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Convenient Synthesis of Allylic Thioethers from Phosphorothioate Esters and Alcohols

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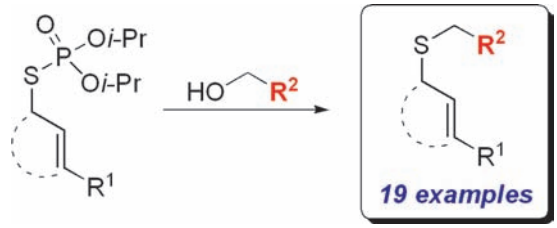
ABSTRACT



The synthesis of allylic thioethers arising from the reaction between phosphorothioate esters and alcohols is described. The synthesis is accomplished in one step by the addition of an exogenous alkoxide to the corresponding allylic phosphorothioate ester. It is demonstrated that this process is amenable to various functional groups and a wide variety of heterocycles. In contrast to conventional methods for thioether synthesis, no malodorous sulfur compounds such as thioacetic acid or thiols are required.

The thioether linkage is present in numerous bioactive natural and pharmaceutical agents. In fact, it has been demonstrated in several instances that replacing a carbon or oxygen atom with sulfur greatly enhances the bioactivity of certain compounds with respect to their oxygenated or carbon counterparts. For instance, structure−activity relationship studies have shown that for diallyl sulfide, which possesses potent anticancer properties,[1] a single sulfur atom bonded to at least one allyl side chain is required for inhibition of carcinogenesis.[2] The thioether functionality has also been implicated in several compounds that possess antagonistic properties against the histamine H_2-receptor.[3] The first of these compounds, burimamide,[4] was significantly less potent than cimetidine (Tagamet),[5] famotidine (Pepcid),[6] or ranitidine (Zantac),[7] each of which replaces a methylene group in the burimamide skeleton with an isosteric thioether linkage.[8] Pyrimidine thionucleosides also exhibit significantly greater inhibitory activity against human cancer cell lines than their corresponding oxygen analogues.[9] Finally, the thioether linkage in the immunoconjugate between doxorubicin and the monoclonal antibody BR96 was demonstrated to be critical to its antitumor properties (Figure 1).[10]

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(3) Ganellin, C. *J. Appl. Chem. Biotechnol.* **1978**, *28*, 183.

(4) Black, J.; Duncan, W.; Durant, C.; Ganellin, C.; Parsons, E. *Nature* **1972**, *236*, 385. (b) Preiss, D.; Code, C. *J. Pharmacol. Exp. Ther.* **1975**, *193*, 614.

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(8) Black, J.; Durant, G.; Emmett, J.; Ganellin, C. *Nature* **1974**, *248*, 65.

(9) Miura, S.; Yoshimura, Y.; Endo, M.; Machida, H.; Matsuda, A.; Tanaka, M.; Sasaki, T. *Cancer Lett.* **1998**, *129*, 103.

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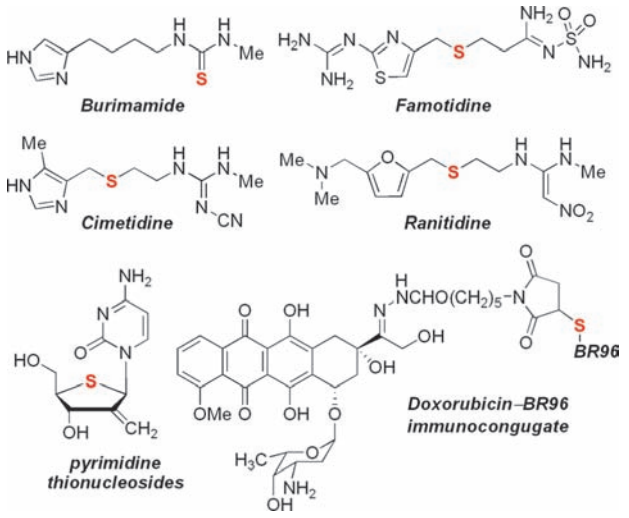
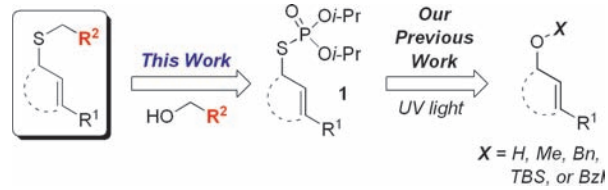


Figure 1. Bioactive sulfur-containing compounds.

