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One-pot synthesis of thia-Michael products from thio acids, epoxides, and electron-deficient alkenes promoted by a silica gel/Et_3N combined catalyst

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This article is dedicated to my dear teacher, Professor Habib Firouzabadi

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ABSTRACT

An efficient method for the one-pot production of thia-Michael adducts using thio acids, epoxides, and electron-deficient alkenes is described. Epoxides quickly underwent nucleophilic ring-opening with thio acids on the silica gel surface at room temperature under solvent-free conditions to yield β-hydroxy thioester intermediates. After addition of an electron-deficient alkene and a catalytic amount of Et_3N to the reaction mixture, the β-acyloxy mercaptans were generated in situ and subsequently underwent thia-Michael addition reactions to produce the corresponding adducts in good to excellent yields.

Organosulfur compounds are important materials in chemistry, biochemistry, and industry.[1] They are prepared by diverse synthetic methods using different starting materials. Thiols are versatile substrates for the synthesis of various organosulfur molecules in many chemical transformations.[2] For instance, thia-Michael adducts, as key intermediates in the synthesis of some bioactive compounds,[3] are prepared through the addition of thiols to electron-deficient olefins. Studies on thia-Michael addition reactions are mainly restricted to modification of the catalysts and conditions for addition of simple, commercially available thiols to the conjugated alkenes.[2,4] For the preparation of structurally diverse thia-Michael adducts, the corresponding thiols must be synthesized initially.

One-pot, multi-stage, and multi-component reactions are important since they represent efficient synthetic routes for the preparation of target molecules. The one-pot synthesis of thia-Michael adducts via addition of in situ generated thiols to electron-deficient olefins using alkyl halides and thiourea has been previously reported.[5] In this Letter, a new procedure for the one-pot synthesis of thia-Michael products using thio acids, epoxides, and Michael acceptors is introduced.

The nucleophilic addition of thio acids to epoxides to produce the corresponding β-hydroxy thioesters is a well-known process.[6] Our recent studies have shown that a β-hydroxy thioester can rearrange to the corresponding β-acyloxy mercaptan isomer using a silica gel/Et_3N combined catalyst.[7] Accordingly, we were interested in exploring a procedure for the one-pot synthesis of thia-Michael adducts using thio acids, epoxides, and electron-deficient alkenes. For this purpose, 2-(phenoxymethyl)oxirane, thioacetic acid, and *n*-butyl acrylate were chosen as model substrates. Thus, silica gel 60 (Merck, 70–230 mesh) (1 g) was added to a mixture of 2-(phenoxymethyl)oxirane (2.1 mmol) and thioacetic acid (2.1 mmol) at room temperature under solvent-free conditions. After 5 min, the addition of thioacetic acid to the epoxide was complete and the corresponding β-hydroxy thioester was obtained. Next, *n*-butyl acrylate (2 mmol) and Et_3N (0.1 mmol) were added to the stirred mixture at 50–60 °C and the stirring was continued for 3 h. During this period, *n*-butyl acrylate was completely consumed and the corresponding thia-Michael adduct was isolated in 92% yield. A similar reaction in the absence of Et_3N proceeded more slowly and produced the desired thia-Michael adduct in only 30% yield after 24 h. Unreacted *n*-butyl acrylate and β-hydroxy thioester were also detected in this reaction mixture, whereas the free thiol was not found. Further experiments showed that the presence of silica gel for in situ generation of thiol from the β-hydroxy thioester was also important; in its absence the reaction failed and both substrates were isolated intact after 24 h. To establish the scope of the method, various Michael acceptors, epoxides, and thioacetic and thiobenzoic acids were examined under the optimized conditions[8] (Table 1).

In accordance with the experiments, a feasible pathway is illustrated in Scheme 1.

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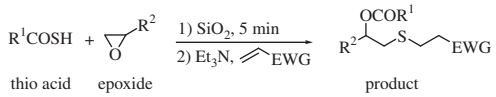
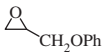
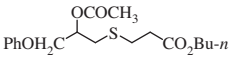
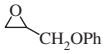
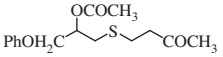
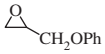
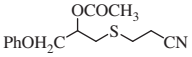
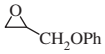
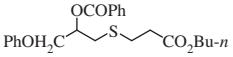
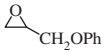
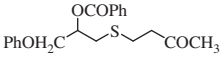
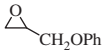
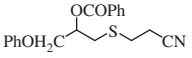
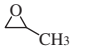
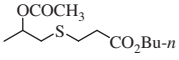
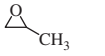
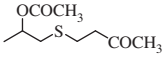
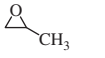
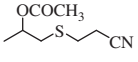
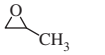
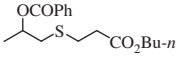
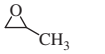
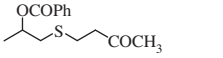
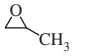
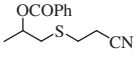
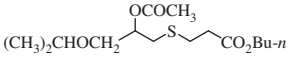
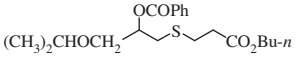
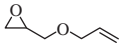
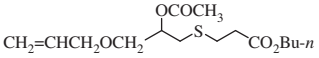
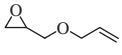
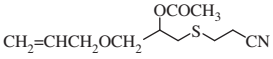
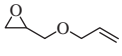
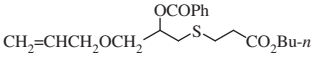
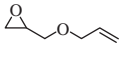
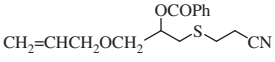
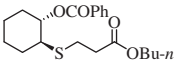
Table 1
One-pot thia-Michael product synthesis using electron-deficient alkenes, thio acids, and epoxides



