}
22		$ZnCl_2$	720	99	C_3/C_2: 87/13^{d,f}
23	TsO 2 3 *n*-Pr **14**	-	1200	2	C_3/C_2: 0^{d,g}
24		$ZnCl_2$	1200	100	C_3/C_2: 93/7^{d,h}

[a] 1.5 mol/equiv. [b] Reaction conversion. [c] For the reactions with a complete conversion, the β-hydroxy sulfide products have been isolated in 94–97% yields. [d] Only *anti* diastereoisomers were found. [e] At 50 °C, 6 h, conversion = 99%; C_3/C_2 83/17. [f] The nucleophilic attack is accompainied by the deprotection of hydroxy group; **15** R = H (87%) and **18** R = H (13%) were the reaction products. [g] At 30 °C, substitution occurred only at C-1; at 50 °C, the conversion was 11% after 168 h, and a mixture of attack at C-3 **15** R = H (80%) and substitution at C-1 (20%) was found. [h] A mixture of **15**, R = Ts (76%), **16** (17%), and **17** (7%).

The presence of $ZnCl_2$ strongly accelerated all the reactions but did not affect the regioselectivity of the

SCHEME 1

	R
12	H
13	TMS
14	Ts

process that, as it is known,[8,9] is mainly determined by the steric and electronic features of the oxirane system. Thus, the C-β attack is the one preferred for alkyl-1,2-epoxides **4**, **5**, and **8** (Table 2, entries 3−6, 11−12), and the C-α attack is preferred for the styrene oxide **3** (Table 2, entries 1 and 2) and for the 1,2-epoxide **6** (Table 2, entries 7 and 8). Interestingly, the epoxyhexanol **9** only gave 6-(phenylthio)hexane-1,5-diol as a product of ring opening at C-β; no products derived from an intramolecular nucleophilic attack of the hydroxy group on the oxirane ring were observed.[16]

2,3-Epoxy alcohol **12** and the related compounds **10**, **11**, **13**, and **14** (Table, entries 15−24) showed a high inherent tendency for ring opening at C-3.

When there are no substituents at C-3, the attack is practically exclusive at this site, while the product of ring opening at C-2 was found with increasing steric hindrance at C-3 (Table 2, entries 19−24). Phenoxy- and trimethylsilyloxyglycidols **10** and **11** reacted easily at 30 °C without hydrolyzing the OPh and OTMS ethereal moieties (Table 2, entries 15−18). The analogous **13**, on the contrary, was much less reactive, and the protective group was hydrolyzed affording a 87:13 mixture of **15** (R = H) and **18** (R = H), respectively (Scheme 1). Epoxy tosyl derivative **14** was practically unreactive when the reaction was carried out without catalyst, while in the presence of ZnCl$_2$, thiophenol attacked all three electrophilic carbons C-1, C-2, and C-3 producing **15** (R = Ts) (76%), **16** (17%), and **17**[8a] (7%), respectively (Table 2, entries 23 and 24). All the 1,2-epoxides considered in this paper gave only *anti*-oxirane ring opening.

Table 3 illustrates the results of ZnCl$_2$-catalyzed thiolyses of 1-methyl-1,2-cyclohexene oxide (**7**) by arylthiophenols in aqueous medium at 30 °C under neutral conditions.

ZnCl$_2$ efficiently catalyzed only the thiolysis by *o*-methylthiophenol (Table 3, entries 1 and 2). Slight catalytic effects were observed when *p*-acetamido- and *o*-metoxycarbonylthiophenol (Table 3, entries 7, 8 and 11, 12) were used. ZnCl$_2$ slowed the reactions of **7** with the other thiols (Table 3, entries 4 vs 3, 6 vs 5, 10 vs 9 and 14 vs 13). Probably, the amino and the carboxy groups,

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(16) The epoxidation of homo- and bis-homoallylic alcohols and the ring-opening of the corresponding oxiranes in organic medium is often accompanied by the formation of hydroxy tetrahydrofuran and tetrahydropyran derivatives.[17] In our case, the preparation of 1,2-epoxide **9** has been performed in water at pH 7.0 by oxidation of the corresponding alkene (10 mmol) with *m*-chloroperbenzoic acid (*m*-CPBA, 30 mmol), and the pH has been kept constant for the entire reaction time (2 h). With this procedure, we did not find any tetrahydrofuran or tetrahydropyrans derivatives as byproducts and the 5,6-epoxy-1-hexanol (**9**) has been obtained in 85% yield after workup of the reaction mixture.

