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ABSTRACT

β-Sulfonyl enoates may be synthesized through a one-pot two-step sequence from ethyl propiolate with good to excellent selectivity for the *Z* isomer. Trialkylamines catalyze thioconjugate additions of aryl thiols, and alkoxides catalyze the addition of aliphatic thiols. Addition of *meta*-chloroperbenzoic acid (*m*CPBA) and $LiClO_4$ to the reaction mixture provides rapid access to the sulfonyl enoates. Yields of the pure Z isomer range from 51 – 90%.

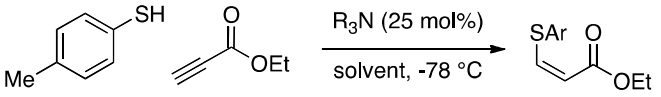
Keywords: conjugate addition, sulfide oxidation, one-pot reactions, enoate, ynoate, dienophile, ethyl propiolate, thiol

Conjugate additions to enoate acceptors are staple reactions in the field of organic synthesis,[1] but conjugate addition reactions of ynoates are undervalued. As part of our development of a one-pot synthesis of chiral esters from ynoates,[2] we required a convenient and rapid synthesis of geometrically enriched β-sulfonyl enoates.[3] We now report the realization of this goal: a one-pot two-step thioconjugate addition-oxidation reaction of ethyl propiolate with various thiols and *meta*-chloroperbenzoic acid (*m*CPBA) in the presence of $LiClO_4$. These convenient electrophiles should find use as building blocks for a variety of scenarios.

Thiols are known to react reliably with ethyl propiolate, providing a predominance of either the *E* or the *Z* enoate product depending upon the reaction conditions.[4] Because our ultimate goal is the development of one-pot methodology, the thioconjugate addition step in our laboratory was subject to the additional requirement of taking place under reaction conditions very similar to those that would be employed in the oxidation step. Accordingly, we conducted our own optimization study for the base-catalyzed conjugate addition of various thiols to ethyl propiolate.[4]

As illustrated in Table 1, we examined a variety of amine bases and organic solvents in the conjugate addition of *p*-toluenethiol to ethyl propiolate. When the reaction was performed in CH_2Cl_2 at -78 °C, selectivity and conversion as measured by ^1H NMR spectroscopy were uniformly high. We chose *i*-Pr_2NEt as the amine base for further study because of the high conversion observed. Geometric selectivity was easily controlled through choice of solvent. Toluene, THF, and Et_2O were all clearly inferior to CH_2Cl_2, with none providing a selectivity of 4:1 or higher.

Table 1
Optimization of thioconjugate addition



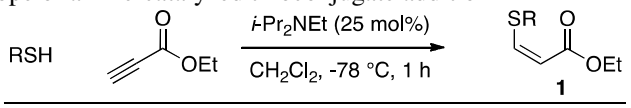
entry	R_3N	solvent	*Z*:*E*[a]	% conv[a]
1	2,6-lutidine	CH_2Cl_2	12:1	90
2	Et_3N	CH_2Cl_2	10:1	92
3	***i*-Pr_2NEt**	**CH_2Cl_2**	**11:1**	100
4	*i*-Pr_2NEt	Toluene	3.3:1	100
5	*i*-Pr_2NEt	THF	2.6:1	90
6	*i*-Pr_2NEt	Et_2O	2.4:1	100

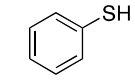
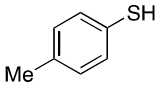
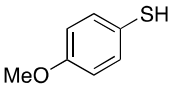
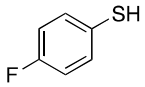
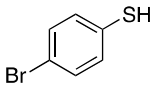
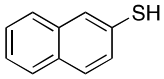
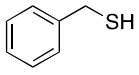
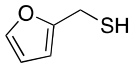
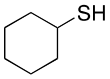
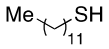
[a]Determined by ^1H NMR spectroscopy of unpurified reaction mixture.

