Pergamon

Tetrahedron Letters 43 (2002) 4649–4652

TETRAHEDRON LETTERS

Chemo- and regioselective oxidation of adamantyl derivatives by dioxiranes

Lucia D'Accolti,[a,b] Ping Kang,[a] Saeed Khan,[a] Ruggero Curci[b] and Christopher S. Foote[a,*]

[a]*Department of Chemistry and Biochemistry, University of California, Los Angeles, CA 90095, USA*
[b]*Dipartimento di Chimica, Università di Bari, via Amendola 173, I-70126 Bari, Italy*

Received 17 April 2002; revised 29 April 2002; accepted 3 May 2002

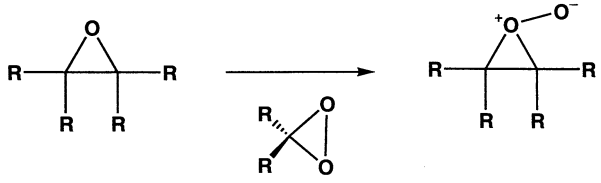
Abstract—Methyl(trifluoromethyl) dioxirane (**1**) gives direct chemo- and regioselective oxidation of methyleneadamantane oxide (**2**) and isopropylideneadamantane oxide (**3**) in high yield under mild conditions. Secondary C–H are not appreciably oxidized and high regioselectivities were observed for attack at tertiary C–H.

Perepoxides have been suggested to be intermediates in the singlet oxygen reaction with certain alkenes. To test the existence of the perepoxide, several groups employed the oxidation of epoxides with oxygen-transfer reagents such as ozone, ozone or pyridine *N*-oxide with irradiation, *m*-chloroperbenzoic acid (MCPBA),[1] and atomic oxygen.[2] The availability of dioxiranes **1** has driven the use of these powerful and selective[3] oxidants to carry out a variety of synthetically useful transformations.[3,4] We wanted to explore the possibility that the dioxiranes might oxidize epoxides to form perepoxides (Scheme 1).

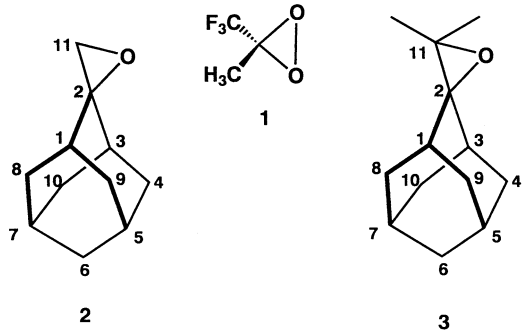
Dioxiranes (**1**) have also been shown to be useful reagents for the selective oxidation of unactivated C–H bonds under mild conditions.[5–8] Regioselective bridgehead functionalization of polycyclic compounds is an important goal in synthesis of non-natural targets. Such systems can further provide access to derivatives bearing quaternary carbon centers, which are difficult to synthesize by other methods.[9,10]

Several groups[3–8,11,12] report that dioxiranes are efficient reagents for electrophilic oxidation. Ab initio calculations have provided an explanation for O-atom insertion into hydrocarbon C–H bonds by electrophiles and peroxides. These studies indicate a non-radical, 'oxenoid' mechanism for the O-atom insertion by the dioxiranes into the unactivated C–H bonds of hydrocarbons.[11,12] Dioxiranes are sensitive to steric and stereoelectronic demands during oxidation.[11]

In this context, it appeared interesting to investigate the reactions of dioxiranes with adamantylidene epoxides. Formation of perepoxides should lead to relatively stable dioxetanes,[13] but if this reaction should fail, oxyfunctionalization would be expected. These target molecules are of interest for mechanistic evaluation[14,15] and the synthesis of novel pharmaceuticals.[16] We report that dioxirane **1** (Scheme 2) does not give dioxetanes with two adamantylidene epoxides but instead gives



Scheme 1.



Scheme 2.