Given the importance of sulfur-containing molecules, it is rather surprising that, in comparison to the amount of effort devoted to the discovery of new methods for preparing C−C, C−O, and C−N bonds, considerably less resources have been allocated to the development of preparing C−S bonds. Many existing methods for synthesizing thioethers require the use of functionalized substrates such as α-halocarbonyl compounds,[11] substrates that contain acidic C−H bonds,[12] α,β-unsaturated carbonyl compounds,[13] or allylic acetates/carbonates.[14] Reports utilizing the latter method for preparing thioethers are still limited because sulfur is known to deactivate late transition metals.[15] The thiol−ene reaction[16] is the anti-Markovnikov addition of thiyl radicals across unactivated alkenes. Although this process was first described in 1905,[17] it has been a surprisingly underutilized transformation. Finally, several groups have utilized stereospecific [3,3]-sigmatropic rearrangements to generate allylic carbamothioates.[18] It is apparent that the development of novel processes for preparing thioethers, and more generally, C−S bonds, would be of great benefit to both chemists and biologists. Herein we report an efficient synthesis of allylic thioethers from the corresponding phosphorothioate esters and alcohols (Scheme 1).

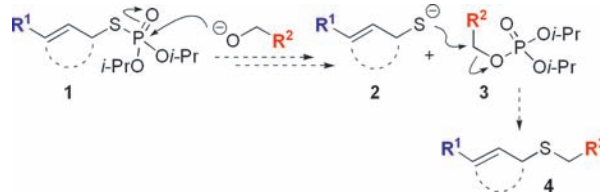
Scheme 1. Two-Step Synthesis of Allylic Thioethers



We recently described a novel method for the photolytic substitution of allylic alcohols, ethers, silyl ethers, and esters to generate phosphorothioate esters **1**.[19] We were also aware of several elegant reports from the research groups of Skowrońska, Krawczyk, and Tanaka in which they converted various phosphorothioate esters to the corresponding alkenes.[20] They proposed a mechanism that proceeds via thermal or phosphine-promoted extrusion of sulfur from thiirane intermediates. Because of the manner in which the requisite phosphorothioate esters were prepared, their methodology is restricted to the use of phosphorothioate esters directly adjacent to carbonyl groups or nitriles.

We proposed that the addition of an exogenous alkoxide to phosphorothioate esters **1**, which are functionally distinct from those used by Skowrońska, Krawczyk, and Tanaka, would initiate a series of events that would lead to the synthesis of thioethers in a single step (Scheme 2). Attack

Scheme 2. Proposed Mechanism for Thioether Synthesis



on phosphorothioate ester **1** by an alkoxide would generate thiolate **2** and phosphate **3**. Nucleophilic displacement of the phosphate would furnish the desired thioether **4**.

In the event, aging a solution of **5** and the corresponding alkoxide generated by deprotonation with NaH in methyl *tert*-butyl ether (MTBE) or THF overnight furnished thioethers **18a**−**l** in good yields (Table 1). The thioether synthesis is compatible with the presence of nitriles (vide infra), esters, and unprotected indole nitrogens, as well as a wide range of nitrogen-, oxygen-, and sulfur-containing heterocycles. Notably, the use of cinnamyl and crotyl alcohol (**8** and **9**) resulted in the formation of only one of two possible regioisomers. Bacon and co-workers reported the use of

