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# $InCl_3$-Catalyzed Regio- and Stereoselective Thiolysis of α,*β*-Epoxycarboxylic Acids in Water

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

*CEMIN, Centro di Eccellenza Materiali Innovativi Nanostrutturati, Dipartimento di Chimica, Università di Perugia, Via Elce di Sotto 8, I-06123 Perugia, Italy*

*luigi@unipg.it; pizzo@unipg.it*

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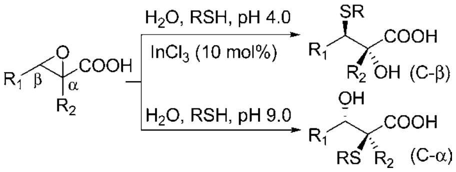
## ABSTRACT



**The thiolysis of α,*β*-epoxycarboxylic acids 1a–e by thiols 2a,b is more efficient in water than in dichloromethane or SFC. At pH 9.0 phenylthiolate generally attacks the C-α carbon while at pH 4.0, and in the presence of $InCl_3$ (10 mol %), the thiolysis is exclusively C-*β* regioselective. In all cases, the processes are completely *anti*-diasteroselective, and the corresponding products 3, 4, and 5 have been isolated in good yields. Both water and catalysts have been recovered and reused.**

According to the urgent need for an efficient and environmentally benign organic chemistry, new catalysts must be found and alternative and safe reaction media should be used to achieve the best selectivities and yields at minimal environmental cost.[1] We have been contributing to the development of a green organic chemistry by realizing organic processes in water,[2] or under solvent-free condition (SFC),[3] and we have generally focused our attention on the definition of one-pot multistep protocols for the synthesis of target molecules.[2a,c−e,3a−c,e] In several cases, we have also realized the recovery and reuse of the catalyst to improve the ecocompatibility of the processes.[2b,e,3d]

By controlling the pH of the aqueous medium, the catalyst's efficiency can be regulated allowing a green, regio- and stereoselective nucleophilic ring-opening of 1,2-epoxides to be realized. We have found that the best catalytic efficiency of a Lewis acid such as In(III), Zn(II), Cu(II), or Al(III) can be reached when the pH is below its $pK_{1,1}$ hydrolysis constant.[4] For example, the synthetic utility of these results has been outlined by realizing the first one-pot regio- and stereoselective synthesis of norstatines in water via Cu(II)-catalyzed azidolysis of α,*β*-epoxycarboxylic acids followed by in situ Cu(II)-catalyzed reduction of the azido group.[2a]

Thiolysis of 1,2-epoxides is an efficient and widely used tool for the synthesis of the *β*-hydroxy sulfide moiety,[2b,d,5]

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(1) (a) Tundo, P.; Anastas, P. T. In *Green Chemistry*: *Theory and Practice*; Oxford University Press: Oxford, UK, 1998. (b) DeSimone, J. M. *Science* **2002**, *297*, 799−803. (c) Tanaka, K.; Toda, F. In *Solvent-free Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2003. (d) Li, C. J.; Chang, T. H. In *Organic Reactions in Aqueous Media*; Wiley: New York, 1997. (e) *Organic Synthesis in Water*; Grieco, P. A., Ed.; Blackie Academic and Professional: London, UK, 1998.

(2) For recent papers see: (a) Fringuelli, F.; Pizzo, F.; Rucci, M.; Vaccaro, L. *J. Org. Chem.* **2003**, *68*, 7041−7045. (b) Fringuelli, F.; Pizzo, F.; Tortoioli, S.; Vaccaro, L. *J. Org. Chem.* **2003**, *68*, 8248−8251. (c) Amantini, D.; Fringuelli, F.; Piermatti, O.; Pizzo, F.; Vaccaro, L. *J. Org. Chem.* **2003**, *68*, 9263−9268. (d) Amantini, D.; Fringuelli, F.; Pizzo, F.; Tortoioli, S.; Vaccaro, L. *Synlett* **2003**, *68*, 2292−2296. (e) Fringuelli, F.; Pizzo, F.; Vaccaro, L. *J. Org. Chem.* **2004**, *69*, 2315−2321.

