

An Oxidatively Removable Protecting Group for Aldehydes and Ketones

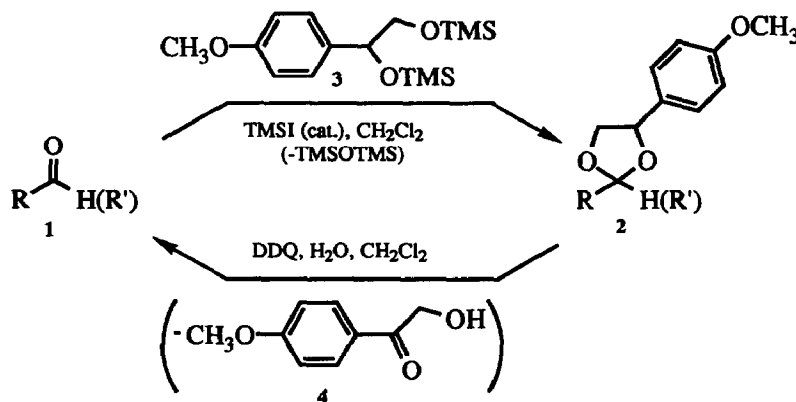
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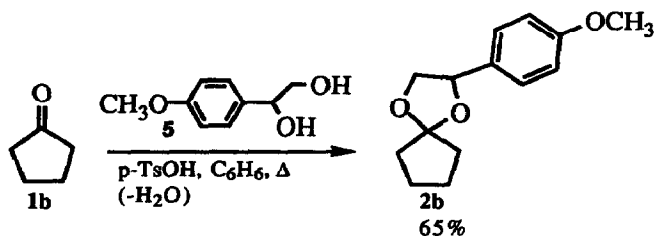
Abstract: Aldehydes and ketones can be converted to the corresponding *p*-methoxyphenylethylene acetals and ketals in good to excellent yield. Deprotection can be accomplished under mild conditions to produce uniformly excellent yields of the original carbonyl compound.

The *para*-methoxybenzyl (PMB) moiety is known to be susceptible to benzylic oxidation under a variety of conditions. Weinreb has utilized anodic oxidation to unmask PMB ethers.¹ Oikawa and coworkers have demonstrated the efficacy of the removal of the PMB group in a very efficient procedure using DDQ (2,3-dichloro-5,6-dicyanobenzoquinone).^{2,3} *Para*-methoxybenzylic cations have been implicated as intermediates in all of the above procedures. We have found that the DDQ protocol can be extended to the deprotection of 4-(4'-methoxyphenyl)-1,3-dioxolanes as shown in Scheme 1 (2 → 1). This reaction is thought to proceed by decomposition of the hemiketal which results from addition of water to the initially formed PMB-stabilized carbocation. Literature perusal indicates a lack of oxidatively removeable protecting groups for aldehydes and ketones.⁴ A protecting group of this nature should be a significant addition to the synthetic chemist's repertoire for construction of complex molecules. It was thus deemed worthwhile to examine the scope of the protection/deprotection sequence outlined in Scheme 1.

Scheme 1



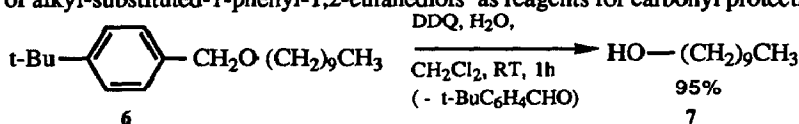
Initial attempts at protection involved treatment of aldehydes and ketones with 1-(4'-methoxyphenyl)-1,2-ethanediol (5)⁵ in benzene with catalytic *p*-toluenesulfonic acid at reflux and azeotropic removal of water. This procedure worked moderately well with cyclopentanone (65%) but produced only modest amounts of product or failed with a variety of other carbonyl compounds.⁶ In cases where the ketone carbonyl failed to react, the diol appeared to polymerize (presumably initiated by acid-catalyzed loss of OH from the *para*-methoxybenzylic



position of 5). Success in the protection reaction was achieved using a variation of Sakurai's procedure for acetalization of carbonyls which utilizes silyl ethers with iodotrimethylsilane catalysis (Scheme 1, 1 + 3 \rightarrow 2).⁷ The requisite bis-trimethylsilyl ether 3 was produced by treatment of the aforementioned diol 5 with 2.5 eq of chlorotrimethylsilane and 5.0 eq of triethylamine.⁸ As shown in Table 1, the protection reaction occurs in moderate to excellent yield for both aldehydes and ketones.⁹ Cycloheptanone, which is known to be substantially less electrophilic than cyclohexanone was quite sluggish with respect to ketalization by this technique.¹⁰ Because protecting groups are useful only in multifunctionalized compounds it was considered appropriate to examine the compatibility of the protection reaction with a variety of functionality/protecting groups (Entries 7-10, Table 1). It can be seen that the alkene functional group as well as the benzoate, benzyl, and tert-butyltrimethylsilyl protecting groups all tolerate the protection reaction quite well. Robust acetals and ketals such as those in glucofuranose 1j¹¹ also survive.

