Thiolysis of Alkyl- and Aryl-1,2-epoxides in Water Catalyzed by $InCl_3$

Francesco Fringuelli,* Ferdinando Pizzo, Simone Tortoioli, Luigi Vaccaro

Dipartimento di Chimica, Università di Perugia, Via Elce di Sotto 8, 06123 Perugia, Italy
Fax: (+39)-075-5855560, e-mail: frifra@unipg.it

Received: October 31, 2001; Accepted: February 14, 2002

Abstract: The pH dependence of thiolysis of 1,2-epoxides with thiophenol in water and the influence of a Lewis acid catalyst is investigated. $InCl_3$ showed a very high efficiency in catalyzing this process at pH 4.0. The regioselectivity of the nucleophilic attack is markedly influenced going from pH 9.0 to pH 4.0. A *one-pot* procedure running solely in water to prepare *trans*-2-(phenylsulphinyl)cyclohexan-1-ol is reported starting from epoxycyclohexane, *via* thiolysis reaction and oxidation with *t*-butyl hydroperoxide.

Keywords: green chemistry; $InCl_3$; Lewis acid catalysis; thiolysis of oxiranes; water

Introduction

Ring opening of 1,2-epoxides with thiol-derived nucleophiles is a well-established route to β-hydroxy sulfides that has been applied for the preparation of allylic alcohols,[1] cyclic sulfides,[2] thioketones[3] and of important intermediates for the synthesis of natural products[4] and compounds of biological and pharmacological interest.[5]

To date, the thiolysis of 1,2-epoxides has been performed fundamentally in two ways: by using thiolates under basic conditions[6,7] or thiols in the presence of a variety of activating agents.[9] In the first case, the reactions occur with good yields in short times under anhydrous conditions. The second strategy uses different kinds of promoting agents including alumina,[9a] silica gel,[9b] Montmorillonite,[9c] polyethylene glycol,[9d] and hydrosulfide exchange resin[9e] as heterogeneous catalysts, or the more common Lewis acids such as $LnCl_3$,[9f] $CoCl_2$,[9g] Ti(O-*i*-Pr)$_4$,[9h, i] $(NH_4)_2Ce(NO_3)_6$,[9j] $LiClO_4$,[9k] $BF_3 \cdot Et_2O$,[9l] SmI_2,[9m] and more complex Lewis acids such as (salen)chromium[9n] and titanium complexes,[9o] tricarbonyl(arene)(thiol)chromium complex,[9p] gallium binaphthoxide complex[9q] and metal tartrates[9r] to carry out enantioselective syntheses. Generally in these cases, the reaction times are long and the yields are not always good.

Our continuing interest in organic synthesis performed exclusively in water[10] stimulated us to investigate the Lewis acid-catalyzed thiolysis of epoxides in aqueous medium.

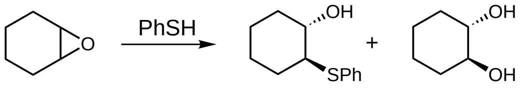
This is a part of a synthetic strategy that we have developed in the azidolysis,[10a] bromolysis,[10b] and iodolysis[10b] in water of alkyl- and aryl-substituted 1,2-epoxides and of α,β-epoxycarboxylic acids and that meets "Click Chemistry" standards as described by Sharpless.[11] The use of water as reaction medium facilitates[12] the nucleophilic addition to epoxides because (i) it responds to the demand for hydrogen bonding of these substrates, (ii) its high heat capacity is a helpful property for processes scaling-up, and (iii) allows the pH to be easily changed and controlled as well as the concentration of aqua ion when the process is catalyzed by a Lewis acid. Recently, we have shown[10a–f] that the Lewis acid catalysis in water is strongly dependent on the pH and by maintaining the pH at a suitable level it is possible to either control the regioselectivity of the reaction or use Lewis acids such as $AlCl_3$, $TiCl_4$ and $SnCl_4$ for which anhydrous conditions are recommended. The thiolysis of 1,2-epoxides catalyzed by Lewis acids in water as the only solvent and the dependence of this reaction on the pH[13] were not previously investigated.

Results and Discussion

First, we investigated the thiolysis of epoxycyclohexane (**1**) with thiophenol in water at different pH values and with various Lewis acid salts. The reactions were performed under heterogeneous conditions at 30 °C in the presence of 10 mol % of catalyst. The pH of the reaction medium was kept constant for the entire reaction time.[14] Reactions in the absence of salt catalyst at the same pH were carried out for comparison purposes. Table 1 illustrates the results. *trans*-2-(Thiophenyl)cyclohexan-1-ol (**2**) and *trans*-1,2-cyclohexanediol (**3**) were the sole reaction products.

