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OXIDATION OF ACETALS, AN ORTHOESTER, AND ETHERS BY DIOXIRANES THROUGH α-CH INSERTION

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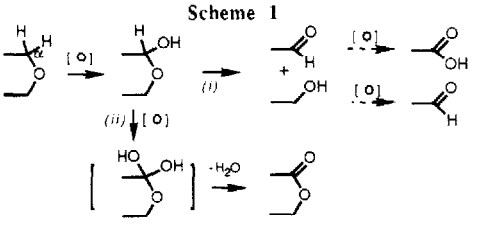
Key Words - Dioxiranes, CH insertion, Oxygen transfer, Acetals, Ethers, Orthoesters, Oxidation, Cleavage.

Abstract. Dimethyldioxirane (**1a**) and methyl(trifluoromethyl)dioxirane (**1b**) efficiently afford cleavage of acetals and of ketals to carbonyl products under mild, neutral conditions. Dialkyl ethers are cleaved to alcohols, aldehydes and/or carboxylic acids, whereas reaction of dioxiranes **1a,b** with medium-ring cyclic ethers transforms the latter into lactones, via the corresponding hemiacetals, with no appreciable formation of ring-opened products. The products can be accounted for on grounds of a remarkably selective *O*-atom insertion by the dioxirane into C-H bonds α to the ether functionality.

Using conventional oxidation reagents, such as lead tetraacetate,[1a] dioxygen,[1b] hydroperoxides,[1c] or ozone,[2] the oxyfunctionalization of ethers and acetals are rarely selective, as they often yield quite complex mixtures of products; with cyclic ethers, products of oxidative cleavage often arise (Scheme 1).[2]

Scheme 1



Metal oxides in their high oxidation states,[3] or LiOCl and catalytic amounts of Ru(II) complexes[4] count among the few reagents which are effective for the selective transformation of primary ethers into esters, without further oxidation of the esters to anhydrides and/or carboxylic acids. Also, metal nitrates - e.g., Cu(II) or Zn(II) nitrate - supported on silicagel have been employed to oxidize ethers under mild conditions to the corresponding ketones or aldehydes, with no further oxidation of the latter;[5] with this method, however, in some cases alkyl nitrites are formed as by-products.[5]

Compared to oxidation methods which use metal oxides stoichiometrically or metal complexes catalytically, oxidations employing either *in situ* [6] or isolated[7] dioxiranes $R^1R^2CO_2$ (**1**), a new class of powerful oxidants,[8] often have the advantages of simple procedures, mild reaction conditions, ease of product isolation, and increased yields. Thus, dimethyldioxirane (**1a**: R^1=R^2=CH_3)[7a,9] and methyl(trifluoromethyl)dioxirane (**1b**: R^1=CH_3, R^2=CF_3)[10] have been applied to perform an impressive variety of useful synthetic transformations.[6-13]

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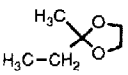
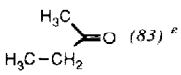
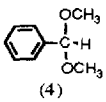
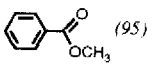
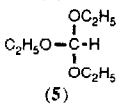
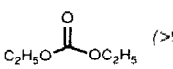
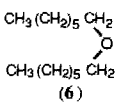
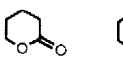
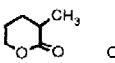
Table 1. Oxidation of acetals and ethers by dioxiranes (**1a,b**).

