Mild water-promoted selective deacetalisation of acyclic acetals†

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Various aliphatic and aromatic dimethyl and diethyl acetals and ketals were found to hydrolyse in essentially quantitative yield when heated to 80 °C in neat water or aqueous medium without a catalyst or any other additive, while cyclic acetals were stable under these conditions. Selective deprotection is possible when both types of acetal are present.

Introduction

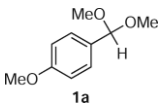
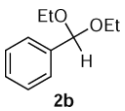
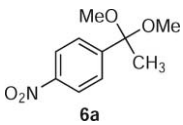
One of the most successful carbonyl protecting strategies is to make use of acetals and ketals.[1] These entities are usually prepared by reaction of the aldehyde or ketone with an alcohol or diol in the presence of a drying agent[2] or by transacetalisation,[3] together with an acid catalyst which may be a Lewis acid such as $Al(OTf)_3$ as we have recently shown.[4] Acetals have varying stabilities; the cyclic species are usually more stable than the acyclic analogs thereof, generating some preference for the cyclic over the acyclic acetals. Despite these reactivity differences, the literature is replete of examples of the use of acyclic acetals as protecting groups.[1]

Deprotection strategies for such acetals vary in their mildness and include, amongst many others, aqueous formic acid[5] and *p*-toluenesulfonic acid in acetone.[1] Super heated water (180 °C, 10 bar pressure) in the presence of $CaCl_2$ has also been used for acetal deprotections.[6] What appears not to be known, and what we disclose in the present manuscript, is that many acetals deprotect spontaneously and rapidly when mixed with neat water at 80 °C and in some cases at ambient temperature, as will become clear. This finding is remarkable given the obvious advantages it holds over other solvent-based acid-catalysed acetal deprotection methods. Our initial work performed when pursuing these investigations made use of tetrahydrofuran/water (4 : 1) mixtures but it was soon established that the use of the organic solvent was unnecessary in most instances.

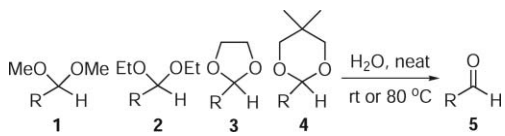
As an extension of our previous work on acetals,[4] we investigated the deprotection of a range of acetals and ketals (Schemes 1 and 2) in neat deionised water (pH 6.4) with various metal triflates (Table 1).[7] In all catalysed cases (Table 1), the free aldehydes were isolated in quantitative yield after one hour reactions at ambient temperature (for the nitrobenzene derivative the reaction was performed at 80 °C since the substrate is solid at ambient temperature).‡ As a control experiment to assess the rate of background spontaneous hydrolysis, the metal triflates were altogether omitted and, astonishingly, the aldehydes and ketones were isolated in excellent yield also within one hour!

To elaborate the scope of the catalyst-free reaction, a range of aromatic and aliphatic acetals and ketals was subjected to these simple deprotection conditions (Table 2). For ease of experimental set-up, and to avoid problems with solid substrates, all subsequent reactions were performed at 80 °C

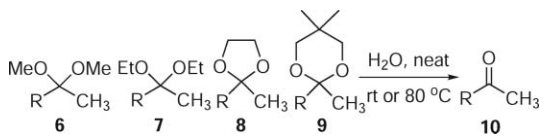
Table 1 Deprotection of acetals[a]

Substrate	Product	Yield (%)[b] $M(OTf)_3$[c]	$Hf(OTf)_4$	No cat.
 1a	**5a**	100	100	97
 2b	**5b**	100	100	75 (100)[d]
 6a	**10a**	100	100[d]	100[d]

[a] 12.5 mmol acetal, 15 mL deionised water, 5 mol% $M(OTf)_x$, 25 °C, 1 h. [b] Yields refer to isolated products. [c] M = Al, In, Sc. [d] Reaction performed at 80 °C.



Scheme 1 Hydrolysis of acetals. **1a**, **2a**, **3a**, **4a**, **5a**: R = 4-MeO-C_6H_4; **1b**, **2b**, **3b**, **4b**, **5b**: R = C_6H_5; **1c**, **2c**, **3c**, **4c**, **5c**: R = 2-MeO-C_6H_4; **1d**, **2d**, **3d**, **4d**, **5d**: R = 2-NO_2-C_6H_4; **1e**, **2e**, **3e**, **4e**, **5e**: R = 2-HO-C_6H_4; **1f**, **2f**, **3f**, **4f**, **5f**: R = $C_6H_5CH{=}CH$; **1g**,**2g**, **3g**, **4g**, **5g**: R = *n*-C_5H_{11}; **1h**, **2h**, **3h**, **4h**, **5h**: R = *n*-C_9H_{19}.



Scheme 2 Hydrolysis of ketals. **6a**, **7a**, **8a**, **9a**, **10a**: R = 4-NO_2-C_6H_4; **6b**, **7b**, **8b**, **9b**, **10b**: R = C_6H_5; **6c**, **7c**, **8c**, **9c**, **10c**: R = 2-naphthyl.

