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A CONVENIENT PREPARATION OF THIOETHERS FROM ALCOHOLS[1]

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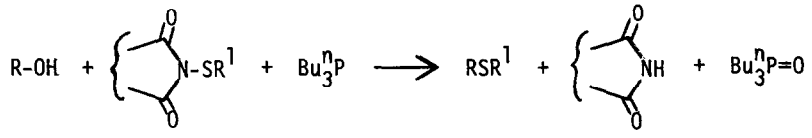
I wish to report a new and convenient method for the direct conversion of alcohols to thioethers in high yields under mild conditions. The method, which offers distinct advantages over recently described procedures[2] for this transformation, comprises reaction of the alcohol with a sulfenimide and tri-n-butylphosphine according to the equation:



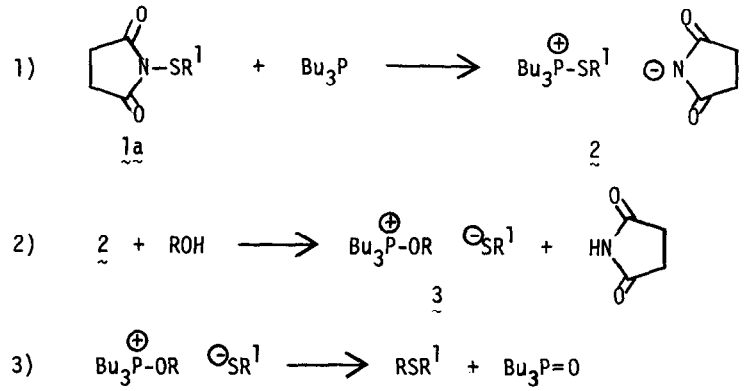
1

The required sulfenimides are readily accessible from thiols[3] or disulfides.[3,4] The reaction is convenient, manipulatively simple, and in most cases occurs rapidly at room temperature using essentially stoichiometric amounts of reagents in benzene or THF. The use of a reagent 1a derived from succinimide results in the water soluble by-products succinimide and tri-n-butylphosphine oxide, making isolation of the thioether particularly simple in most cases.

As will be seen from the Table, the reaction is general for primary and secondary alcohols, and proceeds with inversion. High yields are obtained even when elimination might be expected to compete, e.g. Examples 4 and 5 where only traces of trans-stilbene were observed. The highly stereospecific nature of the reaction was revealed by the use of steroidal alcohols. Both 3α- and 3β-pregnanolone (Examples 8 and 9) react to give exclusively the product of inversion. Even more striking is the reaction with cholesterol, where the 3α-derivative (81%) is the sole thioether product, together with small amounts of cholestadiene. The formation of mixtures of products, due to participation of an i-steroid intermediate, is well known[5] in displacements of Δ^5-sterols. The stereospecific and regiospecific nature of the reaction with cholesterol is in contrast to the non-specific nature of related reactions activated by phosphorus.[6,7]

In further contrast, the present reaction using tri-n-butylphosphine[8] is relatively insensitive to steric factors, unlike some related displacement reactions of alcohols using triphenylphosphine.[9,10]

Maximum yields of arylthioethers are obtained when the phosphine and 1 (R^1 = aryl) are mixed prior to addition of the alcohol. The proposed mechanism is outlined below:



The sulfenimide 1 reacts rapidly with the phosphine in benzene or THF to give a stable reagent formulated as 2. Addition of water at this point produces the thiol R^1SH. Addition of an alcohol converts 2 into an alkoxyphosphonium salt 3, with the succinimide anion acting as a base to liberate $R^1S^{\ominus}$. Formation of the thioether then occurs by cleavage of the alkoxy bond with inversion at carbon. When the alcohol is present during mixing of the reagents, significant amounts of disulfide (R^1SSR^1) are formed. This presumably arises by reaction of $R^1S^{\ominus}$ liberated in Step 2 above with unreacted sulfenimide 1, and results in a reduced yield of thioether. The absence of disulfide when 2 is preformed before addition of water or alcohol strengthens the conclusion that $R^1S^{\ominus}$ is not formed in Step 1, in agreement with the conclusions of Harpp[11] in a similar system. The reagent 2 (R^1 = aryl) is stable for extended periods at room temperature and remains reactive toward alcohols even after 24 hours, albeit in slightly diminished yields. When R^1 is primary or secondary alkyl, the known desulfurization[11] of 1 by phosphines to produce N-alkyl imides precludes the mixing of these reagents before addition of the alcohol. In the presence of an alcohol the above desulfurization is not observed, but the competing formation of disulfide R^1SSR^1 requires the use of a larger excess of reagents and/or slow addition of a solution of 1 to the reaction mixture to maximize yields of thioether.

