

A Mild, Efficient, and Inexpensive Protocol for the Selective Deprotection of TBDMS Ethers Using KHSO_4

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(Received June 21, 2004; CL-040704)

Potassium hydrogensulfate in 30% aq. methanol deprotects a variety of *tert*-butyldimethylsilyl ethers at room temperature in excellent yields.

Hydroxyl groups are widely present in many bioactive organic molecules, sugars, nucleosides etc., hence protection and later deprotection is necessary for multistep transformation, especially in the total synthesis of complex organic molecules. A variety of protective groups have been developed to mask the reactivity of hydroxyl group,¹ however *tert*-butyldimethylsilyl protection is very common, because of its easy incorporation and stability to withstand different reaction conditions.²

Although tetra-*n*-butylammonium fluoride is the most common reagent for the cleavage of TBDMS ethers, the strong basicity³ of fluoride ion limits its application to base sensitive substrates and the phase transfer properties of tetrabutylammonium cations often cause difficulties in the work-up and purification of products. To overcome these difficulties a variety of reagents have been developed, but most of them are oxidizing, strongly acidic or basic in nature, and also require expensive reagents and dry reaction conditions. Some of the acidic reagent employed were aq. $\text{HF}/\text{CH}_3\text{CN}$,⁴ $\text{CF}_3\text{COOH}/\text{H}_2\text{O}/\text{THF}$,⁵ $\text{TsOH}/\text{THF}/\text{H}_2\text{O}$,⁶ H_2SO_4 ,⁷ $\text{BF}_3 \cdot \text{Et}_2\text{O}/\text{CHCl}_3$,⁸ The basic reagents reported other than TBAF were $\text{KF}/18\text{-crown-6}$,⁹ $\text{KF}/\text{alumina}/\text{ultrasound}$,¹⁰ $\text{K}_2\text{CO}_3/\text{kryptofix}/\text{CH}_3\text{CN}$,¹¹ $\text{K}_2\text{CO}_3/\text{ethanol}$,¹² $\text{Cs}_2\text{CO}_3/\text{DMF}/\text{H}_2\text{O}$,¹³ $\text{NaOH}/n\text{-Bu}_4\text{NHSO}_4/\text{dioxane}$,¹⁴ $\text{KF}/\text{alumina}$,¹⁵ and LiOH/DMF .¹⁶ The oxidizing agents like ceric ammonium nitrate,¹⁷ sodium periodate,¹⁸ and oxone¹⁹ were also reported for the deprotection of TBDMS ethers.

As synthetic targets become increasingly complex, selective methods to deprotect TBDMS ethers in the presence of other functional groups are very demanding. So still there is a need to develop a methodology, which might work under mild condition by using economically cheaper and preferably nontoxic reagent. In continuation of our work^{20,21} in exploring the catalytic activity of KHSO_4 we further probed it for the selective deprotection of *tert*-butyldimethylsilyl ethers.²²

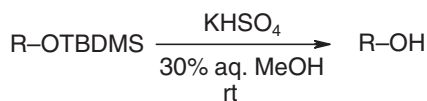
A spectrum of *tert*-butyldimethylsilyl ethers were subjected to our reaction condition. The TBDMS ethers of primary, secondary, and tertiary aliphatic alcohols, and various substituted benzylic alcohols (Table 1) were deprotected selectively during 1.5–4 h in excellent yields. During this exceedingly mild reaction condition neither ester hydrolysis nor transesterification takes place (entries 3–5, 14). The reaction condition does not affect

Table 1. Deprotection of various TBDMS ethers to the corresponding alcohols using KHSO_4 in 30% aq. methanol

| Entry | Substrate | Product ^a | Time/h | Yield/% ^b |
|-------|-----------|----------------------|--------|----------------------|
| 1 | | | 1.5 | 96 |
| 2 | | | 1.5 | 96 |
| 3 | | | 3 | 94 |
| 4 | | | 3 | 97 |
| 5 | | | 3 | 95 |
| 6 | | | 4 | 85 |
| 7 | | | 2 | 96 |
| 8 | | | 2 | 94 |
| 9 | | | 2 | 90 |
| 10 | | | 2 | 90 |
| 11 | | | 2 | 91 |
| 12 | | | 20 | 84 |
| 13 | | | 2 | 75 |
| 14 | | | 2 | 82 |
| 15 | | | 2 | 84 |
| 16 | | | 4 | 85 |

^aAll the products were characterized by IR, NMR, and MS.

^bIsolated Yields.



Scheme 1.

Table 2. Deprotection of N-protected TBDMS ethers of amino alcohols

| Entry | Substrate | Product ^a | Time/h | Yield/% ^b |
|-------|-----------|----------------------|--------|----------------------|
| 1 | | | 1.5 | 90 |
| 2 | | | 1.5 | 92 |
| 3 | | | 1.5 | 95 |
| 4 | | | 1.5 | 93 |

^aAll the products were characterized by IR, NMR, and MS.

^bIsolated Yields.

the acid sensitive ketal group (entry 16). The phenolic TBDMS ether required 20 h and 1 equiv. of KHSO_4 for complete deprotection. Thus in the presence of phenolic TBDMS ether, benzylic ether was cleaved selectively (entry 13).

We next extended our methodology to the deprotection of N-protected TBDMS ethers of amino alcohols (Table 2). The deprotection proceeds smoothly in 1.5 h without affecting the amino protective groups in excellent yields.

We thank the Council of Scientific and Industrial Research, New Delhi, India for financial support.

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- 22 General experimental procedure: To a stirred solution of TBDMS ether (1 mmol) in 3 mL of 30% aq. methanol added 0.4 mmol of KHSO_4 and stirred at room temperature. The progress of the reaction was monitored by TLC. After the disappearance of starting material, methanol was removed, added 5 mL of water and extracted with 20 mL (2×10) of ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and solvent was removed under reduced pressure. The crude product was purified by column chromatography. The alcohol obtained was identical with authentic sample by TLC, IR, NMR, and Mass.