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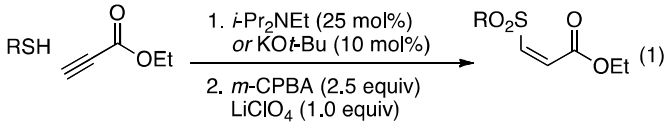
ABSTRACT

Ethyl propiolate undergoes one-pot three-step thioconjugate addition-oxidation-Diels–Alder cycloaddition when treated with a variety of thiols in the presence of catalytic base, *meta*-chloroperbenzoic acid, lithium perchlorate, and cyclopentadiene. The reaction of *S*-aryl thiols is catalyzed by trialkylamines, and the reaction of aliphatic thiols requires catalytic alkoxide base. Yields of the major diastereomer of the conveniently functionalized bicyclic products range from 47 to 81% depending upon the thiol reactant, which compares favorably to yields observed when the entire synthesis is performed step by step.

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

One-pot reaction methodology has generated significant interest in the synthetic community over the past decade.[1] Ynoate esters such as ethyl propiolate are intriguing substrates for one-pot reactions because they are known to act as one-pot bisacceptors in the presence of an excess of a single nucleophile.[2] Our group's long-standing interest in one-pot reactions[3] has led us to the investigation of ynoate esters as platforms for sequential conjugate addition reactions by two disparate nucleophiles.[4] We now report the ability of ethyl propiolate, a representative ynoate ester, to undergo sequential thioconjugate addition and Diels–Alder reaction in one pot.

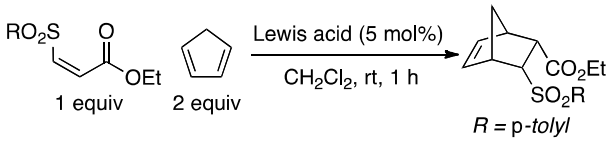
As we have reported in the previous communication,[5] we have developed a one-pot synthesis of (*Z*)-β-sulfonyl enoates from ethyl propiolate (eq 1). Because this class of enoates is known to act as dienophiles in Diels–Alder cycloadditions,[6] we set out to incorporate the Diels–Alder reaction into our one-pot process. The overall process would provide a usefully functionalized building block for further synthetic manipulation.[7]



(1)

The cycloaddition step was first optimized using the independently synthesized and purified *Z* sulfone product derived from *p*-toluenethiol and ethyl propiolate. When the sulfone was stirred with 2 equiv cyclopentadiene in CH_2Cl_2 at reflux for 1 h, 67% conversion to a 3.3:1 (endo:exo) mixture of diastereomers was observed. As illustrated in Table 1, a number of Lewis acids were tested in the reaction as well. In the presence of catalyst (5 mol%), the reaction proceeded at a reasonable rate at room temperature. The two most effective catalysts were $LiClO_4$ and $MgBr_2$•OEt_2, which displayed high selectivity and conversion after only 1 h. Ultimately, $LiClO_4$ was chosen for further study because it displayed slightly higher selectivity and successfully mediated complete conversion to products overnight. Moreover, the $LiClO_4$ catalyst was already known to be compatible with our one-pot β-sulfonyl enoate synthesis (eq 1),[5] so its additional use as cycloaddition catalyst was especially convenient.

Table 1
Optimization of Diels–Alder cycloaddition



entry	Lewis acid	*endo*:*exo*[a]	% conv[a]
1	none	3.3:1	67[b]
2	**$LiClO_4$**	**5.1:1**	**63**
3	$MgBr_2$•OEt_2	4.2:1	70
4	$ZnBr_2$	5.7:1	38
5	$In(OTf)_3$	3.0:1	27
6	$Sn(OTf)_3$	3.7:1	29
7	$Yb(OTf)_3$	3.1:1	24

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

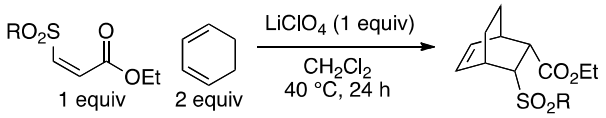
[b]Reaction stirred at 40 °C.

