Cleavage of 2-Methoxyethoxymethyl Ethers Catalyzed by Cerium(IV) Ammonium Nitrate (CAN) in Acetic Anhydride

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The reactions of 2-methoxyethoxymethyl (MEM) ethers **1** with a catalytic amount of cerium(IV) ammonium nitrate (CAN) in acetic anhydride gave the corresponding mixed acetal esters **2** and acetates **3**.

MEM ethers are one of the most important protecting groups in synthetic organic chemistry.[1] The special feature of this protecting group is comparative stability for protic acids and easy removal by Lewis acids such as $ZnBr_2$ and $TiCl_4$. Recently, some mild reagents for deprotection such as $CeCl_3$,[2a] CBr_4/*i*-PrOH,[2b] and $MgBr_2$[2c] have been devised. MEM ethers are also converted into the corresponding acetates by treatment with $FeCl_3$ in Ac_2O.[3]

CAN is a representative oxidizing reagent and many reactions such as oxidation of alcohols, deprotection of dithioacetals, conversion of hydroquinones into quinones, and ligand dissociation from iron carbonyl complexes have been known.[4]

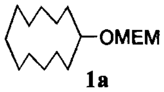
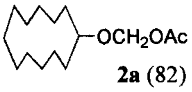
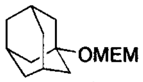
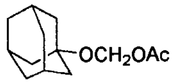
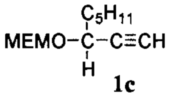
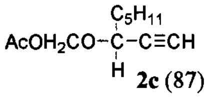
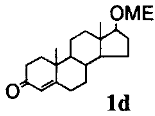
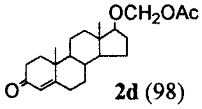
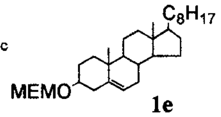
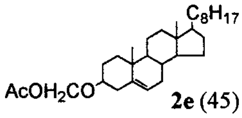
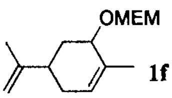
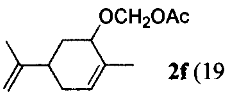
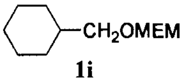
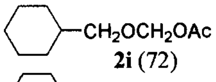
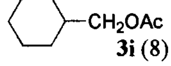
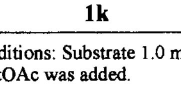
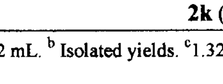
In this paper, we wish to report that MEM ethers **1** react with a catalytic amount of CAN in Ac_2O to give the corresponding mixed acetal esters **2** and acetates **3** which are easily converted into the corresponding alcohols **13** by alkaline hydrolysis.

First, we examined the reactions of a variety of MEM ethers. The results are summarized in Table 1. Cyclododecyl MEM ether (**1a**) was treated with 10 mol% of CAN in Ac_2O at room temperature for 24 h under N_2 to give cyclododecyloxymethyl acetate (**2a**) in 82% yield (Run 1). When 40 mol% of CAN was employed, the reaction time was reduced (Run 2). In CH_3CN, the reaction did not proceed. The reactions of the other secondary and tertiary MEM ethers **1b–f** gave acetal esters **2b–f** (Runs 3–7). The reactions of primary MEM ethers **1** gave mixed acetal esters **2** together with small amounts of acetates **3** except for **1k** which afforded only **2k** (Runs 8–12). In the cases of MEM ethers involving triple bond, enone, benzyl methylene, and acetonide, the products were obtained in good yields (Runs 4, 5, 11, and 12), whereas, MEM ethers **1e** and **1f** possessing double bonds gave acetal esters **2e** and **2f** in low yields because CAN oxidized the double bonds (Runs 6 and 7).[5] Acetal esters **2** were the main products in CAN-catalyzed reactions although the products were acetates **3** in $FeCl_3$–Ac_2O.[3] Acetal esters **2** and acetates **3** were converted into the corresponding alcohols **13** quantitatively by treatment with NaOMe in MeOH.[3b,6]

The reactions of methoxymethyl (MOM) and silyl ethers with CAN in Ac_2O were investigated. The results are given in Table 2. MOM ethers were also cleaved by a catalytic amount of CAN in Ac_2O at room temperature (Runs 1 and 2). *t*-Butyldimethylsilyl (TBDMS) and *t*-butyldiphenylsilyl (TBDPS) ethers were stable under these conditions (Runs 3–6).

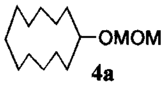
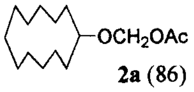
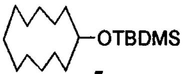
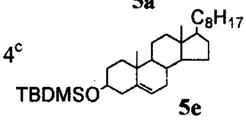
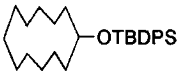
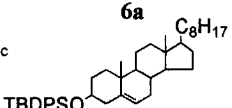
Next, we examined the mechanism of CAN-mediated

Table 1. Conversion of MEM ethers by CAN in Ac_2O[a]

Run	Sunstrate	CAN / mol%	Time / h	Product (Yield[b] /%)
1	 **1a**	10	24	 **2a** (82)
2	**1a**	40	5	**2a** (85)
3	 **1b**	10	24	 **2b** (90)
4	 $MEMO-C(C_5H_{11})(H)-C\equiv CH$ **1c**	40	24	 $AcOH_2CO-C(C_5H_{11})(H)-C\equiv CH$ **2c** (87)
5	 **1d**	40	7	 **2d** (98)
6[c]	 **1e**	40	48	 **2e** (45)
7	 **1f**	40	24	 **2f** (19)
8	$C_{12}H_{25}OMEM$ **1g**	10	24	$C_{12}H_{25}OCH_2OAc$ **2g** (66) $C_{12}H_{25}OAc$ **3g** (27)
9	$C_9H_{19}OMEM$ **1h**	10	24	$C_9H_{19}OCH_2OAc$ **2h** (63) $C_9H_{19}OAc$ **3h** (22)
10	 **1i**	10	24	 **2i** (72)  **3i** (8)
11	$PhCH_2OMEM$ **1j**	10	24	$PhCH_2OCH_2OAc$ **2j** (74) $PhCH_2OAc$ **3j** (19)
12	 **1k**	10	24	 **2k** (82)

[a]Conditions: Substrate 1.0 mmol; Ac_2O 1.32 mL. [b] Isolated yields. [c]1.32 mL of EtOAc was added.

