Tetrahedron Letters, Vol.31, No.21, pp 3067-3070, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

OXIDATIONS BY METHYL(TRIFLUOROMETHYL)DIOXIRANE. 3.[1] SELECTIVE POLYOXYFUNCTIONALIZATION OF ADAMANTANE

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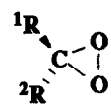
Abstract: Adamantane (**1**) can be converted directly into adamantan-1,3,5-triol (**5**) and into adamantan-1,3,5,7-tetraol (**6**) under remarkably mild conditions by employing an excess of isolated methyl(trifluoromethyl)dioxirane (**3a**) in solution. This new dioxirane species was found to be over 7,000-fold more reactive than dimethyldioxirane (**3b**) in performing adamantane hydroxylations.

THE selective oxyfunctionalization of "unactivated" C-H bonds of saturated hydrocarbons continues to be a subject of great topical concern.[2] In particular, methods making it possible to achieve the functionalization of adamantane (**1**) are relevant, since its derivatives are of interest as energetic materials and pharmaceuticals.[3] However, reagents that allow the direct, selective oxyfunctionalization of this target molecule are scarce. For example, oxygenation by the Gif[4] systems yields adamantan-2-ol and adamantanone (derived from further oxidation of the secondary alcohol), along with adamantan-1-ol. On the other hand, hydroxylations using ozone,[5] peroxy acids,[6] or Cytochrome P-450 models[1,7,8] yield adamantan-1-ol (**2**), in most cases accompained by adamantan-2-ol (and/or adamantanone) in variable amounts. Just "dry" ozonization methods[9] and the new HOF/MeC≡N oxidizing system[10,11] appear promising as for the polyhydroxylation of **1** at the bridgehead positions exclusively.

Recently, we have reported on yet another fruitful approach to hydrocarbon oxyfunctionalization;[1] this came from the remarkable progress recorded by the chemistry of dioxiranes.[3,12] Indeed, once it became estabilished that the reaction of caroate (HSO_5^-, peroxomonosulfate) with ketones generates dioxiranes,[13] the feat[4] of isolation of a few volatile



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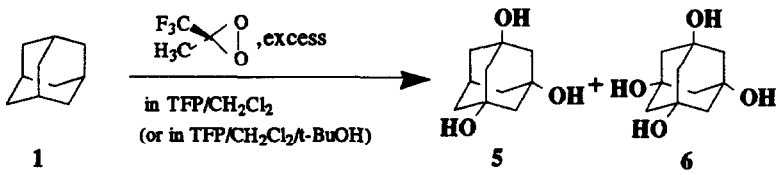
(**3a** : $^1R = CF_3$, $^2R = CH_3$; **3b**: $^1R = {}^2R = CH_3$)

species, such as methyl(trifluoromethyl)dioxirane (**3a**)[15] and dimethyldioxirane (**3b**),[14,16,17] precipitated an intensive utilization of these unique oxidants in synthetic applications.[12] Among these, the most remarkable to-date appears to be the O-atom insertion into unactivated C-H bonds of alkanes.[1,12,18] Indeed, we have employed **3a** (Mello dioxirane)[15] to achieve efficiently the low-temperature oxyfunctionalization of a variety of saturated hydrocarbons.[1] With adamantane (**1**), the highest regioselectivity for tertiary over secondary C-H oxyfunctionalization was recorded ($R_s^t > 250$), so that - with **1** and **3a** in equimolar amounts - adamantan-1-ol (**2**) was the only reaction product.[1]

We now report that the extraordinary reactivity of Mello dioxirane **3a** , coupled to its remarkable capability to discriminate adamantane bridgehead C-H bonds,[1] opens the road to the selective polyoxyfunctionalization of this highly symmetrical tricyclic hydrocarbon. Indeed, the reaction of **1** with dioxirane **3a** in 1,1,1,-trifluoropropanone (TFP, its parent ketone)[15] in a 1:2 molar ratio gave adamantan-1,3-diol (**4**) in good yield.[1]

Then, upon reaction of **1** with larger *excesses* of **3a**, we were able to obtain adamantan-1,3,5-triol (**5**), as well as adamantan-1,3,5,7-tetraol (**6**) (eq 1).



