Perfluoro-*cis*-2,3-Dialkyloxaziridines: Effective Reagents for the Selective Oxidation of Ethers to Carbonyl Compounds

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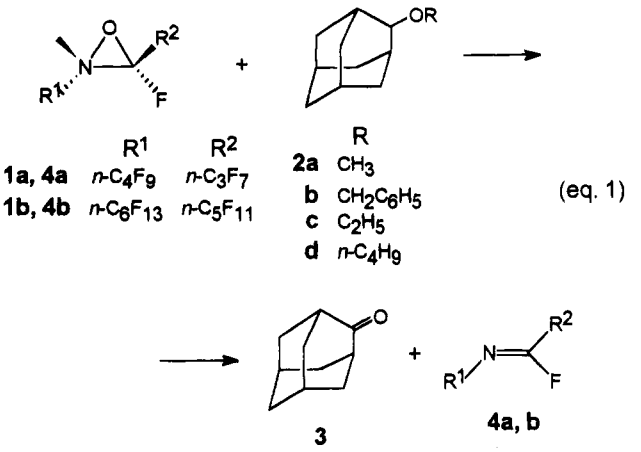
Ethers possessing at least one C–H bond in the position α to the oxygen are susceptible to oxidation. The reaction pattern is quite complex as primary oxidation products may lead to mixtures of cleavage compounds which can in their turn suffer further oxidation. As a result, a wide range of products can be formed in the oxidation of an ether depending on the nature of the substrate, the oxidant, and the adopted experimental conditions.[1] This may account for the fact that only the demethylation of hydroquinone dimethyl ethers[2] and the removal of benzyl ethers[3] belong to the arsenal of the reactions with a wide synthetic usefulness. Reagents which have assumed a synthetic importance are the oxides of the transition metals chromium[4] and ruthenium,[5] and they usually carry out the transformation of cyclic ethers into lactones.

Few oxidizing agents[6] have been reported to perform the one-step oxidation of dialkyl ethers of secondary alcohols to the corresponding carbonyl products, and only trityl tetrafluoroborate[7] and dimethyldioxirane[8] have been employed not exclusively on model compounds, but also on complex, naturally occurring substances.

Perfluoro-*cis*-2,3-dialkyloxaziridines **1a,b** are new and interesting oxidizing agents which can be used successfully for several transformations.[9] Moving from the observation that they perform the selective oxyfunctionalization of various sites,[10] we thought it could be interesting to prove their effectiveness for the one-step oxidation of *sec*-alkyl ethers to corresponding ketones.

When 2-methoxyadamantanol (**2a**) was reacted (room temperature, 2 h) with 2.0 equiv of perfluoro-*cis*-2-*n*-butyl-3-*n*-propyloxaziridine **1a** in a Freon-11 solution, 2-adamantanone (**3**) was isolated in 91% yield after crystallization (eq 1). The perfluoro-(*Z*)-4-aza-4-octene[11]



(eq. 1)

(**4a**) was the only "coproduct" formed in the reaction as shown by ^{19}F NMR of crude reaction mixtures.

Strictly similar results were obtained by using the 2-*n*-hexyl-3-*n*-pentyloxaziridine **1b**. 2-Adamantanone (**3**) was isolated in high yields also starting from the (benzyloxy)-, ethoxy-, and *n*-butoxyadamantanes (**2b–d**), but some differences were observed in comparison with methoxyadamantane (**2a**). Irrespective of the employed oxaziridine **1**, longer reaction times were needed mainly when the ethoxy and butoxy substrates were employed (up to 8 h for **2d**). More interestingly, 2-adamantanol was detected (GC analyses) only in trace amounts when the methoxy ether **2a** was used as starting material. On the other hand, 2-adamantanol became a non-negligible intermediate of the oxidation reaction starting from **2c,d**, and it was the main reaction product, at the beginning of the transformation, when the benzyl ether **2b** was used. Despite the fact that the overall transformation observed for **2a–d** is the same, i.e., oxidation of an ether to a ketone, different pathways seem to be operating. For the methoxyadamantane **2a** it seems to be a direct oxidation at the secondary residue of the ether moiety (C-2 of adamantane) to give the carbonyl group (one-step procedure), while for the other substrates it is, at least in part, the deprotection of the adamantyl ether to the corresponding alcohol and its further in situ oxidation to the keto product (two-step, one-pot procedure).[12]

The methyl ethers appeared to be the substrate of choice in order to perform the desired transformation, and they were employed in the other experiments realized for testing the generality of the process. Methoxycyclododecane (**6a**) and 4-methoxycylohexanecarboxylic acid (*cis/trans* mixture, **6b**) were reacted with **1a** under

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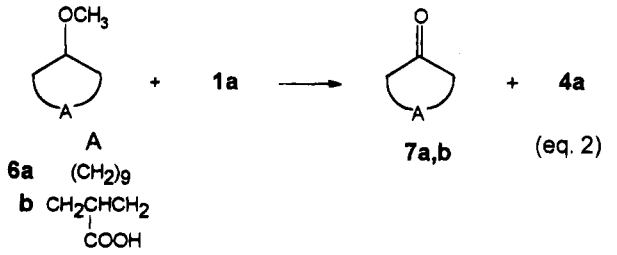
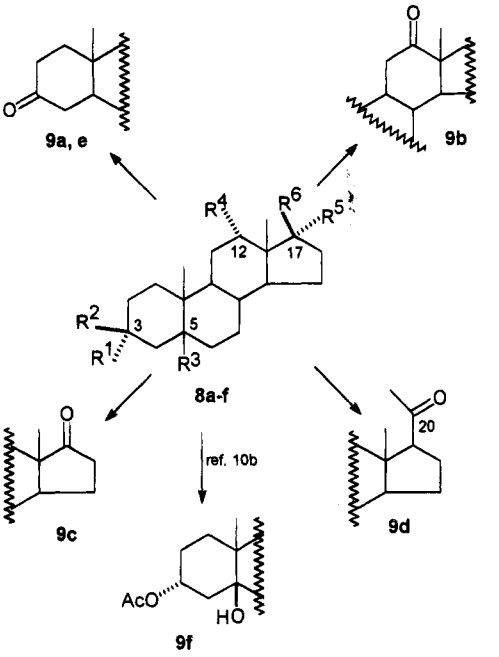
conditions similar to those described above, and corresponding ketones **7a,b** were isolated in 82 and 88% yield, respectively (eq 2).



