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Regioselective Oxyfunctionalization of Bridgehead Adamantane Derivatives

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Abstract: The reactions of bridgehead adamantane derivatives with perfluoro-*cis*-2-*n*-butyl-3-*n*-propyloxaziridine have been studied. The oxyfunctionalization process was found to proceed with excellent regioselectivity affording 3-substituted adamantan-1-ols in preparative chemical yields. The regioselectivity of the reaction was shown to tolerate various organic functional groups such as halogen, haloalkyl, hydroxyl, carboxyl and carboalkoxyl. Mild reaction conditions, simplicity of the experimental procedure, high selectivity and chemical yields render this process an immediately useful and generalized approach to synthetically challenging polyfunctional adamantane derivatives. © 1997 Elsevier Science Ltd.

Introduction

The study of new synthetic approaches to hydroxyadamantanes is of considerable interest and numerous preparative methods for their syntheses have been developed. From the synthetic point of view they are good precursors of biologically and industrially important adamantanes.[1] The ability to activate tertiary C-H bonds in adamantane either in radical or an ionic mode is common to most of the existing oxidizing agents. With all the methods developed so far, the major problem is not the low reactivity of the adamantane molecules themselves, but the difficulty to achieve a selective oxidation. As a result, wide range of products can be formed in the oxidation of adamantane and related compounds depending on the experimental conditions and the nature of substrates and oxidants. Along with older methods[1] some more recent oxidizing systems have been employed to insert an oxygen atom at bridgehead position of adamantane. For example, oxidation of adamantane by the Gif system yields adamantan-2-ol and adamantan-2-on, derived from further oxidation of the secondary alcohol, along with adamantan-1-ol.[2] On the other hand oxidation using ozone[3], peracids[4], molecular oxygen with catalyses of iron and ruthenium,[5] copper[6] or cobalt[7] salts, cytochrome P-450 models[8] yield, in most cases,

variable amounts of adamantan-1-ol accompanied by adamantan-2-ol, adamantan-2-on and adamantan-1,3-diol. Dry ozonation method[9] and $HF/CH_3CN/H_2O$ oxidizing system[10] are efficient for selective hydroxylation of adamantane, but these procedures require the reagent to be prepared before use. Methyl(trifluoromethyl)dioxirane appears promising for the polyhydroxylation of adamantane.[11]

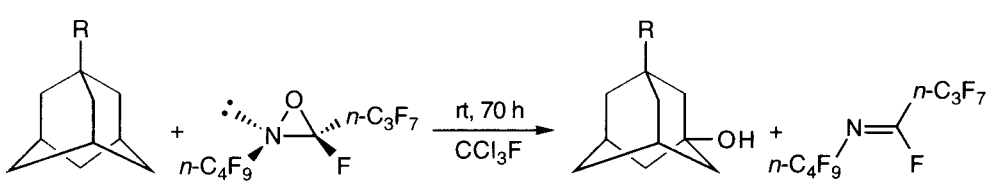
Recently perfluoro-*cis*-2,3-dialkyloxaziridines have been successfully employed for the hydroxylation of unsubstituted adamantane at bridgehead position exclusively.[12] Perfluoro-*cis*-2,3-dialkyloxaziridines are indefinitely stable at room temperature and work as selective oxidizing agents under neutral conditions and in aprotic or protic solvents.[13] They are readily accessible in large amounts from inexpensive commercially available perfluoroalkylamines.[14] The purpose of this study was to explore the hydroxylation of bridgehead adamantane derivatives with perfluoro-*cis*-2,3-dialkyloxaziridines as a new and effective approach to polyfunctional adamantanes.

Results and Discussion

We have found that for the oxyfunctionalization of 1-substituted adamantanes, the starting substrate **1a-h** to perfluoro-*cis*-2-*n*-butyl-3-*n*-propyloxaziridine (**2**) ratio 1:1.2 and a prolonged reaction time (70 h), instead of few minutes as in the case of more reactive adamantane,[12] are crucial to obtain high conversion of the starting compounds. 1-Bromomethyladamantane (**1a**) reacted smoothly with 1.2 equiv. of oxaziridine **2** at room temperature for 70 h to give 3-bromomethyladamantan-1-ol (**3a**) in 94% yield after purification by chromatography (Scheme 1) (Table 1, entry 1). The high regioselectivity of the oxygen atom insertion at the tertiary over the secondary C-H bonds was observed and adamantanol **3a** was the only reaction product as shown by GC analysis of crude reaction mixture. Ring expansion, to give homoadamantane derivatives, as well as the other side reactions which usually plague regioselective oxyfunctionalization of adamantane derivatives were not detected.