1 **5** **6** (1)

As illustrated by the examples collected in Table 1, the appropriate choice of dioxirane to substrate ratio, mixed solvent and reaction times allows one to obtain either **4**, **5**, or **6** as the main product.

Table 1. Hydroxylation of Adamantane by Methyl(trifluoromethyl)dioxirane (**3a**) at -20 °C.

R.[a] (3a/1)	Mixed solvent (composition)	Reactn time	% Con-version[b]	% Yield of Products[c]			
				Ad(OH) (2)	$Ad(OH)_2$ (4)	$Ad(OH)_3$ (5)	$Ad(OH)_4$ (6)
2.0	CH_2Cl_2/TFP (2:1)	2 min	96	38	60		
2.3	"	40 min	>97	4	93[d]		
3.2	"	7 h	96	-	43	55	
4.1	"	2 h	98	-	18	80	-
6.0	"	2 h	98		8	90[e]	-
12.2	CH_2Cl_2/t-BuOH/TFP (2:2:1)	6 h	96		-	58	40
20.	"	3 h	98		-	24	73[f]

[a] Initial molar ratio of dioxirane to substrate. [b] As determined by glc using a SE 30 (or OV 101), 30 m × 0.25 μm i.d. capillary column. [c] Product distributions and yields were determined by glc and/or gc/ms (Hewlett-Packard GC 5890A/MSD 5970B instrument) after treatement of the reaction products with Ac_2O/Py, converting each of the polyols into the corresponding acetates (see text). [d] 91% isolated yield of $Ad(OAc)_2$ (**4'**) by column (silicagel) chromatography; 86% isolated yield of $Ad(OH)_2$ (**4**) upon recrystallization (MeOH/n-hexane) from the reaction mixture. [e] 90% isolated yield of $Ad(OAc)_3$ (**5'**) after column (silicagel) chromatography; 88% isolated yield of $Ad(OH)_3$ (**5**) upon transesterification of **5'** using MeOH/BF_3 (see text). [f] 72% isolated yield of $Ad(OAc)_4$ (**6'**), and 70% isolated yield of $Ad(OH)_4$ (**6**), by the same procedures outlined in note (*e*).

Solutions of 0.5-0.8 M dioxirane **3a** in TFP or 0.03-0.07 M dioxirane **3b** in acetone could be obtained according to a protocol that has been described in detail.[1,14,17,19] Then, performing adamantane hydroxylations simply involved addition of a cold aliquot of standardized[1,17] dioxirane **3a** solution in TFP (or TFP/CH_2Cl_2) to the hydrocarbon **1** in dry CH_2Cl_2 (or CH_2Cl_2 / t-BuOH) at -20 °C, so that to have the appropriate dioxirane excess and solvent composition (Table 1). After ≥ 96% substrate conversion, removal of the volatile solvents in vacuo and treatment of the residue with excess Ac_2O/Py converted the polyols into the corresponding acetates, allowing gc (or gc/ms) product analyses. Then, column chromatography (silicagel, petroleum ether/Et_2O) easily afforded the individual acetates, i.e. $Ad(OAc)_2$ (**4'**),[20] $Ad(OAc)_3$ (**5'**),[21] and

$Ad(OAc)_4$ (**6'**),[22,23] separated from t-BuOAc derived from residual t-BuOH cosolvent, if any (Table 1). Transesterification (dry MeOH/BF_3)[24] of each of the pure polyacetates, removal in vacuo of AcOMe, and washing of the residue with cold Et_2O containing Me_2S (in order to sequester any residual BF_3), yielded pure samples of **4**,[1] **5**,[25] and **6** [23,26] (Table 1).