Encouraged by the optimization of the conjugate addition of *p*-toluenethiol, we set out to determine the reaction scope. Table 2 summarizes our results. Electron-rich aromatic thiols performed best, as illustrated by entries 1-3. Electron-poor aromatic thiols were capable nucleophiles, but selectivity suffered slightly. Because the geometric selectivity of the conjugate addition is determined by the protonation of the allenolate intermediate, the less acidic electron-rich thiols may be more selective acids. Although selectivity generally favored the *Z* isomer, geometric purity degraded during chromatography, sometimes dramatically. This observation emphasizes the importance of the development of a one-pot reaction wherein a second synthetic step occurs in situ, while the *Z*:*E* ratio is maximized.

Table 2

Scope of amine-catalyzed thioconjugate addition



entry	RSH	product	*Z*:*E*[a,b]	yield (%)[c]
1		**1a**	3.9:1 (*12:1*)	94
2		**1b**	3.0:1 (*10:1*)	93
3		**1c**	15:1 (*16:1*)	95
4		**1d**	6:1 (*6:1*)	97
5		**1e**	9:1 (*9:1*)	86
6		**1f**	4.2:1 (*11:1*)	91
7		**1g**	3.4:1 (*4.2:1*)	96
8		**1h**	3.3:1 (*8:1*)	91
9		**1i**	4.2:1 (*6:1*)	67[d]
10		**1j**	2.9:1 (*5:1*)	29[e]

[a]Determined by ^{1}H NMR spectroscopy.

[b]Values in parentheses show the *Z*:*E* ratio prior to purification on silica gel.

[c]Isolated yield of a mixture of *Z* and *E* isomers for reaction performed on 2 mmol scale.

[d]Reaction performed at 0 °C.

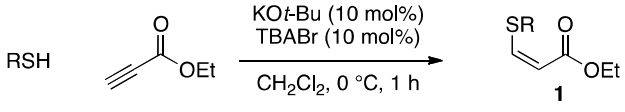
[e]Reaction performed at ambient temperature.

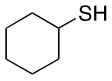
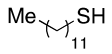
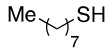
Aliphatic thiols proved to be more challenging substrates. Nonetheless, 1 h at -78 °C proved sufficient to achieve a very high yield (Table 2, entry 7) with acceptable geometric selectivity (4:1 *Z*:*E*) when benzyl mercaptan was used as the nucleophile. The electronically analogous 2-furanmethanethiol behaved very similarly (entry 8), but purely aliphatic thiols did not perform consistently well under amine-catalyzed conditions (entries 9 and 10). Resonance donation of the sulfur lone pairs in the product to the conjugated enoate system, presumably a much more significant factor in the *S*-alkyl case than for *S*-aryl analogs, may explain the relatively low geometric selectivity. Indeed, we have observed the slow equilibration of neat *S*-alkyl β-thioenoates from the *Z* isomer to an *E*/*Z* mixture overnight even at 5 °C, providing further impetus for the development of a one-pot reaction process to immediately convert these products to more elaborated synthons.

Fortunately, replacement of the amine catalyst with a more basic alkoxides provided a convenient solution for aliphatic thiols. Transesterification and geometric equilibration occurred when NaOMe was employed as base, but the sterically hindered KO*t*-Bu proved to be very effective. Addition of tetrabutylammonium bromide (TBABr) to the reaction mixture rendered the reaction homogeneous and allowed the reactions to proceed at 0 °C with acceptable geometric selectivity. Under these modified reaction conditions, both sterically encumbered secondary thiols (Table 3, entry 1) and long-chain aliphatic thiols (entries 2 and 3) performed well, providing high yields of the conjugate addition adducts.

Table 3

Scope of alkoxide-catalyzed thioconjugate additions



entry	RSH	product	*Z*:*E*[a,b]	yield (%)[c]
1		**1i**	4.2:1 (*4.7:1*)	90
2		**1j**	2.7:1 (*3.5:1*)	81
3		**1k**	4.0:1 (*4.1:1*)	88

[a]Determined by ^{1}H NMR spectroscopy.