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which is present in many biologically active molecules[6] and offers high synthetic versatility. A representative example is given by Diltiazem, one of the most potent calcium antagonists known, which is prepared by using as a key step the thermally induced thiolyses of the appropriate cinnamic ester oxides.[6d,f]

In the past few years we have reported new and environmentally friendly procedures for the thiolysis of 1,2-epoxides showing that In(III) and Zn(II) salts are the most efficient catalysts for this transformation under SFC,[3e,4c] in water at pH 4.0[2d,5f] and pH 7.0.[2b]

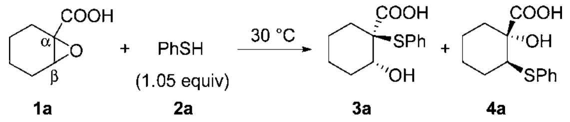
We are currently involved in a project aimed at the *green* preparation of *S*-containing small and medium-size heterocycles via one-pot multistep processes based on the thiolysis of 1,2-epoxides. Within this area we have recently accomplished the one-pot synthesis of new heterocycles such as thiazolopyridinium salts[3e] and 1,4-benzoxathiepin-2-ones[3c] by using as thiols 2-mercaptopyridine and thiosalicylic acid, respectively.

Despite its valuable synthetic utility, thiolysis of $\alpha,\beta$-epoxycarboxylic acids,[7a] $\alpha,\beta$-epoxycarboxyesters,[7b−d] or $\alpha,\beta$-epoxycarboxyamides[7g] has been scarcely studied,[7] and it has never been investigated in water as a reaction medium. Thiolysis of $\alpha,\beta$-epoxycarboxylic acids and their derivatives has been studied in an organic medium under basic or acidic conditions and in the presence or the absence of a Lewis acid ($MgCl_2$,[7c] $CaCl_2$,[7c] $Yb(OTf)_3$,[7f,g] and $Ti(i\text{-}OPr)_4$[7a]). All the processes carried out under basic conditions gave a preferential attack at the C-$\alpha$ position, while under acidic conditions the C-$\beta$ regioisomer was prevailing and thiolysis proceeded with inversion or retention of the configuration of C-$\alpha$ and C-$\beta$ stereocenters.[7]

Currently, our project deals with the study of the thiolysis of $\alpha,\beta$-epoxycarboxylic acids **1a**−**e** by phenylthiol (**2a**) and butylthiol (**2b**) by examining the influence on the regio- and stereoselectivity of the reaction played by (i) the reaction medium, (ii) the catalyst, (iii) the pH of the aqueous medium, and (iv) the thiol employed. We intend to define an efficient and green regio- and stereoselective procedure to access new $\beta$-carboxy sulfides which can be used as precursors for target heterocycles.

We started our study on the thiolysis of 1,2-epoxycyclohexane-1-carboxylic acid (**1a**) by using a stoichiometric amount of phenylthiol (**2a**) at 30 °C, and the results are illustrated in Table 1. We found that this reaction performed at pH 4.0 in the absence of any metal catalyst after 8 h gave only traces of products **3a** and **4a** (Table 1, entry 1). A significantly increased reactivity was observed at pH 9.0 where after 8 h, a complete conversion of **1a** to $\beta$-hydroxy sulfides **3a** and **4a** in a 1/1 ratio was obtained (Table 1, entry 2).

**Table 1.** Thiolysis of 1,2-Epoxycyclohexane-1-carboxylic Acid (**1a**) by Phenylthiol (**2a**)



| entry | reaction medium | catalyst (10 mol %) | *t* (h) | product[a] 3a/4a | |
|---|---|---|---|---|---|
| 1 | $H_2O$ (pH 4.0) | | 8 | traces | |
| 2 | $H_2O$ (pH 9.0) | | 8 | 50 | 50 |
| 3 | $H_2O$ (pH 4.0) | $InCl_3$ | 1.5 | <1 | >99[b] |
| 4 | $H_2O$ (pH 4.0) | $AlCl_3$ | 1.5 | <1 | 68 |
| 5 | $H_2O$ (pH 4.0) | $ZnCl_2$ | 1.5 | <1 | 40 |
| 6 | $H_2O$ (pH 4.0) | $CoCl_2$ | 1.5 | <1 | 14 |
| 7 | $H_2O$ (pH 4.0) | $Cu(NO_3)_2$ | 1.5 | <1 | 3 |
| 8 | DCM | | 1.5 | | |
| 9 | DCM | $InCl_3$ | 1.5 | <1 | 60 |
| 10 | DCM | $InCl_3$ | 4 | <1 | >99 |
| 11 | SFC | - | 1.5 | | |
| 12 | SFC | $InCl_3$ | 1.5 | 4 | 83 |

[a] Ratios measured by GLC analyses, the remaining material was the unreacted **1a**. [b] 96% isolated yield of **4a**.

