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Studies on DMDO-mediated benzylidene acetal oxidation

David K. Mycock [a], Alexandra E. Sherlock [a], Paul A. Glossop [b], Christopher J. Hayes [a,*]

[a] School of Chemistry, University of Nottingham, University Park, Nottingham NG7 2RD, UK
[b] Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent CT13 9NJ, UK

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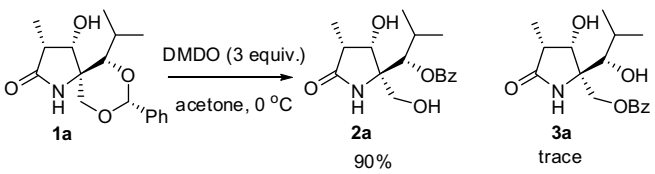
ABSTRACT

We have shown that dimethyldioxirane (DMDO) can be used to effect an oxidative partial deprotection of benzylidene acetals derived from both 1,2- and 1,3-diols to afford hydroxy benzoate products. A wide range of functional groups are tolerated, and good to excellent yields are usually observed. The reactions are easy to perform and produce little waste other than acetone.

Benzylidene acetals are often used to protect 1,2- and 1,3-diols during organic synthesis,[1] and various reductive[2–5] and oxidative[6–14] methods have been examined with different levels of success for their complete or partial deprotection. For example, during our recent total synthesis of (+)-lactacystin,[15] we needed to perform a selective partial deprotection of the benzylidene acetal **1a** in order to access the primary alcohol **2a** (Scheme 1). Unfortunately, none of the available methods were particularly well suited to our needs as they either introduced unwanted functionality (i.e., alkyl bromides when NBS[6] is used) or had issues with regiocontrol (i.e., production of primary benzoates in the case of bipyridinium chlorochromate/*m*-CPBA[12b]). Fortunately, we were able to show that the benzylidene acetal **1a** could be oxidised with DMDO[16] to give the partially deprotected secondary benzoate ester **2a** as the major new product. In this Letter, we report our recent findings on the scope, limitations and mechanistic insight of this oxidative deprotection method.

Our first task was to prepare a range of benzylidene acetals from 1,2- and 1,3-diols and this was readily achieved using well-known methods.[17] Examples were chosen to explore the chemoselectivity and functional group tolerance, as well as the influence of both steric and electronic factors on the regiochemical outcome of the reaction (Table 1). DMDO was prepared and used as a dilute solution (≈0.1 M) in acetone according to the literature procedure,[18] and its concentration was determined via iodometric titration immediately prior to use.



Scheme 1. Previous DMDO oxidation of a benzylidene acetal.

We first chose to examine the oxidation of 1,3-dioxolanes **1b–j** derived from 1,2-diols (Table 1). Thus, 1 equiv of DMDO (0.1 M in acetone) was added to each acetal, and the resulting solution was stirred at 0–4 °C for 20 h. Removal of the volatiles in vacuo then gave the crude product from which the ratio of secondary **2b–j** to primary **3b–j** benzoate esters was determined by ^{1}H NMR. The materials were then purified by column chromatography and the isolated yields were recorded.

We were pleased to see that excellent conversion was observed in all cases, and good to excellent yields of the ester products were obtained. It can be seen from the results in Table 1 that regiocontrol in this reaction is a subtle balance of both steric and electronic factors. For example, acetals **1b**, **1c** and **1d** give the secondary benzoates **2b, 2c** and **2d** as the major regioisomers, whilst the 4,4-dimethyl-1,3-dioxolane **1e** gave the primary benzoate **3e** as the major product. It appears that in simple mono-substituted acetals (i.e., **1b–d**) there is a preference for the formation of the more hindered secondary benzoate ester, but when the steric demand becomes too great, as in the case of product **2e**, then there is a reversal of selectivity to give the least hindered benzoate **3e**. Electronic effects were then probed by using acetals **1f–j** in the oxidation, and in all cases the primary benzoate esters **3f–j** were the major products (Table 1).

The nature of the aromatic group present in the acetal was also examined and we were pleased to see that both electron-donating (*para*-methoxy in **1g**) and electron-withdrawing (*para*-nitro in **1h**) substituents were well tolerated without adversely affecting either yield or regiochemical distribution.

