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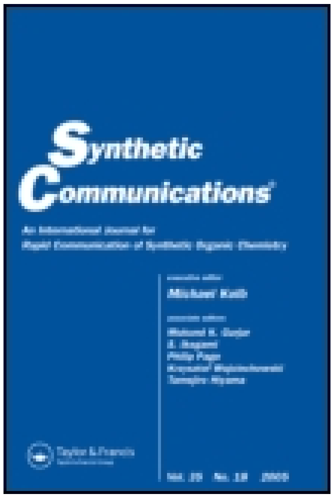

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Phenyl Sulphonyl Acetaldehyde Diethyl Acetal: A New Robust 1,2-Diol Protective Group

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Phenyl Sulphonyl Acetaldehyde Diethyl Acetal: A New Robust 1,2-Diol Protective Group[#]

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ABSTRACT

A simple preparation of a novel resilient protective group for 1,2-diols is described herein which is remarkably stable in the presence of extremely harsh basic conditions as well as acidic media. The title reagent's versatility is detailed with numerous examples.

Key Words: 1,2-Diols; Acetals; Robust.

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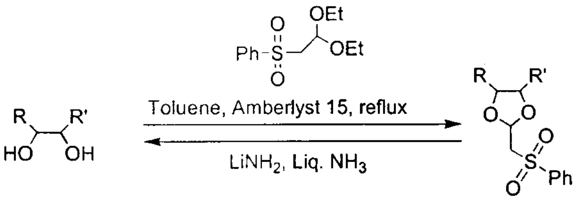
INTRODUCTION

The 1,2-diol group is a commonly encountred functionality especially in the polyol class of natural products. Like any other functionality, this too demands special protective groups, which would mask it efficiently during a long synthetic scheme. Several protective groups[1] have been documented in the literature for existing functionalities, which could also be cleaved under essentially mild conditions. Often, synthetic chemistry requires a protection tool, which is robust and stable to various drastic reagents. Acetal classes of protective groups with appendage are limited and no systematic study has been carried out in detail.[2] Not much work has been reported in this direction.

RESULTS AND DISCUSSION

Herein we report the utility of α-phenyl sulfonyl acetaldehyde diethyl acetal as a novel, robust protective group for 1,2-diols (Sch. 1). Interestingly, this protective group is stable to 60% AcOH,[3] 6M-HCl and 0.1 M H_2SO_4 as well.

The reagent, phenyl sulfonyl acetaldehyde diethyl acetal,[4] prepared from sodium phenyl sulfinate[5] and bromoacetaldehyde diethyl acetal was treated with cyclooctane diol and Amberlyst® 15 in dry toluene (reflux) to furnish the protected diol **1b**. This was treated with the non-nucleophilic base DBU to check if deprotection could be achieved through β-elimination.[6] Surprisingly however, after several hours of stirring with excess of DBU, the protection was intact. Intrigued by this, the action of a few other bases such as NaOH, NaOMe, NaH and LDA was attempted without any success. This protective group was however successfully cleaved when exposed to $LiNH_2$ in liquid NH_3 at −33°C as well as by *n*-butyl lithium at 35°C (Table 1). The interesting robustness of this new protective group prompted us to study



Scheme 1.

Table 1.

Entry	Acid/base employed[a]	Result
1	DBU/anhydrous DCM/r.t./12 h	Stable
2	DBU/anhydrous DCM/reflux/8 h	Stable
3	DBU/H_2O/DCM/PTC/r.t./6 h	Stable
4	DBU/H_2O/DCM/PTC/reflux/8 h	Stable
5	SmI_2/anhydrous THF/r.t./6 h	Stable
6	NaOMe/anhydrous MeOH/r.t./12 h	Stable
7	Bu_3SnH/AIBN/anhydrous benzene/reflux/6 h	Stable
8	LDA/anhydrous THF/−78°C/6 h	Stable
9	NaH/anhydrous DMF/sonication/4 h	Stable
10	aqueous NaOH/sonication/6 h	Stable
11	DBU/anhydrous DCM/sonication/6 h	Stable
12	NaOMe/anhydrous MeOH/sonication/4 h	Stable
13	NaH/anhydrous DMF/r.t./8 h	Stable
14	Na-Naphthalenide/−78°C/4 h	Cleaved
15	*n* BuLi/r.t./2 h	Cleaved
16	$LiNH_2$, liquid NH_3/4 h	Cleaved
17	60% AcOH, r.t./8 h	Stable
18	0.1 N H_2SO_4, MeOH, r.t./8 h	Stable
19	6 N HCl, THF/6 h	Stable

