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Remarkable Deprotection of THP and THF Ethers Catalysed by Cerium Ammonium Nitrate (CAN) Under Neutral Conditions

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Abstract: The catalytic deprotection of a range of functionalised THP and THF ethers can be efficiently performed, under neutral conditions, using as little as 3 mol% CAN in MeCN/borate buffer (pH = 8). © 1999 Elsevier Science Ltd. All rights reserved.

The protection-deprotection of alcohol functionalities is of paramount importance in organic chemistry, as testified by the plethora of imaginative reagents and methods that have been devised to accomplish this key functional group interconversion.[1] The amount of work dedicated to this area is hardly surprising since, more often than not, the success of a total synthesis endeavour crucially depends upon the compatibility and selective unravelling of carefully chosen protecting groups. Amongst the wealth of reagents typically employed to shelter a hydroxyl function, the tetrahydropyranyl- (THP) and tetrahydrofuranyl- (THF) ethers still occupy a prominent position.[1] However, their removal usually entails rather harsh acidic conditions which are rarely compatible with sensitive substrates.[2]

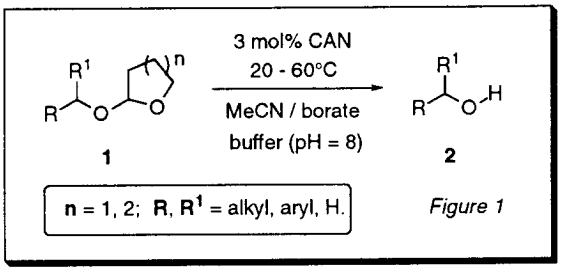

Figure 1

In a preceding communication, we have reported that cerium ammonium nitrate (CAN) was an effective reagent for the unmasking of ketones and aldehydes from the corresponding ketals and acetals under mild conditions.[3] Unfortunately, the large amounts of CAN required in this early protocol (2.5 eq) provided a serious impediment to its use on large scale. In order to alleviate this limitation, we have explored catalytic versions of this unusual deprotection technique[4] and discovered that minute quantities of CAN (3 mol%), in the presence of a borate buffer (pH = 8), smoothly and efficiently unravelled a range of acetals and ketals.[5,6] In this Article, we wish to disclose the results of our investigations in the application of this novel, **CAN-catalysed protocol,** for the removal of THP and THF protecting groups, **under neutral conditions** (Figure 1).

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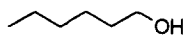
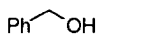
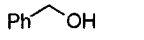
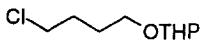
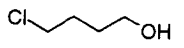
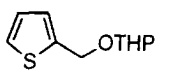
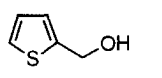
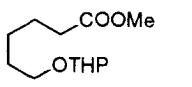
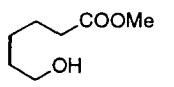
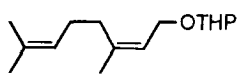
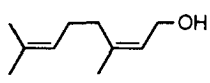
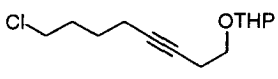
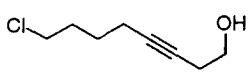
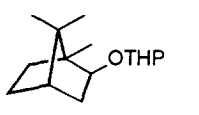
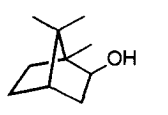
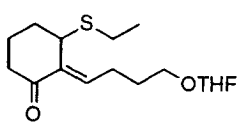
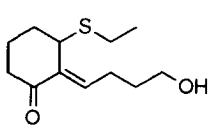
When a tetrahydropyranyl- or tetrahydrofuranyl-ether was reacted with catalytic amounts of CAN (3 mol%), in a mixture of MeCN/borate buffer (pH = 8), at room temperature or 60°C, gentle unveiling of the protecting groups occurred in high yields. Some selected examples are collected in Table 1.

Table 1. CAN-Catalysed Deprotection of THP- and THF-Ethers

Entry	Substrate	Product	Yield[a]
1			94%
2			87%
3			91%[b]
4			86%
5			91%
6			82%
7			86%[c]
8			94%[d]
9			87%
10			99%[e]

(a) All yields are for pure, isolated products. Unless otherwise stated, the deprotections were performed according to the Typical Experimental Procedure. (b) This deprotection was slightly slower than that of the corresponding THP-ether. (c) Decomposition occured under a variety of acid-catalysed conditions. (d) A 60% conversion can be realised in this case by refluxing the substrate in acetone with 5% TsOH, for 24 hrs. Further addition of TsOH did not improve the conversion. (e) Decomposition of this highly sensitive substrate occurred under acidic conditions.

As can be seen from Table 1, a wide range of alcohols can be quantitatively deprotected from their corresponding THP and THF ethers. It is noteworthy that under these conditions, no oxidation of benzylic alcohols (Entries 2 and 3), aromatic (Entry 5) and even aliphatic sulfides (Entry 10) is observed. Although a strong oxidant, the Ce(IV) reagent behaves solely as a powerful and highly selective Lewis acid. Furthermore, the catalyst also tolerates a variety of functional groups, including esters, nitriles, ketones, enones, halides,

sulfides, alkenes and alkynes. Moreover, owing to the neutral conditions employed in this unique protocol, the unmasking of highly acid-sensitive substrates can be performed in high yield without decomposition or rearrangement. For example, THP-protected nerol can be smoothly and efficiently converted into nerol using 3 mol% CAN in MeCN/borate buffer (Table 1, Entry 7). In stark contrast, deprotection of the same compound under mild acidic conditions resulted in extensive decomposition. The superiority of the CAN-catalysed methodology is further illustrated by the competent exposure of a range of substrates resilient to most of the known acidic procedures (Table 1, Entries 8 and 10 and Figure 2).