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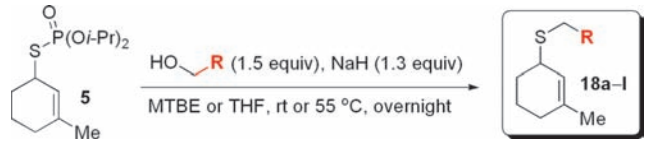
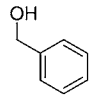
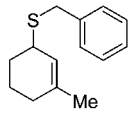
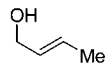
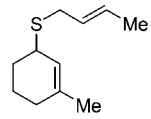
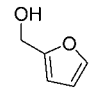
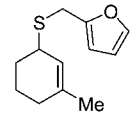
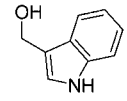
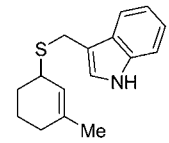
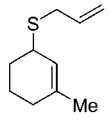
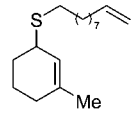
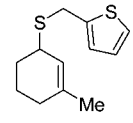
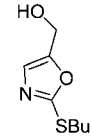
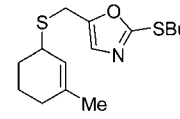
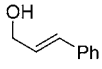
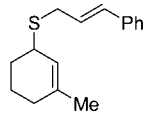
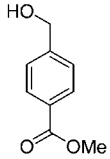
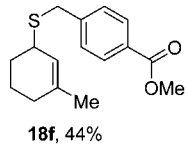
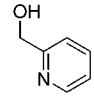
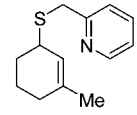
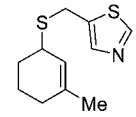
(17) Posner, T. *Ber. Dtsch. Chem. Ges.* **1905**, *38*, 646.

(18) (a) Overman, L. E.; Roberts, S. W.; Sneddon, H. F. *Org. Lett.* **2008**, *10*, 1485. (b) Crich, D.; Yang, F. *J. Org. Chem.* **2008**, *73*, 7107. (c) Minville, J.; Girardin, M.; Spino, C. *Can. J. Chem.* **2007**, *85*, 603. (d) Spino, C.; Boisvert, L.; Douville, J.; Roy, S.; Lauzon, S.; Minville, J.; Gagnon, D.; Beaumier, F.; Chabot, C. *J. Organomet. Chem.* **2006**, 5336.

(19) Han, X.; Zhang, Y.; Wu, J. *J. Am. Chem. Soc.* **2010**, *132*, 4104.

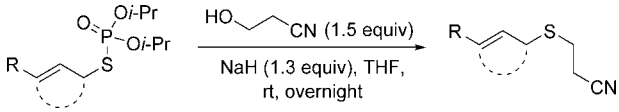
Table 1. Scope of the Alcohol

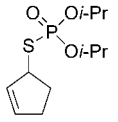
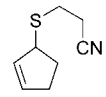
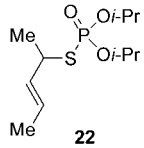
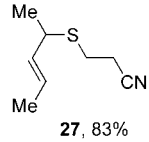
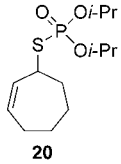
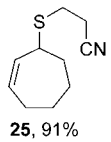
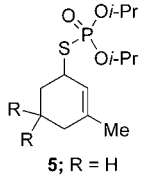
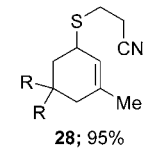
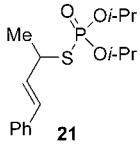
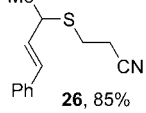


alcohol	thioether	alcohol	thioether	alcohol	thioether	alcohol	thioether
 6	 **18a**, 91%[a]	 9	 **18d**, 87%	 12	 **18g**, 93%	 15	 **18j**, 50%
 7	 **18b**, 81%	 10	 **18e**, 64%	 13	 **18h**, 93%	 16	 **18k**, 84%
 8	 **18c**, 92%	 11	 **18f**, 44%	 14	 **18i**, 86%	 17	 **18l**, 85%

[a] Isolated yield.

