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CCl_3CN: A Crucial Promoter of *m*CPBA-Mediated Direct Ether Oxidation

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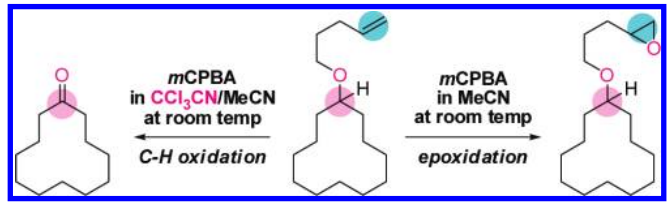
ABSTRACT



The direct oxidation of ether sp^3 C−H bonds using the new reagent system *m*CPBA/CCl_3CN/MeCN has been developed. CCl_3CN in MeCN drastically alters the reactivity of *m*-chloroperbenzoic acid (*m*CPBA), and chemoselective transformation of methyl ethers to ketones was realized under mild conditions. Radical-based *m*CPBA-mediated oxidation was suggested as the reaction mechanism. The present new reaction expands the utility of methyl ethers as stable synthetic precursors of carbonyl compounds and of *m*CPBA as a radical-based C−H oxidizing agent.

Oxidation of organic compounds is of fundamental importance in chemistry.[1] Among the numerous oxidants, *m*-chloroperbenzoic acid (*m*CPBA) is one of the most frequently used reagents in synthetic laboratories.[2] Its unique reactivity is characterized by a weak O−O bond and a nucleophilic OH group. The O−O bond of *m*CPBA transfers an oxygen atom to electron-rich substrates, such as alkenes, sulfides, selenides, and amines, while the nucleophilic attack of *m*CPBA on ketones and aldehydes results in insertion of an oxygen atom to generate esters (Baeyer−Villiger oxidation). Under these oxidation conditions, the sp^3 C−H bonds of substrates are completely inert.[3,4] In this paper, we describe *m*CPBA-mediated oxidation of sp^3 C−H bonds of ethers by applying newly developed conditions. CCl_3CN in MeCN drastically alters the reactivity of *m*CPBA without the aid of a metal catalyst, and chemoselective transformation of stable ethers to ketones is realized at room temperature through a radical-based mechanism.[5−7] The present findings broaden the synthetic utility of *m*CPBA as a C−H oxidizing agent.

The conditions for *m*CPBA-mediated sp^3 C−H oxidation of ethers were screened and optimized using cyclododecyl methyl ether **1a** (Table 1). Treatment of **1a** with *m*CPBA (2

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(2) *Handbook of Reagents for Organic Synthesis: Oxidizing and Reducing Agents*; Burke, S. D., Danheiser, R. L., Eds.; Wiley: Chichester, 1999; pp 84−89.

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(4) The more reactive CF_3CO_3H has been applied to C−H bond oxidation. (a) Deno, N. C.; Messer, L. A. *J. Chem. Soc., Chem. Commun.* **1976**, 1051. (b) Moody, C. J.; O'Connell, J. L. *Chem. Commun.* **2000**, 1311. (c) Camaioni, D. M.; Bays, J. T.; Shaw, W. J.; Linehan, J. C.; Birnbaum, J. C. *J. Org. Chem.* **2001**, *66*, 789.

(5) For a review of metal-free C−H functionalizations, see: Fokin, A. A.; Schreiner, P. R. *Adv. Synth. Catal.* **2003**, *345*, 1035.

(6) For direct ether oxidation using dioxirane and oxaziridine, see: (a) Curci, R.; D'Accolti, L.; Fiorentino, M.; Fusco, C.; Adam, W.; González-Nuñez, M. E.; Mello, R. *Tetrahedron Lett.* **1992**, *33*, 4225. (b) van Heerden, F. R.; Dixon, J. T.; Holzapfel, C. W. *Tetrahedron Lett.* **1992**, *33*, 7399. (c) Arnone, A.; Bernardi, R.; Cavicchioli, M.; Resnati, G. *J. Org. Chem.* **1995**, *60*, 2314.