In the absence of Lewis acid catalysts (Table 1, entries 1, 3, 8, 10) the best result (100% of **2** after 3 h)

Table 1. Thiolysis by thiophenol of epoxycyclohexane (**1**) in water at 30 °C.



1 **2** **3**

Entry	pH	Catalyst [10 mol %]	t [min]	C[a] [%]	Products [%][b]	
					2	**3**
1	2.0	none	15	99	25	75
2	2.0	$InCl_3$	3	99	100	0
3	4.0	none	1440	90	94	6
4	4.0	$InCl_3$	10	99	100	0
5	4.0	$Cu(NO_3)_2$	240	99	32	68
6	4.0	$Sc(OTf)_3$	420	33	73	27
7	4.0	$AlCl_3$	240	37	75	25
8	7.0	none	480	95	100	0
9	7.0	$InCl_3$	45	99	100	0
10	9.0	none	180	99	100	0
11	9.0	$InCl_3$	120	99	100	0

[a] Reaction conversion.

[b] GC ratios of the products; when the conversion is quantitative and **2** was the sole reaction product, it was isolated with 93 – 95% yield.

was achieved, as expected, under basic conditions (pH 9.0), namely, when a high concentration of phenylthiolate was present (p*K*a of PhSH = 6.5).[15]

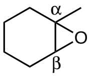
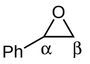
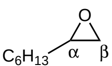
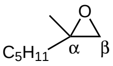
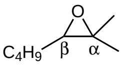
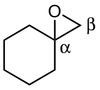
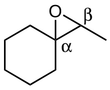
At pH 2.0, there was a considerable Brønsted catalysis (Table 1, compare the results of entry 1 and entry 8) but the reaction was not chemoselective and the diol **3** was the prevailing compound. At pH 2.0 (Table 1, entry 2) the $InCl_3$-catalyzed reaction was complete after 3 min, and the absence of diol **3** (Table 1, compare entry 1 with 2) should indicate that the indium ion coordinates both the epoxide and the nucleophile which is then delivered to the oxirane carbon. Under these last conditions a contribution of Brønsted catalysis to the formation of **2** cannot be excluded.

At pH 4.0 $InCl_3$ is the best catalyst with respect to $Cu(NO_3)_2$, $Sc(OTf)_3$, and $AlCl_3$ (Table 1, entries 4 – 7), and in this case the proton catalysis is negligible (Table 1, compare entries 3 and 4).

At pH 7.0 (Table 1, entries 8 and 9) $InCl_3$ is able to catalyze the reaction too, although less efficiently, while it is practically ineffective under more basic conditions (Table 1, entries 10 and 11).

The investigation was then extended to a variety of unsymmetrical 1,2-epoxides to evaluate the regioselectivity of the reaction. Table 2 illustrates the results of the reactions carried out at 30° and at pH 4.0 in the presence of 10 mol % of $InCl_3$ and at pH 4.0 and 9.0 in the absence of catalyst. The epoxides were prepared by epoxidation of the corresponding alkenes with MCPBA in pH-controlled aqueous medium according to our previously reported procedure[16] and the structures of the products of thiolysis were proven by ^1H and ^{13}C NMR analyses and comparison with authentic samples.[8a,9g,17] The hydroxy sulfides from the attack of C-α of **6** and **7** and the two sulfide regioisomers resulting from the thiolysis of **8** are new compounds and are described in the experimental section. All reactions were performed under heterogeneous conditions. The sole formation of *trans*-β-hydroxy sulfides from thiolysis of **4** indicates that the reaction is *anti* diastereoselective. The experimental procedure has been found to be efficacious even on a large scale. The reaction under catalyzed acidic conditions of **5** and the reaction under uncatalyzed basic

Table 2. Thiolysis by thiophenol of 1,2-epoxides **4 – 10** in water at 30 °C.

