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Methylenephenylsulfone Appended Acetals and Ketals : New Class of Carbonyl Protective Groups Cleavable by DBU

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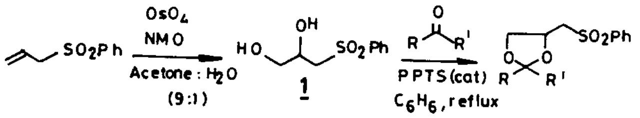
Abstract : 3-phenylsulfonyl 1,2 propane diol, readily obtainable by dihydroxylation of commercially available allylphenylsulfone, acts as an efficient and new protection reagent for both aldehydes and ketones. This protective group is elegantly removed by use of 1,8-diazabicyclo[5.4.0]-7-undecene (DBU), under nonaqueous conditions.

Carbonyl functionality occupies an important position in organic synthesis and it generally needs to be protected[1] in a long synthetic scheme as the group is sensitive to various reagents. The existing protective groups, O,O-acetals and S,S-acetals are generally cleaved by acid hydrolysis or by use of heavy metal such as Hg salts respectively. However due to creation of unwanted complications during their removal, second generation acetals have been developed wherein an appropriate appendage is added into the acetal skeleton, so that removal conditions are more flexible. These include bromomethyl ethylene acetals,[2] 5-(2-pyridyl)-1, 3-dioxanes,[3] 4-pentenyl acetals.[4] The first one requires refluxing methanol and Zn dust for deprotection, the second requiring a two step process and the third requires NBS which limits the use if an olefinic group is present. The recent additions include, silyl appended acetals[5] which can be cleaved by mild fluoride ion and offer many advantages. The only photolabile group in the form of o-nitro phenyl ethylene acetal,[6] though is mild, requires high dilutions. An ongoing programme to address the issue of introducing new or modified protocols in the area of protective groups[7] has prompted us to study the possibility of using 3-phenylsulfonyl 1,2-propane diol[8] as a protective group (**equation 1**). The results are disclosed herein (**Table 1**).



eq.1

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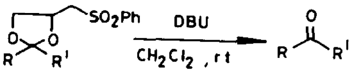
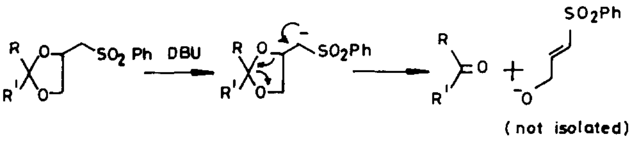
We reasoned a suitable base (DBU in present context) would initiate a β-elimination (**equation 2 & 3**) and deprotection is facilitated. Incidentally, the only known base sensitive carbonyl protective group has been the diacetate.[9]



eq. 2

The prerequisite diol **1** is obtained in quantitative yield as a white solid on simple dihydroxylation of allylphenylsulfone.[10] Treatment of **1** with benzaldehyde (**entry 1**) under standard acid catalyzed azeotrope furnished the 1,3-dioxolane derivative **1a**. This on treatment with DBU in CH$_2$Cl$_2$ at ambient temperature for 12 hr has resulted in 90% recovery of parent benzaldehyde. Of the several bases attempted, DBU was found to be optimal and being non-nucleophilic inhibits its participation further. The other readily available carbonyl substrates *viz.*, phenyl propanaldehyde (**entry 2**), cinnamaldehyde (**entry 3**), cyclohexanone (**entry 8**) and camphor sulfonamide (**entry 10**) were equally well behaved. Further, the mildness of the reaction is proved on sensitive substrates such as silyl ether (**entry 4**), tosyl ester (**entry 5**), THP-ether (**entry 6**), carboxylic ester (**entry 7**), and benzoate (**entry 9**). All these substrates entertained the protection as well as deprotection with equal ease. Most of the phenylsulfone appended acetals are solids and very stable unlike other appended acetals.[11]