(7) For a recent Mn-catalyzed direct ether oxidation, see: (a) Kamijo, S.; Amaoka, Y.; Inoue, M. *Chem. Asian J.* **2010**, *5*, 486. (b) Kamijo, S.; Amaoka, Y.; Inoue, M. *Synthesis* **2010**, 2475.

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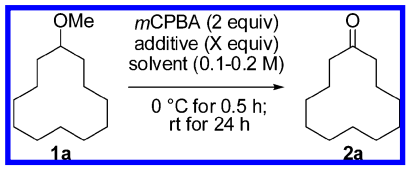
Table 1. Screening of Additives and Solvents for the Oxidation of Methyl Ether **1a**[a]



entry	additive (*X* equiv)	solvent	yield, %[b] (recovery)
1[c]	-	$CHCl_3$	9.8 (63)
2	-	MeCN	<1.0 (99)
3	CCl_3CN (2)	MeCN	68[d] (15[d])
4	Cl_2CHCN (2)	MeCN	trace (98)
5	$(CCl_3CO)_2O$ (2)	MeCN	7.9 (89)
6	-	CCl_3CN/MeCN (1/1)	88[d] (10[d])
7	-	CCl_3CN	<1.0 (99)
8	4,4′-thiobis(6-*t*-butyl-*m*-cresol) (0.1)	CCl_3CN/MeCN (1/1)	1.4 (98)
9[e]	$(C_6H_5COO)_2$ (0.1)	MeCN	13 (84)

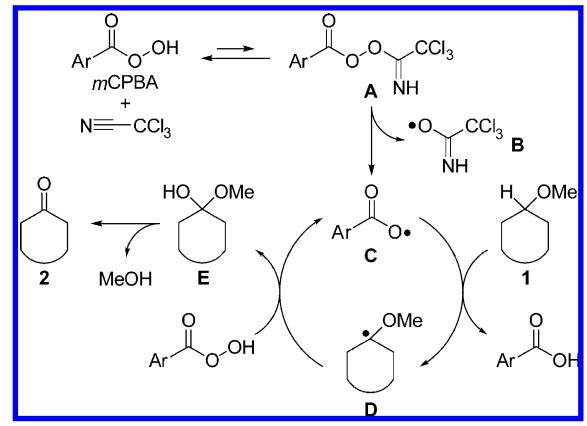
[a] Conditions: methyl ether **1a**, *m*CPBA (2 equiv; 70 wt %), additive (X equiv), solvent (entries 3−5, 0.1 M; entries 1, 2, 6−9, 0.2 M), 0 °C for 0.5 h then rt for 24 h. [b] NMR yield. [c] The reaction was performed at 60 °C for 24 h. [d] Isolated yield. [e] The reaction was performed under a desk lamp.

equiv) in $CHCl_3$ generated only a small amount of ketone even at elevated temperature (entry 1), and negligible formation of **2a** occurred in MeCN (entry 2). In sharp contrast to these results, addition of 2 equiv of CCl_3CN in MeCN significantly promoted the conversion of **1a** into ketone **2a** at room temperature (68% yield, entry 3). Thus, the reaction mode appeared to become different only by addition of CCl_3CN. Interestingly, Cl_2CHCN and trichloroacetic anhydride, which are less electrophilic reagents than CCl_3CN, exhibited a much smaller effect as promoters (entries 4 and 5). The yield of **2a** was increased to 88% in a solvent mixture of CCl_3CN and MeCN (entry 6), whereas use of CCl_3CN as a sole solvent produced just a trace amount of **2a** (entry 7). These data demonstrated that *m*CPBA, CCl_3CN, and MeCN are essential for the ether oxidation.[8,9]

The radical scavenger 4,4′-thiobis(6-*t*-butyl-*m*-cresol) (0.1 equiv)[10] inhibited the *m*CPBA oxidation of **1a** in CCl_3CN/MeCN (entry 8), while the radical initiator benzoyl peroxide (0.1 equiv) promoted formation of **2a** even in the absence of CCl_3CN when irradiated by a fluorescent lamp (entry 9). It is likely, therefore, that a radical-based mechanism is operating in the direct ether oxidation.