With the intention of steering the thiol attack to the C-$\beta$ position of **1a**, we have performed the reaction of **1a** with **2a** in the presence of 10 mol % of $InCl_3$, $AlCl_3$, $ZnCl_2$, $CoCl_2$, and $Cu(NO_3)_2$ which in our hands have proved to be the most efficient catalysts for the nucleophilic oxirane ring-opening processes in water at pH 4.0.[4] Since all the p$K_{1,1}$ hydrolysis constants of these Lewis-acid catalysts are larger than 4, they should be able to express a high catalytic efficiency under this pH condition.

The best result was obtained by using $InCl_3$ (10 mol %) in water at pH 4.0, where at 30 °C in only 1.5 h *trans*-1-hydroxy-2-(phenylthio)cyclohexane-1-carboxylic acid (**4a**)

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(5) Among many others: (a) Posner, G. H.; Rogers, D. Z. *J. Am. Chem. Soc.* **1977**, *79*, 8208−8213. (b) Iida, T.; Yamamoto, N.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1997**, *119*, 4783−4784. (c) Wu, M. H.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 5252−5254. (d) Yadav, J. S.; Reddy, B. V. S.; Baisha, G. *Chem. Lett.* **2002**, 906−907. (e) Devan, N.; Sridhar, P. R.; Prabhu, K. R.; Chandrasekaran, S. *J. Org. Chem.* **2002**, *67*, 9417−9420. (f) Fringuelli, F.; Pizzo, F.; Tortoioli, S.; Vaccaro, L. *Adv. Synth. Catal.* **2002**, *344*, 379−384. (g) Sasaki, M.; Tanino, K.; Hirai, A.; Miyashita, M. *Org. Lett.* **2003**, *5*, 1789−1791. (h) Fringuelli, F.; Pizzo, F.; Tortoioli, S.; Vaccaro, L. *Green Chem.* **2003**, *5*, 436−440 (i) Bandini, M.; Fagioli, M.; Melloni, A.; Umani-Ronchi, A. *Adv. Synth. Catal.* **2004**, *246*, 573−578. (j) Leong, P.; Lautens, M. *J. Org. Chem.* **2004**, *69*, 2194−2196.

(6) (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) Corey, E. J.; Clark, D. A.; Marfat, A.; Goto, G. *Tetrahedron Lett.* **1980**, *21*, 3143−3146. (c) Sharma, S.; Mesic, T. M.; Matin, R. A. *Tetrahedron* **1994**, *50*, 9223−9228. (d) Wipf, P.; Jeger, P.; Kim, Y. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 351−356. (e) Sauders, J. In *Top Drugs, Top Synthetic Routes*; Oxford University Press: Oxford, UK, 2000, and refereces cited therein. (f) Martinelli, M. J.; Vaidyanathan R.; Van Khau, V.; Staszak, M. A. *Tetrahedron Lett.* **2002**, *43*, 3365−3367. (g) Furutani, T.; Imashiro, R.; Hatsuda, M. *J. Org. Chem.* **2003**, *67*, 4599−4601. (h) Magdalou, J.; Fournel-Gigleux, S.; Testa, B.; Ouzzine, M. In *The Practice of Medical Chemistry*, 2nd ed.; Wermuth, C. G., Ed.; Academic Press: San Diego, CA, 2004; p 541.