Epoxide	pH	Cat. [10 mol %]	t [min]	C[a] [%]	α/β[b]	Yield[c] [%]
 **4**	9.0	none	120	99	3/97	90
	4.0	none	120	99d	55/45	
	4.0	$InCl_3$	3	99	55/45	30
 **5**	9.0	none	20	90	75/25	55
	4.0	none	720	99	70/30	
	4.0	$InCl_3$	5	99	97/3	91
 **6**	9.0	none	120	90	2/98	85
	4.0	none	2160	19	5/95	
	4.0	$InCl_3$	10	99	13/87	75[e]
 **7**	9.0	none	120	98	5/95	88
	4.0	none	2160	60	30/70	
	4.0	$InCl_3$	10	99	39/61	50[e]
 **8**	9.0	none	2880	93	1/99	80
	4.0	none	1440	98	63/37	
	4.0	$InCl_3$	10	99	65/35	50
 **9**	9.0	none	20	99	1/99	95
	4.0	none	1440	99	82/18	
	4.0	$InCl_3$	5	99	88/12	78
 **10**	9.0	none	1440	87	18/82	60
	4.0	none	1440	13	34/66	
	4.0	$InCl_3$	5	99	40/60	50

[a] Reaction conversion.

[b] GC ratios of the products.

[c] Yield of the isolated main reaction product.

[d] 30% of diol **3** was present.

[e] The α-adduct was characterized by using a chromatographically enriched mixture.

conditions of **6** have been performed on a 100 mmol scale without encountering any problems and obtaining the same results than those reported for the 1 mmol scale.

The uncatalyzed reaction at pH 9.0 proceeds *via* an S_N2 mechanism mainly or exclusively at the less substituted β-carbon of all the epoxides with the exception of styrene oxide **5**, in which the attack of the nucleophile is driven predominantly, as expected, at the benzylic α-carbon by electronic effects. At pH 4.0, in the absence of $InCl_3$ the α-regioselectivity of the reaction strongly increased and in some cases the β-hydroxy-α-thiophenyl sulfide was the prevalent product (compounds **4**, **8**, and **9**), but long reaction times (2 – 36 h) were generally required. The presence of 10 mol % of $InCl_3$ strongly accelerated the reactions that were completed within 3 – 10 min and likewise greatly changed the regioisomeric ratio as compared to the reactions carried out at pH 9.0. Thus, the α-regioselectivity of thiolysis of **4**, **8**, and **9** increased by 40, 186, and 733 times and that of the other epoxides by 3 – 12 times.

The rationalization of the strong catalytic effect of $InCl_3$ and the increased α-regioselectivity requires further investigations. At present, these results can be justified considering that the aqua species $In(H_2O)_6^{3+}$, present in high concentration at pH 4.0,[18] coordinates to the epoxide resulting in a considerable positive charge on the more substituted α-carbon, thereby favoring the nucleophilic attack according to an S_N2-*borderline* mechanism.

The metal-complexation of epoxide probably causes a greater polarization of more substituted α-carbon of oxirane than that produced by protonation. The regioselectivities of the ring-opening observed in the proton- and indium-catalyzed reactions are roughly the same, indicating that the charge density ratio on C-α and C-β of protonated epoxide is very similar to that of indium-complexed epoxide.

Several years ago, we reported that sulfoxides can be easily prepared with excellent yields by oxidation of sulfides with *t*-butyl hydroperoxide in water under acidic conditions.[19] Coupling that procedure with the thiolysis reported here, β-hydroxyphenyl sulfoxides can be prepared from epoxides by a *one-pot* procedure[20] in aqueous medium. For example, the *trans*-2-(phenylsulfinyl)-cyclohexane-1-ol was obtained as a 7:3 mixture of two sulfoxide diasteroisomers[1a] from epoxycyclohexane (**1**) in quantitative yield. The procedure does not require any organic co-solvent since the sulfoxides precipitated from the aqueous medium and were isolated by simple filtration.

Conclusion

In summary, the reactivity and regioselectivity of thiolysis of alkyl- and aryl-1,2-epoxides with thiophenol in water as the only solvent is strongly affected by the pH and by the presence of Lewis acids. Under basic conditions (pH 9.0) and without catalyst, the reaction is generally slow (up to 48 h) and occurs prevalently (82 – 99%) at the less substituted β-carbon of unsymmetrical epoxides, except when the substituent is a phenyl group (25%). At pH 4.0 and in the presence of 10 mol % of $InCl_3$, the reaction is very fast (3 – 10 min) and a higher amount of α-adduct is observed (13 – 97%).

These results open the route to the synthesis of building blocks of synthetic interest such as allylic alcohols and ketones (either racemic or enantiopure) by an environmentally benign procedure. Moreover, this is a rare case[10e, 21] in which the reaction of a monodentate substrate is catalyzed in water alone by a Lewis acid.