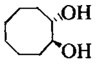
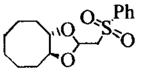
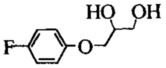
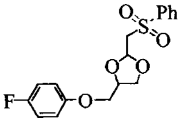
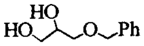
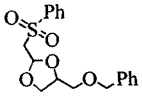
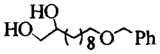
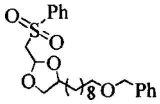
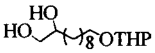
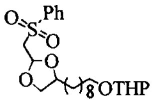
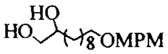
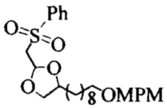
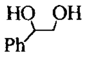
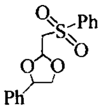
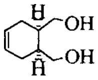
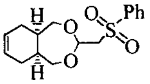
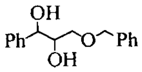
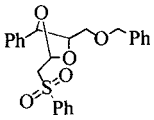
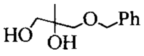
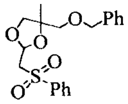
[a] Entries 1, 2, 8 and 10 of Table 2 were subjected to these conditions.

a few other substrates (Table 2). The *p*-fluorophenol derivative (Entry 2) was protected and subjected to cleavage to recover the parent diol in 84% isolated yield. Similarly, the benzyloxy derivative of undecanediol also behaved well during protection (87%) as well as deprotection (73%). Various other diol derivatives were subjected to the above-mentioned protocol to prove the consistency of the present reaction conditions. To check the acid stability of this novel protective group an equimolar mixture of the isopropylidene derivative of cyclooctanediol and **1b** (Sch. 2) was stirred in 60% AcOH, as well as 0.1 M H_2SO_4 in MeOH to observe clean recovery of **1b** whereas the isopropylidene derivative was hydrolyzed back to **1a**.

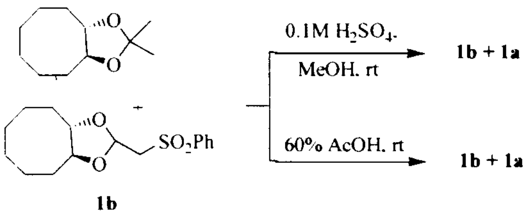
CONCLUSION

We have demonstrated the unique robustness of phenyl sulfonyl acetaldehyde diethyl acetal as a protective reagent for 1,2-diols which is not only stable to harsh basic conditions but also maintains its

Table 2.

Entry	Diol substrate	Protected diol	Protection yield (%)[a]	Deprotection yield (%)[a]
1	 1a	 1b	71	75
2	 2a	 2b	74	84
3	 3a	 3b	78	74
4	 4a	 4b	87	73
5	 5a	 5b	75	74
6	 6a	 6b	79	76
7	 7a	 7b	82	86
8	 8a	 8b	76	72
9	 9a	 9b	69	79
10	 10a	 10b	85	76

[a]Yields calculated after column chromatography of the products.



Scheme 2.

resilience in an acidic environment (60% AcOH, 0.1 M H_2SO_4, MeOH; 6 M HCl, THF). This protocol would find applications in polyol chemistry.

EXPERIMENTAL SECTION

General Methods: Crude products were purified by column chromatography on silica gel of 60–120 mesh. ^{1}H NMR were obtained in $CDCl_3$ at 200 MHz. Chemical shifts are given in ppm with respect to internal TMS, and J values are quoted in Hz. Infrared spectra were obtained neat, and only the most significant absorptions in cm^{-1} are indicated. Toluene was distilled over P_2O_5 and stored over sodium. All reactions were carried out under an atmosphere of nitrogen using dry glassware.

Procedure for the preparation of Reagent: An equimolar mixture of sodium phenylsulphinate (5 g, 30.4 mmol) and bromoacetaldehyde diethyl acetal (5.97 g, 30.4 mmol) in dry DMF (25 mL) was stirred at 70°C for 12 h. The reaction mixture was extracted with ether (3 × 50 mL). The organic layer was washed with water (10 mL), brine (10 mL) and dried over anhydrous Na_2SO_4. The volatiles were removed on a rotary evaporator to give the crude reagent. Purification by chromatography (silica gel, *n*-hexane:ethyl acetate, 30:1) to yield colourless liquid (6.2 g, 79%).^{1}H NMR ($CDCl_3$): δ 7.85 (d, 2H, $J = 5.7$ Hz), 7.65–7.45 (m, 3H), 4.87 (t, 1H, $J = 4.5$ Hz), 3.50–3.30 (m, 6H), 1.00 (t, 6H, $J = 6.8$ Hz). δ ^{13}C NMR ($CDCl_3$): δ 139.96, 133.22, 128.67, 127.82, 97.30, 61.73, 59.47, 14.58. MS (M^-): 258.