TABLE 3. ZnCl$_2$-Catalyzed Thiolyses of 1-Methyl-1,2-cyclohexene Oxide (7) by Arylthiophenols in Water at 30 °C and pH 7.0
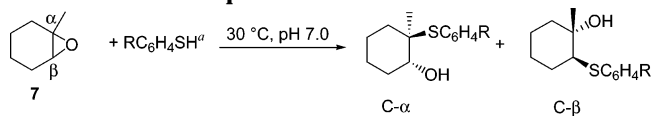
entry	R	ZnCl$_2$ (10 mol %)	time (min)	$C^{b,c}$ (%)	regioselectivity α/β
1	*o*-Me		4300	52	10/90
2		ZnCl$_2$	5	98	44/56
3	*o*-NH$_2$		600	100[d]	1/99
4		ZnCl$_2$	720	100[e]	1/99
5	*p*-NH$_2$		1200	97	4/96
6		ZnCl$_2$	1380	100	6/94
7	*p*-NHAc		720	100[f]	12/88
8		ZnCl$_2$	180	98	10/90
9	*o*-CO$_2$H		420	100	1/99
10		ZnCl$_2$	600	100	1/99
11	*o*-CO$_2$Me		2900	87[g]	2/98
12		ZnCl$_2$	1800	98	1/99
13	*p*-CO$_2$H		10	100[h]	7/93
14		ZnCl$_2$	20	100[h]	2/98

[a] 1.5 mol/equiv. [b] Reaction conversion. [c] For the reaction with a complete conversion, the β-hydroxy sulfide products have been isolated in 94−97% yields. [d] Diol 30%. [e] Diol 12%. [f] Diol 13%. [g] Diol 9%. [h] Diol 10%.

when present as substituents to thiophenol, strongly bind to Zn^{2+} inhibiting its catalytic activity. Increasing the amount of catalyst to 20% did not modify the reaction results. The thiolysis of **7** has also been performed with butanethiol (3 mol/equiv) as a representative alkylthiol; at pH 7.0, ZnCl$_2$ catalyzed this reaction that was finished in 12 h with α/β = 7/93 and 2% of diol, while the uncatalyzed process gave after 48 h only 45% of conversion and 73% of diol.

We observe that the increasing C-α attack, found in the catalyzed thiolysis of 1-methyl-1,2-cyclohexene oxide (**7**) with thiophenol and *o*-methylthiophenol (Table 2, entries 9 and 10, and Table 3, entries 1 and 2) cannot be ascribed to a C$_\alpha$−O bond polarization induced by Zn(II); indeed, the regiochemical courses for Zn-catalyzed and uncatalyzed reactions are identical for all the other substrates. This small effect found in the case of **7** is probably due to a different conformational equilibrium for the Zn-complexed 1,2-epoxide **7** with respect to the uncomplexed one. For a better understanding of this result further investigations are necessary.

The structures of new β-hydroxy sulfides **15** (R = Ts) and **16** and those derived from the thiolyses of **9** and **11** with thiophenol and of **7** with butanethiol were confirmed by ^{1}H and ^{13}C NMR, GC−MS and IR data (see the Supporting Information).

Finally, we investigated the recycling of the aqueous medium and of the catalyst (mother liquors from extractions) in subsequent thiolyses, for example, thiolysis of 1,2-octene oxide (**4**) with thiophenol (Table 4).

