

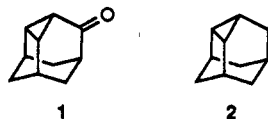
Oxidation of 2,4-Didehydroadamantane

David S. Teager and Roger K. Murray, Jr.*

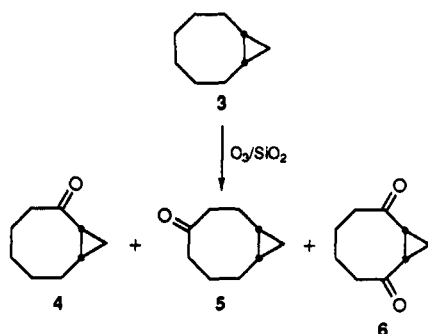
Department of Chemistry and Biochemistry, University of Delaware, Newark, Delaware 19716

Received May 10, 1993

In principle, 8,9-didehydro-2-adamantanone (1), which has been prepared in seven steps from norbornadiene¹ and in three steps from tropylium tetrafluoroborate² in overall yields of 2% and 21%, respectively, should be accessible by oxidation of 2,4-didehydroadamantane³ (2).

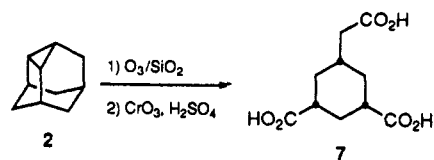


Only two general methods have been reported for the direct synthesis of a conjugated cyclopropyl ketone from the corresponding hydrocarbon. De Meijere and his co-workers have noted that "dry ozonation" of a hydrocarbon adsorbed on silica gel leads to preferential oxidation of the position(s) α to the cyclopropyl group.⁴ For example, dry ozonation of *cis*-bicyclo[6.1.0]nonane (3) proceeds with 97% conversion to give *cis*-bicyclo[6.1.0]nonan-2-one (4), *cis*-bicyclo[6.1.0]nonan-4-one (5), and *cis*-bicyclo[6.1.0]nonane-2,7-dione (6), in yields of 88%, 7%, and 2%, respectively.⁴ In the alternative Yamada procedure, the



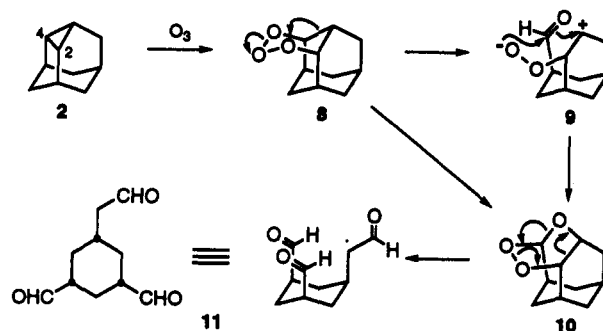
hydrocarbon is oxidized with ruthenium tetroxide, which is generated *in situ* from ruthenium trichloride hydrate or ruthenium dioxide hydrate and sodium metaperiodate in a solvent mixture of acetonitrile, carbon tetrachloride, and water.⁵ Treatment of 3 under these conditions affords 4 in 50% yield.⁵ We have investigated the oxidation of 2 by each of these methods.

When ozone is passed for 100 min through silica gel bearing 0.85% by weight of 2, a complex mixture of products is obtained that contains formyl and carboxyl functional groups. Jones oxidation of this material gives (*cis,cis*-3,5-dicarboxycyclohexyl)ethanoic acid (7) as the only isolated product in 69% yield from 2. Consistent

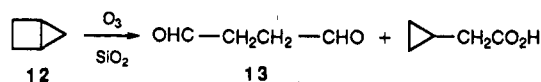


with the presence of a plane of symmetry in 7, the ¹³C NMR spectrum of 7 contains only seven resonances.

The formation of 7 from 2 can be rationalized by the initial addition of ozone across the C-2 to C-4 bond of 2 to give the 1,2,3-trioxane derivative 8. The rearrangement of 8 to the 1,2,4-trioxane derivative 10 may be concerted,

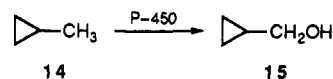


or it may proceed by initial formation of zwitterion 9 followed by an intramolecular 1,4-dipolar cycloaddition of the zwitterion to the formyl group. A [2 + 2 + 2]-cycloreversion of 10 would afford trialdehyde 11 which then could be oxidized further under the reaction conditions to give the observed mixture of products. A similar mechanism has been suggested to account for the formation of 13 in the dry ozonation of bicyclo[2.1.0]pentane (12).⁶



In contrast to the reaction of ozone with 2, oxidation of 2 with ruthenium tetroxide that is generated *in situ* from ruthenium dioxide hydrate and sodium metaperiodate proceeds with 73% conversion of 2 to give 1 as the sole isolated product, but only in 8% yield.