Keywords: dioxiranes; epoxides; oxidation; insertion; chemoselectivity; regioselectivity.

* Corresponding author.

0040-4039/02/$ - see front matter
PII: S0040-4039(02)00876-6

regioselective monooxyfunctionalization of methyleneadamantane oxide (**2**)[17] and isopropylideneadamantane oxide (**3**).[18]

Treatment of **2** with a 0.69 M solution of **1** (1.4 equiv.) under the conditions given below[19] resulted in ca. 95% substrate conversion within 2 h (Scheme 3), yielding the monoalcohol *Z*-5-hydroxymethyleneadamantane oxide (**4a**)[20] (90%) and the other stereoisomer, *E*-7-hydroxymethyleneadamantane oxide (**4b**)[21] (10%) (GC analysis). Column chromatography of this mixture on silica gel gives 401 mg of **4a** (78% isolated yield) and 100 mg of a mixture of **4a** and **4b**.

For **4a**, only the tertiary C–H was oxidized to an OH. In fact, the ^{13}C NMR spectrum showed two C–H signals (δ 37.98, 29.37) and three C–O signals (δ 67.30, 62.95, 54.29). However we could not differentiate which tertiary hydrogen (C_5-H or C_7-H) was oxidized by NMR analysis. The structure of **4a** was therefore established unambiguously by X-ray crystallography (Fig. 1).[22]

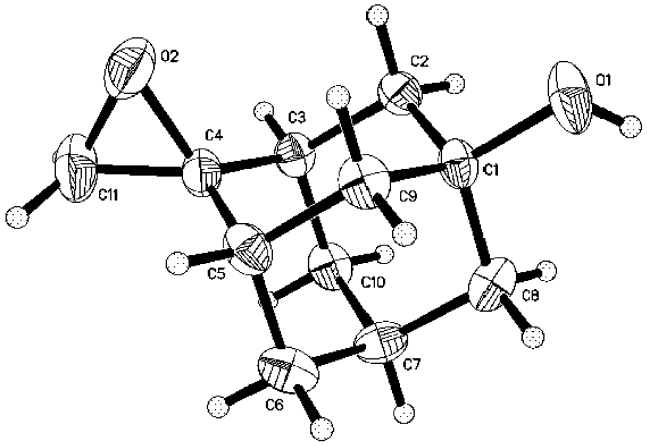


Figure 1. Structure of compound **4a**.

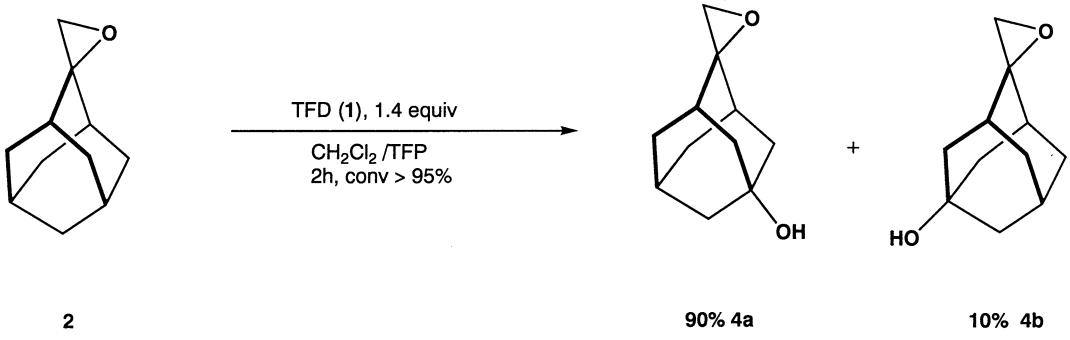
Unfortunately, chromatographic purification of the minor isomer **4b** was unsuccessful. The ^{13}C NMR spectrum of the mixture of **4a** and **4b** shows eight ^{13}C NMR signals different from **4a**: two C–H signals (δ 37.19, 29.19,) and three C–O signals (δ 67.56, 63.54, 54.88).

