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Remarkably Efficient Deprotection of Cyclic Acetals and Ketals¥

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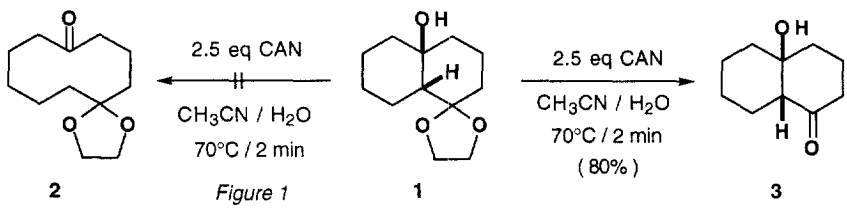
Abstract: A simple and mild procedure for the efficient deprotection of cyclic acetals and ketals, using cerium ammonium nitrate (CAN) is reported. The method tolerates a range of functional and protecting groups and is suitable for acid-labile substrates.

¥ Dedicated fondly to Dr. Victor Matassa for his continuous support

During the course of some studies directed towards the total synthesis of natural products containing a medium-ring system, we had the opportunity to examine the radical-mediated fragmentation of hydroxy-ketal **1** (Figure 1).[1] Numerous reagents able to generate alkoxy radicals from hydroxyl functions have been described in the literature.[2] Amongst these, we selected cerium ammonium nitrate (CAN) and reacted it with substrate **1** under the reported conditions.[3] Upon addition of CAN to ketal **1** in wet acetonitrile, at 70°C, a deep red colour developed instantaneously which vanished within 2 minutes. TLC analysis revealed the complete disappearance of the starting material **1** and the quantitative formation of a single, new compound. Unexpectedly, this product proved to be the keto-alcohol **3** and not the desired 10-membered ring ketone **2** (Figure 1).[4]



2 *Figure 1* **1** **3**

Although CAN is a well-known reagent for the oxidative removal of S,S and O,S acetals,[5] as well as for the deprotection of TBS ethers[6] and ^{t}BOC groups[7], to the best of our knowledge, it has never been used for the deprotection of acetals and ketals.[8] The surprisingly rapid and efficient transformation of ketal **1** into ketone **3** prompted us to investigate in greater detail the scope of this novel deprotection method.

Some pertinent results are collected in Table 1. As can be seen from the Table, a wide variety of ketals and acetals can be smoothly and efficiently deprotected into the corresponding aldehyde or ketone. The crude products, which are sufficiently pure for further use without subsequent purification, are usually obtained in quantitative yields.[9] Ketals derived from both cyclic and acyclic ketones or aldehydes are deprotected with equal facility. The reaction conditions are compatible with a wide range of functional and protecting groups. For example, the presence of another ketone or enone function in the same substrate is perfectly compatible with the deprotection of the dioxolane moiety (Table 1, Entries 2 and 7). Similarly, the removal of the ketal group can be smoothly effected in the presence of a benzyl or acetyl protecting group (Table 1, Entries 8 and 9). Interestingly, CAN-mediated deprotection of enone-derived ketals proceeds efficiently, affording in high yield the desired

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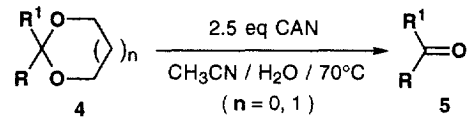
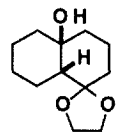
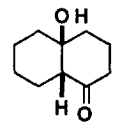
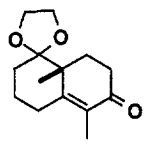
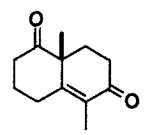
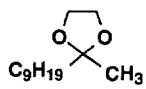
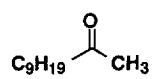
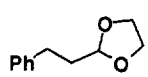
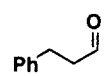
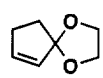
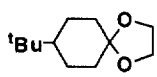
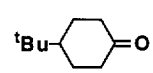
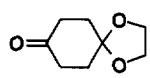
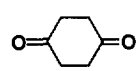
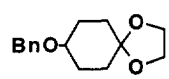
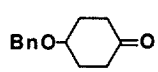
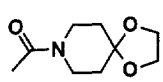
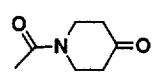
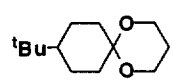
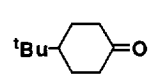
Table 1. CAN-Mediated Deprotection of Ketals and Acetals