Experimental Section

General Remarks

All chemicals were purchased and used without any further purification. GC analyses were performed with an SPB-5 fused silica capillary column (30 m, 0.25 mm diameter) an "on column" injector system, a FID detector, and hydrogen as the carrier gas. GC/MS analyses were carried out with 70 eV electron energy. Column chromatographies were performed on silica gel (0.040 – 0.062 mm). ^1H and ^{13}C NMR spectra were recorded at 200, 101.2, 50.6 MHz respectively, in $CDCl_3$ as solvent with TMS as internal standard. Epoxides **1**, **5**, and **6** are commercially available, epoxides **4**, **7**, **8**, **9**, and **10** were synthesized by oxidation of the corresponding alkene with *m*-chloroperoxybenzoic acid (MCPBA).[16] In a typical procedure MCPBA (77%; 22 mmol) was added to an aqueous suspension of the alkene (20 mmol) in 130 mL of 0.3 N aqueous $NaHCO_3$ at 0 °C over 10 min. The heterogeneous mixture was stirred for 2 – 4 h and then extracted with Et_2O (4 × 40 mL); the organic phase was washed two times with a cold 1.5 M aqueous solution of NaOH, dried (Na_2SO_4) and concentrated under reduced pressure furnishing the epoxide in 80 – 90% yield. The hydroxy sulfides arising from thiolysis of **1**,[9a,17b] **4**,[17a,17b] **5**,[17b,9g] **9**,[17c,17d] **10**,[17e,17f] and those coming from the attack at C-β of **6**,[8a] **7**,[17g] are known compounds.

The hydroxy sulfides from the attack at C-α of **6** and **7** and the two sulfides regioisomers resulting from the thiolysis of **8** are new compounds.

Thiolysis of 1,2-Epoxides in the Absence of $InCl_3$

In a flask thermostatted at 30 °C, equipped with a magnetic stirrer and pH-stat apparatus, thiophenol (0.15 mL, 1.5 mmol) was dissolved in water (2.0 mL). The resulting pH was 4.5. By adding some drops of a concentrated aqueous solution of H_2SO_4 or NaOH the pH was adjusted at the desired value. The epoxide (1.0 mmol) was added under stirring and the pH was kept constant at the fixed value by adding a 10% aqueous H_2SO_4 solution. After the times reported in Tables some drops of concentrated NaOH solution were added and the mixture was extracted with Et_2O (3 × 2 mL). The combined organic layers were dried and evaporated under reduced pressure to give the β-hydroxy sulfide which was purified by column chromatography.

Thiolysis of 1,2-Epoxides in the Presence of $InCl_3$ at pH 4.0

In a flask thermostatted at 30 °C, equipped with a magnetic stirrer and pH-stat apparatus, thiophenol (0.15 mL, 1.5 mmol) and 1.0 mL of a 0.1 M aqueous solution of the $InCl_3$ (0.1 mmol) were added to 0.7 mL of water. The resulting pH was 1.8. By addition of 100 μL of an aqueous 0.5 M solution of NaOH the pH was brought at 4.0. The epoxide (1.0 mmol) was then added under stirring and the pH was kept constant at the fixed value by adding a 10% aqueous H_2SO_4 solution. After the times reported in Tables the reaction mixture was worked-up as above.

2-(Thiophenyl)octan-1-ol: Prepared under acidic conditions (pH = 4.0, $InCl_3$) from **6**. The chromatographic purification of this product is difficult because it is present at 13% in the reaction mixture. It is identified by using an enriched mixture obtained by column chromatography on silica gel eluting with 95/5, *n*-hexane/EtOAc; yield: see Table 2. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.87$ (t, $J = 6.4$ Hz, 3H, H-8), 1.27 – 1.54 (m, 10H, H-3, -4, -5, -6, -7), 1.87 (br s, 1H, OH), 3.13 – 3.17 (m, 1H, H-2), 3.52 (dd, $J = 11.5$, 6.3 Hz, 1H, H-1a), 3.62, (dd, $J = 11.5$, 5.0 Hz, 1H, H-1b), 7.19 – 7.41 (m, 5H, H-aromatic); ^{13}C NMR (101.2 MHz, $CDCl_3$): $\delta = 14.0$, 22.5, 26.9, 29.1, 31.2, 31.6, 52.5, 63.8, 127.3, 128.9, 132.7, 133.7.

