Pergamon

Tetrahedron Letters 42 (2001) 7087–7090

TETRAHEDRON LETTERS

On the hydroxylation of bicyclo[2.1.0]pentane using dioxiranes

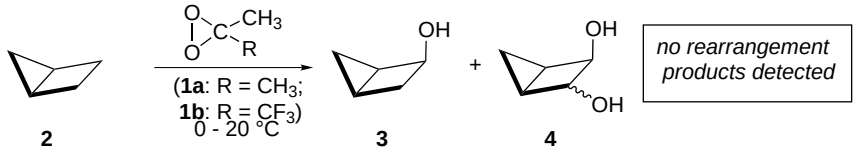
Ruggero Curci,* Lucia D'Accolti and Caterina Fusco

Centro C.N.R. 'M.I.S.O.', Department of Chemistry, University of Bari, v. Amendola 173, I-70126 Bari, Italy

Received 21 May 2001; revised 27 July 2001; accepted 3 August 2001

Abstract—The oxidation of bicyclo[2.1.0]pentane by isolated dimethyldioxirane and by the more powerful methyl(trifluoromethyl)dioxirane, affords selectively, the corresponding *endo*-2 alcohol along with the 2,3-diol in high yield, and no rearrangement products; this suggests that a concerted *O*-insertion mechanism should be preferred over radical pathways.

Dioxiranes,[1] especially the isolated dimethyldioxirane (DMD)[2] (**1a**) and methyl(trifluoromethyl)dioxirane (TFD) (**1b**)[3] in the isolated form, are nowadays well established as useful oxidants for a variety of oxyfunctionalizations of organic substrates. The efficient oxyfunctionalization of unactivated alkane C–H bonds of alkanes under extremely mild conditions undoubtedly ranks as a landmark in dioxirane chemistry.[3b] It has been noted that the selective hydroxylation of alkanes by cytochrome P-450 enzymes[4] and by dioxiranes present several features in common; in both cases, the mechanism does not seem to involve *free*-radicals (i.e. radicals freely diffusing through the solution).[5] With this in mind, we have now applied both dioxiranes **1a** and **1b** to the oxidation of bicyclo[2.1.0]pentane (BCP) (**2**).



(1)

For the dioxiranes, an alternative to the established 'oxenoid' *O*-insertion into alkane C–H bonds consists in an initial *H*-abstraction to give a radical pair $\|R^{\bullet}HO\text{-}CR^1R^2\text{-}O^{\bullet}\|$;[6] this would be followed by fast in-cage collapse to products, similar to the 'oxygen rebound' envisaged for the iron-containing cytochrome P-450 enzymes.[4,5] For the latter, bicyclo[2.1.0]pentane (**2**) has been employed as a calibrated[7a] free-radical 'clock' in order to determine the rate of oxygen rebound (k_{OH}) by measuring the ratio of the unrearranged alcohol insertion product **3** to the amount of rearranged cyclopent-3-enol resulting from capture of a hydroxyl radical by a cyclopent-3-enyl radical. Ortiz de Montellano and Stearns examined the P-450 hydroxylation of **2** and established a 7:1 ratio of unrearranged to rearranged (U/R) alcohols,[7a] indicating a rate for oxygen rebound of $k_{OH}=1.7\times10^{10}$ M^{-1} s^{-1} based on the known rate for the ring opening of the bicyclo[2.1.0]pent-2-yl radical.[7b,c]

Representative results of the dioxirane hydroxylation of BCP (**2**) are collected in Table 1.

Dimethyldioxirane (**1a**) (ca. 0.1 M in acetone) and methyl(trifluoromethyl)dioxirane (**1b**) [0.5–0.8 M in 1,1,1-trifluoropropanone (TFP)] solutions were prepared as already reported in detail.[2,3] The substrate **2** was synthesized and purified by a given literature procedure;[8] to this, dioxirane **1a** or **1b** was added in acetone or TFP solution, respectively. The reactions were carried out under the conditions given in Eq. (1) and Table 1 on a 5–20 mL scale, and monitored by GC and GC–MS. It should be noted that dioxirane oxidations of probe **2** were run under pseudo-first order conditions using a large excess of substrate over dioxirane in order to minimize secondary reactions and over oxidation.