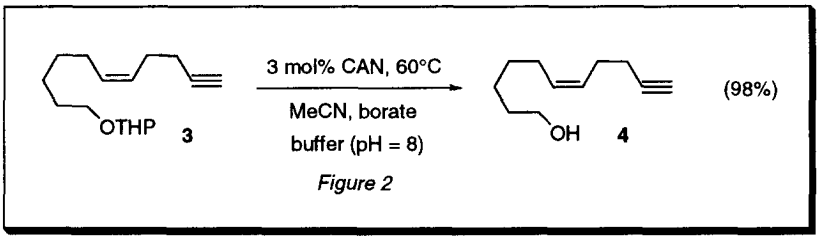


Figure 2

As an illustration, attempted cleavage of the THP group of enyne **3**, under a variety of conditions, completely failed to provide the desired alcohol **4**. Remarkably, using our CAN-catalysed protocol, quantitative unmasking of **3** occurred, affording product **4** in 98% yield. In addition to being a mild and selective reagent for the removal of THP and THF ethers, CAN displays some remarkable selectivities towards several protecting groups (Figure 3).

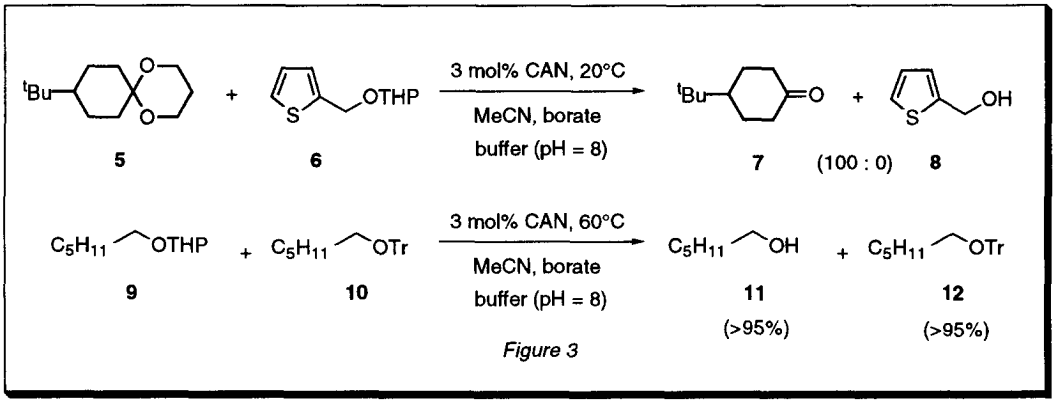


Figure 3

For instance, treatment of an equimolar mixture of ketal **5** and THP-ether **6** with catalytic quantities of CAN resulted in the complete and chemoselective unmasking of the ketal functionality. Even more interesting is the observation that trityl ethers, usually highly labile under acidic conditions, are totally inert when submitted to our CAN protocol. This striking behaviour allows, for the first time, the selective deprotection of a THP group in the presence of a trityloxy-substituent.

In summary, we have developed a novel and efficient CAN-catalysed procedure for the removal of a range of THP- and THF-protecting groups.[7] The reaction occurs under essentially neutral conditions and is particularly well-suited for acid-labile substrates. Furthermore, the catalyst tolerates a broad range of

functionalities, including aliphatic and aromatic sulfides. Moreover, CAN displays unprecedented reactivity towards several protecting groups, allowing unusual and chemoselective unmasking to be readily performed. Future work is directed towards broadening the scope of this novel deprotection and investigating further applications of this unique Lewis acid.

Acknowledgements.

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6. The deprotection of THP ethers using a modified CAN derivative has been reported: Iranpoor, N.; Salehi, P. *Iran. J. Chem. & Chem. Eng.*, **1996**, *15*, 8-10. Under these conditions, however, acid-catalysed cleavage of the acetal cannot be ruled out.
7. **Typical Experimental Procedure**. Deprotection of 1-tetrahydropyrannyloxy-8-chloro-oct-3-yne (Table 1, Entry 8).
   Solid CAN (0.42 g, 0.77 mmol, 3 mol%) was added to a stirred solution of 1-tetrahydropyrannyloxy-8-chloro-oct-3-yne (7g, 25.7 mmol) dissolved in 77 mL of MeCN and 77 mL of borate buffer (pH = 8) and maintained at 70°C. After 2 hrs at 70°C, the reaction mixture was cooled to 20°C and extracted three times with 100 mL of CH_2Cl_2. The combined organic phase was washed three times with 50 mL of saturated $NaHCO_3$, dried over $MgSO_4$ and the solvents were removed *in vacuo*. The crude product was purified by silica gel column chromatography (petroleum ether : ether, 1:1, $R_f = 0.32$). Pure 1-hydroxy-8-chloro-oct-3-yne was obtained as a colourless oil (3.9 g, 94%). ^1H NMR (200 MHz, $CDCl_3$) δ : 1.6 (m, 2H), 1.8 (m, 2H), 2.2 (tt, J = 2.3, 7 Hz, 2H), 2.4 (tt, J = 2.3, 6.3 Hz, 2H), 2.56 (s, 1H), 3.6 (t, J = 6.5 Hz, 2H), 3.7 (t, J = 6.3 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ : 19.5; 24.5; 27.5; 33.0; 46.0; 62.7; 78.7; 82.9. IR (neat) ν : 3354, 2945, 2869, 1046 cm^{-1}. MS (CI, CH_4-N_2O) *m/z* (relative intensity) 163 (20%), 161 (60%).