2-Methyl-2-(thiophenyl)-heptan-1-ol: Prepared under acidic conditions (pH = 4.0, $InCl_3$) from **7**. It is identified by using an enriched mixture obtained by chromatography on silica gel and purified by chromatography on silica gel, eluting with 95/5 petroleum ether/ Et_2O: oil; yield: see Table 2. ^{1}H NMR ($CDCl_3$, 200 MHz) $\delta = 0.86 – 0.93$ (t, $J = 6.8$ Hz, 3H, H-7), 1.14 (s, 3H, Me), 1.20 – 1.55 (m, 8H, H-3, -4, -5, -6), 2.20 (s, 1H, OH), 3.20 – 3.25 (m, 2H, H-1), 7.26 – 7.39 (m, 3H, H-aromatic), 7.46 – 7.51 (m, 2H, H-aromatic); ^{13}C NMR ($CDCl_3$, 50.6 MHz): $\delta = 14.0$, 22.1, 22.6, 23.5, 36.9, 55.8, 66.9, 67.9, 126.2, 128.9, 129.1, 130.2; MS (EI, 70 eV): m/z = 238 (M$^+$, 2), 218 (90), 185 (17), 154 (20), 109 (100), 65 (45); anal. calcd. for $C_{14}H_{22}OS$ (238.14): C 70.54, H 9.30, S 13.45%; found: C 70.48, H 9.29 S 13.51%.

2-Methyl-2-(thiophenyl)-heptan-3-ol: Prepared under acidic conditions (pH = 4.0, $InCl_3$) from **8** and purified by column chromatography on silica gel eluting with 95/5, *n*-hexane/ EtOAc: oil; yield: 50%. IR ($CHCl_3$): ν = 3488 (w), 3067 (w), 2961 (s), 1462 (m), 1390 (m), 1304 (m), 1272 (m), 1057 (w) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.90$ (t, $J = 6.9$ Hz, 3H, H-7), 1.21 (s, 3H, Me), 1.26 (s, 3H, Me), 1.3 – 1.6 (m, 6H, H-4, -5, -6), 2.97 (s, 1H, OH), 3.28 (d, $J = 8.6$ Hz, 1H, H-3), 7.2 – 7.4 (m, 3H, H-aromatic), 7.5 – 7.6 (m, 2H, H-aromatic); ^{13}C NMR (50.6 MHz, $CDCl_3$): $\delta = 14.1$, 22.0, 22.8, 25.9, 29.5, 30.2, 55.7, 75.1, 128.7, 129.1, 130.5, 137.4; MS (EI, 70 eV): *m/z* = 238 (M$^+$, 9), 151 (100), 110 (89), 69 (26), 43 (12); anal. calcd. for $C_{14}H_{22}OS$ (238.14): C 70.54, H, 9.30, S 13.45%; found: C 70.58, H 9.36, S 13.35%.

2-Methyl-3-(thiophenyl)-heptan-2-ol: Prepared under acidic conditions (pH = 4.0, $InCl_3$) from **8** and purified by column chromatography on silica gel eluting with 95/5, *n*-hexane/ EtOAc: oil; yield: 80%. IR ($CHCl_3$): ν = 3497 (w), 2929 (s), 1467 (m), 1373 (m), 1337 (m), 1256 (m), 1166 (w), 1114 (s), 1093 (s) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.87$ (t, $J = 6.9$ Hz, 3H, H-7), 1.23 (s, 3H, Me), 1.26 (s, 3H, Me), 1.3 – 1.5 (m, 6H, H-4, -5, -6), 2.70 (br s, 1H, OH), 3.03 (dd, $J = 10.9$, 1.9 Hz, 1H, H-3), 7.14 – 7.3 (m, 3H, H-aromatic), 7.4 – 7.5 (m, 2H, H-aromatic); ^{13}C NMR (50.6 MHz, $CDCl_3$): $\delta = 13.9$, 22.5, 25.9, 27.1, 30.5, 32.3, 65.4, 73.1, 126.4, 128.9, 130.7, 137.4; MS (EI, 70 eV): *m/z* = 238 (M$^+$, 11), 180 (83), 123 (41), 110 (100), 59 (46), 43 (26); anal. calcd. for $C_{14}H_{22}OS$ (238.14): C 70.54, H 9.30, S 13.45%; found: C 70.49, H 9.28, S 13.37%.