Based upon these results, we postulate that the mechanism of the reaction involves initial CH-oxidation[19] of the benzylidene acetal methine to afford the corresponding hemiorthoacetal **4** (Scheme 2). This intermediate then collapses to give **5** and/or **6** as transient intermediates, with the relative proportion of each

* Corresponding author. Tel.: +44 0115 951 3045; fax: +44 0115 951 3564.
E-mail address: chris.hayes@nottingham.ac.uk (C. J. Hayes).

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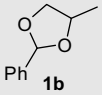
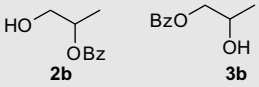
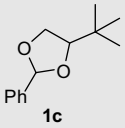
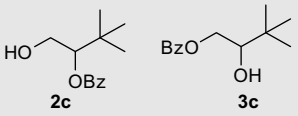
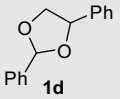
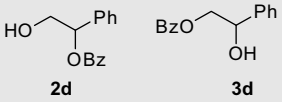
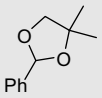
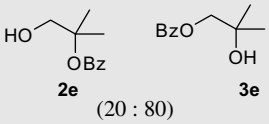
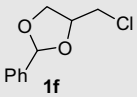
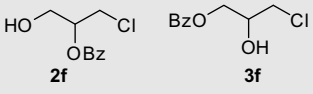
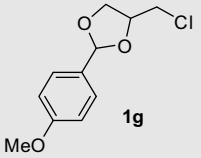
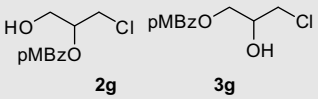
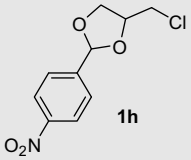
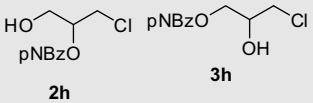
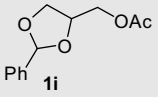
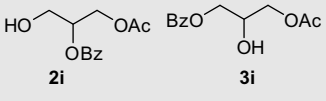
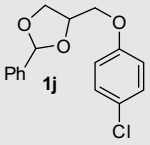
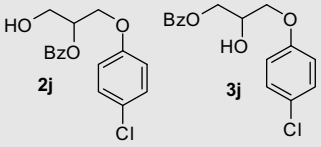
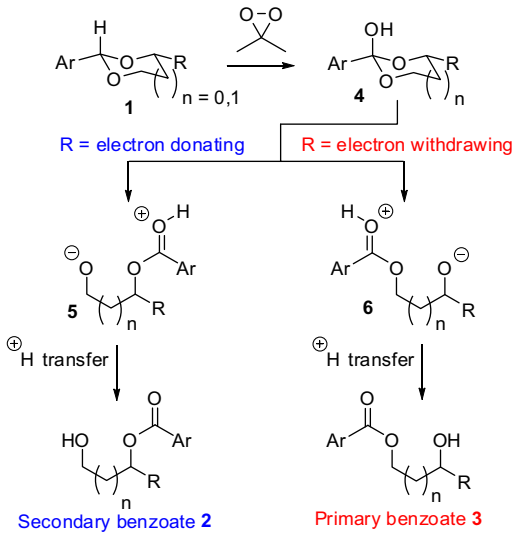
Table 1
DMDO-mediated oxidation of 1,3-dioxolanes[a]

Entry	Acetal (cis:trans)	Products (ratio **2**:**3**)	Yield[b] (%)
1	 **1b** (1 : 1)	 **2b** **3b** (89 : 11)	76
2	 **1c** (2 : 1)	 **2c** **3c** (90 : 10)	85
3	 **1d** (1 : 1)	 **2d** **3d** (71 : 29)	83
4	 **1e**	 **2e** **3e** (20 : 80)	81
5	 **1f** (1 : 1)	 **2f** **3f** (7 : 93)	84
6	 **1g** (1 : 1)	 **2g** **3g** (7 : 93)	92
7	 **1h** (1 : 1)	 **2h** **3h** (8 : 92)	74
8	 **1i** (1 : 1)	 **2i** **3i** (7 : 93)	79
9	 **1j** (1 : 1)	 **2j** **3j** (7 : 93)	73

[a] Conditions: DMDO (0.1 M, 1 equiv), acetone, 0 °C.
[b] Combined isolated yield.

