Tetrahedron Letters,Vol.30,No.49,pp 6867-6868,1989   0040-4039/89 $3.00 + .00
Printed in Great Britain   Pergamon Press plc

AN UNEXPECTED DIFFICULTY IN THE USE OF MEM AS A PROTECTIVE GROUP FOR PHENOLIC HYDROXYL

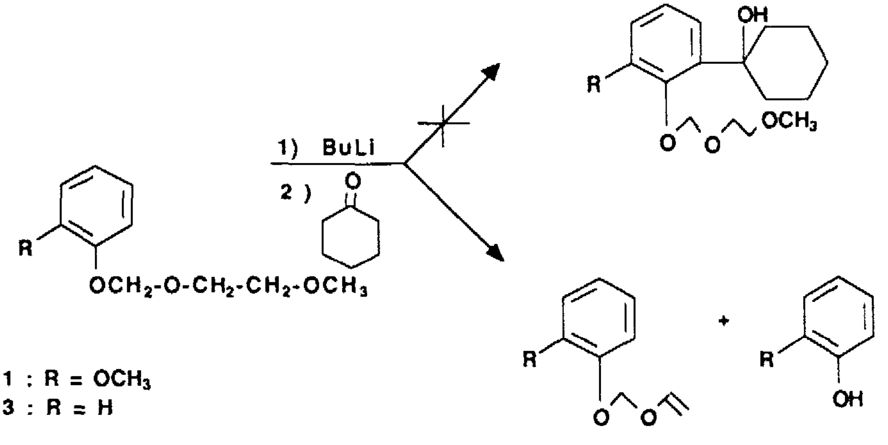
Joëlle MAYRARGUE, Mustapha ESSAMKAOUI and Henri MOSKOWITZ*
Faculté de Pharmacie, Laboratoire de Chimie Organique, associé au CNRS,
Rue J.B. Clément, 92296 Châtenay-Malabry, France.

Summary : The ortholithiation of methoxyethoxymethyl (MEM) protected phenolic groups leads to an intramolecular attack of the MEM group instead of the expected condensation.

In a study of polycyclic phenolic structures, it was necessary to protect reversibly the aromatic hydroxyl groups. Methoxymethyl (MOM) chloride was at first conveniently used: however, due to its toxicity, it is no longer commercially available and, as a replacement, we have studied methoxyethoxymethyl (MEM) chloride used as a protective group for OH since the work of COREY *et al* [1].

MEM chloride was used in the case of guaiacol and compound 1 was obtained in good yield, as described in (1). Literature data [2,3], suggested a high stability in a basic medium and an easy cleavage by acids could be expected.

Compound 1 was reacted with i) butyllithium and ii) cyclohexanone (1/1/1 or 1/2/1) aiming at the synthesis of a tertiary alcohol. Only the ether 2[4] (51 %), the deprotected phenol 5 (16 %) and the MEM derivative 1 (23%) could be isolated.

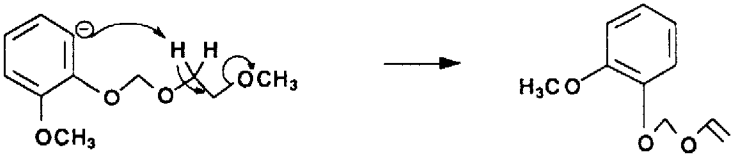


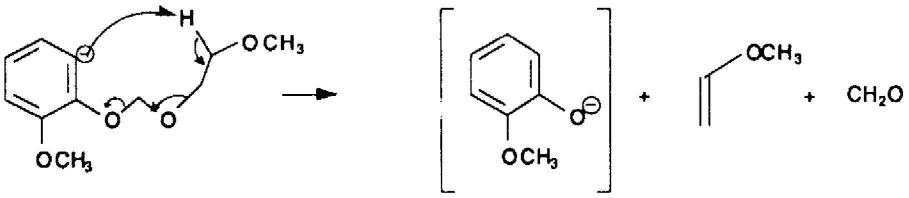
1 : R = OCH_3
3 : R = H

2 : R = OCH_3
4 : R = H

5 : R = OCH_3

Lithiation occuring in *ortho* of the O-MEM rather than of O-CH_3 group[5], the formation of compound **2** and the deprotection of **1**[6], unexpected in a basic medium, can be explained by the following processes:





A similar interaction is possible when MOM is used as the protective group, but in the absence of possible cleavage, the *ortho* lithiated derivative can react with cyclohexanone leading to the expected alcohol.

We have checked that MEM was not attacked directly by butyllithium : in the same experimental conditions, the MEM derivatives of alcohols do not undergo any elimination process. Furthermore, the methoxy group of guaiacol does not seem to interfere, since the MEM derivative of phenol **3** leads, in the same way, to enol ether **4**. In the reaction of the enol ether **2** with i) BuLi and ii) cyclohexanone, no transformation occurs ; this could be related to the formation of unreactive carbanion strongly stabilized by the electron pairs of oxygen atoms and π bond. It must, however, be noted that **1** reacted with BuLi, cyclohexanone and 12-crown-4-ether (added before or after BuLi) did not undergo any attack and was recovered unchanged.

It appears from this study that the MEM group cannot be used to protect a phenolic function in a process of *ortho*lithiation.

REFERENCES AND NOTES

1 - E.J. Corey, J.L. Gras and P. Ulrich, Tetrahedron Lett., 809 , (1976).

2 - E.J. Corey, R.L. Danheiser, S. Chandrasekaran, P. Siret, G.E. Keck and J.L. Gras, J. Am. Chem. Soc., **100**, 8031, (1978).

3 - J. Quick, R. Ramachandra, Synth. Commun., **8** , 511, (1978).

4 - N-butyllithium (0,011 mole) was added under nitrogen to 20 ml of an anhydrous THF solution of **1** (0,01 mole) at -5 °C and the mixture stirred at room temperature for 1,5 h. After addition of cyclohexanone (0,01 mole) at -5 °C, the mixture was stirred for another 2 h. at room temperature. MeOH was then added and after evaporation of the solvents, the residue was extracted with H_2O/Et_2O. The deprotected phenol was isolated from the aqueous solution and product **2** from the organic layer. Compound **2** was isolated on a silicagel column (toluene-acetone 8/2). ^1H NMR (60 MHz) d : 3.9 (s, CH_3) ; 4.3 and 4.7 (2q, CH_2) ; 5.5 (s, CH_2) ; 6.65 (q, CH) ; 7.1 (m, ArH). Correct C, H, N analysis.

5- S.H. Rosenberg and H. Rapoport, J. Org. Chem., **49**, 56, (1984).

6- This mechanism was suggested by the referee of a first version of this manuscript; we thank him (or her) for this suggestion. The formaldehyde evolved was characterized with chromotropic acid.

(Received in France 24 July 1989)