Substrate	Dioxi-rane	Solvent	T (°C)	Reactn time	Conver-sion (%)[a]	Products (% Yield)[b]
 (2)	**1a**[d]	CH_2Cl_2/acetone (30:70)	0	24 h	35	 *(95)*
	1b[d]	CH_2Cl_2/TFP (60:40)	0	2 h	98	*(>95)*
 (3)	**1b**[d]	CH_2Cl_2/TFP (60:40)	0	30 min	80	 *(83)* [e]
 (4)	**1a**[c]	CH_2Cl_2/acetone (30:70)	18	96 h	50	 *(95)*
 (5)	**1a**[d]	CH_2Cl_2/acetone (30:70)	0	2 h	95	 *(>95)* [e]
 (6)	**1a**[c]	CH_2Cl_2/acetone (30:70)	0	3 h	50	$CH_3(CH_2)_5CH{=}O$ *(38)* $CH_3(CH_2)_5CO_2H$ *(44)* $CH_3(CH_2)_5CH_2OH$ *(17)*
t-BuO-CH_3 (7)	**1b**[c]	CCl_4[f]	0	10 min	98	t-BuOH *(>90)* [e]
 (8)	**1a**[c]	CH_2Cl_2/acetone (50:50)	0	70 h	65	 (9) (10) (**9**:**10** = *50* :*20*)[g]
	1b[c]	CH_2Cl_2/TFP (60:40)	0	10 min	98	(**9**:**10** = *65* :*30*)
 (11)	**1b**[c]	CH_2Cl_2/TFP (50:50)	0	15 min	94	 (12) (13) (**12**:**13** = *82* :*8*)
 (14)	**1a**[c]	CH_2Cl_2/acetone (40:60)	18	96 h	30	 (15) (16) (**15**:**16** = *30* :*55*)
	1b[c]	CH_2Cl_2/TFP (60:40)	- 10	15 min	85	(**15**:**16** = *38* :*58*)

[a] As determined (± 2%) by gc (DB5, 0.20 μm film thickness, 15 m × 0.32 mm i.d., wide-bore capillary column). [b] Unless noted otherwise, yields were determined by gc or gc/ms (Hewlett-Packard mod. 5970 mass selective detector and mod. 5890 gas chromatograph) and based on the amount of substrate consumed; products were identified upon comparison of their ^1H nmr spectra (Varian XL 200), and/or gc/ms or gc/ftir (Perkin-Elmer FT-IR mod. 1710 and mod. 8700 gas chromatograph) with those of commercially available materials or independently synthesized authentic samples. [c] Dioxirane to substrate molar ratio (hereafter D/S) = 2.2 : 1. [d] D/S = 1.2 : 1. [e] As determined (± 4%) upon analysis of ^1H nmr spectra of the reaction mixture. [f] Ketone-free dioxirane **1b** solution (cf., ref. 10c). [g] Ring-cleavage products $HOCH_2CH_2CH_2CH{=}O$ and $HOCH_2CH_2CH_2CO_2H$ also detected by ^1H nmr.

In the course of a recent study on the oxidation of alcohols to carbonyl compounds by dioxiranes,[11,12] we observed that acetals and hemiacetals[11] undergo easily oxidative cleavage to carbonyl-containing products by these reagents. We present herein some further examples concerning the latter transformation, along with the oxyfunctionalization of simple ethers. Representative results are shown in Table 1.

Solutions of 0.06-0.09 M dimethyldioxirane (**1a**) in acetone or of 0.5-0.8 M methyl(trifluoromethyl)dioxirane (**1b**) in 1,1,1-trifluoropropanone (its ketone precursor, hereafter TFP) were obtained by following the reported protocol .[7a,9,10] The oxidations simply entailed addition of cold aliquots of standardized [9,10] dioxirane solution to the substrates (acetal, ether or orthoester) in dry CH_2Cl_2 (kept at 0 °C, in the majority of cases), at the dioxirane excess and solvent composition given in Table 1. The reaction progress was monitored by gc/ms; in some cases (entries 2, 4,and 6, Table 1) ^1H NMR spectra were run periodically on the reaction mixture directly, in which case CD_2Cl_2 was employed in place of CH_2Cl_2 as solvent.

The first two entries in Table 1 estabilish the dioxiranes as excellent agents for the oxidative cleavage of ethylene ketals **2** and **3**[14] under mild conditions; as expected,[11] the oxidation rates are much higher with dioxirane **1b**,[10a] which is several thousand-fold more reactive[15] than dimethyldioxirane (**1a**). This method should be synthetically useful for the deprotection of masked carbonyl compounds (acetals, orthoesters) *in the absence of acid catalyst* .

