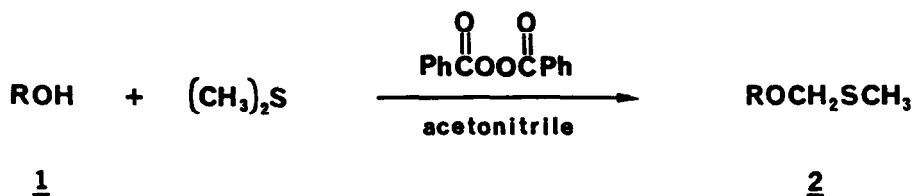


A MILD METHOD FOR THE CONVERSION OF ALCOHOLS TO METHYLTHIOMETHYL ETHERS

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Summary. Alcohols can be easily transformed to their corresponding methylthiomethyl ethers under mild conditions by treatment with methyl sulfide and benzoyl peroxide in acetonitrile.

Methylthiomethyl (MTM) ethers are now well-established as protecting groups for alcohol functionalities,¹ but their use in organic synthesis has been limited by a number of problems associated with their formation. For example, MTM ethers can be prepared directly from alcohols using acetic acid-acetic anhydride in dimethyl sulfoxide,² but this procedure requires long reaction times and strongly acidic conditions. The direct alkylation of an alcohol with $\text{ClCH}_2\text{SCH}_3$ -sodium hydride³ harbors some of the typical problems encountered in substitution reactions, and therefore is generally restricted to primary alcohols and phenols. A recent modification of the direct alkylation procedure utilizing $\text{AgNO}_3/\text{ClCH}_2\text{SCH}_3$ /triethylamine, while applicable to primary, secondary and tertiary alcohols, affords only modest yields of MTM ethers.⁴ Two indirect methods for preparing alkylthiomethyl ethers, including MTM ethers, by an interconversion of MEM and/or MOM ethers with $(\text{CH}_3)_2\text{BBR}/\text{CH}_3\text{SNa}$ ⁵ or $(\text{iPrS})_2\text{BBR}$ ⁶ have also been described. We now report a simple method for the direct conversion of alcohols to MTM ethers under very mild conditions using methyl sulfide and benzoyl peroxide.



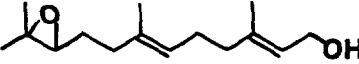
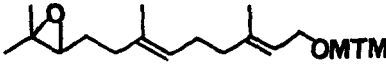
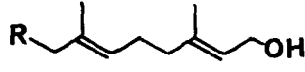
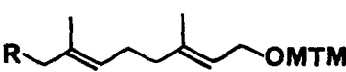
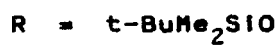

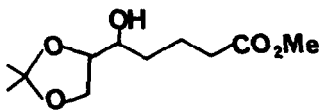
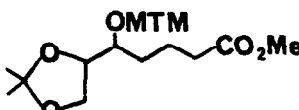
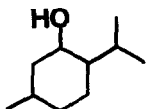
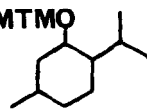
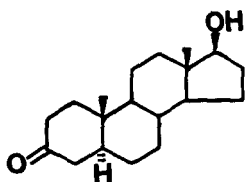
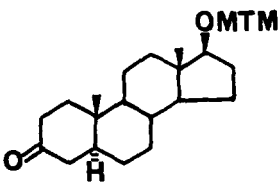
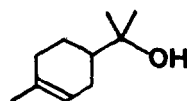
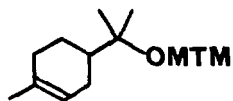
The following illustrates the simplicity of the procedure for the preparation of MTM ethers: To a solution of 1 mmol of alcohol 1d in 4 mL of anhydrous acetonitrile at 0 °C was added 0.58 mL (8 equiv) of methyl sulfide followed by the portionwise addition of 986 mg (4 equiv) of benzoyl peroxide over a 20 min period. After stirring for 2 h at 0 °C, the mixture was diluted with Et₂O and washed with 1 N aqueous sodium hydroxide solution; then brine; and dried over anhydrous magnesium sulfate. Evaporation of solvent, followed by chromatography on silica gel in 1:10 ethyl acetate/hexane (R_f 0.53) afforded an 88% yield of the MTM ether 2d.