Table 2. Scope of the Phosphorothioate Ester

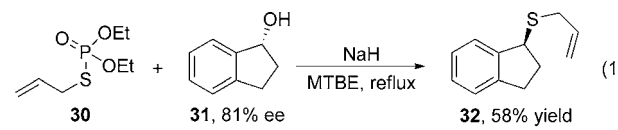


phosphorothioate	product	phosphorothioate	product
 19	 **24**, 88%[a]	 22	 **27**, 83%
 20	 **25**, 91%	 **5**; R = H **23**; R = Me	 **28**; 95% **29**; 89%
 21	 **26**, 85%		

[a] Isolated yield.

phosphorodithioate esters but their scope was limited to only four aliphatic alcohols and yields ranged from poor to moderate.[21] The scope of the phosphorothioate component was then investigated (Table 2). Again, the range was quite broad and was amenable to five-, six-, and seven-membered cycloalkenes as well as symmetrically and unsymmetrically substituted acyclic substrates.

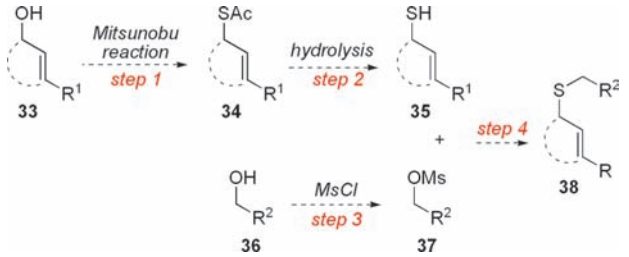
Because the mechanism of C−S bond formation is likely to proceed by an S_N2 displacement, in principle, we should be able to generate enantioenriched thioethers by utilizing chiral secondary alcohols. To investigate this hypothesis, thioether formation was carried out between allyl diethyl phosphorothioate ester **30** and scalemic secondary alcohol **31** that was prepared via Corey−Bakshi−Shibata (CBS) reduction of indanone (eq 1). We were delighted to observe near-perfect transfer of stereochemical information from starting material to product.



The two-step process for preparing thioethers described above represents a significant improvement to current methodology. Conventional methods for carrying out the same synthesis would involve Mitsunobu displacement of

the allylic alcohol with thioacetic acid followed by hydrolysis to the thiol (Scheme 3).[22] It would then be necessary to

Scheme 3. Thioether Synthesis Utilizing Conventional Methods



activate the other alcohol for nucleophilic displacement by conversion to a sulfonate ester. The reaction between thiol **35** and **37** would furnish thioether **38** in a four-step process, as compared to only two steps using our chemistry. Direct Mitsunobu reaction with thiols is unusual and limited to the availability of the corresponding thiol. Transition-metal-mediated allylic substitution with sulfur nucleophiles is also possible, but because thiols can poison late transition metals, reports of this kind are rare.[15]

Furthermore, the Mitsunobu reaction is an inherently non-atom-economical process that produces stoichiometric amounts of hydrazine dicarboxylate and triphenylphosphine oxide byproduct, of which the latter can sometimes be difficult to separate from the final product. In contrast, the byproduct generated in our procedure is a phosphate salt that can be readily removed upon basic aqueous workup. Our method also avoids the handling of malodorous compounds such as thioacetic acid or thiols. As described in our previous report, phosphorothioate esters are stable, odorless compounds that can be chromatographed and stored for extended periods without any special precautions.[19]

In conclusion, we have described an expedient method for the synthesis of allylic thioethers starting from the corresponding phosphorothioate esters and alcohols. This chemistry is compatible with a wide range of functional groups and heterocycles. We have also demonstrated that this is a highly stereospecific process capable of delivering enantioenriched thioethers from the corresponding chiral secondary alcohols. Future work will focus on exploring the scope of the stereospecific thioether synthesis and extending the methodology to include intramolecular variants to provide access to tetrahydrothiophene and thiane derivatives.

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Supporting Information Available: Experimental procedures and spectra for compounds **5**, **18a**−**l**, **19**−**29**, and **32**. This material is available free of charge via the Internet at http://pubs.acs.org.

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