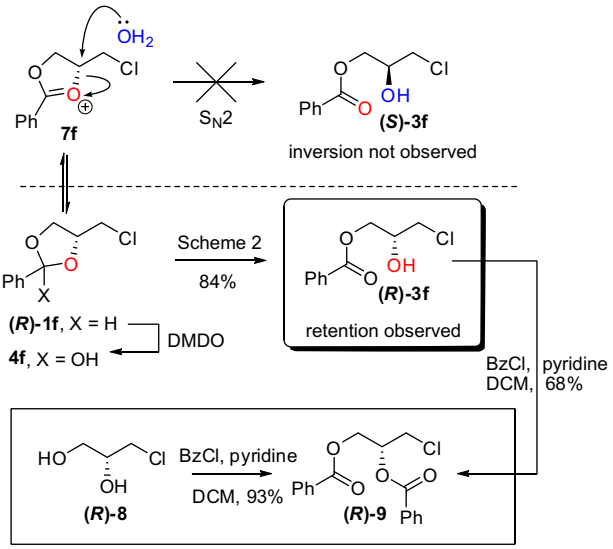
being determined by the stability of the alkoxide leaving group. In the case of R being electron-donating (i.e., R = alkyl), the primary alkoxide **5** is more stable than the secondary alkoxide **6**, hence the secondary benzoate **2** is favoured over the primary benzoate **3**. Conversely, if R is electron-deficient (i.e., R = CH_2Cl, CH_2O), the secondary alkoxide **6** is favoured over the primary alkoxide **5** and the primary benzoate **3** is the major product. The only exception to this trend is example **1e**, where steric hindrance dominates over the electronic effect.



Scheme 2. Proposed mechanism for DMDO acetal oxidation.

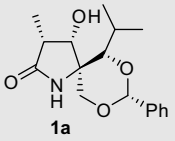
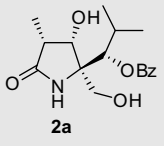
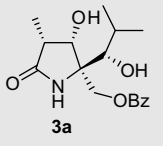
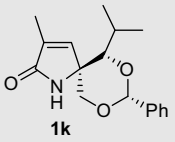
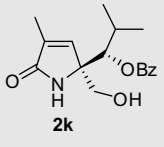
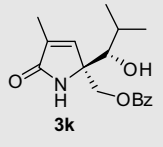
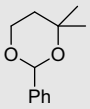
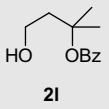
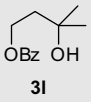
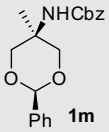
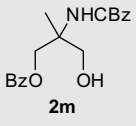
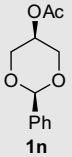
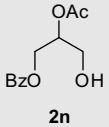
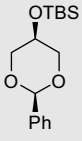
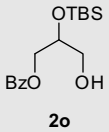
An alternative mechanism involving S_N2 substitution of an intermediate oxocarbenium ion[20] was discounted by performing the DMDO oxidation on the (*R*)-enantiomer of **1f**, which was prepared from the commercially available diol (*R*)-**8** (Scheme 3). Thus, (*R*)-**1f** gave the expected secondary alcohol product **3f** upon exposure to DMDO. The stereochemistry at the secondary hydroxyl centre was determined to be (*R*) (>95% ee) by chiral HPLC of its dibenzoate derivative **9**. An authentic sample of (*R*)-**9** was prepared from (*R*)-**8** in good yield, and a racemic standard was prepared from our previous racemic sample of **3f**.

These results clearly support the mechanism presented in Scheme 2 as the reaction proceeds with >95% retention of stereochemistry at the secondary hydroxyl stereocentre. If the



Scheme 3.

Table 2
DMDO-mediated oxidation of 1,3-dioxanes[a]

Entry	Acetal	Products (ratio **2**:**3**)	Yield[b] (%)
1	 **1a**	 **2a**  **3a** (100 : 0)	90
2	 **1k**	 **2k**  **3k** (100 : 0)	52
3	 **1l**	 **2l**  **3l** (20 : 80)	60
4	 **1m**	 **2m**	74
5	 **1n**	 **2n**	70
6	 **1o**	 **2o**	93

[a] Conditions: DMDO (0.1 M, 1 equiv), acetone, 0 °C.
[b] Combined isolated yield.

oxocarbenium ion **7f** was involved in producing **3f**, we would expect to see either inversion of stereochemistry resulting from S_N2 attack of water (Scheme 3), or loss of stereochemistry via an equivalent S_N1 pathway (not shown).