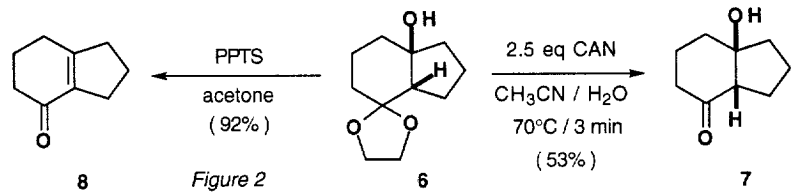
4 5

Entry	Substrate	Product	Yield[a]	Time
1			80%	2 min
2			98%	2 min
3			83%	4 min
4			70%	5 min[b]
5			84%	5 min
6			71%	4 min
7			71%	3 min
8			97%	2 min
9			60%	4 min
10			65%	5 min

(a) All yields refer to pure, homogeneous products. In all cases, the crude yield of essentially pure product (>95%) is quantitative. (b) Performed using a borate buffer (pH = 8)

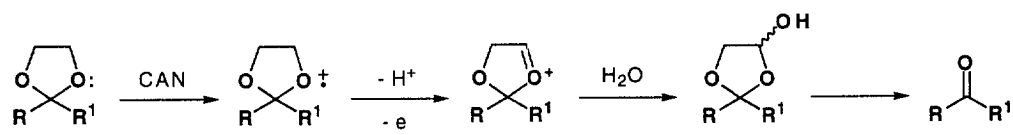
enone (Table 1, Entry 5). Finally, not only a five-membered ring ketal but also a six-membered ring ketal can be deprotected with equal ease and efficiency (Table 1, Entry 10). It is noteworthy that dimethylketals and TBS protecting groups are incompatible with this protocol.[10] That the reaction conditions are particularly mild is further illustrated by the example shown in Figure 2. Attempted deprotection of the hydrindane derivative **6** under a variety of acid-catalysed conditions led repeatedly to enone **8.**

In striking contrast, CAN-mediated removal of the dioxolane protecting group afforded quantitatively the desired hydroxyketone **7**. Aldol **7** is extremely sensitive to acidic conditions and rapidly eliminates water under the slightest provocation, generating enone **8**. For example, rapid purification of **7** by column chromatography on silica gel resulted in reduced yields due to dehydration of keto-alcohol **7** into **8**. It is remarkable to note that no epimerisation of *cis*-**7** took place under these mild conditions to afford *trans*-**7**.[11]



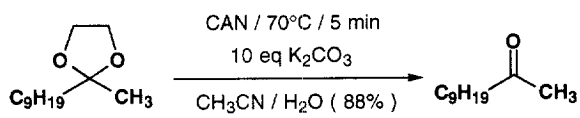
8 *Figure 2* **6** **7**

Though the intimate mechanistic details of this novel deprotection reaction are not yet fully understood, a feasible pathway might involve the removal of an electron from the dioxolane moiety by the cerium oxidant, affording the radical cation **9** (Figure 3).[12] Further loss of a proton and an electron then generates the oxonium cation **10** which is intercepted by water, producing the hemiketal **11**. Subsequent collapse of **11** then liberates the desired carbonyl derivative **5**.



4 **9** *Figure 3* **10** **11** **5**

In order to demonstrate that the deprotection reaction is not an acid-catalysed process,[11] the cleavage of ketal **12** was effected under basic conditions (Figure 4). In the presence of K_2CO_3 (10 eqs.) and CAN, smooth release of the ketone **13** could be accomplished in excellent yield.



12 *Figure 4* **13**

In summary, we have shown that CAN is a powerful reagent for the efficient and rapid deprotection of cyclic ketals and acetals. In most cases, the disappearance of the initial red-colour (2-5 min) signals the end of the reaction.[13] The method also tolerates a range of protecting and functional groups. Finally, we have demonstrated for the first time that cyclic ketals can be cleaved **under basic conditions**. Further work is directed towards delineating the scope of this novel deprotection protocol and understanding the intimate mechanism of this useful reaction.[14]