Scale-Up of Thiolysis of Epoxides 5 and 6

The thiolysis under catalyzed acidic conditions of **5** and that under uncatalyzed basic conditions of **6** have been performed on a 100 mmol scale following the above described experimental procedures and obtaining the same yields and selectivities reported in Table 2 but with longer reaction times (10 min and 4 h, respectively).

One-Pot Synthesis of *trans*-2-(Phenylsulfinyl)-cyclohexan-1-ol

In a flask thermostatted at 30 °C, equipped with a magnetic stirrer and pH-stat apparatus, thiophenol (0.3 mL, 3.0 mmol) and 2.0 mL of aqueous 0.1 M $InCl_3$ (0.2 mmol) were dissolved in 2.0 mL of water. The resulting pH value was 1.8. By the addition of 100 μL of an aqueous 5 M solution of NaOH the pH was adjusted at 4.0. Epoxide **1** (0.2 mL, 2.0 mmol) was added. During the reaction the pH was kept constant by adding a 10% aqueous solution of H_2SO_4. After 10 min 70% aqueous solution of *t*-butyl hydroperoxide (1.5 mL, 12 mmol) was added, the pH adjusted to 4.0 and the resulting mixture heated at 70 °C for 4 hours. The mixture was cooled to room temperature and filtered to give the hydroxy sulfoxides in quantitative yield as a mixture of two diastereoisomers: major isomer (70%): ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 0.90 – 1.53$ (m, 6H, H-3, -4, -5), 1.56 – 1.82 (br m, 2H, H-1), 2.70 – 2.83 (ddd, $J = 4.4$, 9.7, 11.9 Hz, 1H, H-2), 4.06 (m, 1H, H-1), 7.49 – 7.55 (m, 3H, H-aromatic), 7.67 – 7.72 (m, 2H, H-aromatic); minor isomer (30%): ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 0.90 – 1.53$ (m, 6H, H-3, -4, -5), 2.03 – 2.20 (br m, 2H, H-1), 2.60 (dd, $J = 15.7$, 10.0 Hz, 1H, H-2), 3.92 (m, 1H, H-1), 7.49 – 7.55 (m, 3H, H-aromatic), 7.67 – 7.72 (m, 2H, H-aromatic).

Acknowledgements

The Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST), the Consiglio Nazionale delle Ricerche (CNR) and the Università di Perugia are thanked for financial support. The Consorzio Interuniversitario Nazionale Metodologie e Processi Innovativi di Sintesi (CINMPIS) is thanked for scholarship accorded to Dr. Simone Tortoioli.

References and Notes

[1] a) V. Kesavan, D. Bonnet-Delpon, J.-P. Bégué, *Tetrahedron Lett.* **2000**, *41*, 2895 – 2898; b) R. B. Mitra, Z.

Muljiani, A. R: A: S: D, Deshmukh, V. S. Joshi, S. R. Gadre, *Synthetic Commun*. **1984**, 14, 101–112.

[2] a) S. Ozaki, E. Matsui, H. Yoshinaga, S. Kitagawa, *Tetrahedron Lett.* **2000**, *41*, 2621–2624; b) B. M. Adger, J. V. Barkley, S. Bergeron, M. W. Cappi, B. E. Flowerdew, M. P. Jackson, R. McCague, T. C. Nugent, S. M. Roberts, *J. Chem. Soc. Perkin Trans. 1* **1997**, 3501–3507.

[3] J.-P. Bégué, D. Bonnet-Delpon, A. Kornilov, *Synthesis* **1996**, 529–532.

[4] a) P. Wipf, P. Jeger, Y. Kim, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 351–356; b) V. Jaeger, D. Schroeter, B. Koppenhoefer, *Tetrahedron* **1991**, *47*, 2195–2210; c) M. Chini, P. Crotti, L. A. Flippin., A. Lee, F. Macchia, *J. Org. Chem.* **1991**, *56*, 7043–7048; d) P. Meffre, L. Vo Quang, Y. Vo Quang, F. Le Goffic, *Tetrahedron Lett.* **1990**, *31*, 2291–2294; e) V. Jaeger, W. Huemmer, *Angew. Chem.* **1990**, *102*, 1182–1183.

[5] a) A. Scwartz, P. B. Madan, E. Mohacsi, J. P. O' Brien, L. J. Todaro, D. L. Coffen, *J. Org. Chem.* **1992**, *57*, 851–856; b) A. Conchillo, F. Cramps, A. Messeguer, *J. Org. Chem.* **1990**, *55*, 1728–1735; c) J. R. Luly, N. Yi, J. Soderquist, H. Stein, J. Cohen, T. J. Perun, J. J. Plattner, *J. Med. Chem.* **1987**, *30*, 1609–1616; c) E. J. Corey, D. A. Clark, A. Marfat, G. Goto, *Tetrahedron Lett.* **1980**, *21*, 3143–3146.

