Tetrahedron Letters No. 1, pp 65 - 66, 1976. Pergamon Press. Printed in Great Britain.

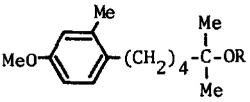
PROTECTION OF TERTIARY HYDROXYL GROUPS AS METHYLTHIOMETHYL ETHERS

Kiyoyuki Yamada,* Kaneyoshi Kato, Hiroshi Nagase, and Yoshimasa Hirata

Department of Chemistry, Faculty of Science, Nagoya University, Chikusa, Nagoya, Japan

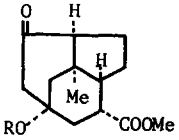
(Received in Japan 20 October 1975; received in UK for publication 20 November 1975)

The protection of hydroxyl groups is frequently required in the transformation of various polyfunctional compounds. Although a variety of methods of protecting hydroxyl groups is known,[1,2] few of them can satisfactorily be applied to tertiary hydroxyl groups, owing to their unreactive nature and, in many cases, their property susceptible to acid-catalyzed dehydration. In the present paper, preparation, cleavage, and utility of a methylthiomethyl (MTM = $-CH_2SMe$) ether grouping for the protection of tertiary hydroxyl groups are described. Very recently, the protection of primary hydroxyl groups as MTM ethers and their usefulness were reported by Corey and Bock.[3]



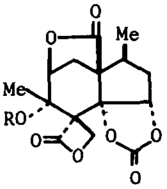
1a : R = H

1b : R = MTM



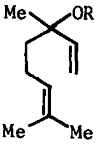
2a : R = H

2b : R = MTM



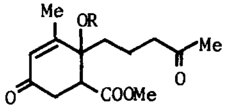
3a : R = H

3b : R = MTM



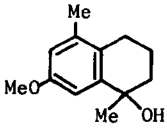
4a : R = H

4b : R = MTM

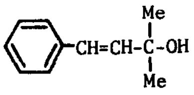


5a : R = H

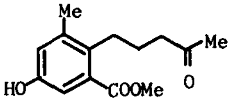
5b : R = MTM



6



7



8

When a tertiary alcohol was treated with a mixture of acetic anhydride and DMSO at room temperature, an MTM ether was formed[4] in good yield [(1a)[5] → (1b)[5], 90%; (2a)[6] → (2b)[5], 90%; (3a)[7] → (3b)[5] (mp 199—202°), 80%]. The characteristic signals of the MTM ethers in the nmr spectra are singlets due to -SMe (δ 2.1 — 2.4) and $-OCH_2S-$ (δ 4.4 — 4.7), respectively. It is noteworthy that an allylic tertiary alcohol can also be converted to the corresponding MTM ether [e.g. linalool (4a) → (4b)[5], (30—40% isolated yield, 60% yield by nmr spectral analysis of the reaction mixture); (5a)[5] → (5b)[5], 88%]. Dehydration took place in certain benzylic tertiary alcohols and the related compounds [e.g. (6), (7)] under the reaction conditions. In the alcohol (6), the MTM ether would be formed and subsequently undergo elimination, because on treatment of (6) with acetic anhydride in the absence of DMSO, the alcohol (6) was recovered unchanged.

The cleavage of the MTM ethers to regenerate the tertiary alcohols was effected by mercuric chloride—cadmium carbonate in acetonitrile—water (50°, 3 hr)[8,9] usually in high yield. It is essential to keep the reaction mixture neutral in order to obtain tertiary alcohols in good yield. These reaction conditions could be applied for the cleavage of the labile MTM ether (5b), although the yield was moderate: the MTM ether (5b) afforded the tertiary alcohol (5a) (60%) and an aromatic compound (8) (22%) resulting from dehydration.

Experimental procedures for the preparation and the cleavage of MTM ethers are as follows.

Preparation of the MTM ether (5b): A solution of a diastereomeric mixture of (5a) (3.4 g, 12.7 mmol) in acetic anhydride (60 ml) and anhydrous DMSO (60 ml) was stirred at room temperature for 30 hr. The solution was evaporated under reduced pressure (2 mmHg) using a Dry Ice—acetone trap below 50°, and the resulting oil was dissolved in benzene. The benzene solution was washed twice with a saturated $NaHCO_3$ solution, once with a saturated NaCl solution, dried (Na_2SO_4), and concentrated. Chromatography of the oily residue on silicic acid ($CHCl_3$) gave a diastereomeric mixture of (5b) (3.7 g, 88%) as colorless oil, which could be separated by repetition of preparative layer chromatography (plc) (silica gel, benzene—ether, 1:1) to give each of two diastereomers in pure state.

Cleavage of the MTM ether (1b): A suspension of (1b) (20 mg, 0.071 mmol), $HgCl_2$ (57 mg, 0.21 mmol) and $CdCO_3$ (72 mg, 0.42 mmol) in acetonitrile—water (10:1, 1.1 ml) was stirred at 50° for 3 hr. The mixture was diluted with EtOAc and filtered. The filtrate was evaporated under reduced pressure. The chloroform solution of the residue was washed with a saturated NaCl solution, dried (Na_2SO_4), and concentrated. Plc (silica gel, $CHCl_3$) afforded pure (1a) (15 mg, 94%).

REFERENCES

1. J. F. W. McOmie in "Advances in Organic Chemistry, Methods and Results, Vol. 3," R. A. Raphael, E. C. Taylor, H. Wynberg, Ed., Interscience Publishers, 1963, pp. 191-294.
2. C. B. Reese in "Protective Groups in Organic Chemistry," J. F. W. McOmie, Ed., Plenum Press, 1973, pp. 95-143.
3. E. J. Corey and M. G. Bock, Tetrahedron Lett., 3269 (1975). We thank Professor Corey for making his results available to us prior to publication.
4. Formation of methylthiomethyl ethers as by-products of the Moffatt oxidation and the related reactions of secondary alcohols have been known: J. G. Moffatt in "Oxidation, Vol. 2," R. L. Augustine, D. J. Trecker, Ed., Marcel Dekker, Inc., 1971, pp. 1-64.
5. The ir, nmr, and mass spectral data for this new compound were in accord with the structure assigned. Satisfactory microanalyses or high resolution mass spectral data were obtained.
6. K. Yamada, M. Suzuki, Y. Hayakawa, K. Aoki, H. Nakamura, H. Nagase, and Y. Hirata, J. Amer. Chem. Soc., **94**, 8278 (1972).
7. K. Yamada, S. Takada, S. Nakamura, and Y. Hirata, Tetrahedron, **24**, 199 (1968).
8. Cleavage of the MTM ethers of tertiary alcohols was examined at room temperature,[3] but the MTM ethers were recovered to a various extent after 15 hr.
9. *cf*. Hydrolysis of thioketals by mercuric chloride: E. J. Corey and B. W. Erickson, J. Org. Chem., **36**, 3553 (1971); E. J. Corey and D. Crouse, ibid., **33**, 298 (1968).