General Procedure for the protection of diol as described for 1a: To diol **1a** (1 g, 6.9 mmol) in dry toluene (15 mL) was added phenyl sulfonyl acetaldehyde diethyl acetal (1.79 g, 6.9 mmol), Amberlyst® 15 (0.01 g), and refluxed for 12 h. The resin was then filtered off and the volatiles removed under reduced pressure. The residue was dissolved in ethyl acetate (50 mL) and washed with water (25 mL), brine (25 mL) and dried over anhydrous

Na_2SO_4. The volatiles were removed *in vacuo* to afford crude **1b.** Purification by silica gel chromatography (hexane:ethylacetate, 15:1), yielded **1b** (1.323 g, 71%).

General procedure for deprotection of protected diol as described for 1b using Lithium amide: To a stirred solution of lithium amide (0.1 g, 4.3 mmol) in liq. NH_3 (10 mL), was added **1b** (0.5 g, 1.6 mmol) in dry THF (10 mL) and stirred for 10 min after which the excess of liq NH_3 was allowed to evaporate. The liberated diol was isolated by quenching with saturated NH_4Cl solution and extracting with diethyl ether. The organic layer was washed with water (5 mL), brine (5 mL) and dried over anhydrous Na_2SO_4. The volatiles were removed under vacuum to afford parent diol **1a** (0.174 g, 75%).

General procedure for deprotection of protected diol using *n*BuLi: To a stirred solution of **1b** (0.5 g, 1.6 mmol) in dry THF (10 mL) at 0°C was added butyl lithium 2.5 M in Hexane (1.62 mL, 4.03 mmol) allowing the reaction mixture to warm to room temperature and stirred for 2 h. After monitoring by TLC the diol was isolated by quenching with saturated NH_4Cl solution and extracting with diethyl ether. The organic layer was washed with water (5 mL), brine (5 mL) and dried over anhydrous Na_2SO_4. The volatiles were removed under vacuum to afford parent diol **1a** (0.162 g, 70%).

Compound **1b:** Colourless liquid. ^{1}H NMR ($CDCl_3$): δ 7.90 (d, 2H, $J = 7.6$ Hz), 7.65–7.45 (m, 3H), 5.3(t, 1H, $J = 5.1$ Hz), 3.75–3.55(m, 2H), 3.35(d, 2H, $J = 5.1$ Hz), 1.85–1.65(m, 4H), 1.45–1.10(m, 8H); IR (neat): 1083, 1130, 1309 cm^{-1}. MS (M^+): 310; HRMS (M^++1) Calcd. for $C_{16}H_{22}SO_4$: 311.1317 found 311.1318.

2b: Colourless liquid. ^{1}H NMR ($CDCl_3$): δ 7.90 (d, 2H, $J = 7.0$ Hz), 7.65–7.47 (m, 3H), 7.0–6.85 (m, 2H), 6.77–6.67 (m, 2H), 5.35 (t, 1H, $J = 5.8$ Hz), 4.40–4.27 (m, 1H), 4.0–3.68 (m, 4H), 3.40 (d, 2H, $J = 5.8$ Hz); IR (neat): 1041, 1083, 1134, 1210, 1506 cm^{-1}. MS (M^+): 352; HRMS (M^++1) Calcd. for $C_{17}H_{17}SO_5F$: 353.0858 found 353.0857.

3b: Colourless liquid. ^{1}H NMR ($CDCl_3$): δ 7.90 (d, 2H, $J = 6.9$ Hz), 7.65–7.45 (m, 3H), 7.35–7.15 (m, 5H), 5.35 (t, 1H, $J = 5.5$ Hz), 4.40 (s, 2H), 4.20–3.65 (m, 5H), 3.40 (d, 2H, $J = 5.5$ Hz); IR (neat): 1151, 1249, 1309, 1450, 2927 cm^{-1}. MS (M^+): 348; HRMS (M^++1) Calcd. for $C_{18}H_{20}SO_5$: 349.1109 found 349.1110.