Epoxide **3** was reacted with a 0.22 M solution of **1** under the same conditions as **2** (Scheme 4). The GC/MS analysis revealed that after 1 h the conversion was 70%.[19] Column chromatography of this mixture on silica gel gives 150 mg of **3** followed by 245 mg (60% isolated yield) of *Z*-5-hydroxyisopropylideneadamantane oxide (**5a**)[23] and 135 mg (40% isolated yield) of *E*-7-hydroxyisopropylideneadamantane oxide (**5b**)[24] (*Z*/*E* assignments were made by analogy with **4**).

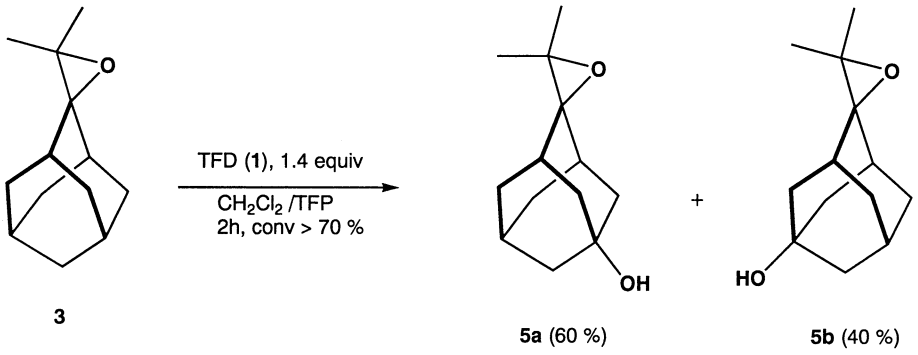
For each compound the ^{13}C NMR shows nine signals, three quaternary carbons bonded to oxygen, two tertiary C–H, three secondary CH_2 and one CH_3. These spectra are similar to those of **4a** and **4b** except for the methyl group. The fact that only a single methyl appears in each shows that hydroxylation occurs on the symmetry plane.

The structural information obtained from NMR and X-ray analysis was further confirmed by the identification of the carbonyl compounds resulting from the cleavage of these oxides with periodic acid. Following the general procedure described by Ceruti et al.,[25] 0.4 mol equiv. of the corresponding oxide were added to a suspension of periodic acid (10 mL), and the mixture was stirred at room temperature until reaction was complete (TLC, silica gel plate monitoring). The crude reaction mixture was examined with ^1H NMR. The cleaved product shows signals at 2.62 ppm (2H), α to C=O and 2.35 ppm (1H), tertiary C–H at C-7 for 5-hydroxy-2-adamantanone (**6**)[26] (Scheme 5).

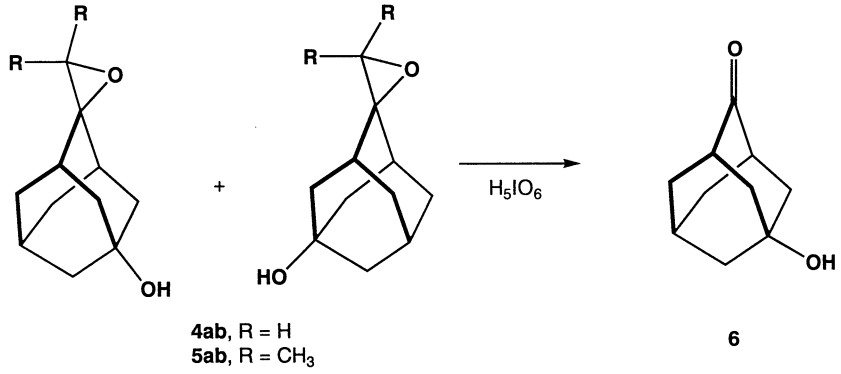
The chemo- and regioselective oxidation of unactivated C–H bonds to alcohols is difficult to achieve in good yield using common oxidizing agents.[27] The data presented demonstrate that the application of dioxirane **1** to the chemoselective oxidation of adamantyl epoxides leads to epoxy alcohols in good yields, without any undesired side reactions. High regioselectivity for tertiary over secondary C–H insertion in the oxidation of substrates **2** and **3** was obtained, in agreement with the literature.[6,7] It appears that the oxiranil ring has a significant deactivating effect (presumably electrostatic) on the nearby hydrogens, leading to the exclusive oxidation of C_5-H and C_7-H with *Z*/*E* diastereoselectivity in a concerted 'oxenoid' O-insertion by dioxiranes. The high *Z*-diastereoselectivity in attack on **2** is surprising; previous work has shown a preference for *Z* attack to



