CHEMISTRY LETTERS, pp. 1277-1278, 1979. Published by the Chemical Society of Japan

A MILD AND CONVENIENT METHOD FOR THE PREPARATION OF METHYLTHIOMETHYL ETHERS: PROTECTION OF HYDROXYL GROUPS

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Methylthiomethyl (MTM) ethers of various types of alcohols were prepared under mild conditions by using chloromethyl methyl sulfide and silver nitrate.

Methylthiomethyl (MTM) ethers are known as the very valuable protective group for the hydroxyl functions because of their unique stability characteristics and the selective cleavage under mild conditions.[1-3] For the preparation of MTM ethers the following three methods have so far been reported: (1) halomethyl methyl sulfide — sodium hydride,[1a,b] (2) acetic anhydride — DMSO,[2] and (3) acetic acid — acetic anhydride — DMSO.[3] However, the first method requires a strong base such as sodium hydride and is suitable only for primary alcohols[1a] and phenols[1b]. The second method is restricted to tertiary alcohols because primary or secondary alcohols are partly oxidized to carbonyl compounds. In the third method, the oxidative side-reaction is suppressed to a considerable extent, but still not completely eliminated. In this paper we wish to describe a mild and convenient method for the preparation of MTM ethers under non-oxidative conditions.

The reaction was carried out by mixing alcohols and chloromethyl methyl sulfide with silver nitrate in the presence of triethylamine at room temperature $\sim$ 80°C. The results are summarized in Table 1.

$$ROH \xrightarrow[Et_3N \ / \ Benzene \text{ or } Cyclohexane]{ClCH_2SCH_3,\ AgNO_3} ROCH_2SCH_3$$

As is shown in the table the MTM ethers of primary and secondary alcohols were smoothly produced. The MTM ether of α-phenylethanol, for example, was obtained by this method in good yield, while the method by Pojer et al.[3] produced a significant amount of acetophenone as a by-product (entry 5). In the case of tertiary alcohol the yield was low (entry 9). Allylic alcohols such as geraniol or linalool could be converted into the corresponding MTM ethers without any rearrangement of double bonds (entries 2 and 9).

The reaction seems to proceed with the help of the electrophilic catalysis of silver ion. Other silver salts such as silver cyanide, silver fluoride, silver perchlorate, or silver tetrafluoroborate were less effective. For the solvent, hydrocarbons such as cyclohexane or benzene gave good results. With the polar solvents (acetonitrile, acetone, HMPA etc.) the reaction was very fast but the yield was unsatisfactory.[4] Triethylamine proved to be the best base for this reaction.

Table 1. Preparation of MTM Ethers[a)]

	Alcohol	Solvent	Temp (°C)	Time (h)	Yield[b)] (%)		Recovered alcohol (%)[b)]
1	1-Octanol	Benzene	80	9	81[c)]		
2	Geraniol	Benzene	80	24	75[c)]		17
3	THPO⌒O⌒OH	Benzene	80	24	60[c)]		31
4	Cyclohexanol	Benzene	60	5	80	(90)	7
		Cyclohexane	rt	26		(98)	
5	α-Phenylethanol	Benzene	60	4	69[c,d)]	(82)	11
		Cyclohexane	rt	8.5		(83)	
6	2-Octanol	Benzene	70	24	59[c)]		28
7	1-Hexyn-3-ol	Benzene	rt	27	60[c)]	(82)	
8	Cholesterol	Benzene	80	24	44[c)]		45[e)]
9	Linalool	Benzene	65	46	32		65

a) $ClCH_2SCH_3$ (1.2 eq.), $AgNO_3$ (1.1 eq.), and Et_3N (1.2 eq.) were used vs. ROH. b) Isolated yield. GLPC yields were given in parentheses. c) These are new compounds and gave correct elemental analyses. Structures were confirmed by PMR spectra. d) An experiment carried out according to Pojer's method[3)] gave the MTM ether (53%) besides a significant amount of acetophenone (30%). e) Dicholesteryl methylene acetal was also isolated (4%). Mp 187-188°C; MS (m/e) 784 (M^+).[c)]

Among other bases examined [pyridine, 2,6-lutidine, dicyclohexylethylamine, DBU, 1,8-bis-(dimethylamino)-naphthalene, or calcium carbonate] only 2,6-lutidine gave fairly good results (80% GLPC yield for cyclohexyl methylthiomethyl ether).

A typical example is as follows. A solution of α-phenylethanol (60 µl, 0.5 mmol) and chloromethyl methyl sulfide (50 µl, 0.6 mmol) in dry benzene (250 µl) was added to a stirred mixture of silver nitrate (94 mg, 0.55 mmol), triethylamine (84 µl, 0.6 mmol), and dry benzene (250 µl), and the mixture was then heated at 60°C. Formation of the MTM ether was followed by GLPC by addition of bromomesitylene as an internal standard. After four hours the amount of the ether became constant with 82% yield. For isolation of the ether, the reaction mixture was filtered through a dry Celite column. The filtrate was washed successively with 3% aqueous phosphoric acid, saturated aqueous sodium hydrogencarbonate solution, and water, dried, concentrated, and purified by preparative TLC (silica gel).

This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education.

References and Notes

1) a) E. J. Corey and M. G. Bock, Tetrahedron Lett., 1975, 2643, 3269; b) R. A. Holton and R. G. Davis, ibid., 1977, 533.
2) K. Yamada, K. Kato, H. Nagase, and Y. Hirata, Tetrahedron Lett., 1976, 65.
3) P. M. Pojer and S. J. Angyal, Tetrahedron Lett., 1976, 3067.
4) Cyclohexyl methylthiomethyl ether was produced in 48% yield in acetonitrile at -20°C in 1 h. The use of excess reagents did not improve the yield.

(Received August 13, 1979)