Keywords: dioxiranes; bicyclo[2.1.0]pentane; free-radical 'clock'; insertions; oxenoids; radicals.

* Corresponding author. Fax: +39-080-5442924; e-mail: csmirc17@area.ba.cnr.it

0040-4039/01/$ - see front matter
PII: S0040-4039(01)01434-4

Table 1. Hydroxylation of bicyclo[2.1.0]pentane (**2**) by dimethyldioxirane (**1a**) and methyl(trifluoromethyl)dioxirane (**1b**)[a]

Entry	Dioxirane (M)	BCP (2) (M)	Temp. (°C)	Reaction time (min)	Conversion (%)[b]	(% Yield of products)[c]	
						Alcohol (**3**)	Diol (**4**)
1	(**1a**) 0.018	0.181	20	60	40	89	11
2	(**1a**) 0.018	0.181	20	150	75	70	30
3	(**1a**) 0.002	0.181	20	15	60	>99	–
4	(**1a**) 0.002	0.181	20	27	82	>99	–
5	(**1a**) 0.024	0.028	20	150	70	>99	–
6	(**1a**) 0.002	0.028	20	120	25	>99	–
7	(**1a**) 0.002	0.033	20	90[d]	35	>99	–
8	(**1b**) 0.002	0.209	0	5	95	79	21
9	(**1b**) 0.001	0.002	0	30	35	92	8

[a] All reactions were run in stoppered flasks under an air blanket (unless noted otherwise), using as solvent the ketone parent of the dioxirane, i.e. acetone for dioxirane **1a** and 1,1,1-trifluoropropanone for dioxirane **1b**. Residual dioxirane was determined either by iodometry and/or by a reported GC method (Ref. 3b).

[b] Substrate conversion is referred to a stoichiometric amount of dioxirane (limiting reagent) consumed; it was determined by GC [VOCOL, 60 m×0.53 mm ID, 3.0 mm film thickness; 40°C (20 min), 40–220°C (6°C/min); t_R: 4.3 min] by using *n*-dodecane external standard and A112 (1,2,2-trichloro-1,2,2-trifluoroethane) as internal standard.

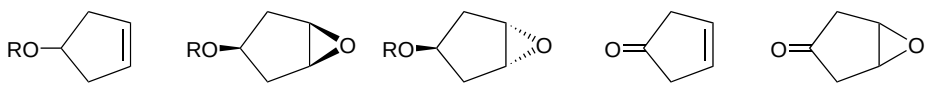
[c] Yields are based on the amount of substrate converted and were determined by GC at the conditions in footnote b (t_R: 11.60 and 14.65 min, for **3** and **4**, respectively) using *n*-dodecane as external standard; products were identified by GS–MS [Hewlett–Packard mod. 5970 (EI 70 eV), and mod. 5890 GC (SPB-1, 30 m×0.25 mm ID, 0.25 μm film thickness)].

[d] Reaction run using solutions purged with pure, oxygen-free nitrogen gas.