The observed data indicated that the radical chain reaction is involved in the conversion of **1** to **2**. Scheme 1 illustrates the mechanistic hypothesis of the reaction. Due to the strongly electrophilic nature of CCl_3CN, a mixture of

Scheme 1. Suggested Radical Mechanism for Direct Ether Oxidation



*m*CPBA and CCl_3CN in polar solvent (MeCN) is in equilibrium with minute amounts of the highly unstable peroxyimidate **A**.[11] The O−O bond of **A** is more activated by the attached imidate than that of *m*CPBA[12] and consequently is more prone to undergo homolytic cleavage. Thus, the low concentration of radical initiator **A** would continuously liberate oxyradical **C** at room temperature. Next, **C** abstracts hydrogen from **1** to generate ArCOOH and radical **D**, which in turn reacts with *m*CPBA to generate **E**.[13] In this step, oxyradical **C** is regenerated to propagate the chain reaction. Lastly, ejection of MeOH from **E** furnishes the product **2**. NMR monitoring of the reaction revealed that production of the end compounds in Scheme 1 (MeOH, ArCOOH, and **2**) was in accordance with consumption of ether **1a** and therefore supported the suggested mechanism.[14] Overall, *m*CPBA has two roles in this radical chain reaction: it functions as an oxyradical precursor through **A** and as an oxygen atom donor upon formation of **E**.

To explore the substrate scope and chemoselectivity of the present transformation, variously substituted ethers were treated under the optimized conditions (Table 2). First, oxidation of cyclododecyl ethers was investigated (entries 1−7). Similar to the case of methyl ether **1a** (entry 1), oxidations of the octyl **1b**, isopropyl **1c**, and benzyl ethers **1d** all produced ketone **2a** (entries 2−4). The sterically more demanding *t*-butyl group of **1e**, on the other hand, impeded the oxidation (entry 5). 4-Pentenyl ether **1f** and the cyclohexanone analogue **1g** were both converted into **2a** (entries

(8) Light or O_2 had a small effect for the reaction in entry 6 because **2a** was consistently produced under the conditions strictly without light or O_2.

(9) Oxidations of butylbenzene and triphenylmethane were not successful under the same conditions as shown in entry 6.

(10) Kishi, Y.; Aratani, M.; Tanino, H.; Fukuyama, T.; Goto, T. *J. Chem. Soc., Chem. Commun.* **1972**, 64.

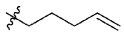
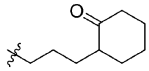
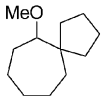
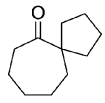
(11) For peroxyimidate derived from H_2O_2 and CCl_3CN known as an epoxidation reagent, see: (a) Payne, G. B.; Deming, P. H.; Williams, P. H. *J. Org. Chem.* **1961**, *26*, 659. (b) Arias, L. A.; Adkins, S.; Nagel, C. J.; Bach, R. D. *J. Org. Chem.* **1983**, *48*, 888.

(12) The dissociation energy of the O−O bond generally decreases upon attachment of electron-withdrawing groups [e.g., AcO-OH (40.6 kcal/mol), AcO−OAc (33.5 kcal/mol), and AcO-ONO_2 (31.4 kcal/mol)]. See: Molecular Structure and Spectroscopy. In *Handbook of Chemistry and Physics*, 87th ed.; Lide, D. R., Ed.; CRC Press: Boca Raton, FL, 2006; p 64.

(13) For oxygen donation of *m*CPBA to a carbon radical, see ref 3e.

(14) **B** should abstract a hydrogen to give $CCl_3C(O)NH_2$. Detection of **A** and $CCl_3C(O)NH_2$ by NMR analysis has not yet been successful. Since only 0.1 equiv of the radical inhibitor completely inhibited the oxidation (entry 8, Table 1), we assumed that the concentrations of **A** and the resulting $CCl_3C(O)NH_2$ are extremely low in the reaction mixture.