[6] a) M Romdhani Younes, M. M. Chaabouni, A. Baklouti, *Tetrahedron Lett.* **2001**, *42*, 3167–3169; b) J. C. Justo De Pomar, A. Soderquist, *Tetrahedron Lett.* **1998**, *29*, 4409–4412; c) C. H. Behrens, K. B. Sharpless, *J. Org. Chem.* **1985**, *20*, 5696–5704.

[7] The deprotonation of thiols has been also catalyzed by using onium salts.[8]

[8] a) D. Albanese, D. Landini, M. Penso, *Synthesis* **1994**, 34–36; b) T. Nishikubo, T. Izawa, M. Shimojo, T. Kato, A. Shiina, *J. Org. Chem.* **1990**, *55*, 2536–2542; c) T. Iizawa, A. Goto, T. Nishikubo, *Bull. Chem. Soc. Jpn.* **1989**, *62*, 597.

[9] a) G. H. Posner, D. Z. Rogers, *J. Am. Chem. Soc.* **1977**, *99*, 8208–8214; b) P. Raubo, J. Wicha, *Pol. J. Chem.* **1995**, *69*, 78–84; c) A. K. Maiti, G. K. Biswas, P. Bhattacharyya, *J. Chem. Res., Synop.* **1993**, 325; d) A. K. Maiti, P. Bhattacharyya, *Tetrahedron*; **1994**, *50*, 10483–10490; e) J. Choi, N. M. Yoon, *Synthesis*, **1995**, 373–375; f) A. E. Vougioukas, H. B. Kagan, *Tetrahedron Lett.* **1987**, *28*, 6065–6068; g) J. Iqbal, A. Pandey, A. Shukla, R. R. Srivastava, S. Tripathi, *Tetrahedron* **1990**, *46*, 6423–6432; h) J. M. Chong, K. B. Sharpless, *J. Org. Chem.* **1985**, *50*, 1560–1563; i) G, Lin, Z. Shi, C. Zeng, *Tetrahedron Asymmetry* **1993**, *4*, 1533–1536; j) N. Iranpoor, I. M. Baltork, F. S. Zardalao, *Tetrahedron* **1991**, *47*, 9861–9866; k) M. Chini, P. Crotti, E. Giovani, F. Macchia, M. Pineschi, *Synlett* **1992**, 303–305; l) P. N. Guivisdalsky, R. Bittman, *J. Am. Chem. Soc.* **1989**, *111*, 3077–3079; m) J. W. J. Still, L. J. P. Martin, *Synthetic Commun.* **1998**, *28*, 913–923; n) M. H. Wu, E. N. Jacobsen, *J. Org. Chem.* **1998**, *63*, 5252–5254; o) J. Wu, X.-L. Hou, L.-X. Dai, L.-J. Xia, M.-H. Tang, *Tetrahedron Asymmetry* **1998**, *9*, 3431–3436; p) S. Fukuzawa, H. Kato, M. Ohtaguchi, Y. Hayashi, H. Yamazaki, *J. Chem. Soc. Perkin Trans. 1* **1997**, 3059–3063; q) T. Iida, N. Yamamoto, H. Sasai, M. Shibasaki, *J. Am. Chem. Soc.* **1997**, *119*, 4783–4784; r) H. Yamashita, *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1213.

