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Phenylsulfonylethylidene (PSE) acetals as atypical carbohydrate-protective groups

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Abstract

We introduce a new class of arylsulfonylated cyclic acetals derived from carbohydrate structures which are synthesized with high yields under basic conditions. Deprotection methods for such acetals are also investigated.

Selective introduction–expulsion of protective groups still remains a major concern in carbohydrate chemistry strategies.[1,2] An impressive part of the chemistry of carbohydrates has dealt with cyclic acetals (mainly 1,3-dioxolanes and 1,3-dioxanes). Besides being useful for selective protection of monosaccharides, cyclic acetals can display a number of interesting reactions — this is particularly true for benzylidene acetals which can undergo regiospecific oxidative[3] and reductive[4,5] openings. Hence, studies of new cyclic acetals showing atypical properties remain an important topic because of the uncommon synthetic features they can bring out. Within the frame of our continuous exploration of thiofunctionalized sugars, we have started to investigate the preparation and the reactivity of arylsulfonyl acetals as carbohydrate-protective groups.

1,2-Bis(phenylsulfonyl) alkenes — already known as powerful electrophilic partners for Diels–Alder or Michael reactions — are well-suited reagents for this purpose.[6] As an extension of recent literature results,[7] we have demonstrated that phenylsulfonylethylidene (PSE) acetals can be readily prepared from unprotected glycosides under basic conditions (Fig. 1).

Following a double Michael addition pathway, either *Z*- or *E*-1,2-bis(phenylsulfonyl) ethylene[8] reacted at room temperature with diverse α- and β-diols in THF, using NaH as the base and Bu_4NBr as the phase transfer catalyst.[9] Saccharidic polyols reacted similarly in DMF, using *t*BuOK as the base. In all cases, the initial Michael addition of an alkoxide ion is followed by eliminative expulsion of a phenylsulfinate ion. The resulting transient alkoxy vinyl sulfone then undergoes Michael addition of a second alkoxide ion.

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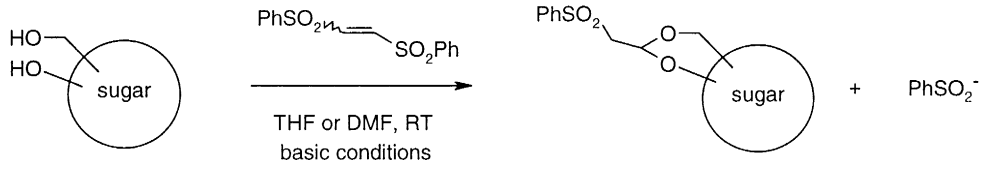


Fig. 1. Synthesis of PSE acetals

Various diols and polyols derived from pyrano- and furano-sugars have been submitted with success to the above reaction conditions[10] (Figs. 2 and 3).

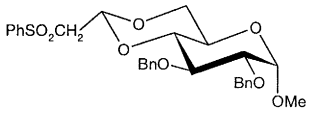
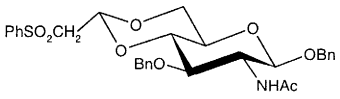
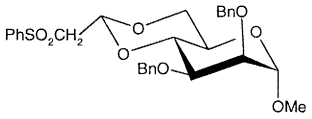
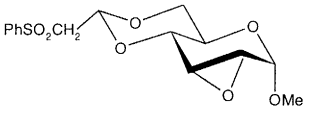
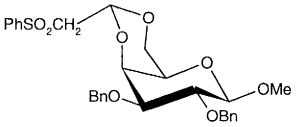
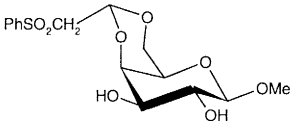
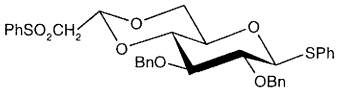
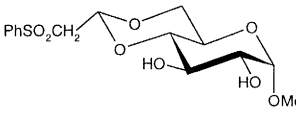
	compound	yield		compound	yield
1		99 %	**5**		70 %
2		87 %	**6**		83 %
3		97 %	**7**		81 %
4		83 %	**8**		96 %

Fig. 2. Pyrano-sugar derived PSE acetals

As expected, β-diols gave, exclusively, the equatorially-configurated cyclic acetals in conformity with the well-documented case of 4,6-*O*-benzylidene derivatives. In contrast, the diastereoselectivity of dioxolane-type acetals is quite poor (Fig. 3; entries 9, 10 and 11).

