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Thiolysis of 1,2-epoxides by thiophenol catalyzed under solvent-free conditions

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Abstract—Thiolysis of alkyl- and aryl-1,2-epoxides was investigated under solvent-free conditions in the presence of Lewis and Brønsted acid and base catalysts ($InCl_3$, *p*-TsOH, *n*-Bu_3P, K_2CO_3). Five mol% of catalyst was sufficient and the best results were obtained by using $InCl_3$ and K_2CO_3. β-Hydroxy sulfide was isolated in excellent yields.

To minimize the amount of harmful organic solvents used in chemical processes, much attention has been devoted to the use of alternative reaction media.[1] Besides the use of supercritical fluids, water, and ionic liquids, the possibility of performing chemical processes in the absence of solvent (solvent-free conditions) has been receiving more attention.[1b,2] For historical and cultural reasons, organic reactions have generally been developed in solution while, a higher chemical efficiency would be expected if there were no medium interposed between the reactants. The examples reported demonstrate that no-solvent reactions are generally faster, give higher selectivities and yields, and usually require easier work-up procedures and simpler equipment.[2,3]

For many years, we have been interested in using alternative reaction media to contribute to the development of an environmentally-responsible chemistry and our research has been focused on the use of water as reaction medium.[4] We have found that Lewis acids catalyze the regio- and stereoselective iodolysis and azidolysis of α,β-epoxycarboxylic acids in water[5] and we have also shown that $InCl_3$ is an efficient catalyst for the thiolysis of oxiranes in water at pH 4.0.[6] In the area of solvent-free reactions, we have recently reported[7] the trimethylsilylation of alcohols catalyzed by tetramethylammonium bromide,[7a] and the [4+2] cycloaddition reaction between 3-nitrocoumarins and vinyl ethers.[7b]

The thiolysis of 1,2-epoxides is a convenient synthetic tool for preparing β-hydroxy sulfides, which are an important class of intermediates in organic synthesis.[8] To the best of our knowledge there has only been one report of the thiolysis of 1,2-epoxides performed under solvent-free conditions; Penso et al. used tetrabutylammonium fluoride (5 mol%) as a basic catalyst.[9]

In this letter we report the catalytic efficiency of Lewis and Brønsted acid and base catalysts in a solventless thiolysis of alkyl- and aryl-1,2-epoxides. The reactions were carried out at 30°C in the presence of 5 mol% catalyst using 1.05 mol equiv. of thiophenol.

$InCl_3$ was chosen as a representative Lewis acid, *p*-toluensulfonic acid (*p*-TsOH) as a Brønsted acid, *n*-Bu_3P as a Lewis base, and K_2CO_3 as a Brønsted base. Alkyl- and arylsubstituted-1,2-epoxides **1**–**7** were selected as substrates and the results are reported in Table 1. After 2 weeks (336 h) the reactions performed in the absence of catalyst only gave a small % of conversion (see Table 1, footnote a).

$InCl_3$ was chosen because it is a very efficient catalyst for this transformation in water[6] and in dichloromethane, as recently reported by Yadav et al.[10] This salt was generally more efficient under solvent-free conditions than under solvent conditions; lower catalyst loadings (5 mol% versus 10 mol%) could be used. Complete conversions were obtained in all the reactions in 1 min with the exception of the thiolyses of **4**, **6** and **7**. With a 5 mol% loading the reaction of **6** stopped at 51% conversion (entry 23) but with 10 mol% of $InCl_3$ the conversion reaction reached 80% (entry 24). In the case of 1,2-epoxide **7** the reaction was complete in 10

Keywords: 1,2-epoxides; Lewis catalysts; Brønsted catalysts; solvent-free conditions.

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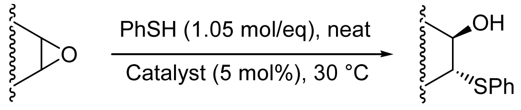
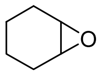
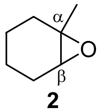
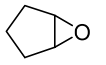
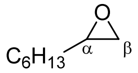
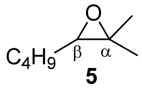
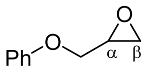
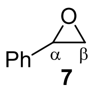
min (entry 28) but the side-product 1,2-bis(phenylthio)-ethylbenzene (**8**) (50% of the mixture) was also found (see Table 1, footnote e). By reducing the amount of $InCl_3$ from 5 to 1 mol%, the side-product **8** was reduced to 8% of the reaction mixture (entry 29, footnote f).

p-TsOH showed a poor catalytic effect in the reaction of 1,2-epoxides **2**, **3**, **5**, and **7** (Table 1, entries 6, 11, 19, and 30) while the effect was completely unsatisfactory for substrates **4** and **6** (entries 15 and 25). The highest efficiency was shown in the thiolysis of **1**; after 48 h the corresponding β-hydroxy phenylsulfide was obtained in quantitative yield (entry 2). When the same reaction was performed in dichloromethane, less than 2% conversion was obtained after 48 h. In the case of 1,2-epoxide **7**, the reaction was complete in 48 h (entry 30) but due to the very high reactivity of benzylic system, the additional side-product **8** (17% of the mixture) was also found (see Table 1, footnote g). Under these reaction conditions we suppose that the thiiranium ion was formed and reacted with phenylthiol to give **8**.