(7) (a) Chong, J. M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1560−1563. (b) Schwartz, A.; Madan, P. B.; Mohacsi, E.; O'Brien, J. P.; Todaro, L. J.; Coffen, D. L. *J. Org. Chem.* **1992**, *57*, 851−856. (c) Inoue, H.; Nagao, T. *Chron. Drug Discovery* **1993**, 207−238. (d) Jacobsen, E. N.; Deng, L.; Furukawa, Y.; Martinez, L. E. *Tetrahedron* **1994**, *50*, 4323−4334. (e) Woydowski, K.; Fleischhauer, J.; Shiffer, J.; Liebsher, J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 149−153. (f) Aggarwal, V. K.; Hynd, G.; Picoul, W.; Vasse, J.-L *J. Am. Chem. Soc.* **2002**, *124*, 9964−9965. (g) Tosaki, S.; Tsuji, R.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 2147−2155.

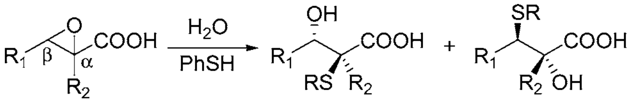
was totally regio- and stereoselectively formed (Table 1, entry 3). With $AlCl_3$, **4a** was exclusively formed but only a 68% conversion was reached (Table 1, entry 4). All the other Lewis acid catalysts employed gave lower conversions (3−40%) (Table 1, entries 5, 6, and 7).

The reaction of **1a** with **2a** was performed in dichloromethane (DCM) and under SFC also. In the absence of $InCl_3$ no conversion at all was observed in both cases (Table 1, entries 8 and 11). The efficiency of $InCl_3$ was lower in DCM and the process required 4 h to give product **4a** (Table 1, entries 9 and 10). Under SFC, when $InCl_3$ was used as catalyst, a 87% conversion was obtained after 1.5 h, and **3a** and **4a** were formed in a 5/95 ratio (Table 1, entry 12). Water proved to be superior to the organic reaction medium (DCM) and to SFC allowing the best efficiency to be achieved.

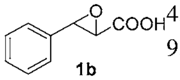
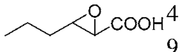
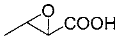
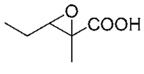
These results open the route to the first catalytic *β*-regio- and *anti*-stereoselective thiolysis of α,*β*-epoxycarboxylic acids in water.

The protocols for pH 4.0-$InCl_3$-catalyzed and for the pH 9.0-promoted thiolysis by phenylthiol (**2a**) were then applied to variously substituted 1,2-epoxides **1b**−**e** (Table 2). The efficiency of the aqueous medium was confirmed both under basic conditions at pH 9.0 and at pH 4.0 in the $InCl_3$-catalyzed process. The pH played a dramatic role in directing the regioselectivity of these reactions. Under acidic conditions (pH 4.0) the thiolysis of α,*β*-epoxycarboxylic acids **1b**−**e** in the presence of 10 mol % of $InCl_3$ gave adducts **4b**−**e** exclusively, coming from the attack at the C-*β* position (Table 2, entries 1, 3, 5, and 7). *β*-Hydroxy sulfides **3** and **4** were obtained in relatively short times, with complete *anti* diasteroselectivity and in all cases with excellent yields (85−95%). At pH 9.0 at 30 °C **2a** preferentially attacked the α-carbon of **1c**, **1d**, and **1e** (Table 2, entries, 4, 6, and 8), while as expected, preferential attack at the C-*β* benzylic position was observed in the case of 1,2-epoxide **1b** (Table 2, entry 2). Under basic conditions the observed regiochemistry can be justified by invoking an $S_N2$ mechanism while at pH 4.0 an $S_N2$ *borderline* mechanism should be operating. In the latter case electrophilicity at C-*β* is higher than that at C-α since a partial positive charge at the *β*-carbon is induced by the protonation of the oxirane ring, or by the complexation of the carboxylic and oxirane oxygens by In(III).