After 10 min, the reaction was finished and then the pH of the aqueous mixture was adjusted to 9−9.5 by adding NaOH aqueous solution. Zn(II) and the unreacted thiophenol were completely soluble in the aqueous medium as tetrahydroxy zincate and thiolate ions, respec-

TABLE 4. Reuse of the Aqueous Medium and of the Catalyst
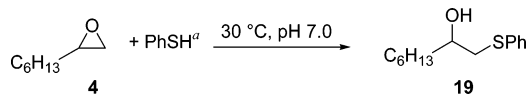
run	time (min)	yield[b] (%)
I	10	95
II	10	95
III	15	95
IV	20	90

[a] 1.5 mol/equiv in the first run and 1.0 mol/equiv in the subsequent runs. [b] Yield of isolated product.

tively. This allowed the β-hydroxysulfide **19** to be extracted uncontaminated by the catalyst and nucleophilic species. The mother liquors were then reused as follows: (i) a new amount of thiol was added,[18] (ii) the pH was adjusted to 7.0, and (iii) the epoxide **4** was again charged. The same aqueous medium was used for four runs without significant variations in the reaction time and yield (Table 4). No catalyst was added after the first run.

In summary, $ZnCl_2$ (10 mol %), which has been recommended to be used under anhydrous conditions in organic processes, in our hands, in an aqueous mixture and under neutral conditions (pH 7.0), strongly accelerates the thiolysis of 1,2-epoxides with a variety of thiols with the exception of those bearing strong coordinating groups such as amino or carboxy goups. The aqueous medium and the catalyst have been recovered and reused several times without significant variations in the reaction times, selectivities, and yields.

(17) (a) Janda, K. D.; Shevlin, C. G.; Lerner, R. A. *J. Am. Chem. Soc.* **1995**, *117*, 2659−2660. (b) Mihailović, M. Lj; Marinković, D. *Croat. Chem. Acta* **1986**, 109−120. (c) Mousseron-Canet, M.; Levallois, C.; Huerre, H. *Bull. Soc. Chim. France* **1966**, 658−660.
(18) In the first run, 1.5 equiv of thiophenol was used according to the standard procedure (see the Experimental Section). In the subsequent runs, 1.0 equiv of thiol was used and the reaction conversion was 100%.

Experimental Section

$ZnCl_2$-Catalyzed Thiolysis. General Procedure. Thiol (1.5 mmol) and 0.1 M aqueous solution of $ZnCl_2$ (1 mL, 0.1 mmol) were dissolved in water (0.7 mL), in a flask thermostated at 30 °C and equipped with a magnetic stirrer. The pH of the aqueous mixture was adjusted to 7.0 by adding some drops of 5 M NaOH aqueous solution. The 1,2-epoxide (1.0 mmol) was then added under stirring. The pH tended to increase and was kept constant at 7.0 by adding some drops of 10% aqueous H_2SO_4. After the reaction times reported in the tables, some drops of 5 M NaOH aqueous solution were added to the reaction mixture to reach pH 9−9.5 and the aqueous basic solution was extracted with Et_2O (3 × 2 mL). The combined organic layers, evaporated at reduced pressure, furnished the β-hydroxy sulfide that was purified by recrystallization or by column chromatography.

Uncatalyzed Thiolysis. General Procedure. Thiol (1.5 mmol) dissolved in water (1.8 mL) was put in a flask thermostated at 30 °C and equipped with a magnetic stirrer. The pH was adjusted to 7.0 by adding some drops of 5 M NaOH aqueous solution. The 1,2-epoxide (1.0 mmol) was added under stirring that continued for the time reported in the tables. The final reaction mixture was then worked up as reported above.

Reuse of Aqueous Medium and of $ZnCl_2$ Catalyst. Thiol (1.0 mmol) was added to the basic mother liquors remaining after the extraction of β-hydroxy sulfide and the pH was adjusted to 7.0 by adding some drops of 10% aqueous H_2SO_4. After 30 min, the 1,2-epoxide (1.0 mmol) was then added and the mixture stirred at 30 °C the times reported (Tables 1−3). The reaction mixture was worked-up as above and the mother liquors could then be recycled (Table 4).

Supporting Information Available: Full characterization (^1H NMR, ^{13}C NMR, IR, GC−MS, R_f) for compounds **15** (R = Ts) and **16** and compounds deriving from the thiolysis of **7** with butanethiol and from the thiolyses of **9** and **11** with thiophenol. This material is available free of charge via the Internet at http://pubs.acs.org.

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