When cyclopentadiene was replaced with the less reactive cyclohexadiene, we were surprised to observe that $LiClO_4$ was the only catalyst tested that displayed any reactivity at all, providing

the endo product in 50% conversion after reflux overnight. Diastereoselectivity was extremely high, greater than 20:1 in favor of the endo isomer in every trial. More surprisingly, CH_2Cl_2 was the only solvent in which reactivity occurred. Similar results were observed for substrates derived from other thiols (Table 2). Unfortunately, in no case was an isolated yield greater than 25% observed, despite seemingly clean reaction as determined by thin layer chromatography and ^{1}H NMR spectroscopy. Other dienes tested (isoprene, furan, *N*-methylpyrrole, *N*-BOC-pyrrole, 2-methylthiophene) showed no reactivity under our conditions.

Table 2

Diels–Alder cycloaddition with cyclohexadiene



entry	R	*endo*:*exo*[a]	% conv[a]
1	Ph	>20:1	30
2	*p*-Me-C_6H_4	>20:1	50
3	Bn	>20:1	80

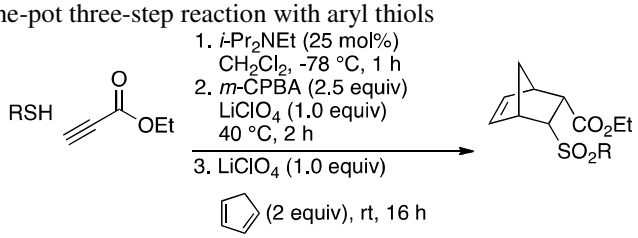
[a]Determined by ^{1}H NMR spectroscopy of the unpurified reaction mixture. Isolated yields never exceeded 25%.

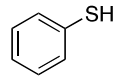
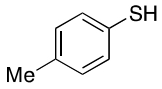
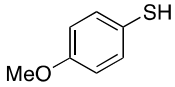
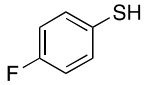
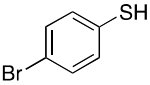
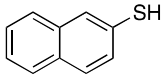
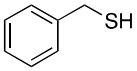
With these results in hand, we chose to concentrate our efforts toward development of the reaction with cyclopentadiene. Final optimization of the one-pot three-step heteroconjugate addition-oxidation-Diels–Alder cycloaddition reaction proceeded apace. Reaction solvent and catalyst were completely compatible with our previously developed (*Z*)-β-sulfonyl enoate synthesis.[5] Nonetheless, residual amine or alkoxide base and *m*-CPBA derivatives present in the reaction mixture during the one-pot three-step reaction required an increase in catalyst loading for the cycloaddition step (1 equiv vs. 5 mol%). Given the inexpensive nature of the catalyst, we found this increase acceptable.

As displayed in Table 3, we found the reaction to be general and reliable for *S*-aryl thiols with only minor changes in the reaction conditions from case to case. In a typical reaction procedure, the *S*-aryl thiol and amine base were mixed in CH_2Cl_2 at room temperature, then cooled to -78 °C and treated with ethyl propiolate. After 1 h, *m*-CPBA and $LiClO_4$ were added and the reaction mixture was warmed to room temperature. After stirring at reflux for 2 h, cyclopentadiene and additional $LiClO_4$ were added, and the reaction was stirred at room temperature overnight. Aqueous workup and column chromatography provided the pure major endo diastereomer in good yields. Electron-rich aryl thiols were the most successful substrates (entries 1-3). In some cases, the addition of a second equivalent of $LiClO_4$ during the cycloaddition step was unnecessary to achieve high yield and selectivity.[8] In the case of *p*-bromothiophenol, the reaction was performed in 1,2-dichloroethane in order to achieve a higher reflux temperature during the oxidation step, ensuring full oxidation to the sulfone. In general, halogenated thiophenol derivatives appear to react somewhat less selectively than their counterparts, which corresponds to lower isolated yields of the major cycloaddition adduct. Benzyl mercaptan reacted analogously to the *S*-aryl thiols, providing the major isomer in 67% yield. Diastereoselectivity varied somewhat from substrate to substrate, ranging from 3:1 (major endo isomer:Σminor isomers) for *p*-bromothiophenol to 15:1 for *p*-methoxythiophenol. Both the exo isomer derived from the *Z* enoate and diastereomers resulting from the cycloaddition of the *E* enoate were frequently observed as minor products, but in all cases the major endo isomer was easily purified by column chromatography.