In addition to the oxidation of 1,3-dioxolanes, we also performed a series of experiments using 1,3-dioxanes as substrates (Table 2). As observed previously in the dioxolane series, oxidation of the alkyl-substituted acetals **1a** and **1k** afforded the secondary benzoates **2a** and **2k** as the major products. Both examples also show that the oxidation can be performed in the presence of hydroxyls, electron-deficient alkenes and amide NH groups. Acetal **1l** gave a reversal of regioselection and afforded the primary benzoate **3l** as the major product. This is a similar behaviour to that seen with **1e** (Table 1) in the dioxolane series, and its formation can be rationalised in a similar way (i.e., the tertiary ester **2l** is sterically hindered). The acetals **1m–o** demonstrate good functional group compatibility with the oxidation conditions, with acetate **1n**, OTBS **1o** and NHCBz **1m** groups being well tolerated.

In conclusion, we have shown that DMDO can be used to effect an oxidative partial deprotection of benzylidene acetals derived from both 1,2- and 1,3-diols.[21] A wide range of functional groups are tolerated, and good to excellent yields are usually observed. The reactions are easy to perform and produce little waste other than acetone, and as a consequence this method could find use in a number of synthetic applications.

Acknowledgements

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20. This mechanism is invoked for the NBS-mediated cleavage of benzylidene acetals (see Ref. 6).
21. *Typical procedure*: Benzylidene acetal **1c** (82.4 mg, 0.40 mmol) was treated with a solution of DMDO (4 mL of a 0.10 M solution in acetone, 1 equiv) and the mixture was stirred at 0 °C for 20 h. The solution was allowed to reach room temperature and was then concentrated in vacuo. The crude material was purified by column chromatography using petroleum ether 40–60 and EtOAc (3:1) to give benzoates **2c** and **3c** as a 90:10 mixture (75 mg, 85%). (Data for **2c**): ν_{max}/cm^{-1} ($CHCl_3$) 2972, 1710, 1279, 911; δ_H (400 MHz; $CDCl_3$) 8.10–8.07 (2H, m, ArH), 7.61–7.57 (1H, m, ArH), 7.49–7.45 (2H, m, ArH), 4.96 (1H, dd, *J* 7.9 and 2.5, C*H*OBz), 3.98 (1H, dd, *J* 12.2 and 2.5, HOCH*H*), 3.78 (1H, dd, *J* 12.2 and 8.8, HOC*H*H), 1.05 (9H, s, $C(CH_3)_3$); δ_C (100 MHz; $CDCl_3$) 167.5 (C), 133.1 (CH), 130.2 (C), 129.7 (CH), 128.5 (CH), 83.6 (CH), 62.9 (CH_2), 34.0 (C) 26.3 (CH_3); *m/z* (ESI+) (M+Na, $C_{13}H_{18}NaO_3$ requires 245.1148. Found 245.1143). (Data for **3c**): ν_{max}/cm^{-1} ($CHCl_3$) 3012, 2965, 1718, 1276, 909; δ_H (270 MHz; $CDCl_3$) 8.09–8.03 (2H, m, ArH), 7.60–7.55 (1H, m, ArH), 7.50–7.45 (2H, m, ArH), 4.55 (1H, dd, *J* 11.3 and 2.4, CH*H*OBz), 4.25 (1H, dd, *J* 11.3 and 8.6, C*H*HOBz), 3.66 (1H, dd, *J* 8.9 and 2.4, HOC*H*), 1.03 (9H, s, $C(CH_3)_3$); δ_C (100 MHz; $CDCl_3$) 167.0 (C), 133.2 (CH), 130.0 (C), 129.7 (CH), 128.5 (CH), 77.5 (CH), 67.1 (CH_2), 34.1 (C) 25.9 (CH_3); *m/z* (ESI+) (M+Na, $C_{13}H_{18}NaO_3$ requires 245.1148. Found 245.1142).