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A new synthetic route for the preparation of β-acyloxy mercaptans via the addition of thioacids to epoxides

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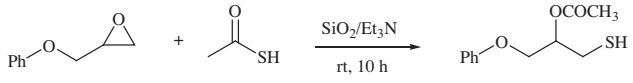
ABSTRACT

A new synthetic route for the preparation of *S*-benzylated β-acyloxy mercaptans starting from the one-pot reaction of thioacids and epoxides using a silica gel/Et_3N combined catalyst is described. The thiol functionality in the crude product is then protected via benzylation and the corresponding thioethers are isolated after chromatography.

The synthesis of sulfur-containing molecules has attracted significant attention due to their application in industry, medicine, and organic chemistry.[1] Thiolic precursors are fundamental substrates for the synthesis of many organosulfur compounds.[2] Thioesters are considered as masked thiols since they can be readily transformed into the thiol functionality by hydrolysis or acyl group transfer reactions under mild conditions.[3] The addition of thioacids to epoxides is a convenient method for the synthesis of β-hydroxy thioesters and thus the corresponding thiols in organosulfur synthesis. The synthesis of thiols starting from epoxides is synthetically valuable since epoxides are readily available either commercially, or by a variety of procedures. The addition of thioacids to epoxides is not suitably developed and is limited to a few reports.[4] Therefore, further studies on the addition of thioacids to epoxides using easily available catalysts (to develop new efficient methods) are important in organic synthesis.

Herein, we report a simple method for the one-pot generation of β-acyloxy mercaptans from the reaction of thioacids with epoxides.

The reaction of thioacetic acid with 2-(phenoxymethyl)oxirane under solvent-free conditions was chosen as a model reaction and several attempts were made to find the best catalyst and optimize the conditions. The corresponding β-acyloxy mercaptan was synthesized in 89% yield at room temperature in the presence of an Et_3N/SiO_2 combined catalyst after 10 h.



In this study, silica gel (1 g) and Et_3N (0.1 mmol) were added to a stirred mixture of thioacetic acid (2 mmol) and 2-(phenoxymethyl)oxirane (2 mmol) at room temperature. According to TLC and IR analysis of the reaction mixture, the reactants were completely converted into the corresponding β-hydroxy thioester during the first 5 min. By continuing the stirring, β-hydroxy thioester gradually rearranged into the corresponding β-acyloxy mercaptan via acyl group transfer from oxygen to sulfur. It should be noted that the presence of the Et_3N/silica gel combined catalyst in this reaction is crucial; similar reactions in the presence of only one of the catalysts yielded the corresponding β-hydroxy thioester after 24 h. Also, when β-hydroxy thioester was treated individually with Et_3N or SiO_2

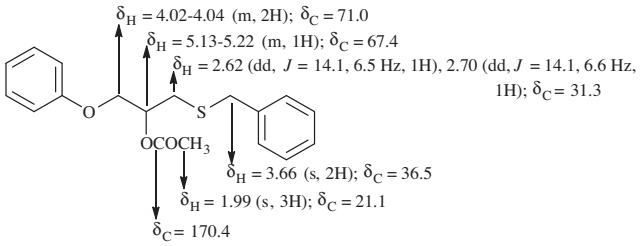


Figure 1. Selected NMR data for compound **2**.

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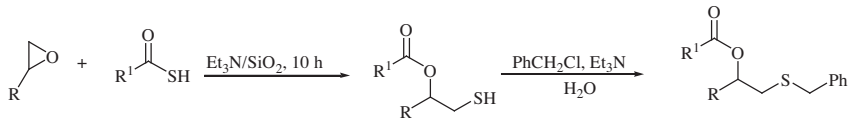
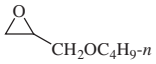
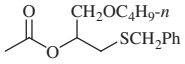
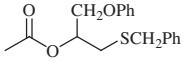
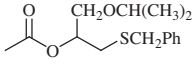
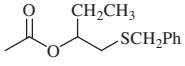
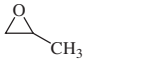
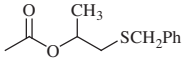
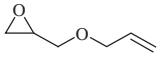
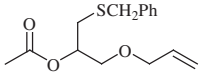
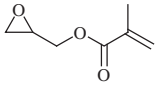
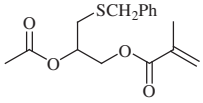
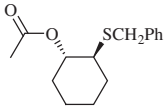
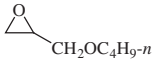
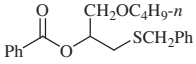
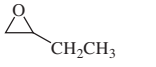
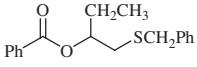
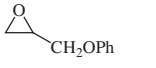
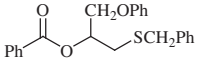
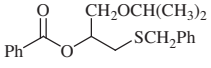
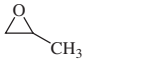
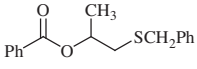
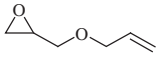
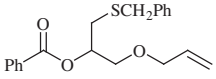
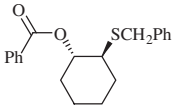
Table 1
One-pot synthesis of β-acyloxy mercaptans from the reaction of epoxides with thioacids in the presence of SiO_2/Et_3N combined catalyst followed by –SH protection