Scheme 3.



Scheme 4.



Scheme 5.

oxygen substituents,[7] but not so large. The difference in the stereoselectivity of attack on **2** and **3** is unexplained so far. We are continuing to explore the cause of the high selectivities observed in these reactions.

References

1. Ito, Y.; Matsuura, T. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1871–1873.
2. Jefford, C. W.; Knopfel, W.; Smith, L. C.; Kohmoto, S.; Almquist, K. A.; Jiminez Estrada, M.; Barchietto, G. In *Oxygen and Oxy-radicals in Chemistry and Biology*; Rodgers, M. A. J.; Powers, E. L., Eds.; Academic Press: New York, 1981; pp. 397–407.
3. Curci, R.; Dinoi, A.; Rubino, M. F. *Pure. Appl. Chem.* **1995**, *67*, 811–822.
4. Adam, W.; Hadjiarapoglou, L. P.; Curci, R.; Mello, R. In *Organic Peroxides*; Ando, W., Ed.; Wiley: New York, 1992; pp. 195–219.
5. Mello, R.; Fiorentino, M.; Fusco, C.; Curci, R. *J. Am. Chem. Soc.* **1989**, *111*, 6749–6757.
6. Yang, D.; Wong, M. K.; Wang, X. C.; Tang, Y. C. *J. Am. Chem. Soc.* **1998**, *120*, 6611–6612.
7. González-Nuñez, M. E.; Royo, J.; Castellano, G.; Andreu, C.; Boix, C.; Mello, R.; Asensio, G. *Org. Lett.* **2000**, *2*, 831–834.
8. Curci, R.; D'Accolti, L.; Fusco, C. *Tetrahedron Lett.* **2001**, *42*, 7087–7090.
9. Kuck, D.; Schuster, A.; Fusco, C.; Fiorentino, M.; Curci, R. *J. Am. Chem. Soc.* **1994**, *116*, 2375–2381.
10. D' Accolti, L.; Fusco, C.; Lucchini, V.; Carpenter, G. B.; Curci, R. *J. Org. Chem* **2001**, *66*, 9063–9066.
11. Bach, R. D.; Andres, J. L.; Su, M. D.; McDouall, J. J. W. *J. Am. Chem. Soc.* **1993**, *115*, 5768–5775.
12. Du, X. H.; Houk, K. N. *J. Org. Chem.* **1998**, *63*, 6480–6483.
13. Poon, T. H.; Pringle, K.; Foote, C. S. *J. Am. Chem. Soc.* **1995**, *117*, 7611–7618 and references cited therein.
14. Bobek, M. M.; Brinker, U. D. *J. Am. Chem. Soc.* **2000**, *122*, 7430–7431.
15. Mukherjee, A.; Wu, Q.; Noble, W. J. *J. Org. Chem.* **1994**, *59*, 3270–3274.
16. Scholtissek, C.; Quack, G.; Klenk, H. D.; Webster, R. G. *Antiviral Res.* **1998**, *37*, 83–95.
17. Schleyer, P. von R.; Nicholas, R. D. *J. Am. Chem. Soc.* **1961**, *83*, 182–186.
18. Lopez, L.; Mastrorilli, P.; Mele, G.; Nobile, C. F. *Tetrahedron Lett.* **1994**, *35*, 3633–3636.
19. The oxidations were carried out by addition of an aliquot (4–8 mL) containing **1**, 1.4 equiv. of a standardized cold solution of dioxirane **1** to a stirred solution of 1 equiv. of substrate in 5–10 mL of the solvent. The reaction progress was monitored by GC or GC/MS. After solvent removal in vacuo, the products were separated by flash chromatography (silica gel, starting eluent pentane/Et_2O 4:1).
20. ***Z*-5-Hydroxymethyleneadamantane oxide** (**4a**): Colorless needles (ether/pentane 80:20), mp 170–172°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.68 (s, 2H), 2.19 (m, 1H), 2.03 (d, 2H, 12 Hz), 1.77–1.59 (m, 11H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 67.30, 62.95, 54.29, 44.56, 42.55, 37.98, 35.32, 29.37; FTIR in CCl_4 (cm^{-1}) 3708 (m), 3608 (s), 3036 (m),