That the efficiency displayed by Mello dioxirane **3a** in adamantane oxyfunctionalizations is unmatched by dimethyldioxirane (**3b**) could be verified by kinetic experiments. These were performed by monitoring (glc) the disappearance of the hydrocarbon substrate, according to a technique already described.[1] With initial concentrations of adamantane (**1**) and of dioxirane **3a** both in the range 0.02 - 0.04 M in TFP/CH_2Cl_2 (95:5) at -12.4 °C, a clean second-order rate-law was obeyed to over 75% reaction, yielding $k_2 = 0.78 \pm 0.02$ $M^{-1}s^{-1}$. The oxidation of **1** by dimethyldioxirane **3b** was run in acetone/CH_2Cl_2 (95:5) at the same temperature (-12.4 °C) under pseudo-first order conditions, with $[\mathbf{1}]_o = (2.0 - 2.3) \times 10^{-3}$ M and $[\mathbf{3b}]_o = (4.6 - 4.2) \times 10^{-2}$ M. The $\ln(c_o/c)$ vs. time plots were linear to over 80% substrate conversion, yielding $k_1 = (0.49 \pm 0.02) \times 10^{-5}$ s^{-1}; from this a k_2 value of 0.106×10^{-3} $M^{-1}s^{-1}$ could be estimated as $(k_1/[\mathbf{3b}]_o)$. Thus, Mello dioxirane (**3a**) is over 7,000-fold more reactive than dimethyldioxirane (**3b**) in attacking adamantane.

The ability to insert an O-atom into "unactivated" C-H bonds of saturated hydrocarbons, either in an ionic or radical mode, is a feature displayed by a number of recent hydroxylation systems.[2-10] However, the achievement of selective polyhydroxylation is rare, since the OH functionality first introduced would lower the electon-density of C-H bonds or repress radical or radical-chain processes.[2,27] Clearly, for such difficult cases Mello dioxirane (**3a**) should be the reagent of choice. Indeed, although the data in Table 1 hint at a diminished efficacy of **3a** toward the substrate as OH functionalities are sequentially introduced, this reagent still makes it possible the exhaustive, one-pot oxyfunctionalization of all four bridgehead C-H bonds in adamantane. This feat seems to be unmatched by other reagents.[2-12,18]

Acknowledgement. This work was supported by the Italian National Research Council (C.N.R.) and by the "Progetto Finalizzato - C.F.S. II" (C.N.R.). One of us (R.M.) is grateful to the Alexander von Humboldt - Stiftung for a fellowship spent (June 1989-June 1990) at University of Würzburg (F.R.G.).

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(20) **1,3-Diacetoxyadamantane (4')**: white solid (deliquescent), mp 36-38 °C (not corrected); ^{1}H nmr ($CDCl_3$, 200 MHz) δ 1.49 (br t, 2H, $^6CH_2$, J = 2.7 Hz), 1.90 (s, 6H, CO-CH_3), 2.01 (br, 8H, CH_2), 2.25 (br m, 2H, CH), 2.38 (s, 2H, $^2CH_2$); cf. ref. 23b.