A thorough examination of deprotection conditions for the PSE acetals have shown interesting results. Classical hydrolysis or alcoholysis in acidic medium at 60–80°C — CH_3COOH 80% or H_2SO_4 0.7 N or $BF_3 \cdot Et_2O/CH_2Cl_2/MeOH$ — proved totally ineffective: no degradation could be observed and the starting material was entirely recovered. What is more, when PSE acetal **1** was submitted to 9:1 TFA:H_2O (60°C, 2 h), the benzyl groups were expelled, whereas the PSE acetal remained unaffected (Fig. 4).

The reluctance of PSE acetals to acid-catalyzed hydrolysis may be connected with the fact that both acetalic oxygen atoms become harder (therefore more difficult to be protonated) because of the presence of a sulfonyl group; this behaviour was previously observed in the case of other acetals bearing electron-withdrawing groups.[11]

Nevertheless, PSE acetals can be readily deprotected under classical reductive conditions: for example, treatment of **1** by $LiAlH_4$ in Et_2O (optionally in the presence of $AlCl_3$) delivers the corresponding 4,6-diol with 75–85% yield. In contrast, milder reducing systems such as $NaBH_3CN$/TFA proved ineffective.

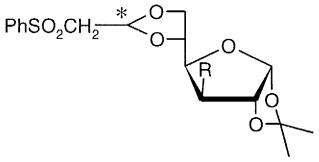
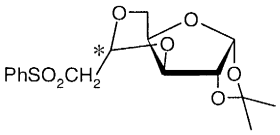
compound		R	yield	* epimeric ratio
	**9**	R = H	94 %	6 : 4
	10	R = OH	84 %	5 : 4
	11	R = OBn	91 %	5 : 4
	**12**	-	86 %	1 : 0

Fig. 3. Furano-sugar derived PSE acetals

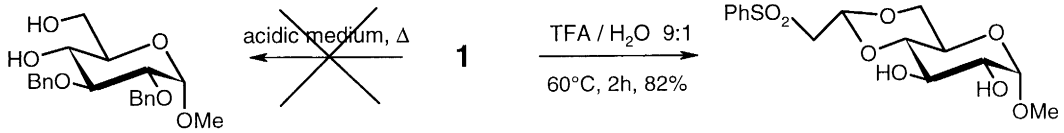


Fig. 4.

In summary, a new class of cyclic acetals have been synthesized under basic conditions, with high yields and high regio- and stereoselectivity. These compounds present abnormal properties when compared to classic benzylidene acetals: they resist acid hydrolysis and can be deprotected under reductive conditions.

Further broad range exploration of the chemical behaviour of carbohydrate-derived PSE acetals is currently being performed in our laboratory.

Acknowledgements

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9. In a typical procedure, 2 equivalents of NaH were added at 0°C to a THF solution of the diol; after 15 min, 1 equivalent of 1,2-bis(phenylsulfonyl)ethylene and a few crystals of Bu_4NBr were added. After 12 h stirring at room temperature, the mixture

was treated with brine and extracted with AcOEt. The combined organic phases were dried over $MgSO_4$, concentrated under reduced pressure and the crude product was purified by silica gel column chromatography.

10. Fully satisfactory NMR and mass spectrometry data were obtained for all new compounds. Selected data for **1**: ^{1}H NMR δ 3.34 (s, 3H, OMe), 3.35 (dd, 1H, H-4, J_{4-5}=9.6), 3.43 (dd, 1H, H-6b, J_{5-6b}=10.1), 3.47 (dd, 1H, H-2), 3.48 (d, 2H, CH_2SO_2), 3.59 (ddd, 1H, H-5), 3.85 (dd, 1H, H-3, J_{2-3}=J_{3-4}=9.1), 4.00 (dd, 1H, H-6a, J_{5-6a}=4.7, J_{6a-6b}=10.1), 4.51 (d, 1H, H-1, J_{1-2}=3.8), 4.64 and 4.81 (2d, AB system, 2H, J_{gem}=12.1, PhCH_2O), 4.74 and 4.78 (2d, AB system, 2H, J_{gem}=11.2, PhCH_2O), 4.98 (t, 1H, H-7, J=4.9), 7.29–7.61 (m, 13H, H-Ar), 7.89–7.93 (m, 2H, *ortho*-H-Ar *Ph*SO_2), ^{13}C NMR δ 55.8 OMe, 60.3 CH_2SO_2, 62.0 C-5, 69.0 C-6, 74.2 PhCH_2O, 75.2 PhCH_2O, 78.5 C-3, 79.4 C-2, 82.3 C-4, 97.0 C-7, 99.5 C-1, 126.3–134.2, 15*CH, 138.4, 139.1, 140.2, 3*C_{IV} Ph, MS (Ionspray®): $[M+Na]^+$=563, $[\alpha]_D$=+23 (*c* 1, $CHCl_3$).
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