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Table 2 Hydrolysis of acetals in water[a]

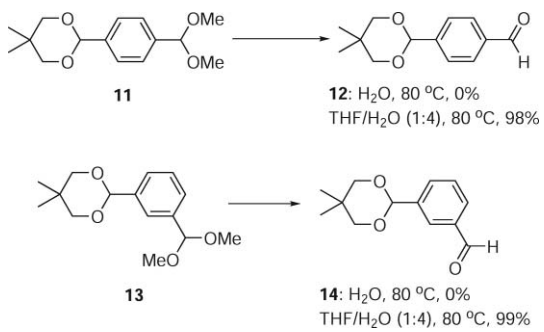
Entry	Substrate: acetal type[b]	Product	Yield (%)[c]
1	**1a**: OMe	**5a**	97
2	**2a**: OE	**5a**	100
3	**3a**: EG	**5a**	<5[d]
4	**4a**: PG	**5a**	0[d]
5	**1b**: OMe	**5b**	100
6	**2b**: OEt	**5b**	100
7	**3b**: EG	**5b**	<5[d]
8	**4b**: PG	**5b**	0[d]
9	**1c**: OMe	**5c**	93
10	**2c**: OEt	**5c**	100
11	**3c**: EG	**5c**	0[d]
12	**4c**: PG	**5c**	0[d]
13	**1d**: OMe	**5d**	<5[d]
14	**2d**: OEt	**5d**	<5[d]
15	**3d**: EG	**5d**	<5[d]
16	**4d**: PG	**5d**	0[d]
17	**1e**: OMe	**5e**	97
18	**2e**: OEt	**5e**	95
19	**4e**: PG	**5e**	0[d]
20	**1f**: OMe	**5f**	100[e]
21	**2f**: OEt	**5f**	100[e]
22	**3f**: EG	**5f**	100[e]
23	**4f**: PG	**5f**	17[d]
24	**1g**: OMe	**5g**	100[f]
25	**2g**: OEt	**5g**	100[f]
26	**3g**: EG	**5g**	0[d,f]
27	**4g**: PG	**5g**	0[d,f]
28	**1h**: OMe	**5h**	100[f]
29	**2h**: OEt	**5h**	100[f]
30	**3h**: EG	**5h**	0[d,f]
31	**4h**: PG	**5h**	0[d,f]
32	**6a**: OMe	**10a**	100 (50)[g]
33	**7a**: OEt	**10a**	98 (7)[g]
34	**8a**: EG	**10a**	0[d]
35	**9a**: PG	**10a**	0[d]
36	**6b**: OMe	**10b**	100
37	**7b**: OEt	**10b**	100
38	**8b**: EG	**10b**	5[d]
39	**9b**: PG	**10b**	0[d]
40	**6c**: OMe	**10c**	100 (<5)[g]
41	**7c**: OEt	**10c**	100 (10)[g]
42	**8c**: EG	**10c**	<5[d]
43	**9c**: PG	**10c**	0[d]

[a] 12.5 mmol acetal, 15 mL deionised water, 80 °C, 2 h. [b] OMe = dimethyl acetal; OEt = diethyl acetal; EG = acetal of 1,2-ethanediol (ethylene glycol); PG = acetal of 3,3-dimethyl-1,3-propanediol (propylene glycol). [c] Yields refer to isolated products. [d] 24 h reaction. [e] rt, 2 h. [f] 10 : 4 : 1 $Et_2O/THF/H_2O$, 8 bar nitrogen pressure (autoclave reactor), 80 °C. [g] rt, 24 h.

(in a few instances room temperature comparisons are given). With the exception of the 2-nitrobenzaldehyde derivatives and the aliphatic acetals (Table 2, entries 13–16, 24–31), all methyl and ethyl acetals tested were susceptible to virtually complete hydrolysis in neat water at 80 °C. The aliphatic acetals (Table 2, entries 24–31) were rather resistant to hydrolysis even after extended periods of reaction at elevated temperature, most probably as a result of their hydrophobicity. Such rate-retarding effects are well-known in biphasic hydroformylation reactions with alkenes of varying chain lengths reacting at widely different rates, if negligibly for longer chain substrates. This reflects their solubility in the aqueous medium.[8] The use of THF/H_2O mixtures failed to improve the outcomes but $Et_2O/THF/H_2O$ mixtures contained in stainless steel reactors (to contain the volatile solvents) at 80 °C under 8 bar nitrogen pressure afforded excellent hydrolyses (Table 2, entries 24, 25, 28, 29). In the case of the 2-nitrobenzaldehyde derivatives (Table 2, entries 13–16; compare with the 2-OMe analog results in entries 9–12), the lack of reactivity can be explained by the electron-withdrawing effect of the 2-nitro group which would destabilise cationic intermediates presumably formed during the hydrolysis.[9] 4-Nitroacetophenone derivatives (Table 2, entries 32–33) were not plagued by this lack of reactivity, possibly because of a reduction in the electron-withdrawing inductive and field effects[10] due to the remoteness of the electron-withdrawing group from the active site of the acetal. Such a reduction in the net effect of the nitro group would pose less of a destabilising influence of that group on cationic intermediates. In the case of the acetals of cinnamaldehyde (Table 2, entries 19–21), three of the acetal substrates were so reactive that the hydrolyses could be performed at ambient temperature. The particular reactivity presumably arises as a direct consequence of the presence of the alkene which would act to resonance stabilise the cationic intermediates usually expected of the standard acetal hydrolysis mechanism (S_N1-type).[8]