The oxidation of several steroids was also studied (Scheme 1). For some substrates the reactions were quite fast (**8a,b,e**, 2 h, room temperature), for others longer reaction times (**8d**, 24 h, room temperature) or high temperatures (**8c,d**, 85 °C, 30 min) were needed. In all cases good yields were obtained, and the presence of a ketone (e.g., **8a,b**) or a carboxylic acid or ester (e.g., **6b**, **8c,d**) did not interfere with the oxidation.

The process was effective in the oxidation of a methoxy residue on C-3, C-12, C-17, and C-20 of different classes of steroids (androstanes, pregnanes, cholanic acids) belonging to either the 5α or the 5β series. The differences described above in the experimental conditions show how the oxidation is quite sensitive to steric hinderances. Some interesting selectivities were observed. While 5β-cholanic acid 3α-ol 3-acetate methyl ester (**8f**) is cleanly oxyfunctionalized to give corresponding 5β-hydroxy product,[10b] the oxidation of the 3α,12α-diol 3-acetate 12-*O*-methyl analogue **8c** occurs chemoselectively at C-12. No concomitant attack at C-5 is observed, and the 12-oxocholanic ester **9c** is isolated in high yield, thus proving that the methyl ether of a secondary alcohol undergoes preferential oxidation with respect to an unactivated tertiary hydrocarbon site.[14] Furthermore, 5α-pregnane-3β,20β-diol 3,20-di-*O*-methyl ether **8e** undergoes exclusive attack at C-3, while the 3-acetate 20-*O*-methyl ether **8d** is oxidized at C-20. The selective oxidation of a single methoxy residue in a dimethoxylated substrate can therefore be performed and the attack at the less favored site of a polyfunctional substrate can be realized by changing the ether functionality at the preferencial oxidation site into an ester one.

Scheme 1



	R^1	R^2	R^3	R^4	R^5	R^6	Isolated Yields (%)
8a	OCH_3	H	αH	H	O		84
8b	O		αH	H	H	OCH_3	91
8c	OAc	H	βH	OCH_3	H	$CH(CH_3)CH_2CH_2CO_2CH_3$	76
8d	H	OAc	αH	H	H	$CH(CH_3)\beta OCH_3$	79
8e	H	OCH_3	αH	H	H	$CH(CH_3)\beta OCH_3$	82
8f	OAc	H	βH	H	H	$CH(CH_3)CH_2CH_2CO_2CH_3$	70[10b]

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Supplementary Material Available: Experimental procedure for oxidation of **8c,e** and their spectroscopic characterization (^1H, ^{13}C NMR) (2 pages).

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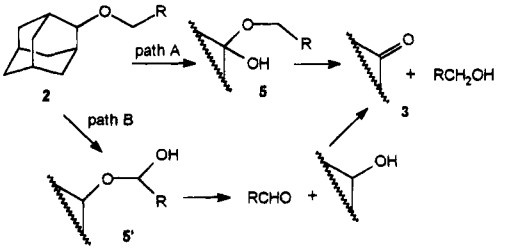
(12) In order to rationalize this difference, we may think that the transformation occurs in all cases through an oxidation reaction α to the ether oxygen to give an intermediate hemiketal which evolves spontaneously to the corresponding ketone and alcohol. In the oxyfunctionalization of unactivated hydrocarbons, oxaziridines **1** showed a remarkable tertiary to secondary selectivity and reaction at a methyl group was never observed (ref 10a,b). In the reaction of 2-methoxyadamantane (**2a**) the two competitive sites of oxidation are a methyl group and a methyne group (C-2 of adamantane). A nearly complete selectivity for the tertiary hydrogen can be expected (path A) to give the hemiketal **5** which decomposes to adamantanone (**3**). Starting from ethoxy- and butoxy-adamantanes **2c,d** the two potential sites of oxidation are a methylene and a methyne. A lower selectivity for the tertiary hydrogen can be envisaged, so that some attack of the methylene (path B, R = methyl, propyl) can occur to give the hemiketal **5'** which affords 2-adamantanol through hydrolysis. This latter product can be furtherly oxidized to 2-adamantanone **3** under adopted reaction conditions (for the oxidation of secondary alcohols to ketones see ref 9c). Similarly, it can be argued (ref 13) that the preferential site of oxidation of 2-(benzyloxy)adamantane (**2b**) is the benzyl position so that substantial amounts of 2-adamantanol are formed.



(13) In the oxidation of alkyl benzyl ethers, the preferencial attack at the benzylic position is a rule (ref 3).

(14) The same selectivity is revealed by the oxidation of 2-adamantyl ethers which undergo attack at C-2 to give adamantanone **3** while adamantane reacts at C-1 to give 1-hydroxyadamantane (ref 10a).