From runs performed under the conditions given in entry 5, the product was isolated in mixture with unreacted BCP and gave MS and a ^{1}H NMR spectra in good agreement with those reported for the unrearranged *endo*-C-2 alcohol **3**.[7a] Since the reactions were run on relatively small scale using excess substrate, the amount of the C-2,C-3 diol **4** formed (entries 1, 2, 8 and 9) was not sufficient to permit isolation; however, this compound was characterized by GC–MS. In fact, its mass spectrum exhibits an intense $M^{+\bullet}$ peak at *m*/*z* 100 (22%), and HRMS (CI^+ mode) $[M+H]^+$ at 101.0603 (calcd: 101.0603).[9] This is at variance with the parent alcohol **3**, which presents a prominent $[M-H]^+$ peak at *m*/*z* 83 (53%) rather than a $M^{+\bullet}$ peak (*m*/*z* 84, 6%). The above MS fragmentation pattern of **4** is characteristic of cyclic *vic*-diols, presenting inter alia the base peak at *m*/*z* 41 $[C_3H_5]^+$ (100%) and relevant peaks at *m*/*z* 82 $[M-H_2O]^+$ (54%) and 72 $[M-C_2H_4]^+$ (44%), *m*/*z* 57 $[M-C_2H_3O]^+$ (32%), and *m*/*z* 70 $[M-CH_2O]^+$ (70%). The latter is typical of strained-ring *trans*-1,2-diols such as *trans*-cyclobutane-1,2-diol, being markedly less abundant for the corresponding *cis*-cyclobutane-1,2-diol.[10] Thus, the *trans* configuration is more likely for diol **4**. The prevalent *anti* stereoselectivity observed in the bis hydroxylation of BCP might be rationalized in terms of dipole orientation of the incoming dioxirane with respect to the initially introduced OH moiety, so that *O*-insertion into the adjacent C–H from the opposite face becomes favored by electrostatic interactions.[11] Work is in progress in order to establish unambiguously the exact stereochemistry of the *vic*-diol formed.

Ensuing hydroxylation of BCP to the *endo*-C-2 alcohol **3** and formation of the C-2,C-3 diol **4** is remarkable. In fact, the dioxirane oxidation of *sec*-alcohol functionalities to carbonyls is normally 50–100 times faster than hydroxylation of 'unactivated' alkane C–H bonds.[1f] In contrast, overoxidation of alcohol **3** to the corresponding carbonyl is precluded in the case at hand, most likely because of unfavorable angle strain in the bicyclic C-2 ketone.

More remarkable is the lack of rearrangement products derived from radical pathways. Indeed, the main oxidation product expected from the ultra-fast ring opening of cyclopent-3-enyl radicals is the rearranged cyclopentenol **5a**;[12a] possible products from further oxidation of **5a** include epoxyalcohols **6a** and **7a**,[12b] ketone **8**,[12c] and in turn from this epoxyketone **9**.[12d]



5a,b **6a,b** **7a,b** **8** **9**

a: R = H; **b**: R = Ac

Authentic samples of these compounds were obtained;[12b–d] then, acetates **5b**–**7b** were readily prepared upon reaction of the appropriate alcohol with Ac_2O and pyridine. The latter reference compounds were also made available because of the artifactual claim[13] that the dioxirane oxidation of alkanes might lead to acetate products by an out-of cage radical-chain sequence.[13b] In this respect, it is quite telling that none of the putative products above could be detected by GC and GC–MS analyses of the reaction mixtures. Control experiments showed that compounds **5**–**9** are ade-

quately stable to the reaction conditions to permit detection; we could determine a minimum GC detection limit of less than 0.2% for authentic admixtures of **5**–**9**. Therefore, the ratio of U/R products presented by the dioxirane oxidation of BCP exceeds 500:1. On this ground, given the precise horology available for the ring opening of the bicyclo[2.1.0]pent-2-yl radical ($k_r = 2\times10^9$ s^{-1} at 25°C),[7c] one can estimate that, if a radical pair mechanism were to take place, the in-cage 'oxygen rebound' would have to take place at a rate $k_{OH} \geq 1\times 10^{12}$ M^{-1} s^{-1}. This is roughly in the same range with the estimate produced by Newcomb et al.;[14] actually, these authors could assess[14a] an even higher limit of $k_{OH} \geq 4\times 10^{12}$ M^{-1} s^{-1} by examining the DMD oxidation of *trans*-2-phenyl-ethylcyclopropane, a hypersensitive radical probe.[14]