Acknowledgements

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References and Notes

1. Ates, A.; Markó, I.E. Manuscript in preparation.
2. For some leading references, see: (a) Barton, D.H.R.; Akhtar, M. *J. Am. Chem. Soc.*, **1964**, *86*, 1528. (b) Suarez, E.; Conception, J.I.; Francisco, C.G.; Hernandez, R.; Salazard, J.A. *Tetrahedron Lett.*, **1984**, *25*, 1953. (c) Arigoni, D.; Cainelli, G.; Mihailovic, M.L.; Jeger, O. *Helv. Chim. Acta*, **1959**, *42*, 1124. (d) Walling, C.; Padwa, A. *J. Am. Chem. Soc.*, **1961**, *83*, 2207. (e) Barton, D.H.R.; Beaton, J.M.; Geller, L.E.; Peclet, M.M. *J. Am. Chem. Soc.*, **1961**, *83*, 4076. (f) Suarez, E.; Francisco, C.G.; Leone, E.I.; Moreno, P. *Tetrahedron Asymmetry*, **1998**, *9*, 2975.
3. (a) Ho, T.-L. Cerium(IV) *Oxidation of Organic Compounds in Organic Syntheses by Oxidation with Metal Compounds*; Mijs, W.J.; deJonge, C.R.H.I. Eds., Plenum Press, New York, 1986. (b) Trahanovsky, W.S.; Young, M.G.; Nave, P.M. *Tetrahedron Lett.*, **1969**, *10*, 2501. (c) Ho, T.-L. *Synthesis*, **1973**, 347.
4. Remarkably, epimerisation of the *cis*-fused decaline **3** into the more stable *trans*-isomer did not occur under these reaction conditions.
5. Ho, T.-L.; Ho, C.H.; Wong, C.M. *J. Chem. Soc., Chem. Commun.*, **1972**, 791.
6. DattaGupta, A.; Singh, R.; Singh, V.K. *Synlett*, **1996**, 69.
7. Hwu, J.R.; Jain, M.L.; Tsay, S.-C.; Hakimelahi, G.H. *Tetrahedron Lett.*, **1996**, *37*, 2035.
8. For other deprotections using CAN, see for example: (a) Matsumoto, T.; Katsuki, M.; Jona, H.; Suzuki, K. *J. Am. Chem. Soc.*, **1991**, *113*, 6982. (b) Schreiber, S.L.; Kiessling, L.L. *Tetrahedron Lett.*, **1989**, *30*, 433. (c) Choi, J.-R.; Han, S.; Cha, J.K. *Tetrahedron Lett.*, **1991**, *32*, 6469. (d) Cotelle, P.; Catteau, J.-P. *Tetrahedron Lett.*, **1992**, *33*, 3855.
9. The discrepancy in yields between the crude products and the analytically pure compounds mostly reflects the mechanical losses encountered during the purification step. The crude products are sufficiently pure (>95% purity) to be used directly in a subsequent transformation.
10. The cleavage of TBS ethers by CAN does not occur in CH_3CN/H_2O mixture but can be efficiently performed in $MeOH/H_2O$. The authors suggest the intermediacy of a MeOH.Ce(IV) complex as the active catalyst (cf. Reference 6). Under these conditions, TBS ethers are cleaved chemoselectively in the presence of ketal groups. For the removal of ketals by $CeCl_3$, see: Marcantoni, E.; Nobili, F.; Bartoli, G.; Bosco, M.; Sambri, L. *J. Org. Chem.*, **1997**, *62*, 4183.
11. The pH of the reaction medium is only mildly acidic, possibly due to a buffering effect by the CH_3CN solvent. For substrates that are highly sensitive to acidic conditions, a borate buffer (pH = 8) can be successfully employed (see Table 1, Entry 4).
12. For electron-transfer reactions using CAN, see for example: Baciocchi, E.; Giacco, T.D.; Rol, C.; Sebastiani, G.V. *Tetrahedron Lett.*, **1989**, *30*, 3573.
13. The deep red colour that develops during these reactions is probably due to the formation of a 1:1 complex between CAN and the ketal protecting group. No such colour is observed when CAN is dissolved in H_2O or H_2O/CH_3CN mixture. For the formation of red-coloured complexes between CAN and alcohols, see: (a) Young, L.B.; Trahanovsky, W.S. *J. Am. Chem. Soc.*, **1969**, *91*, 5060. (b) Littler, J.-S.; Waters, W.A. *J. Chem. Soc.*, **1960**, 2767.
14. Typical Experimental Procedure: Deprotection of ketal **1**
To a stirred solution of ketal **1** (100 mg; 0.47 mmol) in 1 mL of CH_3CN at 70°C under inert atmosphere was added in one portion a solution of CAN (650 mg; 1.78 mmol; 2.5 eq.) in 2 mL of H_2O. A deep red colour appeared immediately which discharged within 2 min. The crude reaction mixture was poured into H_2O (15 mL) and the keto-alcohol **3** was extracted into ether (2 x 15 mL). The organic layer was dried over $MgSO_4$ and the solvent eliminated under reduced pressure affording essentially pure product **3** (79 mg; ± 100%). Further purification by sgc chromatography (PE/EA: 2/1) gave analytically pure **3** (63 mg; 80%).
IR (KBr) 3437 (OH), 2934 and 2864 (C-H), 1707 (C=O), 1450 1353, 1141 cm^{-1}; **^{1}H NMR** 300 MHz ($CDCl_3$) δ 1.14-1.92 (m, 9H) and 1.93-2.52 (m, 6H); **^{13}C NMR** 300 MHz ($CDCl_3$) δ 20.55 (CH_2), 22.65 (CH_2), 23.68 (CH_2), 25.65 (CH_2), 33.72 (CH_2), 38.23 (CH_2), 38.32 (CH_2), 59.14 (CH), 74.62 (C), 212.66 (C); **MS** (EI, 70 eV) *m/z* (relative intensity) M* 168.1 (100), 150 (50), 139.2 (20), 125.1 (26), 113 (30), 55 (12); **Anal.** Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 70.93; H, 9.70.