Entry	Epoxide	R^1	Product		Yield (%)
1[a]		CH_3		**1**	85
2[a]		CH_3		**2**	87
3[a]		CH_3		**3**	84
4[a]		CH_3		**4**	80
5[a]		CH_3		**5**	81
6[a]		CH_3		**6**	88
7[a]		CH_3		**7**	73[c]
8[a]		CH_3		**8**	79
9[b]		Ph		**9**	79
10[b]		Ph		**10**	78
11[b]		Ph		**11**	85
12[b]		Ph		**12**	85
13[b]		Ph		**13**	80
14[b]		Ph		**14**	80
15[b]		Ph		**15**	76

[a] The reactions were conducted at room temperature.
[b] The reactions were conducted at 50–60 °C.
[c] The corresponding Michael product was not obtained.

at room temperature and at 60 °C, it was recovered intact from the reaction mixture after 24 h. The crude product was extracted using EtOAc, concentrated and before purification by chromatography on silica gel, the –SH functionality was protected. The crude product was added to a mixture of benzyl chloride (2 mmol) and Et_3N (2 mmol) in water (2 mL). The mixture was then stirred at 50–60 °C until the mercaptan was completely consumed (1.5–2 h). The product was extracted and subjected to column chromatography (silica gel 70–230 mesh) using EtOAc/hexane (1:20) as eluent to afford 2-(benzylsulfanyl)-1-(phenoxymethyl)ethyl acetate (**2**) in 87% yield. This compound was obtained as colorless oil and its structure was established by spectroscopic and analytical techniques. The IR spectrum of the product showed the characteristic signal of an ester (1742 cm^{-1}). The ^1H NMR spectrum of this compound consisted of two singlets at 1.99 and 3.66 ppm which correlated to the resonances of CH_3 and benzylic CH_2 protons, respectively. The multiple resonances between 4.02–4.04 and 5.13–5.22 ppm were due to CH_2O and CH hydrogens, and the two doublets of doublet resonances at 2.62 and 2.70 ppm were assigned to the diastereotopic hydrogens on CH_2S linked to methine carbon. Also, 10 aromatic

hydrogen atoms were appeared as multiplet resonances between 6.78 and 7.23 ppm. The ^{13}C NMR spectrum contained 14 resonances, which were assigned to methyl (δ = 21.1), methylenes (δ = 31.3, 36.5, 71.0), methine (δ = 67.4), aromatic (δ = 114.7, 121.3, 127.2, 128.6, 129.0, 129.5, 137.9, 158.4), and carbonyl (δ = 170.4) carbons (Fig. 1).

This protocol was applied for the synthesis of structurally diverse *S*-benzylated β-acyloxy mercaptans.[5] The results are summarized in Table 1.

These results clearly prove that the reaction of thioacids with epoxides in the presence of SiO_2/Et_3N combined catalyst can be used for the one-pot synthesis of valuable bifunctional β-acyloxy mercaptans in high yields. It can be concluded from the results that the less-hindered carbon atom of epoxides is attacked by thioacids.

In conclusion, we have developed an efficient one-pot procedure for the synthesis of β-acyloxyl mercaptans via the addition of thioacids to epoxides in the presence of silica gel/Et_3N combined catalyst. This method is particularly important because it provides a short route to obtain derivatives of non-commercially available thiols. It is also noteworthy given its experimental simplicity, high generality, and the low cost of the catalyst system.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.03.045.

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5. General procedure: Silica gel 60 (70–230 mesh) (1 g) and Et_3N (0.1 mmol) were added to a stirred mixture of an epoxide and a thioacid at room temperature under solvent-free conditions. The progress of the reaction was monitored by TLC and IR spectroscopy. After 5 min, the starting epoxide had been completely converted into the corresponding β-hydroxy thioester. However, stirring was continued for another 10 h at rt (for reactions using thioacetic acid) or at 50–60 °C (for thiobenzoic acid including reactions). During this time, β-hydroxy thioester was mainly converted into the corresponding β-acyloxy mercaptan. Next, the crude β-acyloxy mercaptan product was extracted using EtOAc (3 × 3 mL) and after concentration was directly subjected to –SH benzylation in H_2O (2 mL) using benzyl chloride (2 mmol) and Et_3N (2 mmol). This mixture was stirred at 50–60 °C until the mercaptan had been completely consumed (1.5–2 h). The product was extracted with EtOAc (3 × 2 mL). The organic layers were combined, washed with HCl (1 M, 3 mL), dried over Na_2SO_4, filtered, and concentrated to yield the crude product. This product was then further purified by chromatography on silica gel using *n*-hexane/EtOAc (20:1) as eluent to provide the desired pure product in good to excellent yield (Table 1).