Table 3

One-pot three-step reaction with aryl thiols



entry	RSH	product	dr[a]	yield (%)[b]
1		**1**	70:30	75
2		**2**	76:24	81[c,d]
3		**3**	87:13	81
4		**4**	76:24	56
5		**5**	71:29	57[e]
6		**6**	80:20	60
7		**7**	76:24	67[c]

[a]dr = diastereomer ratio = (major isomer:Σminor isomers), determined by ^{1}H NMR spectroscopy of the unpurified reaction mixture.

[b]Isolated yield of major endo diastereomer for reaction performed on 2 mmol scale.

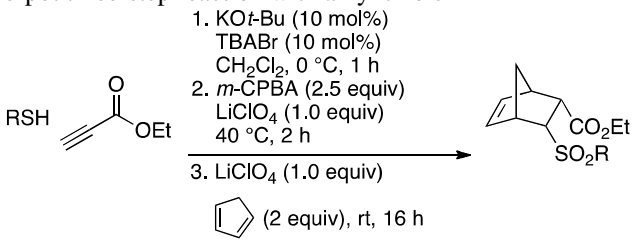
[c]No $LiClO_4$ added during third step.

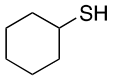
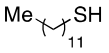
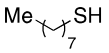
[d]0.5 equiv $LiClO_4$ used.

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

For purely aliphatic thiols, similar reaction conditions were employed, differing only in the substitution of catalytic *i*-Pr_2NEt with catalytic KO*t*-Bu and phase transfer catalyst tetrabutylammonium bromide (TBABr). As illustrated in Table 4, these challenging substrates performed reliably, providing consistent yields of the major endo diastereomer.

Table 4
One-pot three-step reaction with alkyl thiols



entry	RSH	product	dr[a]	yield (%)[b]
1		**8**	74:26	47
2		**9**	81:19	51
3		**10**	84:16	57

[a]dr = diastereomer ratio = (major isomer:Σminor isomers),, determined by ^{1}H NMR spectroscopy of the unpurified reaction mixture.

[b]Isolated yield of major diastereomer for reaction performed on 2 mmol scale.

A one-pot process provides inherent advantages over step-by-step synthesis, most obviously in the limitation of time and material costs associated with multiple purification steps. To be truly useful, however, the yield, selectivity, and purity of the final product must be comparable to what would be achieved by step-by-step synthesis. A mathematical comparison of two routes to product **2** shows that our one-pot process is favorable compared to the step-by-step synthesis, as measured by the yield of the major isomer. To wit, the yield of the purified, isolated major endo diastereomer of product **2** as generated through our one-pot three-step reaction was 71%, which corresponds to an average of 89% yield for each of the three steps. Figure 1 shows a comparison of this approach to a traditional step-by-step synthesis also performed in our laboratory. In the step-by-step synthesis, the yield for the thioconjugate addition step was 93%, the yield of the *Z* isomer after oxidation to the sulfone was 87%, and the yield for the Diels–Alder step was 82%. The overall yield for the entire step-by-step synthesis was 66%, which demonstrates that the one-pot process is superior in overall yield as well as in convenience. Although any complex one-pot reaction sequence is prone to loss of yield through side reactions occurring under the complex reaction conditions, in the present case those complexities have been more than compensated by the prevention of product loss during multiple purification steps. One advantage of the step-by-step process is that less $LiClO_4$ catalyst is necessary to achieve the final product, because no catalyst is necessary to scavenge residual amine during the oxidation step.[5] Nonetheless, that advantage is more than offset by the convenience, speed, and economic advantages of our one-pot reaction.