4b: Colourless viscous liquid. ^{1}H NMR ($CDCl_3$): δ 7.95 (d, 2H, $J = 7.0$ Hz), 7.70–7.50 (m, 3H), 7.35–7.25 (m, 5H), 5.35 (t, 1H, $J = 4.7$ Hz), 4.50 (s, 2H), 4.02–3.85 (m, 2H), 3.50–3.34 (m, 5H), 1.65–1.15 (m, 16H); IR (neat): 1083.8, 1126, 1152, 1310, 2930 cm^{-1}. MS (M^+): 460; HRMS (M^++1) Calcd. for $C_{26}H_{36}SO_5$: 461.2361 found 461.2360.

5b: Colourless liquid. ^{1}H NMR (CDCl$_3$): δ 7.90 (d, 2H, $J = 8.1$ Hz), 7.70–7.45 (m, 3H), 5.30 (t, 1H, $J = 4.6$ Hz), 4.55 (t, 1H, $J = 2.3$ Hz), 3.95–3.70 (m, 7H), 3.40 (d, 2H, $J = 4.6$ Hz), 1.65–1.15 (m, 22H); IR (neat): 1079, 1132, 125, 1308, 1438, 2926 cm^{-1}. MS (M$^+$): 454.

6b: Colourless viscous liquid. ^{1}H NMR (CDCl$_3$): δ 7.95 (d, 2H, $J = 7.5$ Hz), 7.70–7.50 (m, 3H), 7.30–7.17 (m, 2H), 6.9–6.8 (m, 2H), 5.30 (t, 1H, $J = 5.0$ Hz), 4.40 (s, 2H), 4.10–3.80 (m, 5H), 3.80 (s, 3H), 3.40 (d, 2H, $J = 5.0$ Hz), 1.65–1.15 (m, 16H); IR (neat): 1085, 1150, 1252, 1312, 1448, 2922 cm^{-1}. MS (M$^+$): 490.

7b: Colourless liquid. ^{1}H NMR (CDCl$_3$): δ 7.95 (d, 2H, $J = 7.6$ Hz), 7.65–7.45 (m, 3H), 7.35–7.15 (m, 3H), 7.12–7.0 (m, 2H), 5.45 (t, 1H, $J = 5.1$ Hz), 4.95 (t, 1H, $J = 7.6$ Hz), 4.10 (d, 2H, $J = 5.1$ Hz), 3.5 (d, 2H, $J = 6.2$ Hz); IR (neat): 1083, 1150, 1310, 2928 cm^{-1}. MS (M$^+$): 304.

8b: Colourless liquid. ^{1}H NMR (CDCl$_3$): δ 7.90 (d, 2H, $J = 7.0$ Hz), 7.70–7.50 (m, 3H), 5.55 (s, 2H), 5.20 (t, 1H, $J = 4.7$ Hz), 3.60 (d, 2H, $J = 4.7$ Hz), 3.45 (d, 2H, $J = 4.7$ Hz), 3.35 (d, 2H, $J = 4.7$ Hz), 2.15–1.85 (m, 6H); IR (neat): 997, 1083, 1131, 1149, 1308, 2901 cm^{-1}. MS (M$^+$): 308; HRMS (M$^+$+1) Calcd. for $C_{16}H_{20}SO_4$: 309.1160 found 309.1160.

9b: Colourless viscous liquid. ^{1}H NMR (CDCl$_3$): δ 7.95 (d, 2H, $J = 7.0$ Hz), 7.65–7.45 (m, 3H), 7.40–7.15 (m, 10H), 5.70 (t, 1H, $J = 4.7$ Hz), 4.85 (d, 1H, $J = 8.2$ Hz), 4.55 (d, 2H, $J = 7.0$ Hz), 4.02–3.82 (m, 1H), 3.65 (d, 2H, $J = 4.7$ Hz), 3.55 (d, 2H, $J = 4.7$ Hz); IR (neat): 1024, 1083, 1151, 1309, 2929 cm^{-1}. MS (M$^+$): 425; HRMS (M$^+$) Calcd. for $C_{24}H_{24}SO_5$: 425.1422 found 425.1421.

10b: Colourless liquid. ^{1}H NMR (CDCl$_3$): δ 7.90 (d, 2H, $J = 7.1$ Hz), 7.65–7.45 (m, 3H), 7.35–7.15 (m, 5H), 5.40 (t, 1H, $J = 4.8$ Hz), 4.40 (s, 2H), 3.90 (s, 2H), 3.50 (s, 2H), 3.35 (d, 2H, $J = 4.8$ Hz), 1.25 (s, 3H); IR (neat): 1043, 1083, 1123, 1150, 1309 cm^{-1}. MS (M$^+$): 362.

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