Most likely, the oxidative cleavage is initiated by *O*-atom insertion into C-H bonds of the 1,3-dioxolane moiety of ketals **2** and **3**. Similarly, initial *O*-insertions by the dioxirane into the methyne C-H of benzaldehyde dimethylacetal (**4**) and of triethylorthoformate (**5**) are also involved in the high yield transformation of these substrates into methylbenzoate and diethylcarbonate, respectively (entries 3 and 4, Table 1).

The products which arise from the cleavage of the simple, unbranched dialkyl ether such as **6** (Table 1) are also envisaged to derive from preliminary *O*-insertion *selectively* at methylene C-H α to the ether moiety (Scheme 1). In accordance with these results, exposure of t-butyl methyl ether (**7**) to the action of the more powerful dioxirane **1b** brings about cleavage into formic acid and tert-butanol (which is resistant to further oxidation[11]).

Interestingly, cleavage is not the main course of the dioxirane oxidation of medium-ring ethers **8**, **11**, and **14** (entries 7-9, Table 1). Rather, by using carefully dried dioxirane solutions (molecular sieves 5Å), an alternative route - i.e., oxidation to lactones (path *ii* , Scheme 1) - becomes the main process. In most of the cases, the lactones are accompanied by variable amounts of the corresponding acetals, the intermediate oxidation products (Table 1). Of interest is 3-methyltetrahydropyran (**14**) as substrate (entry 9, Table 1), for which insertion takes place exclusively at the two α-CH_2 positions to afford α-methyl δ-valerolactone (**15**)[16] and its γ-methyl regioisomer (**16**).[17]

The high selectivity for the observed α functionalization speaks for a non-radical C-H insertion, akin to that envisaged for the dioxirane oxyfunctionalization of alcohols.[11] In fact, also some β attack would be expected in a classical radical pathway involving RO• radicals; for instance, approximately 13% attack at β-CH_2 was found for the reaction of tetrahydrofuran (**8**) with HO•.[18] Concerning this, it should be noted that for 3-methyltetrahydropyran (**14**) insertion at the β position should be encouraged by the presence of a tertiary C-H; however, even in this case no product derived from β-oxidation was detected.

The results reported herein on the oxidations with dioxiranes provide a new entry into the cleavage of acetals to the corresponding carbonyl products under mild conditions, as well as the direct conversion of cyclic ethers into lactones. In view of the synthetic utility of these transformations, further studies concerning the elucidation of mechanistic details of these C-H insertions are warranted.

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16. (a) **3-Methyl-tetrahydropyran-(*2H*)-2-one (15)**: bp 71-75 °C (6 mmHg)[16b]; ft-ir: 1776 (C=O str.), 1141 (C-O str.) cm^{-1}, etc.; ^1H nmr ($CDCl_3$, 200 MHz) δ 1.22 (d, 3 H, CH_3, J = 6.9 Hz), 1.3 - 2.2 (complex m, 3 H), 2.55 (m, 2 H, CH_2), 4.25 (m, 2 H); ms (70 eV) *m/z* (r. i.) 114 (28, M^+), 99 (4), 70 (15, $^{\bullet}CH_2CH(CH_3)C{\equiv}O^+$), 55 (100, [*m/z* 70-CH_3]), 42 (98), etc.. (b) Kurata, K.; Tanaka, S.; Takahashi, K. *Chem. Pharm. Bull. (Tokio)* **1976**, *24*, 538.

17. (a) **5-Methyl-tetrahydropyran-(*2H*)-2-one (16)**: bp 86 °C (2 mmHg)[17b]; ft-ir: 1781 (C=O str.), 1144 (C-O str.) cm^{-1}, etc.; ^1H nmr ($CDCl_3$, 200 MHz) δ 0.98 (d, 3 H, CH_3, J = 6.6 Hz), 1.2 - 2.2 (m, 3 H), 2.40 (m, 2 H, CH_2), 3.90 (m ,2 H, CH_2); ms (70 eV) *m/z* (r. i.) 114 (14, M^+), 84 (16), 70 (17), 56 (81, $^{\bullet}CH_2CH_2C{=}O^+$), 55 (51), 42 (100), etc.. (b) Surzur, J.-M.; Teissier, P. *Bull. Soc. Chim. France* **1970**, 653.

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