The hydroxylation reaction has been successfully extended to 1-haloadamantanes **1b-d**. Using these conditions we have achieved almost quantitative conversion of substrates **1b-d** to afford resulting tertiary alcohols **3b-d** (Table 1, entries 2-4) in high isolated yields. In the oxyfunctionalization of 1-haloadamantanes **1b-d** the two competitive sites for attack of oxaziridine **2** are tertiary C-H bonds and C-halogen bond. As it follows from the experimental results, oxaziridine **2** shows remarkable regioselectivity and the reaction at the C-halogen bond was never observed. The mechanistic rationale for the oxygen atom insertion into C-H bond was proposed for hydrocarbons oxidation with perfluorooxaziridine **2**.[12] It seems reasonable to explain the observed selectivity through higher electron donor nature of the C-H bond over the carbon-halogen bond. The classical approach to 3-haloadamantan-1-ols is a multistep sequence based on the cyclization of 7-

Scheme 1



1a-h **2** **3a-h** **4**

R = CH_2Br (**a**); F (**b**); Cl (**c**); Br (**d**); OH (**e**); CH_2CO_2H (**f**); CO_2H (**g**); CO_2CH_3 (**h**)

methylidenbicyclo[3.3.1]nonan-3-one with hydrochloric or hydrobromic acids.[1] More recently, fluorinations of adamantan-1-ol with CF_3OF[15] or F_2O[16] have been used to synthesize 3-fluoroadamantan-1-ol (**3b**). However, the fluorination reactions have poor selectivity; 3,5-difluoroadamantan-1-ol and adamantan-1,3-diol were also formed in these reactions that necessitated careful chromatographic separations to isolate the desired product. The methodology here described makes it possible to obtain 3-haloadamantan-1-ols **3b-d** in preparatively valuable yields by a single procedure step from readily available 1-haloadamantanes **1b-d**.

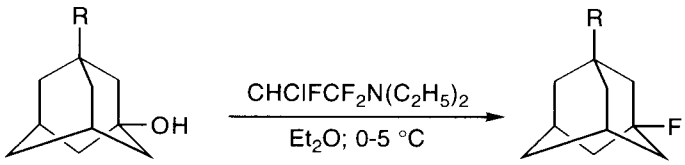
Table 1. Oxyfunctionalization of 1-Substituted Adamantanes **1a-h** with Perfluorooxaziridine **2**[a]

entry	Starting compound	R	Product[b]	Yield, %[c]
1	**1a**	CH_2Br	**3a**	94
2	**1b**	F	**3b**	82
3	**1c**	Cl	**3c**	85
4	**1d**	Br	**3d**	89
5	**1e**	OH	**3e**	85
6	**1f**	CH_2COOH	**3f**	90
7	**1g**	COOH	**3g**	82
8	**1h**	$COOCH_3$	**3h**	85

[a] All reactions were run in CCl_3F at the room temperatures (18-22 °C); adamantane **1a-h**/perfluorooxaziridine **2** ratio 1:1.2. [b] All resultant compounds **3a-h** were identified by comparison of their physical properties and NMR spectra with those reported in the literature. [c] Yields refer to isolated yields of products of greater than 95% purity.

To further demonstrate the synthetic usefulness of this method, the reactions of oxaziridine **2** with bridgehead adamantane derivatives **1e-h**, containing various oxygenated functional groups were examined. When adamantan-1-ol (**1e**) was treated with 1.2 equiv. of oxaziridine **2** in trichlorofluoromethane at room temperature, adamantan-1,3-diol (**3e**) was obtained in 85% yield (Table 1, entry 5). The carboxylic acids **1f,g** and ester **1h** also reacted with oxaziridine **2** to give tertiary hydroxy compounds **3f-h** in high yields (Table 1, entries 6-8). The oxidation procedure involves addition of excess oxaziridine **2** to the trichlorofluoromethane solution of the substrate and stirring the resulting mixture at room temperature. Carboxylic acids **1f,g** have low solubility in trichlorofluoromethane, but the hydroxylation process occurs nicely despite the fact that a two-phase system is used. It should be emphasized that product isolation is attractively simple since both starting oxaziridine **2** and azaalkene **4**, a co-product of the oxidation process, are easily removable volatile compounds. Similarly to the oxyfunctionalization of 1-bromomethyladamantane (**1a**) and 1-haloadamantanes **1b-d** with perfluorooxaziridine **2**, the reactions of adamantane derivatives **1e-h** occurred in a highly regioselective manner without involvement of the secondary C-H bonds of the adamantane cage or the side chains of **1e-h**.