It is clear from Table 2 that the cyclic acetals of all substrates but one, namely of cinnamaldehyde, were resistant to hydrolysis under these conditions, mostly giving negligible hydrolysis. This particular observation leads to the useful insight that cyclic and acyclic acetals may be differentially deprotected simply by heating the substrate in water to remove the acyclic acetal (OMe and OEt acetal types in Table 2) under these mild conditions while retaining the cyclic protecting group.

Such selective deprotection was shown with substrates **11**[11] and **13** where only the acyclic acetal in the system spontaneously hydrolysed while the cyclic protecting group was retained intact in both cases (Scheme 3). Here, neat water failed to effect the desired hydrolysis but the addition of 20% THF to the aqueous mixture readily facilitated the deprotection reaction in essentially quantitative yield. It is clear from this example that the new finding holds significant potential, especially for otherwise acid- and base-sensitive protecting groups.



Scheme 3 Selective hydrolysis of acyclic acetals.

Conclusions

This paper highlights the facile uncatalysed deprotection of dimethyl and diethyl acetals in neat water under mild conditions. Under identical conditions, cyclic acetals are found to be stable and only starting materials are recovered. This differential reactivity enables easy discrimination between the deprotection of

cyclic and acyclic acetals. This allowed the exclusive deprotection of an acyclic acetal leaving the cyclic counterpart intact.

Acknowledgements

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Notes and references

‡ Typical experimental procedure for the hydrolysis of acetals. The reactions were performed in neat deionised water unless otherwise indicated. No special precautions were taken to exclude oxygen and standard round bottomed flasks were used. To 12.5 mmol of the acetal were added 15 mL of deionised water. The reaction vessel was heated to 80 °C for the determined period of time after which the water was simply removed by evaporation thereof. Alternatively, diethyl ether (3 × 5 mL) could be used with which to extract the organic material from the aqueous layer. The organic phase was dried with anhydrous magnesium sulfate and the volatile component removed under vacuum. In all cases the products were isolated directly in >98% purity as determined by ^{1}H NMR and GC analyses without further need for purification. The aldehyde or ketone products were compared spectroscopically with their commercially available counterparts.
In instances where the reactions were performed under pressure, stainless steel autoclaves fitted with a PTFE liner, a pressure gauge, filler fitting with a tap valve (needle type) and pressure relief safety device were used (**caution**: high pressure reactions should be performed only by suitably trained personnel who understand the risks involved, making use of appropriate pressure vessels). The acetal was weighed directly into the PTFE liner which was then placed inside the pressure vessel. The relevant aqueous solvent mixture as indicated in the main text of this manuscript was added to the acetal and the pressure vessel sealed and pressurised with nitrogen from a high pressure cylinder. The vessels was heated in an oil bath to the temperature and for the time indicated in the main text of this article. At the end of the reaction the pressure vessel was cooled and de-pressurised inside a fume hood. The reaction contents were then treated as usual (see above) to isolate the products.

1 P. G. W. Wuts and T. W. Greene, *Protective Groups in Organic Synthesis*, 4th edn, Wiley-Interscience, Hoboken, New Jersey, 2007, ch. 4.
2 D. Crich, W. Cai and Z. Dai, *J. Org. Chem.*, 2000, **65**, 1291.
3 D. R. McPhail, J. R. Lee and B. Fraser-Reid, *J. Am. Chem. Soc.*, 1992, **112**, 1905.
4 D. B. G. Williams and M. Lawton, *Green Chem.*, 2008, **10**, 914.
5 P. Maunder, P. M. Finglas, A. I. Mallet, F. A. Mellon, M. A. Razzaque, B. Ridge, L. Vahteristo and C. Witthöft, C., *J. Chem. Soc., Perkin Trans. 1*, 1999, 1311.
6 K. Sato, T. Kishimoto, M. Morimoto, H. Saimoto and Y. Shigemasa, *Tetrahedron Lett.*, 2003, **44**, 8623.
7 B. T. Gregg, K. C. Golden and J. F. Quinn, *J. Org. Chem.*, 2007, **72**, 5890.
8 R. M. Deshpande, Purwanto, H. Delmas and R. V. Chaudhari, *Ind. Eng. Chem. Res.*, 1996, **35**, 3927.
9 MM. Kreevoy and R. W. Taft, Jr., *J. Am. Chem. Soc.*, 1955, **77**, 3146; M. M. Kreevoy and R. W. Taft, Tr, *J. Am. Chem. Soc.*, 1955, **77**, 5590.
10 J. D. Roberts and W. D. Moreland, Jr., *J. Am. Chem. Soc.*, 1953, **75**, 2167.
11 H. Nao, K. Kiyoshi, S. Hisashi and S. Tsuneo, *Synlett*, 2004, **6**, 1074.