2962 (s), 2925 (s), 2855 (m), 1418 (m), 1255 (s), 1217 (m), 1093 (s), 1010 (s); HRMS (EI) for $C_{11}H_{16}O_2$ experimental: 180.1148, calculated: 180.1550.

21. ***E*-7-Hydroxymethyleneadamantane oxide (4b)**: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.65 (s, 2H), 2.17 (m, 1H), 1.95–1.86 (m, 2H), 1.77–1.59 (m, 11H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 67.56, 63.54, 54.88, 44.96, 43.77, 37.19, 33.56, 29.19.
22. X-Ray crystallography was carried out on a Bruker Smart 1000-CCD Diffractometer with Oxford Cryosystem Nitrogen Gas. The HRMS (EI) spectra were obtained on an AEI Ltd Model MS-902 sector filled double focusing spectrometer, Mo X-ray source. Crystal data for **4a**: $C_{11}H_{16}O_2$, orthorhombic, space group *Pbcn*, $Z=8$; unit cell dimensions: $a=22.371(5)$, $b=9.484(2)$, $c=9.070(2)$ Å; $\beta=90°$; molecular weight 180.24; calculated density 1.244 Mg/m^3; absorption coefficient $\mu=0.084$. Further details of the crystal structure investigation can be obtained from the Cambridge Crystallographic Data Centre.
23. ***Z*-5-Hydroxyisopropylideneadamantane oxide (5a)**: White solid, mp 134–136; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.30–1.37 (m, 14H), 1.39 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 69.21, 67.41, 63.40, 44.00, 42.17, 35.26, 34.90, 29.49, 20.38; FTIR in CCl_4 (cm^{-1}) 3607 (m), 3583 (m), 3060 (m), 2927 (m), 2853 (m), 1449 (m), 1250 (s), 1216 (m), 1117 (m), 1006 (m); HRMS (EI) for $C_{13}H_{20}O_2$ experimental: 208.1463, calculated: 208.1463.
24. ***E*-7-Hydroxyisopropylideneadamantane oxide (5b)**: White solid, mp 135–136°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.26 (m., 1H), 1.95–1.59 (m, 13H), 1.38 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 69.78, 67.64, 63.52, 44.55, 43.68, 33.86, 33.28, 29.42, 19.93; FTIR in CCl_4 (cm^{-1}) 3608 (m), 3585 (m), 3040 (m), 2926 (m), 2855 (m), 1453 (m), 1255 (s), 1217 (m), 1102 (m), 1005 (m); HRMS (EI) for $C_{13}H_{20}O_2$ experimental: 208.1463, calculated: 208.1463.
25. Ceruti, M.; Viola, F.; Dosio, F.; Cattel, L.; Bouvier-Navé, P.; Ugliengo, P. *J. Chem. Soc., Perkin Trans. 1* **1988**, 461–469.
26. Geluk, H. W.; Schlatmann, J. L. *Tetrahedron* **1968**, *24*, 5369–5377.
27. Sheldon, R. A.; Kochi, J. K. *Metal Catalyzed Oxidation of Organic Compounds*; Academic Press: New York, 1991.