[b]Values in parentheses show the *Z*:*E* ratio prior to purification on silica gel.

[c]Isolated yield of a mixture of *Z* and *E* isomers for reaction performed on 2 mmol scale.

In order to render these β-thioenoate products more useful as synthetic building blocks, we sought to increase their electrophilicity through conversion to sulfones in situ. Initial studies with purified thioether **1b** showed the *m*CPBA was a promising oxidant, readily providing the sulfone when 3 equiv of the oxidizing agent were used.[5]

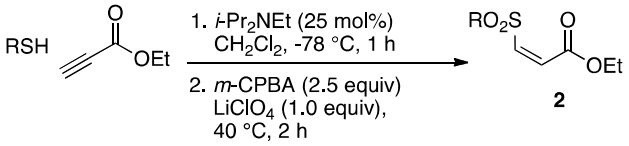
Unfortunately, residual catalytic base in the one-pot version of the reaction led to significant byproduct formation and low yield (15%) when the one-pot two-step thioconjugate addition-oxidation sequence was attempted. In order to mitigate the effect any residual base might have on the oxidation step, $LiClO_4$ was added as an amine- or alkoxide-sequestering agent. Under these conditions, yield increased dramatically and the amount of *m*CPBA could be reduced to 2.5 equiv.[6]

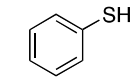
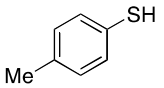
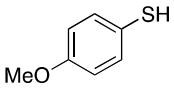
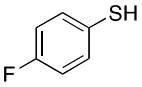
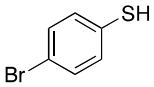
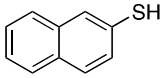
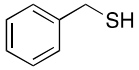
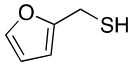
As illustrated in Table 4, aryl thiols again proved to be superior substrates in the presence of trialkylamine catalyst, although some drop in yield was observed for halogenated arenes (entries 4 and 5). Benzyl mercaptan also performed well, but the 2-furyl derivative proved unstable under the oxidizing conditions. Gratifyingly, *Z*:*E* ratios for the sulfone products are very similar to those observed for the simple conjugate addition reactions, demonstrating that very little geometric equilibration occurs under the one-pot two-step reaction conditions. Indeed, geometric purity is generally higher for the sulfones than for the analogous thioethers purified immediately after the thioconjugate addition step. Conveniently,

the *Z* and *E* isomers of the sulfones could be easily separated via column chromatography.

Table 4

Scope of amine-catalyzed one-pot thioconjugate addition-oxidations



entry	RSH	product	*Z*:*E*[a]	yield of *Z* (%)[b]
1		**2a**	12:1	71[c]
2		**2b**	8:1	81[d]
3		**2c**	10:1	90
4		**2d**	10:1	70
5		**2e**	3:1	51[e]
6		**2f**	10:1	84
7		**2g**	5:1	64
8		**2h**	–	*decomp.*

[a]Determined by ^{1}H NMR spectroscopy.

[b]Isolated yield of *Z* isomer for reaction performed on 2 mmol scale.

[c]0.5 equiv $LiClO_4$ used.

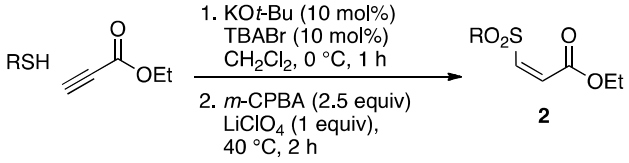
[d]0.5 equiv $LiClO_4$ used.

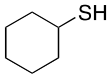
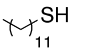
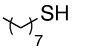
[e]Modified reaction conditions: 1,2-dichloroethane used as solvent; second step at 83 °C.