Scheme 2



3c,d

5 (R = Br)
6 (R = Cl)

It is worth noting that the electron-withdrawing nature of the oxygenated functional groups in substrates **1e-h** is expected to decrease oxyfunctionalization reaction rates,[12] but the efficient transformation under the standard reaction conditions was nevertheless possible also for the carboxyl and carbomethoxyl substituted compounds **1g,h** to give the corresponding hydroxy derivatives in a highly regioselective manner and good chemical yields (Table 1). The presence of electron-withdrawing substituents on the adamantane cage might decrease the reactivity of such derivatives toward electrophilic species. In contrast, the experimental data presented here demonstrate that high conversions and regioselectivity were obtained for the oxyfunctionalization of all substrates **1a-h** with oxaziridine **2** regardless of the nature of the substituent on the adamantane moiety. Accordingly, these data would support a radical or ion-radical mechanism of this oxyfunctionalization process.[13a]

The synthetic usefulness of readily available by this method 3-haloadamantan-1-ols **3b-d** has been demonstrated with an efficient preparation of synthetically challenging 1-bromo- and 1-chloro-3-fluoroadamantanes **5** and **6**.[17] The hydroxy group of compounds **3c,d** was replaced with fluorine by using commercially available *N,N*-diethyl-(2-chloro-1,1,2-trifluoroethyl)amine (*Yarovenko* reagent) in anhydrous ether at 5 °C to afford corresponding fluoroadamantanes **5** and **6** in good isolated yields (Scheme 2).

Conclusions

Perfluoro-*cis*-2-*n*-butyl-3-*n*-propyloxaziridine (**2**) has been shown to be a powerful oxidizing agent for the efficient oxyfunctionalization of bridgehead adamantane derivatives. The advantages of the oxidation with perfluorooxaziridine **2** are high regioselectivities, practically quantitative conversion of substrates, simplicity of the experimental procedure, and exclusive formation of monooxygenated products. The achieved reaction features are quite rare for the transformations of heteroatom-containing adamantane derivatives since the heteroatom lowers the electron density of the tertiary C-H bonds to such extent that they become practically immune to attack by known oxidizing reagents. Mild reaction conditions, high regioselectivity and chemical yields render the process presented here an immediately useful and generalized approach to synthetically challenging polyfunctional adamantane derivatives.

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Experimental Section

^1H, and ^{19}F NMR spectra were recorded on Varian VXR-300 (300 MHz ^1H, 282 MHz ^{19}F MMR) spectrometer using tetramethylsilane and $CFCl_3$ as internal standards. Chemical shifts are reported in ppm. IR

spectra were recorded on Specord M-80 spectrophotometer, and are reported in cm^{-1}. Column chromatography was performed using silica gel 60 (Fluka). Melting points are uncorrected and were determined in sealed capillaries.

General Procedure for the Synthesis of Hydroxy Adamantane Derivatives 3a-h with Oxaziridine 2. To a mixture of adamantane derivative **3a-h** (0.25 mmol) and $CFCl_3$ (0.4 mL) oxaziridine **2** (0.135 g, 0.30 mmol) was added. The reaction mixture was stirred at room temperature for 70 h and then evaporated under the reduced pressure (0.1 mm Hg). The residue was purified by column chromatography on silica gel to give hydroxy derivatives **3a-h**. The yields of **3a-h** are given in Table 1.

3-Bromomethyladamantan-1-ol (3a). Chromatography: hexane/ethyl acetate 2.5:1; mp 88 °C (lit.[18] 88 °C); IR (KBr): 3336 (OH); ^1H NMR (DMSO-D_6): 1.39-1.50 (m, 12H), 2.11 (s, 2H), 3.33 (s, 2H), 4.51 (s, 1H, OH).

3-Fluoroadamantan-1-ol (3b). Chromatography: hexane/ethyl acetate 5:1; mp 188-189 °C (lit.[15] 182-185 °C); IR (CH_2Cl_2): 3591 (OH); ^1H NMR (CCl_4/C_6D_6 6:1): 1.36-1.44 (m, 3H), 1.52 (s, 4H), 1.66-1.76 (m, 6H), 2.25 (s, 2H); ^{19}F NMR ($CDCl_3$): 133.70 (s).