Then, the considerations and conclusions presented by Newcomb et al.[14a] concerning the mechanism of dioxirane oxyfunctionalization of alkane C–H bonds can be endorsed in full. In fact, much evidence has been accumulated that allows one to dismiss[5a,6b,c] the claim that under normal conditions dioxirane oxidation of alkanes could involve diffusively *free* radicals.[13] As for the intermediacy of radical pairs, we first recognized[6a] that the in-cage 'oxygen rebound' of radical pairs could constitute the only viable alternative to a mechanism of dioxirane direct *O*-insertion into C–H bonds, but concluded that the evidence available at that early stage of dioxirane mechanistic studies weighed heavily for the simpler insertion mechanism. After much debate[5a,6b,c,13,14] and controversial data,[13,15] current evidence demonstrates that our initial view still holds. In fact, recent high level computational studies have shown that dioxirane hydroxylations occur by insertion-type transition states that only exhibit *biradicaloid* character;[16] *after* the transition state, bifurcation[17] is energetically feasible and could yield either the collapse products (alcohol and ketone) or radical pairs (in essence, the 'leakage' model[6b] that we envisaged). However, the results now coming from the application of fast radical probes, i.e. the BCP probe reported herein and Newcomb's *trans*-2-phenyl-ethylcyclopropane, demonstrate that the radical-pair mechanism is less likely. Indeed, Newcomb et al. have pointed out[14a] that their radical-clock allows one to estimate that the radical pairs engaged in the 'rebound' process would have a life-time of only 0.2 ps, which is practically indistinguishable from the lifetime of a transition state calculated from transition state theory (0.17 ps).

In envisaging novel mechanisms for dioxirane hydroxylation of alkane C–H bonds, one should not neglect the evidence coming from the application of fast radical probes which stringently argues in favor of a substantially concerted insertion process.

Acknowledgements

Partial support of this work by the Ministry of University, Scientific and Technological Research of Italy (National Project: 'Activation of Peroxide Species in Innovative Selective Oxidation Processes') is gratefully acknowledged. Thanks are due to Dr. R. Mello (University of Valencia, Spain) for performing the HRMS analyses.