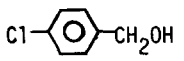
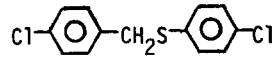
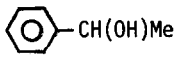
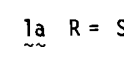
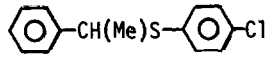
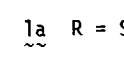
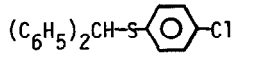
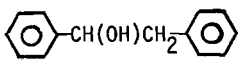
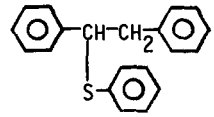
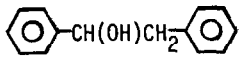
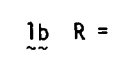
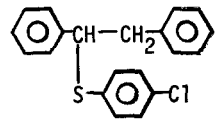
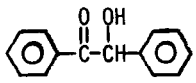
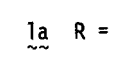
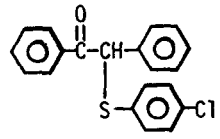
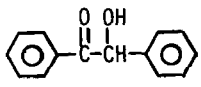
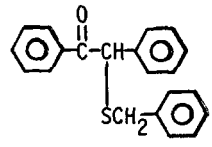
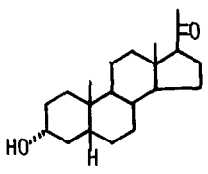
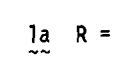
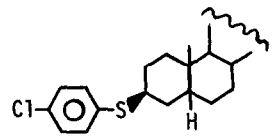
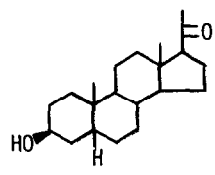
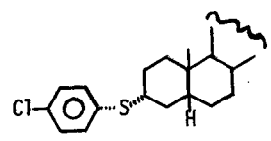
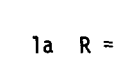
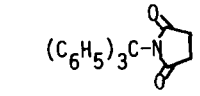
Although most reactions are complete within 1 hour at room temperature using 1.1 equivalents of 1 and Bu_3P, Examples 7, 8 and 9 required overnight reaction (18 hours) and 1.3 equivalents of reagents. The use of a nitrogen atmosphere in such cases is beneficial to prevent oxidation of the thiol.

Whereas ordinary tertiary alcohols do not undergo displacement in this system, triphenyl carbinol rapidly gave a product identified as triphenylmethylsuccinimide with very little thioether formation. Further aspects of this latter reaction and of the above synthetic method are being investigated.

A general procedure follows:

To a stirred solution of tri-n-butylphosphine (2.22 g, 11 m eq) in benzene (30 ml) at room temperature is added solid N-(phenylthio)succinimide (2.56 g, 11 m eq) in one portion. After stirring for five minutes at room temperature, the alcohol (10 m eq) is added all at once. Stirring is continued at room temperature until the reaction is complete, the solvent is evaporated and the residue treated with water (100 ml). (The addition of a few ml of hexane

TABLE

Example	ROH	I	Product	Yield[d]
1[a]		1a R = 		94%
2[a]		1a R = 		97%
3[a]	$(C_6H_5)_2CHOH$	1a R = 	$(C_6H_5)_2CH$- 	88%
4[a]		1a R = Sø		92%
5[a]		1b R = 		95%
6[a]		1a R = 		93%
7[b]		1a R = 		64%
8[c]		1a R = 		92%
9[c]		1a R = 		96%
10[c]	Cholesterol	1a R = Sø	3α-phenylthiocholest-5-ene	81%
11[a]	$(C_6H_5)_3C$-OH	1a R = 	$(C_6H_5)_3C$- 	21%

Footnotes to Table

[a]1.1 equivalents of tri-n-butylphosphine (commercial reagent) and the sulfenimide were used at room temperature in benzene.

[b]1.5 equivalents of reagents used.

[c]1.3 equivalents of reagents used under nitrogen.

[d]Figures quoted are isolated yields. Commercial reagents or alcohols were used without purification. Known products are in agreement with literature physical constants. All products gave satisfactory analyses and spectroscopic data in accordance with the assigned structure.

to dissolve traces of R^1SH or R^1SSR^1 may give cleaner crystalline products.) The product is isolated by filtration or extraction (hexane), washed well, and purified if necessary by conventional procedures.

References and Notes

1. Contribution No. 496 from the Institute of Organic Chemistry, Syntex Research, Palo Alto, California 94304.
2. I. Nakagawa and T. Hata, Tetrahedron Letters, 1409 (1975); Y. Tanigawa, H. Kanamaru and S. Murahashi, Tetrahedron Letters, 4655 (1975); W. T. Flowers, G. Holt, F. Omogbai and C. P. Poulos, J. Chem. Soc. Perkin I, 2394 (1976); I. M. Downie, H. Heaney and G. Kemp, Angew. Chem. Internat. Ed., 14, 370 (1975); R. S. Davidson, J. Chem. Soc. (C), 2131 (1967); and H. Loibner and E. Zbiral, Helv. Chim. Acta, 59, 2100 (1976).
3. M. Behforouz and J. E. Kerwood, J. Org. Chem., 34, 51 (1969).
4. K. H. Büchel and A. Conte, Chem. Ber., 100, 1248 (1967).
5. L. F. Fieser and M. Fieser, "Steroids," Reinhold Publ. Corp., New York, 1959, p. 314.
6. A. K. Bose and B. Lal, Tetrahedron Letters, 3937 (1973); and R. Aneja, A. P. Davies and J. A. Knaggs, Tetrahedron Letters, 67 (1974), 1033 (1975).
7. However, a very recent paper[9a] reports high stereospecificity in a phosphorus-activated displacement of cholesterol by azide.
8. Triphenylphosphine is ineffective in this reaction at room temperature. Tris(dimethylamino)phosphine reacts much more slowly.
9. (a) B. Lal, B. N. Pramanik, M. S. Manhas and A. K. Bose, Tetrahedron Letters, 1977 (1977); (b) A. K. Bose, B. Lal, W. A. Hoffman and M. S. Manhas, Tetrahedron Letters, 1619 (1973).
10. However, it has recently been shown[12] that certain hindered steroidal alcohols undergo phosphorus-activated displacement using the triphenylphosphine-diethyl azodicarboxylate system when benzene is used as solvent.
11. D. N. Harpp and B. A. Orwig, Tetrahedron Letters, 2691 (1970).
12. H. Loibner and E. Zbiral, Helv. Chim. Acta, 60, 417 (1977).