Table 2. Reactions of MOM and Silyl ethers catalyzed by CAN in Ac_2O[a]

Run	Sunstrate	CAN / mol%	Time / h	Product (Yield[b] /%)
1	 **4a**	40	5	 **2a** (86)
2	$C_{12}H_{25}OMOM$ **4g**	40	4	$C_{12}H_{25}OCH_2OAc$ **2g** (72) $C_{12}H_{25}OAc$ **3g** (21)
3[c]	 **5a**	40	8	No Reaction
4[c]	 **5e**	40	8	No Reaction
5[c]	 **6a**	40	8	No Reaction
6[c]	 **6e**	40	8	No Reaction

[a] Conditions: Substrate 1.0 mmol; Ac_2O 1.32 mL. [b] Isolated yields. [c] 1.32 mL of EtOAc was added.

cleavage of MEM ethers. The generation of CH_3CO^+ is supposed in the reactions using Lewis acids such as $FeCl_3$, TMSCl, and $BF_3 \cdot OEt_2$ in Ac_2O.[7] Benzene rings were acetylated during the reactions using $FeCl_3$–Ac_2O.[2a] Interestingly, *o*-nitrotoluene (59%) and *p*-nitrotoluene (37%) were obtained from the reactions of CAN with toluene in Ac_2O. We propose that the reactions might be catalyzed by NO_2^+. In order to confirm the intermediacy of NO_2^+ in CAN-mediated reactions, we examined the reaction of MEM ether **1a** with NO_2BF_4 (40 mol%) in Ac_2O. Acetal ester **2a** (16%) and acetate **3a** (40%) were obtained from the reaction catalyzed by NO_2BF_4 although only 2a (82%) was formed by the CAN–Ac_2O system. The reason for the difference of the products is not clear now.

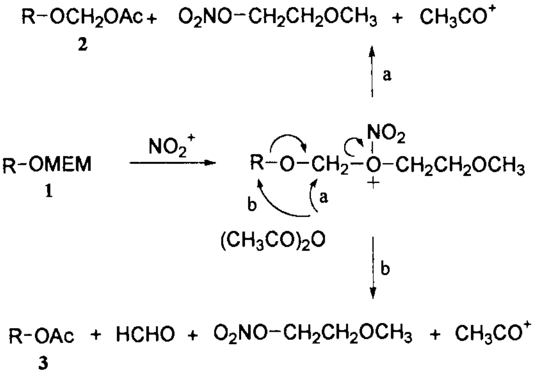
$$\underset{\mathbf{7}}{(NH_4)_2[Ce(NO_3)_6]} + \underset{\mathbf{8}}{(CH_3CO)_2O}$$

$$\longrightarrow \underset{\mathbf{9}}{(NH_4)_2[Ce(NO_3)_5(OCOCH_3)]} + \underset{\mathbf{10}}{CH_3COONO_2}$$

$$\underset{\mathbf{10}}{CH_3COONO_2} \rightleftharpoons \underset{\mathbf{11}}{CH_3COO^-} + \underset{\mathbf{12}}{NO_2^+}$$

Scheme 1.

A plausible mechanism for the formation of NO_2^+ is shown in Scheme 1. CAN would cleave Ac_2O to produce **9** and acetyl nitrate **10**. In this process, CAN acts as a Lewis acid. NO_2^+ is formed by the dissociation of acetyl nitrate **10**. Because of the high positive charge of Ce atom, CAN could behave as an effective Lewis acid. Scheme 2 shows the plausible mechanism for the deprotection of MEM ethers **1**. Path a leads to acetal esters **2**, on the other hand, acetates **3** were produced by path b. The fact that silyl ethers are stable under these conditions indicates that the reactions are not catalyzed by protic acids resulting from the hydrolysis of CAN.



Scheme 2.

A typical procedure is as follows: A mixture of MEM ether **1a** (272 mg, 1.0 mmol) and CAN (55 mg, 0.1 mmol) in Ac_2O (1.32 mL) was stirred at room temperature for 24 h under N_2. The mixture was poured into 10% potassium carbonate (20 mL) and extracted with ether. The extracts were washed with water, dried, and evaporated. The residue was purified by column chromatography with 20:1 hexane–EtOAc on silica gel to give **2a** (209 mg, 82%).

The crude **2a** (without purification by column chromatography) was added to a solution of NaOMe (21 mg, 0.4 mmol) in MeOH (4.2 mL) at room temperature. After being stirred for 1 h, Dowex 50 WX2 ion-exchange resin (ca. 0.3 g) was added until the solution becomes neutral. The mixture was filtered and the filtrate was evaporated. The residue was chromatographed with 5:1 hexane–acetone to give cyclododecanol **13a** (148 mg, 80%).

In conclusion, MEM ethers are converted into mixed acetal esters and acetates by a catalytic amount of CAN in Ac_2O. A difference of the positions of cleavage between CAN and the other Lewis acids is interesting.

References and Notes

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