Table 2. Oxidation of Various Ethers[a]

entry	substrate	product	yield, %[b] (recovery)
1	**1a**: R^1 = Me	**2a**	88 (10)
2	**1b**: R^1 = n-C_8H_{17}	**2a**	53 (14)
3	**1c**: R^1 = i-Pr	**2a**	65 (15)
4[c]	**1d**: R^1 = $PhCH_2$	**2a**	42 (43)
5	**1e**: R^1 = t-Bu	**2a**	1.9 (98)
6	**1f**: R^1 = 	**2a**	91 (0)
7	**1g**: R^1 = 	**2a**	51 (0)[d]
8	 **1h**	 **2b**	90
9	**1i**: R^2 = Ac	**2c**	81 (9.6)
10	**1j**: R^2 = Ms	**2d**	86 (13)
11[e]	**1k**: R^2 = TBDPS	**2e**	59 (15)
12[e]	**1l**: R^2 = Tr	**2f**	55 (34)
13[c]	**1m**: *trans*-isomer	**3**	52 (28)
14[c]	**1n**: *cis*-isomer	**3**	38 (38)

[a] Conditions: ether **1**, *m*CPBA (2 equiv; 70 wt %), CCl_3CN/MeCN (1/1; 0.2 M), 0 °C for 0.5 h then rt for 24 h. [b] Isolated yield of ketone and recovery of starting material. [c] Treated with 4 equiv of *m*CPBA in CCl_3CN/MeCN (1/1; 0.1 M). [d] Lactone **4b** was isolated in 32% yield. [e] Treated with 1.2 equiv of *m*CPBA.

6 and 7).[15] Since the *m*CPBA oxidation of olefin **1f** and six-membered ketone **1g** in the absence of CCl_3CN afforded the corresponding epoxide **4a** and seven-membered lactone **4b**, respectively (Figure 1), entries 6 and 7 clearly verified the enhanced reactivity of the *m*CPBA/CCl_3CN/MeCN reagent system.

(15) Neither epoxide **4a** nor the olefinic derivatives were isolated upon treatment of **1f** with the *m*CPBA/CCl_3CN/MeCN reagent system. The olefin and alcohol moieties of the cleaved 4-pentenol were likely to be oxidized to give the mixture of products.

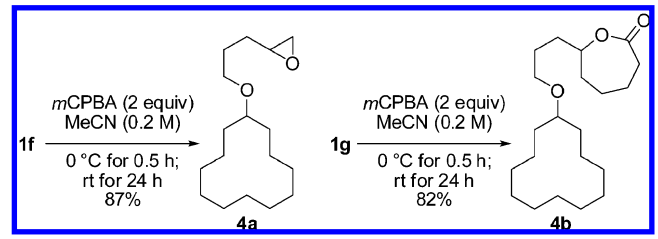


Figure 1. *m*CPBA oxidations of olefin **1f** and ketone **1g** in the absence of CCl_3CN.

Next, the methyl ethers of substituted carboskeletons were subjected to the reaction (Table 2, entries 8−14). The oxidation of the seven-membered ring **1h** gave ketone **2b** in high yield (entry 8). Importantly, only the methyl ethers of the differentially protected diols **1i**−**1l** (entries 9−12) were oxidized to the carbonyl groups of **2c**−**2f**. The electron-withdrawing acetyl (**1i**) and mesyl (**1j**) groups and the sterically bulky TBDPS (**1k**) and trityl groups (**1l**) effectively protected the hydroxy functionalities, demonstrating the high chemoselectivity of the reaction. When 4 equiv of *m*CPBA was applied to *cis*- and *trans*-substituted cyclohexyl methyl ethers **1m** and **1n**, the ether oxidation and the Baeyer−Villiger oxidation occurred simultaneously to generate lactone **3** (entries 13 and 14).

In conclusion, we have developed a method for the direct ether oxidation using the new reagent system *m*CPBA/CCl_3CN/MeCN. Robust methyl ethers were chemoselectively reacted with *m*CPBA in the presence of other potentially reactive oxygen functionalities under mild and operationally simple conditions. The present oxidation expands the synthetic potential of methyl ethers as stable precursors of carbonyl compounds and of *m*CPBA as a radical-based C−H oxidizing agent. Applications of the new reagent system as well as further mechanistic investigations are ongoing in our laboratory.

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Supporting Information Available: Experimental procedures and spectroscopic and analytical data for relevant compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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