Although benzyl mercaptan reacted efficiently under the amine-catalyzed reaction conditions, the other aliphatic thiols examined suffered significant decomposition. When *i*-Pr_2NEt was replaced with KO*t*-Bu, a successful one-pot two-step thioconjugate addition-oxidation sequence was completed for cyclohexanethiol, dodecanethiol, and octanethiol (Table 5), each of which provided useful isolated yields of the *Z* isomer.

Table 5

Scope of alkoxide-catalyzed one-pot thioconjugate addition-oxidations

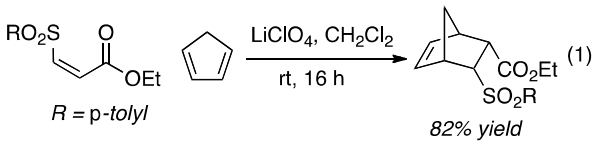


entry	RSH	product	*Z*:*E*[a]	yield of *Z* (%)[b]
1		**2i**	3.5:1	60
2		**2j**	3.1:1	51
3		**2k**	3.0:1	58

[a]Determined by ^{1}H NMR spectroscopy.

[b]Isolated yield of *Z* isomer for reaction performed on 2 mmol scale.

In order to demonstrate the reactivity of these β-sulfonyl enoates, the Diels–Alder cycloaddition of cyclopentadiene to sulfone **2b** was performed. In the presence of $LiClO_4$ at room temperature in CH_2Cl_2, complete conversion to the cycloadduct was observed overnight (eq 1). Column chromatography provided the pure major endo isomer in 82% yield.



In conclusion, we have developed a one-pot two-step thioconjugate addition-oxidation reaction that rapidly generates (*Z*)-β-sulfonyl enoates from ethyl propiolate. Reaction scope includes both aryl and aliphatic thiols. The major Z isomer is easily purified by column chromatography. Expansion of this reaction to include 3-substituted ynoates as well as further demonstrations of the electrophilicity of these compounds is underway.

Acknowledgments

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References and notes

1. For a review of conjugate addition reactions, see: (a) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221-3236. For recent

examples of the conjugate additions of thiol nucleophiles, see: (b) Abe, A. M. M.; Sauerland, S. J. K.; Koskinen, A. M. P. *J. Org. Chem.* **2007**, *72*, 5411-5413. (c) Marigo, M.; Schulte, T.; Franzén, J.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 15710-15710. (d) Peng, A.; Rosenblatt, R.; Nolin, K. *Tetrahedron Lett.* **2012**, *53*, 2712-2714.

2. See succeeding article in this journal.
3. For a synthesis of some aryl thiol-derived sulfonyl enoates by a different route, see: Chen, D.-D.; Hou, X.-L.; Dai, L.-X., *J. Org. Chem.* **2008**, *73*, 5578-5581.
4. For example, the *Z*-selective addition of 4-methylbenzenethiol to an ynoate in the presence of Et_3N is known: (a) Maezaki, N.; Yagi, S.; Yoshigami, R.; Maeda, J.; Suzuki, T.; Ohsawa, S.; Tsukamoto, K.; Tanaka, T. *J. Org. Chem.* **2003**, *68*, 5550-5558. For an example of an *E*-selective reaction in the presence of Et_3N, see: (b) Nishida, A.; Shibasaki, M.; Ikegami, S. *Chem. Pharm. Bull.* **1986**, *34*, 1434-1446.
5. This reaction is precedented. For example, see: (a) Jungheim, L. N.; Barnett, C. J.; Gray, J. E.; Horcher, L. H.; Shepherd, T. A.; Sigmund, S. K. *Tetrahedron* **1998**, *44*, 3119-3126. (b) See also reference 4a.
6. Acceleration of *m*-CPBA oxidations of sulfur atoms by Lewis acids is known: Li, Y.; Matsuda, M.; Thiemann, T.; Sawada, T.; Mataka, S.; Tashiro, M. *Synlett* **1996**, 461-464.

Supplementary Material

Supplementary data (experimental procedures and spectral data) associated with this article can be found, in the online version, at XXX.