Extension of this procedure to the primary, secondary and tertiary alcohols listed in Table I gave good yields of the MTM ethers 2a - 2i.⁷ Noteworthy, the acid-labile tetrahydropyranyl protecting group in 1b and the oxido group in 1c were completely compatible with the reaction conditions. By contrast, these groups did not tolerate the acidic conditions of the standard method using AcOH-Ac₂O-DMSO. The solvent for the reaction was found to be critical. The best yields of MTM ethers were obtained using acetonitrile as the solvent. Other aprotic solvents such as THF, Et₂O, CH₂Cl₂, benzene, and dioxane were less satisfactory than acetonitrile, and reactions were generally incomplete in these solvents even though the benzoyl peroxide was totally consumed. Additionally, we observed that the yield of the MTM ether was unaffected by the presence of bases such as 2,6-lutidine.⁸

The solvent also played an important role in suppressing competitive oxidation of the alcohol to the aldehyde or ketone, and the use of acetonitrile generally restricted the formation of carbonyl compounds to less than 10%. However, it was necessary to use an excess of methyl sulfide to prevent oxidation of the MTM ether by benzoyl peroxide, and a stoichiometric analysis of the conversion of geraniol (1d) using 1:1, 3:1 and 4:1 mole ratios of peroxide-to-alcohol provided 28%, 62% and 88% yields of 2d, respectively. This moderately low conversion efficiency is undoubtedly due to a rapid reaction between methyl sulfide and benzoyl peroxide which, in addition to the MTM ether, affords the products shown in Scheme I.⁹

In view of the formation of these by-products, it is important to note that excess DMSO-benzoic anhydride-benzoic acid in acetonitrile does not readily convert alcohols to MTM ethers; only 5-8% yield after 24 h at 23 °C. Additionally, a solution of DMSO and benzoic anhydride in acetonitrile produces only trace amounts of ester III even after 6 h at 0 °C. Consequently, the sulfoxide, anhydride, and acid derived from methyl sulfide-benzoyl peroxide do not significantly contribute to the formation of either the MTM ether or the MTM ester III.

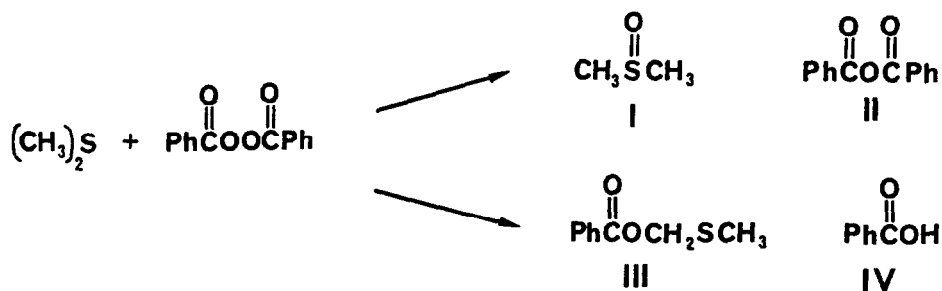
Table I. Conversion of Alcohols **1** to MTM ethers **2** with Me₂S/benzoyl peroxide.

entry	Substrate 1 ^a	Product 2	reaction time (h)	yield(%) ^b
a	CH ₃ (CH ₂) ₆ CH ₂ OH	CH ₃ (CH ₂) ₆ CH ₂ OMTM	4	88
b	THPOCH ₂ CH ₂ C≡CCH ₂ OH	THPOCH ₂ CH ₂ C≡CCH ₂ OMTM	3	84
c			2	77
d			2	88
e			0.25	74
f	4-CH ₃ OC ₆ H ₄ CH ₂ OH	4-CH ₃ OC ₆ H ₄ CH ₂ OMTM	3	81
g			4	86
h ^c			4	96
i			4	86
j ^c			5	85

(a) all reactions were conducted with 1 mmol of substrate at 0 °C. (b) isolated yields of purified products. (c) 6 equiv of benzoyl peroxide were used.

The use of the inexpensive reagents methyl sulfide and benzoyl peroxide, coupled with the mild conditions of the reaction which are compatible with acid-labile groups, should contribute to future use of the procedure disclosed here for introducing the MTM protecting group which is valued for its unique stability characteristics^{1a} and ease of removal¹⁰ under mild conditions.¹¹

Scheme I



References and Notes

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11. We gratefully acknowledge the American Cancer Society and the American Heart Association for the generous support of this work.

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