Tetrahedron Letters No. 6, pp 533 - 534, 1977. Pergamon Press. Printed in Great Britain.

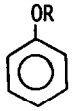
PROTECTION OF PHENOLS AS METHYLTHIOMETHYL ETHERS

Robert A. Holton*[1] and Robert G. Davis
R. B. Wetherill Laboratory of Chemistry, Purdue University
West Lafayette, Indiana 47907

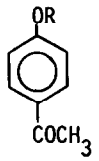
(Received in USA 19 November 1976; received in UK for publication 10 January 1977)

Methylthiomethyl (MTM) ethers have recently been found to serve as protecting groups for primary,[2] secondary[3] and tertiary[3,4] alcohols. It is our belief that phenolic MTM ethers, by virtue of their facile formation and hydrolysis as well as their resistance to a variety of reagents and conditions, constitute a beneficial addition to the synthetic repertoire of organic chemists.

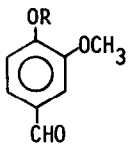
Attempted conversions of phenol into its MTM ether 1 *via* the methods of Angyal[3] or Yamada[4] (DMSO, acetic anhydride, room temperature with or without added acetic acid) were unsuccessful due to the formation of a mixture of products, presumably resulting from competitive C- and O-methylthiomethylation. Treatment of sodium phenoxide with chloromethyl methyl sulfide[5] in ether or THF also failed to generate 1 in a satisfactory manner, owing to the previously ob-



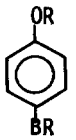
1a, R=MTM, 94%
1b, R=H, 94%



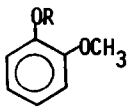
2a, R=MTM, 93%
2b, R=H, 93%



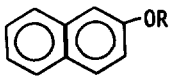
3a, R=MTM, 93%
3b, R=H, 95%



4a, R=MTM, 92%
4b. R=H, 92%



5a, R=MTM, 91%
5b, R=H, 95%



6a, R=MTM, 94%
6b, R=H, 90%

served[2] apparent inertness of chloromethyl methyl sulfide to nucleophilic attack. Aryl MTM ethers 1a-6a[6] could be generated in the indicated high yields[7] through reaction of the corresponding sodium phenoxides with chloromethyl methyl sulfide in hexamethylphosphorictriamide (HMPA) solution at room temperature for 16 hr.

MTM ethers 1a-6a were found to be resistant to the hydrolysis conditions shown to be effective for regeneration of primary alcohols from their MTM ethers[2] ($HgCl_2$, CH_3CN, H_2O, room temperature, 6 hr, led to 93% recovered 1a), allowing the selective hydrolysis of primary alkyl MTM ethers in the presence of aryl MTM ethers. Aryl MTM ethers were also found to be stable to basic and nucleophilic reagents (NaOR, $LiAlH_4$, RMgX), and moderately stable to acidic conditions (acetic acid, THF, H_2O, room temperature, 4 hr, 95% recovered 1a).

Removal of the MTM group to afford phenols 1b-6b could be accomplished in the indicated yields[7] by treatment of the MTM ether with mercuric chloride in acetonitrile-water (4:1) at reflux for 10 hr.

Exemplary experimental procedures for the formation of phenolic MTM ethers and their hydrolysis follow:

Phenyl methylthiomethyl ether (1a): To a solution of 94 mg (1.0 mmol) of phenol in 5 ml of dry HMPA (distilled from CaH_2) under N_2 was added 27 mg (1.1 mmol) of sodium hydride. After stirring at room temperature for 0.5 hr, 106 mg (1.1 mmol) of chloromethyl methyl sulfide was added and stirring at room temperature was continued for 16 hr. The mixture was partitioned between benzene and water; drying and evaporation of benzene extracts gave spectrally and chromatographically homogeneous 1a (145 mg, 94%): nmr ($CDCl_3$) 1.90 (s, 3), 3.68 (s, 2), 6.7-7.4δ (m, 5).

Hydrolysis of phenyl methylthiomethyl ether (1a): To a solution of phenyl methylthiomethyl ether (1a) (154 mg, 1.0 mmol) in 10 ml of a 4:1 acetonitrile-water mixture was added mercuric chloride (271 mg, 1.5 mmol). The resulting suspension was refluxed for 10 hr, diluted with ethyl ether, and filtered through celite. Aqueous extraction followed by drying and solvent evaporation gave spectrally homogeneous phenol (86 mg, 92%), identical to an authentic sample.

Acknowledgement: We thank the Public Health Service (GM-21992-01) for the support of this research.

References and Notes

1. DuPont Assistant Professor of Chemistry.
2. E. J. Corey and M. G. Bock, Tetrahedron Lett., 3269 (1975).
3. P. M. Pojer and S. J. Angyal, ibid., 3067 (1976).
4. K. Yamada, K. Kato, H. Nagase, and Y. Hirata, ibid., 65 (1976).
5. Commercially available from Aldrich Chemical Co. or prepared by the method of W. E. Truce, G. H. Birum, and E. T. McBee, J. Amer. Chem. Soc., 74, 3594 (1952).
6. Structures consistent with all spectral data. All new compounds gave correct C,H analyses.
7. Yields refer to spectrally and chromatographically homogeneous isolated material.