[10] a) F. Fringuelli, F. Pizzo, L. Vaccaro, *J. Org. Chem.* **2001**, *66*, 4719–4722; b) D. Amantini, F. Fringuelli, F. Pizzo, L. Vaccaro, *J. Org. Chem.* **2001**, *66*, 4463–4467; c) F. Fringuelli, F. Pizzo, L. Vaccaro, *Synlett* **2000**, 311–314; d) F. Fringuelli, F. Pizzo, L. Vaccaro, *Synthesis* **2000**, 646–650; e) F. Fringuelli, O. Piermatti, F. Pizzo, L. Vaccaro, *Eur. J. Org. Chem.* **2001**, 439–455; f) F. Fringuelli, F. Pizzo, L. Vaccaro, *Tetrahedron Lett.* **2001**, *42*, 1131–1133; g) Fringuelli, F. Pizzo, L. Vaccaro, *J. Org. Chem.* **2001**, *66*, 3554–3558; h) D. Amantini, F. Fringuelli, F. Pizzo, L. Vaccaro, *J. Org. Chem.* **2001**, *66*, 6734–6737; i) F. Fringuelli, M. Matteucci, O. Piermatti, F. Pizzo, M. G. Burla, *J. Org. Chem.* **2001**, *66*, 4661–4666; j) F. Fringuelli, O. Piermatti, F. Pizzo, *Organic Synthesis in Water*, (Ed.: P. A. Grieco), Blackie Academic and Professional, Glasgow, **1998**, pp. 223–249 and 250–261; k) O. Attanasi, L. De Crescentini, P. Filippine, F. Fringuelli, F. Mantellini, M. Matteucci, O. Piermatti, F. Pizzo, *Helv. Chim. Acta* **2001**, *84*, 513–524; l) F. Fringuelli, R. Germani, F. Pizzo, F. Santinelli, G. Savelli, *J. Org. Chem.* **1992**, *57*, 1198; m) F. Fringuelli, G. Pani, O. Piermatti, F. Pizzo, *Tetrahedron* **1994**, *50*, 11499; n) G. Brufola, F. Fringuelli, O. Piermatti, F. Pizzo, *Heterocycles* **1996**, *43*, 1257 and **1997**, *45*, 1715; o) D. Ye, F. Fringuelli, O. Piermatti, F. Pizzo, *J. Org. Chem.* **1997**, *62*, 3248; p) F. Fringuelli, O. Piermatti, F. Pizzo, L. Vaccaro, *J. Org. Chem.* **1999**, *64*, 6094–6096.

[11] H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2001**, *40*, 2004–2021.

[12] For a list of advantages and disadvantages of water as reaction medium see Ref.[10e]

[13] The stereochemical outcome of the reaction of glutathione and 3,4-epoxyprecocene in H_2O-THF depends on the polarity of solvent and pH. While above pH 13, almost exclusively *trans* adducts were formed, within the pH range 8.5–10.5 a significant portion of *cis* adducts (24%) were obtained.[5b]

[14] At the beginning of the thiolysis the pH of Lewis acid-catalyzed reactions is easier to control if the epoxide is added to the aqueous, pH-stabilized mixture of thiophenol and catalyst.

[15] M. M. Kreevoy, B. E. Eichinger, F. E. Stary, E. A. Katz, J. M. Seellstedt, *J. Org. Chem.* **1964**, *29*, 1641–1645.

[16] F. Fringuelli, R. Germani, F. Pizzo, G. Savelli, *Tetrahedron Lett*. **1989**, *30*, 1427–1428.

[17] a) Y. Gindon, R. N. Young, R. Frenette, *Synth. Commun.* **1981**, *11*, 391–398; b) C. Gabbi, F. Ghelfi, R. Grandi, *Synth. Commun.* **1997**, *27*, 2857–2863; c) D. Craig, K. Daniels, A. R. MacKenzie, *Tetrahedron* **1993**, *49*, 11263–11304; d) K. Hiroi, H. Sato, *Synthesis* **1987**, 811–814; e) P. Brownbridge, P. K. G. Hodgson, R. Shepherd, S. Warren, *J. Chem. Soc. Perkin Trans. 1*, **1976**, 2024–2034; f) T. Cohen, H.-I. Jeong, B. Mudryk, M. Bhupathy, M. M. A. Awad, *J. Org. Chem.* **1990**, *55*, 1528–1536; g) A. Toshimitsu, C. Hirosawa, K. Tamao, *Tetrahedron* **1994**, *50*, 8997–9008.

[18] a) D. T. Richens, in *The Chemistry of Aqua Ions*, Wiley, New York, **1997**; b) C. F. Baes, Jr., R. E. Mesmer, *The Hydrolysis of Cations*, Wiley, New York, **1976**.

[19] F. Fringuelli, R. Pellegrino, F. Pizzo, *Synth. Commun.* **1993**, *23*, 3157 – 3163.

[20] β-Hydroxy sulfoxides were recently prepared by a *one-pot* uncatalyzed procedure in hexafluoroisopropanol (reflux for 28 h under argon atmosphere) followed by *in situ* oxidation (H_2O_2 at 0 °C).[1]

[21] S. Otto, F. Bertoncin, J. B. F. N. Engberts, *J. Am. Chem. Soc.* **1996**, *118*, 7702 – 7707.