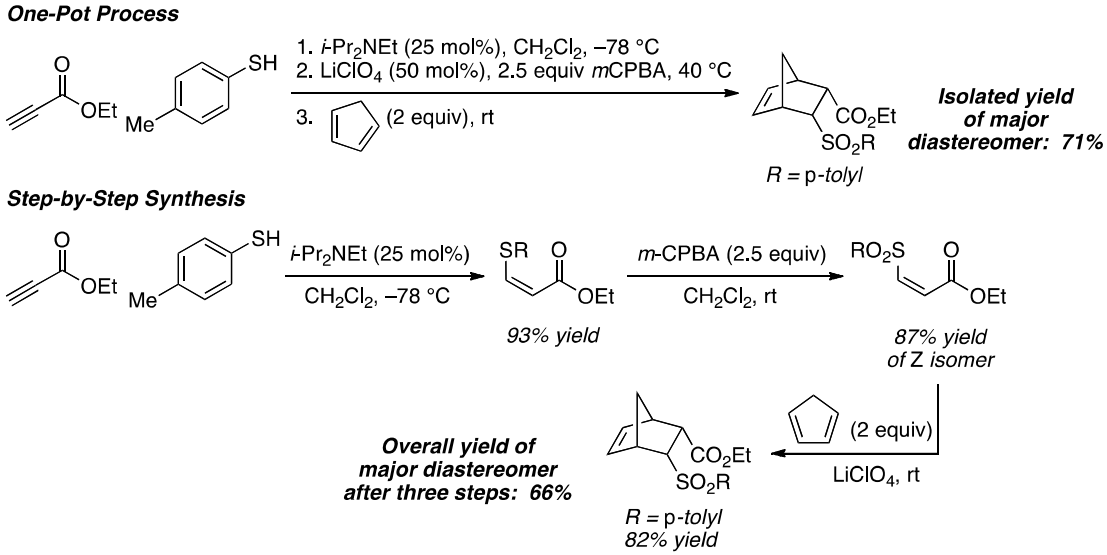


Figure 1. Comparison of one-pot reaction with step-by-step synthesis

In conclusion, this one-pot three-step thioconjugate addition-oxidation-Diels–Alder reaction shows great efficiency for a wide range of thiols when reacted with ethyl propiolate and cyclopentadiene. Expansion of the reaction scope to include less reactive dienes and other ynoate derivatives, including chiral variants, is underway and will be reported in due course.

Acknowledgments

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6. Sulfone- and sulfoxide-substituted enoates are known to undergo Diels–Alder reactions. For examples, see: (a) Buss, A. D.; Hirst, G. C.; Parsons, P. J. *J. Chem. Soc., Chem. Commun.* **1987**, 1836-1837. (b) De Lucchi, O.; Lucchini, V.; Marchioro, C.; Valle, G.; Modena, G. *J. Org. Chem.* **1986**, *51*, 1457-1466.
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8. Table 3, entry 2: Reaction was performed with 0.5 equiv $LiClO_4$ in the second step and no added $LiClO_4$ in the third step. Virtually identical results were obtained when the reaction was performed with 1.0 equiv $LiClO_4$ added during both the second and third steps. Table 3, entry 7: Reaction was performed with no added $LiClO_4$ in the third step. Virtually identical results were obtained when the reaction was performed with 1.0 equiv $LiClO_4$ added during the third step.