Table 1. Acid- or base-catalyzed thiolysis of 1,2-epoxides under solvent-free conditions



Entry	Epoxide	Catalyst (5 mol%)	Time (h)	C[a] (%)	Yield[b] (%)	α/β ratios
1	 **1**	$InCl_3$	0.017	99	95	
2		*p*-TsOH	48	99	95	
3		K_2CO_3	12	99	95	
4		*n*-Bu_3P	309	98	94	
5	 **2**	$InCl_3$	0.017	99	95	55/45
6		*p*-TsOH	144	95[c]	65	43/57
7		K_2CO_3	312	73	68	5/95
8		K_2CO_3	300	99[d]	96	5/95
9		*n*-Bu_3P	500	75	72	1/99
10	 **3**	$InCl_3$	0.017	99	95	
11		*p*-TsOH	500	20	15	
12		K_2CO_3	24	99	95	
13		*n*-Bu_3P	300	99[d]	96	
14	 **4**	$InCl_3$	0.17	90	87	1/99
15		*p*-TsOH	216	1	-	1/99
16		K_2CO_3	18	99	95	1/99
17		*n*-Bu_3P	314	97	94	1/99
18	 **5**	$InCl_3$	0.017	99	95	69/31
19		*p*-TsOH	48	90[c]	60	68/32
20		K_2CO_3	312	60	55	14/86
21		K_2CO_3	300	99[d]	95	14/86
22		*n*-Bu_3P	500	33	27	25/75
23	 **6**	$InCl_3$	0.17	51	47	1/99
24		$InCl_3$	0.17	80[d]	77	1/99
25		*p*-TsOH	168	6	-	1/99
26		K_2CO_3	1	99	95	1/99
27		*n*-Bu_3P	7	97	93	1/99
28	 **7**	$InCl_3$	0.17	99[e]	41	88/12
29		$InCl_3$	0.17	99[f]	85	95/5
30		*p*-TsOH	48	99[g]	73	95/5
31		K_2CO_3	2	99	95	40/60
32		*n*-Bu_3P	20	99	95	37/63

[a] After 2 weeks (336 h) reactions performed in the absence of catalyst only gave a small % of conversion, except in the cases of **3** and **7** where 80 and 42% conversion, respectively, were obtained; [b] yield of the isolated β-hydroxy phenylsulfides; [c] 25-28% of the corresponding vinyl sulfide was formed; [d] 10 mol% of catalyst were used; [e] 50% of the final mixture was made up of **8**; [f] 1 mol% of $InCl_3$ was used and 8% of **8** was found; [g] 17% of **8** was found.

n-Bu_3P was chosen to compare the results with those recently published by Hou et al. who found that this catalyst (used in 10 mol% amount) efficiently catalyzed the ring-opening of 1,2-epoxides and aziridines in water but was not effective when the reactions were carried out in acetonitrile.[11] To confirm these results we repeated the reaction of **1** in dichloromethane and we found that after 200 h ca. 3% conversion was obtained. Our results showed that in the absence of solvent, n-Bu_3P (5 mol%) has a good catalytic efficiency with all the substrates except **3** where 10 mol% of catalyst was used and **5** in which the reaction conversion was only 33% after ca. 500 h (entry 22).

Finally, K_2CO_3 was the best base catalyst, showing a very high catalytic efficiency with complete conversion after 1–24 h except in the less reactive substrates **2** and **5** where expected longer reaction times were observed (entries 7 and 20). By increasing the catalyst amount to 10 mol%, the conversions of **2** and **5** were accomplished after 300 h (entries 8 and 21).

Since this salt is the cheapest catalyst of those tested and is used in very small amounts, these results are very promising in view of scaling-up the process.

As expected, the regioselectivity of the process is strongly dependant on the acidity or basicity of the reaction conditions and the data obtained under solvent-free conditions are comparable to those obtained in aqueous or organic solvent conditions.[6,10] Acidic conditions ($InCl_3$ or p-TsOH as catalysts) favored the nucleophilic attack of thiol at the more-substituted α-carbon, depending on the substituents on the oxirane-ring. An almost complete α-regioselectivity was obtained with **7** (entry 29) while α/β ratios of 55/45 or 69/31 were observed with **2** and **5**, respectively (entries 5 and 18). As expected, under basic conditions (n-Bu_3P or K_2CO_3 as catalysts), the less-substituted β-carbon was more favored and a good to high β-regioselectivity was found. In particular in the case of styrene oxide (**7**) a 40/60 α/β ratio was obtained (entry 31), while in aqueous or organic media, an α-attack was largely predominant.[6,10]

In conclusion we have reported the thiolysis of alkyl- and aryl-1,2-epoxides under solvent-free conditions catalyzed by p-TsOH, $InCl_3$, K_2CO_3 and n-Bu_3P (5 mol%) as representative catalysts. The best results were obtained using $InCl_3$ and K_2CO_3. Under solventless conditions smaller catalyst loadings and reaction times were observed with respect to those obtained in aqueous[6,11] or organic media.[10,11]

In our opinion, these results are extremely promising and work is in progress to improve catalyst efficiency and to apply the solvent-free thiolysis of 1,2-epoxides to the synthesis of target molecules.

Typical experimental procedure: In an oven-dried screw-capped vial thiophenol (1.05 mmol, 0.108 mL) was stirred with the catalyst (5 mol%) for 10 min at 30°C and then 1,2-epoxide (1.0 mmol) was added. After the times reported, the reaction mixtures with $InCl_3$, K_2CO_3 and p-TsOH were treated in diethyl ether, the organic phase was washed with water to remove the catalyst and was worked-up as usual. n-Bu_3P was removed directly by re-crystallization in the cases of solid products, or by filtration through silica gel in the cases of oily products.

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