**Table 2.** Thiolysis of α,*β*-Epoxycarboxylic Acids **1b**−**e** by Phenylthiol (**2a**) in Water



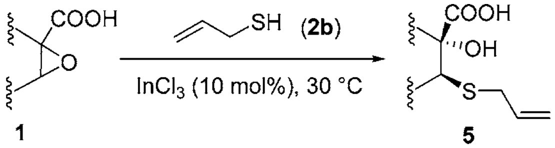
**1** **3** (C-α) **4** (C-β)

| entry | epoxy acid | pH | catalyst (10 mol%) | T (°C) | t[a] (h) | products[b] 3/4 | yield[c] (%) |
|---|---|---|---|---|---|---|---|
| 1 | <br>**1b** | 4.0 | $InCl_3$ | 30 | 0.1 | < 1/> 99 | 95 |
| 2 | | 9.0 | - | 30 | 0.5 | 20/80 | - |
| 3 | <br>**1c** | 4.0 | $InCl_3$ | 55 | 2 | < 1/> 99 | 96 |
| 4 | | 9.0 | - | 55 | 3 | 94/6 | 85 |
| 5 | <br>**1d** | 4.0 | $InCl_3$ | 55 | 1.5 | < 1/> 99 | 94 |
| 6 | | 9.0 | - | 55 | 1 | 97/3 | 92 |
| 8 | <br>**1e** | 4.0 | $InCl_3$ | 55 | 10 | < 1/> 99 | 95 |
| 9 | | 9.0 | - | 55 | 72 | 57/43 | 95[d] |

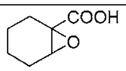
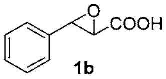
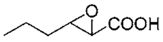
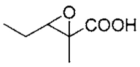
[a] Reaction time relative to a conversion >99%; 1.05 and 1.5 equiv of **2a** were used at pH 4.0 and 9.0, respectively. [b] Ratios evaluated by GLC analyses. [c] Yield of the isolated major product. [d] Isolated yields of **3e** and **4e**.

Considering that alkylthiols have never been used under aqueous acidic conditions, we have also included in our study the thiolysis of representative α,*β*-epoxycarboxylic acids **1a**−**c**,**e** by allylthiol (**2b**). **2b** was chosen as a representative alkylthiol,[8] which possesses the allylic functionality, offering additional possibilities for increasing molecular complexity. The results obtained are illustrated in Table 3. As expected the reactions of **2b** (1.05 equiv) were slower but in all cases $InCl_3$ (10 mol %) was confirmed to be an efficient catalyst

**Table 3.** $InCl_3$-Catalyzed Thiolysis of α,*β*-Epoxycarboxylic Acids **1a**−**c**,**e** by Allylthiol (**2b**) (1.05 molar equiv) at pH 4.0



**1** **5**

| entry | epoxy acid | T (°C) | t[a] (h) | yield[b] (%) |
|---|---|---|---|---|
| 1 | <br>**1a** | 30 | 40 | 75 |
| 2 | <br>**1b** | 30 | 1 | 90 |
| 3 | <br>**1c** | 55 | 48 | 86 |
| 4 | <br>**1e** | 55 | 48 | 85 |

[a] Reaction time relative to a conversion >99%. [b] Yield of the isolated products **5**.

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(8) Alkylthiols, although more efficient nucleophiles than the aromatic ones,[9] rarely have been used due to their high p$K_a$ (ca. 11 while p$K_a$ of aromatic thiols is ca. 6).[9]

(9) (a) Smith, M. B.; March, J. *March's Advanced Organic Chemistry*, 5th ed.; Wiley-Interscience Publication: New York, 2001. (b) Streitwieser, A. *Chem. Rev.* **1956**, *56*, 571, cfr. 582.

and only C-$\beta$ products **5** were regio- and *anti*-stereoselectively formed in high yields. In addition, both the aqueous medium and $InCl_3$ can be recovered and reused with no decrease in the efficiency of the process both in terms of regio- and stereoselectivity and in isolated yields of products.

In conclusion, in this paper we reported that water is an efficient reaction medium in the thiolysis of $\alpha,\beta$-epoxycarboxylic acids **1a−e**. The reactions always occurred stereoselectively and the regiochemistry can be directed by using acidic or basic conditions. The aqueous medium has allowed, for the first time, steering of the thiol attack only at the C-$\beta$ position by using a catalytic amount of a Lewis acid at pH 4.0. $InCl_3$ (10 mol %) turned out to be the most efficient catalyst and a variety of $\alpha$-carboxy-$\beta$-hydroxy sulfides **3** and $\beta$-carboxy-$\alpha$-hydroxy sulfides **4** and **5** were prepared in good to excellent yields.

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**Supporting Information Available:** Detailed experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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