(21) **1,3,5-Triacetoxyadamantane (5')**: pale yellow crystals (deliquescent), mp 59-61 °C (not corrected) [lit[23b]: mp 45-46 °C]; ir (KBr) 2987, 2968, 2925, 2876 (C-H str.), 1735 (C=O str.), 1455, 1376, 1253, 1223, 1035, 1023 (C-O str.) cm^{-1},etc.; ^{1}H nmr ($CDCl_3$, 200 MHz) δ 1.963 (s, 9 H, CO-CH_3), 2.02 (d, 6H, CH_2, J = 3.2 Hz), 2.40 (septet, 1H, ^{7}C-H, J = 3.3 Hz). 2.47 (s, 6H, CH_2); ^{13}C nmr ($CDCl_3$, 50 MHz) δ 20.67 (q, CO-CH_3, J = 125 Hz), 29.12 (d, ^7CH, J = 137 Hz), 38.74 (t, $^6CH_2$,$^8CH_2$, and $^9CH_2$, J = 130 Hz), 43.93 (t, $^2CH_2$, $^4CH_2$, and $^{10}CH_2$, J = 130 Hz), 79.92 (s, ^1C,^3C, and ^5C), 175.62 (s, CH_3-C=O); ms (70 eV) *m/z* (r.i.) 251 (4, M$^+$- OAc), 250 (22), 190 (28), 149 (25), 148 (93), 133 (9), 120 (12), 108 (13), 107 (13), 106 (13), 105 (13), 91 (12), 79 (11), 55 (5), 43 (100), etc.; anal. Calcd for $C_{16}H_{22}O_6$: C, 61.9; H, 7.1 %. Found: C, 62.6; H, 7.9 %.

(22) **1,3,5,7-Tetraacetoxyadamantane (6')**: white solid, mp 161-163 °C (not corrected) [lit.[23a] mp 160.5-162 °C]; ir (KBr) 2850, 2990 (C-H str.), 1743 (C=O str.), 1442, 1380, 1222, 1027 (C-O str.) cm^{-1}, etc.; ^{1}H nmr ($CDCl_3$, 200 MHz) δ 1.96 (s, 12H, CH_3), 2.48 (s, 12H, CH_2); ^{13}C nmr ($CDCl_3$, 50 MHz) δ 22.15 (q, CH_3, J = 125 Hz), 43.20 (t, CH_2, J = 130 Hz), 169.87 (s, C=O); ms (70 eV) *m/z* (r. i.) 309 (3, M$^+$-OAc), 308 (15), 249 (9), 206 (26), 164 (15), 160 (31), 147 (12), 146 (38), 122 (9), 118 (14), 91 (7), 43 (100), etc..

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(25) **1,3,5-Trihydroxyadamantane (5)**: white solid, mp 203-207 °C (not corrected); ir (KBr) 3325 (O-H str.), 2950, 2939, 2912 (C-H str.), 1451, 1352, 1332, 1047 (C-O str.) cm^{-1}, etc.; ^{1}H nmr (CDCl3, 200 MHz) δ 1.35 (d, 6H, CH_2, J = 3.0 Hz), 1.43 (s, 6H, CH_2), 2.11 (septet, 1H, ^7CH, J = 3.2 Hz), 4.46 (br s, 3H, OH); ^{13}C nmr (DMSO-d_6, 50 MHz) δ 29.38 (d, ^7CH, J = 128 Hz), 42.95 (t, $^6CH_2$, $^8CH_2$,and $^9CH_2$, J = 125 Hz), 52.25 (t, $^2CH2$, $^4CH_2$,and $^{10}CH_2$, J = 125 Hz), 69.36 (s, ^1C,^3C, and ^5C); ms ((70 eV) *m/z* (r. i.) 184 (5, M$^+$), 128 (8), 127 (100, M$^+$- $CH_2C(OH)CH_2$), 111 (31), 110 (10), 109(10), 85 (7), 69 (8), 55 (7), 43 (36), 41 (12), 39 (9). To our knowledge this triol had not been described previously.

(26) **1,3,5,7-Tetrahydroxyadamantane (6)**: white solid, mp 313-316 °C (not corrected) [lit.[23a] mp 317-320 °C]; ir (KBr) 3341 (O-H str.), 2956, 2944,2924 (C-H str.), 1459, 1054 (C-O str.) cm^{-1}, etc.; ^{1}H nmr ($CDCl_3$, 200 MHz) δ 1.425 (s, 12H, CH_2), 4.44 (s, 4H, OH, disappears upon exchange with D_2O).

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(Received in UK 29 March 1990)