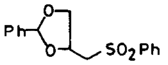
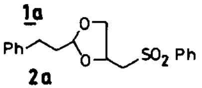
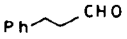
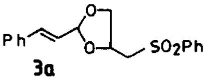
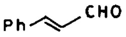
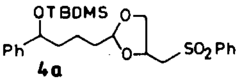
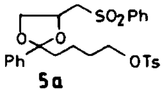
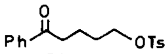
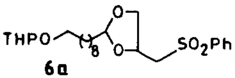
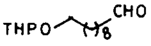
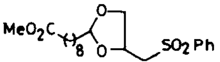
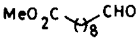
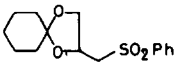
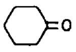
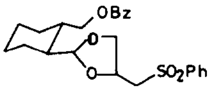
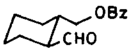
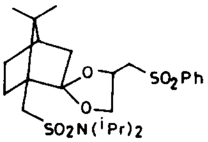
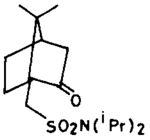
Mechanistically, it is ascribed that DBU picks up the most acidic proton adjacent to phenylsulfone, the β-elimination is triggered and aldehyde is liberated (**equation 3**). Though no attempt has been made to isolate the byproduct, it can be logically concluded that the byproduct is water soluble and never interfered in purification process.



eq.3

In conclusion, a new protective group for carbonyl compounds is introduced which is base labile. Also unlike other acetals, the cleavage is done under nonaquous conditions. Undoubtedly, the solid nature of most products and their shelf stability offers advantages over existing acetal class of protective groups.[12,13]

Table 1 : Deprotection of methylenephenylsulfone appended acetals

Entry	Starting compound	Product	Reaction Time	Yield (%)
1	 **1a**	Ph – CHO **1b**	12h	90[a]
2	 **2a**	 **2b**	36 h	86
3	 **3a**	 **3b**	12h	92
4	 **4a**	 **4b**	36h	78
5	 **5a**	 **5b**	12h	80
6	 **6a**	 **6b**	36h	74
7	 **7a**	 **7b**	36h	76
8	 **8a**	 **8b**	36 h	70[a]
9	 **9a**	 **9b**	36h	86
10	 **10a**	 **10b**	36h	74

[a] - The flash column chromatograpy of products was done using n-pentane and ether as eluent

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8. Ley *et al* have introduced novel spiroketals for protection of 1,2 diols which are cleavable by LiN(TMS)$_2$. Ley, S.V.; Mio, S.; Meseguer, B. *Synlett* **1996**, 791 and references cited therein.
9. Kochhar,K.S.; Bal,B.S.;Deshpande,R.P.; Rajadhyaksha S.N.; Pinnick,H.W. *J.Org.Chem.* **1983**,*48*,1765.
10. (a) Allylphenylsulfone was purchased from Aldrich Chemical company and was used without any further purification. (b) Sato, T.; Okumura, Y.; Itai, J.; Fujisawa, T. *Chem. Lett.* **1988**, *9*, 1537.
11. No attempt was made to determine *de* of the protected carbonyl compounds.
12. **General procedure for protection of carbonyl compounds.** To a solution of carbonyl compound (5 mmol) in benzene, diol **1** (6 mmol) and PPTS (~ 50 mg) were added and refluxed while azeotropically removing water for 14 hr. The reaction mixture was cooled to room temperature and solid NaHCO$_3$ (~ 100 mg) was added, stirred for 10 min, filtered and volatiles were removed under reduced pressure to afford the required acetal/ketal in more than 90% yield as diastereomeric mixture after a short silica gel column.

    General procedure for deprotection. To a solution of acetal (5 mmol) in dry CH$_2$Cl$_2$ (15 mL) DBU (7 mmol) was added and the reaction mixture was stirred at room temperature for the time listed in Table 1. Removal of solvent afforded crude carbonyl compound which was purified by column chromatography.
13. a) All new compounds were characterised by spectral data including ^{1}H NMR, mass, HRMS and /or elemental analysis.

    b) IICT Communication No. 3857.