3-Chloroadamantan-1-ol (3c). Chromatography: hexane/ethyl acetate 5:1; mp 210-211 °C (lit.[19] 205.5 °C); IR (CH_2Cl_2): 3590 (OH); ^1H NMR (CCl_4/C_6D_6 6:1): 1.17 (s, 1H, OH), 1.46-1.48 (m, 2H), 1.56 (s, 4H), 1.94-1.97 (m, 6H), 2.21-2.22 (m, 2H).

3-Bromoadamantan-1-ol (3d). Chromatography: hexane/ethyl acetate 5:1; mp 162-163 °C (lit.[20] 159-160 °C); IR (CH_2Cl_2): 3590 (OH); ^1H NMR (CCl_4/C_6D_6 6:1): 1.50 (s, 2H), 1.59 (s, 4H), 1.65 (s, 1H, OH), 2.14-2.18 (m, 8H).

Adamantan-1,3-ol (3e). Chromatography: ethyl acetate; mp 313-314 °C (lit.[19] 315 °C); IR (KBr): 3216 (OH); ^1H NMR (DMSO-D_6): 1.37 (s, 2H), 1.46-1.50 (m, 10H), 2.11 (s, 2H), 4.43 [s, 2H, $(OH)_2$].

3-Hydroxy-1-adamantyl acetic acid (3f). Chromatography: ethyl acetate; mp 127-128 °C (lit.[21] 127-128 °C); ^1H NMR (DMSO-D_6): 1.46-1.52 (m, 12H), 2.02 (s, 2H), 2.09 (s, 2H), 4.41 (s, 1H, OH), 11.95 (br.s, 1H, COOH).

3-Hydroxyadamantan-1-carboxylic acid (3g). Chromatography: ethyl acetate; mp 203-204 °C (lit.[22] 202-203 °C); ^1H NMR (DMSO-D_6): 1.50 (s, 2H), 1.55 (s, 4H), 1.64 (s, 6H), 2.12 (s, 2H), 4.46 (s, 1H, OH), 11.98 (s, 1H, COOH).

3-Hydroxyadamantan-1-carboxylic acid methyl ester (3h). Chromatography: hexane/ethyl acetate 1:1; oil; IR (CH_2Cl_2): 3691 (OH); ^1H NMR (DMSO-D_6): 1.51(s, 2H) 1.56 (s, 4H), 1.67 (s, 6H), 2.14 (s, 2H), 3.59 (s, 3H), 4.56 (s, 1H, OH). Compound **3h** was identified by comparison of its ^1H NMR spectrum with that of the sample 3-hydroxyadamantan-1-carboxylic acid methyl ester prepared according to the literature procedure.[23]

1-Bromo-3-fluoroadamantane (5). To a stirred solution of 3-bromoadamantan-1-ol (**3d**) (0.2 g, 0.87 mmol) in anhydrous ether (5 mL) *N,N*-diethyl-(2-chloro-1,1,2-trifluoroethyl)amine (0.33 g, 1.7 mmol) was added at 0 °C. The resultant solution was stirred at 5 °C for 10 h. The reaction mixture was washed with aqueous saturated $NaHCO_3$ and then by water. The organic layer was separated, dried (Na_2SO_4) and the solvent was evaporated *in vacuo*. The residue was purified by column chromatography on silica gel, eluent hexane, and then purified by sublimation in vacuum of water pump to give compound **5** (0.187 g, 93%), mp

135-136 °C (lit.[17] 136-137 °C); ^{1}H NMR ($CDCl_3$): 1.60 (s, 2H), 1.89 (s, 4H), 2.23 (s, 4H), 2.38 (s, 2H), 2.46 (m, 2H); ^{19}F NMR ($CDCl_3$): 130.99 (s).

1-Chloro-3-fluoroadamantane (6). The procedure similar to the described for preparation of compound **5** was followed. Starting with chloro-derivative **3c** (0.1 g, 0.54 mmol) compound **6** was obtained in 92% yield (0.092 g); mp 177-178 °C (lit.[17] 177-178 °C); ^{1}H NMR ($CDCl_3$): 1.56 (s, 2H), 1.86 (s, 4H), 2.04 (s, 4H), 2.27-2.28 (m, 2H), 2.39 (s, 2H); ^{19}F NMR ($CDCl_3$): 132.63 (s).

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