References

1. For reviews, see: (a) Adam, W.; Curci, R.; Edwards, J. O. *Acc. Chem. Res.* **1989**, *22*, 205; (b) Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187; (c) Curci, R. In *Advances in Oxygenated Processes*; Baumstark, A. L., Ed.; JAI: Greenwich, CT, 1990; Vol. 2, Chapter I, pp. 1–59; (d) Adam, W.; Hadjiarapoglou, L. P.; Curci, R.; Mello, R. In *Organic Peroxides*; Ando, W., Ed.; Wiley: New York, 1992; Chapter 4, pp. 195–219; (e) Adam, W.; Hadjiarapoglou, L. *Top. Curr. Chem.* **1993**, *164*, 4552; (f) Curci, R.; Dinoi, A.; Rubino, M. F. *Pure Appl. Chem.* **1995**, *67*, 811 and references cited therein.
2. (a) Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847; (b) Cassidei, L.; Fiorentino, M.; Mello, R.; Sciacovelli, O.; Curci, R. *J. Org. Chem.* **1987**, *52*, 699; (c) Adam, W.; Chan, Y.-Y.; Cremer, D.; Gauss, J.; Scheutzow, D.; Schindler, M. *J. Org. Chem.* **1987**, *52*, 2800.
3. (a) Mello, R.; Fiorentino, M.; Sciacovelli, O.; Curci, R. *J. Org. Chem.* **1988**, *53*, 3890; (b) Mello, R.; Fiorentino, M.; Fusco, C.; Curci, R. *J. Am. Chem. Soc.* **1989**, *111*, 6749; (c) Adam, W.; Curci, R.; González Nuñez, M. E.; Mello, R. *J. Am. Chem. Soc.* **1991**, *113*, 7654.
4. *Cytochrome P-450. Structure, Mechanism, and Biochemistry*; Ortiz de Montellano, P. R., Ed.; Plenum: New York, 1986.
5. (a) Vanni, R.; Garden, S. J.; Banks, J. T.; Ingold, K. U. *Tetrahedron Lett.* **1995**, *36*, 7999; (b) Ingold, K. U. *Aldrichim. Acta* **1989**, *22*, 69 and references cited therein.
6. (a) Mello, R.; Cassidei, L.; Fiorentino, M.; Fusco, C.; Hümmer, W.; Jäger, V.; Curci, R. *J. Am. Chem. Soc.* **1991**, *113*, 2205; (b) Curci, R.; Dinoi, A.; Fusco, C.; Lillo, M. A. *Tetrahedron Lett.* **1996**, *37*, 249; (c) Adam, W.; Curci, R.; D'Accolti, L.; Dinoi, A.; Fusco, C.; Gasparrini, F.; Kluge, R.; Paredes, R.; Schulz, M.; Smerz, A. K.; Veloza, L. A.; Weinkötz, S.; Winde, R. *Chem. Eur. J.* **1997**, *3*, 105 and references cited therein.
7. (a) Ortiz de Montellano, P. R.; Stearn, R. A. *J. Am. Chem. Soc.* **1987**, *109*, 3415; (b) Bowry, V. W.; Lusztyk, J.; Ingold, K. U. *J. Am. Chem. Soc.* **1989**, *111*, 1927; (c) Newcomb, M.; Toy, P. H. *Acc. Chem. Res.* **2000**, *33*, 449 an references cited therein.
8. Gasman, P. G.; Mansfield, K. T. *Org. Synth.* **1969**, *49*, 1.
9. The High Resolution MS spectra were run on a VG Autospec instrument (CI^+ with methane as ionizing gas, source temperature 150°C) equipped with a GC BPX5 capillary column, 25 m×0.22 mm ID, 0.25 μm.
10. For instance, see: Barnier, J. P.; Denis, J. M.; Salaun, J.; Conia, J. M. *Tetrahedron* **1974**, *30*, 1397.
11. Fusco, C.; Fiorentino, M.; Dinoi, A.; Curci, R.; Krause, R. A.; Kuck, D. *J. Org. Chem.* **1996**, *61*, 8681.
12. (a) Crandall, J. K.; Banks, D. B.; Colyer, R. A.; Watkins, R. J.; Arrington, J. P. *J. Org. Chem.* **1968**, *33*, 423; (b) D'Accolti, L.; Fiorentino, M.; Fusco, C.; Rosa, A.; Curci, R. *Tetrahedron Lett.* **1999**, *40*, 8023; (c) Ross, A. R.; Pohl, T. M.; Piazza, K.; Thomas, M.; Fox, B.; Whalen, D. L. *J. Am. Chem. Soc.* **1982**, *104*, 1658; (d)

Stensen, W.; Svendsen, J. S.; Hofer, O.; Sydnes, L. K. *Acta Chem. Scand. B* **1988**, *42*, 259.
13. (a) Minisci, F.; Zhao, L.; Fontana, F.; Bravo, A. *Tetrahedron Lett*. **1995**, *36*, 1697; (b) Bravo, A.; Fontana, F.; Fronza, G.; Mele, A.; Minisci, F. *J. Chem. Soc., Chem. Commun*. **1995**, 1573; (c) Minisci, F.; Bravo, A.; Fontana, F.; Fronza, G.; Zhao, L. *J. Org. Chem*. **1998**, *39*, 8187.
14. (a) Newcomb, M.; Choi, S.-Y.; Simakov, P. A. *Tetrahedron Lett*. **1998**, *39*, 8187; (b) Newcomb, M.; Johnson, C. C.; Manek, M. B.; Varick, T. R. *J. Am. Chem. Soc*. **1992**, *117*, 10915; (c) Newcomb, M. *Tetrahedron* **1993**, *49*, 1151 and references cited therein.
15. Freccero, M.; Gandolfi, R.; Sarzi-Amadè, M.; Rastelli, A. *Tetrahedron Lett*. **2001**, *42*, 2739.
16. (a) Bach, R. D.; Glukhovtsev, M. N.; Canepa, C. *J. Am. Chem. Soc*. **1998**, *120*, 10528; (b) Houk, K. N.; Du, X. J. *J. Org. Chem*. **1998**, *63*, 6480 and references cited therein.
17. Rauk, A.; Shustov, G. V. *J. Org. Chem*. **1998**, *63*, 8681.