The deprotection reaction (2 \rightarrow 1) provides excellent yields of the original aldehydes and ketones. Deprotection of the bifunctionalized compounds 2f-j proceeded in an entirely chemoselective manner. This is accomplished by treating the acetal or ketal with DDQ and water in dichloromethane. This reaction is rapid (one to two h) and quite simple to perform. We have found it necessary to use an excess (2.0 eq) of DDQ to ensure complete reaction. A portion of the DDQ reagent is consumed in the further oxidation of alpha-hydroxyketone 4 to the corresponding aldehyde (p-CH₃O-C₆H₄C[O]CHO).⁵ Gas chromatographic analysis of several deprotection reactions indicates that 4 and the aldehyde are usually present in approximately a one to one ratio.

We have recently begun to investigate the possibility of using substituents other than para-methoxy to assist DDQ benzylic oxidations. Thus 4-tert-butylbenzyl ether 6 was deprotected under the usual conditions to provide a 91% yield of decanol after 1 h. We have also found that unsubstituted benzyl ethers react significantly more slowly with DDQ (decyl benzyl ether yielding 95% of 1-decanol after 24 h).¹² Future plans include the examination of alkyl-substituted-1-phenyl-1,2-ethanediols as reagents for carbonyl protection.

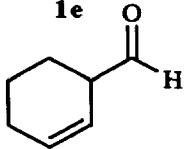
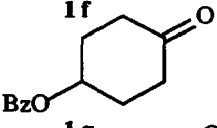
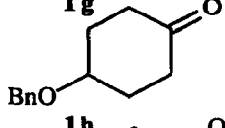
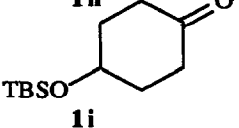
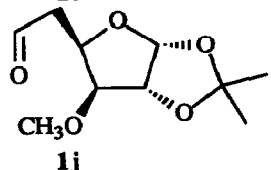


Typical Experimental Procedures

Protection of cyclohexanone: To a solution of cyclohexanone (150 mg, 1.53 mmol) in dry dichloromethane (2.6 mL) was added 574 mg of 3 (1.84 mmol). This solution was cooled to -78°C and 5 drops of iodotrimethylsilane were added via syringe. The medium yellow mixture was stirred for 3 h then gradually warmed to 0°C and stirred for an additional hour. Saturated NaHCO₃ (3 mL) was added and the resultant mixture was extracted with ether (3 X 5 mL). The solvent was then removed under reduced pressure. The oily residue was chromatographed on a 35 X 1 cm column of silica gel with 2% ethyl acetate in hexane as eluant affording 304 mg (1.23 mmol, 80% yield) of the corresponding ketal as a colorless oil. ¹H-NMR (300 MHz,

CDCl₃): δ 1.38-1.74 (10H, m), 3.64 (1H, t, $J = 8.0\text{Hz}$), 3.75 (3H, s), 4.20 (1H, dd, $J = 8.0\text{Hz}$, 5.8Hz), 4.98 (1H, dd, $J = 8.0\text{Hz}$, 5.8Hz), 6.88 (2H, d, $J = 8.4\text{Hz}$), 7.27 (2H, d, $J = 8.4\text{Hz}$). ¹³C-NMR (75 MHz, CDCl₃): δ 23.9, 25.2, 35.5, 36.3, 55.3, 71.4, 77.3, 110.1, 113.9, 127.7, 130.0, 159.4. IR (neat) 3010, 2980, 2900, 1630, 1605, 1580, 1480, 1460, 1370 cm⁻¹. MS (CI) m/z (rel. int.): 249 (MH⁺, 100), 248 (11), 207 (5), 189 (8), 152 (10), 151 (92), 99 (28).

Table 1

Entry	carbonyl	protection ^a	deprotection ^{b,c}
1	cyclohexanone 1a	80%	95% ^d
2	cyclopentanone 1b	90%	93% ^d
3	cycloheptanone 1c	41%	82% ^d
4	4-heptanone 1d	76%	92% ^d
5	decanal 1e	86%	94%
6		97%	92% ^d
7		83%	80%
8		84%	87%
9		82%	90%
10		71%	82%

a. Reaction conditions: 1.2 of 3, TMSI (cat.), CH₂Cl₂ (0.5 M), -78°C--> 0°C.

b. Reaction conditions: 2 DDQ, CH₂Cl₂ (0.2 M), H₂O, R.T..

c. Isolated yields except where noted.

d. Yield determined by gas chromatography.

Deprotection of the ketal of 4-tert-butyltrimethylsilyloxycyclohexanone (2i): Compound 2i (151 mg, 0.399 mmol) was dissolved in 2.0 mL of dichloromethane. To this solution was added 0.2 mL of water and 181 mg (0.798 mmol) of DDQ. This dark green mixture was stirred for 3 h at room temperature. Water was added (2 mL) and the mixture was extracted into ether (3 X 5 mL). After solvent removal the crude mixture was chromatographed on a 35 X 1 cm column of silica gel using 4% ethyl acetate in hexane to provide 82 mg (0.36 mmol, 90%) of known ketone 1i¹³ as a colorless oil.

Acknowledgements

We are grateful to SmithKline Beecham and the Council on Undergraduate Research for their support of this work. We are indebted to Steve Stout of American Cyanamid for obtaining mass spectra and high resolution NMR spectra. We would like to thank Jin Qian and Mary Ann Wagner for participating in the alkyl-substituted benzyl ether studies. We also thank Robert Dugger of Pfizer Inc. for helpful discussions.

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(Received in USA 14 September 1993; revised 20 October 1993; accepted 1 November 1993)