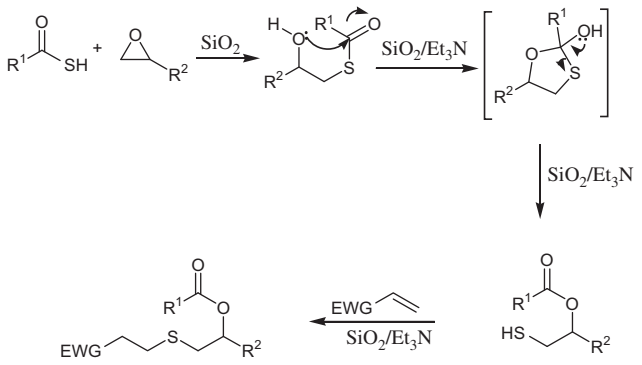
thio acid epoxide product

Entry	R^1	Epoxide	EWG	Product		Yield[a]
1	CH_3		CO_2Bu-*n*		**1**	92
2	CH_3		$COCH_3$		**2**	90
3	CH_3		CN		**3**	94
4	Ph		CO_2Bu-*n*		**4**	90
5	Ph		$COCH_3$		**5**	84
6	Ph		CN		**6**	93
7	CH_3		CO_2Bu-*n*		**7**	87
8	CH_3		$COCH_3$		**8**	84
9	CH_3		CN		**9**	87
10	Ph		CO_2Bu-*n*		**10**	86
11	Ph		$COCH_3$		**11**	85
12	Ph		CN		**12**	82
13	CH_3		CO_2Bu-*n*		**13**	89
14	Ph		CO_2Bu-*n*		**14**	87
15	CH_3		CO_2Bu-*n*		**15**	90
16	CH_3		CN		**16**	85
17	Ph		CO_2Bu-*n*		**17**	91
18	Ph		CN		**18**	90
19	Ph		CO_2Bu		**19**	87
20	Ph		$COCH_3$		**20**	83
21	Ph		CN		**21**	83

[a] Yield refers to isolated product.

Regioselective addition of thio acid to the non-substituted carbon atom of the terminal epoxide is facilitated by silica gel producing the corresponding β-hydroxy thioester. The β-acyloxy mercaptan intermediate is then produced gradually from β-hydroxy thioester due to the acyl group transfer from sulfur to the oxygen atom; this immediately undergoes Michael addition reaction with the electron-deficient alkene. This stage is promoted by the SiO_2/Et_3N combination.

In conclusion, an efficient, straightforward, and high yielding procedure for the one-pot preparation of thia-Michael adducts of



Scheme 1. A possible pathway for the one-pot generation of thia-Michael products using thio acids, epoxides, and Michael acceptors.

β-acyloxy mercaptans using thio acids, epoxides, and electron-deficient alkenes under solvent-free conditions has been developed. In this method, the β-acyloxy mercaptans are generated in situ utilizing thio acid and epoxide substrates and a silica gel/Et_3N combined catalyst. This method is important because it provides a short synthetic route to achieve the corresponding thia-Michael adducts of non-commercial mercaptans using readily available substrates.

Acknowledgement

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Supplementary data

Supplementary data (^1H and ^{13}C NMR spectra of all products) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.05.042.

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8. *General procedure*: silica gel 60 (1 g) was added to a stirred mixture of a thio acid (2.1 mmol) and an epoxide (2.1 mmol) at room temperature under solvent-free conditions. After consumption of the starting materials (less than 5 min), an electron-deficient alkene (2 mmol) and Et_3N (0.1 mmol) were added to the mixture and stirring was continued at 50–60 °C. The reaction progress was monitored by GC or TLC. After complete consumption of the alkene (3 h for reactions using thioacetic acid and 7 h for reactions using thiobenzoic acid), the mixture was extracted with EtOAc, and then concentrated. The crude product was purified by silica gel column chromatography (EtOAc:*n*-hexane = 1:15 v/v) and the corresponding thia-Michael product was isolated in 82–94% yield. Physical, spectral, and analytical data for *butyl 3-{[2-(acetyloxy)-3-phenoxypropyl]sulfanyl} propanoate* (***1***): Colorless oil; ^1H NMR (250 MHz, $CDCl_3$) δ: 7.21–7.13 (m, 2H), 6.88–6.71 (m, 3H), 5.22–5.12 (m, 1H), 4.11–4.50 (m, 2H), 3.99 (t, J = 6.6 Hz, 2H), 2.88–2.69 (m, 4H), 2.54–2.48 (m, 2H), 1.98 (s, 3H), 1.56–1.45 (m, 2H), 1.34–1.17 (m, 2H), 0.83 (t, J = 7.3 Hz, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 171.7, 170.3, 158.4, 129.5, 121.3, 114.6, 71.4, 67.2, 64.5, 34.7, 32.2, 30.6, 27.6, 21.0, 19.1, 13.7; IR (neat): ν (cm^{-1}) = 1735 (C=O ester), 1597 (C=C aromatic); Anal. Calcd for ($C_{18}H_{26}O_5S$): C, 60.99; H, 7.39; S, 9.05. Found: C, 60.76; H, 7.51; S, 8.90.