Given these observations, we were interested in developing an alternative method for the direct oxidation of 2. We were intrigued by the report that oxidation of methylcyclopropane (14) with cytochrome P-450 gives cyclopropylmethanol (15) without the formation of any



rearranged products.⁷ Since some aspects of the chemistry of dioxiranes have been suggested to resemble the behavior of certain monooxygenase enzymes⁸ and dioxiranes also are known to oxidize secondary alcohols to ketones,⁹ we decided to investigate the reaction of 2 with dimethyl-dioxirane.

(1) Baldwin, J. E.; Fogelson, W. D. *J. Am. Chem. Soc.* 1968, 90, 4303.
(2) (a) Murray, R. K., Jr.; Morgan, T. K., Jr.; Babiak, K. A. *J. Org. Chem.* 1975, 40, 1079. (b) Karlovic, G.; Majerski, Z. *J. Org. Chem.* 1978, 43, 746.

(3) (a) Udding, A. C.; Strating, J.; Wynberg, H. *J. Chem. Soc., Chem. Commun.* 1966, 657. (b) Isaev, S. D.; Yurchenko, A. G.; Stepanov, F. N.; Kolyada, G. G.; Novikov, S. S.; Karpenko, N. F. *Zh. Org. Khim.* 1973, 9, 724.

(4) (a) Proksch, E.; de Meijere, A. *Angew. Chem., Int. Ed. Engl.* 1976, 15, 761. (b) Zarth, M.; de Meijere, A. *Chem. Ber.* 1985, 118, 2429.

(5) Hasegawa, T.; Niwa, H.; Yamada, K. *Chem. Lett.* 1985, 1385.

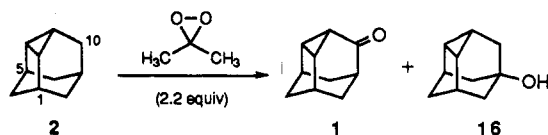
(6) Preuss, T.; Proksch, E.; de Meijere, A. *Tetrahedron Lett.* 1978, 833.

(7) Ortiz de Montellano, P. R.; Stearns, R. A. *J. Am. Chem. Soc.* 1987, 109, 3415.

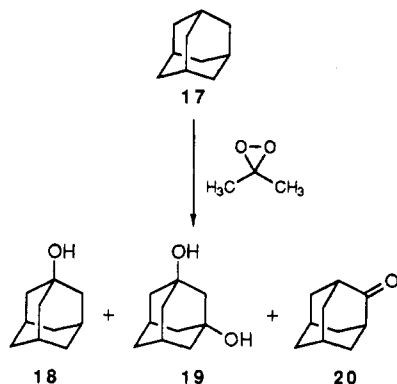
(8) Murray, R. W.; Jeyaraman, R.; Mohan, L. *J. Am. Chem. Soc.* 1986, 108, 2470.

(9) Adam, W.; Chan, Y.-Y.; Cremer, D.; Gauss, J.; Scheutzw, D.; Schindler, M. *J. Org. Chem.* 1987, 52, 2800.

Treatment of **2** with 2.2 equiv of dimethyldioxirane⁹ proceeds with 82% conversion of **2** to give **1** and 7-hydroxy-2,4-didehydroadamantane¹⁰ (**16**) in yields of 29% and 21%,

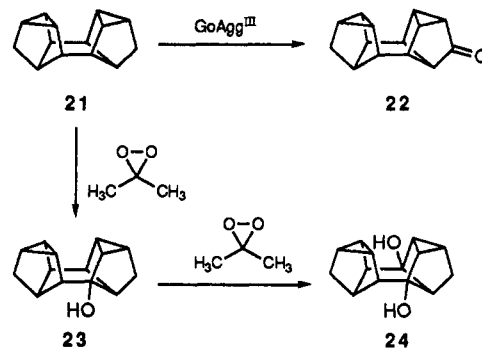


respectively. In contrast to this result, the reaction of dimethyldioxirane with adamantane (**17**) provides 1-adamantanol (**18**) in 87% yield and a mixture of 1,3-adamantanediol (**19**) and 2-adamantanone (**20**) in a combined yield of 2.6%.⁸ Thus, the cyclopropyl moiety



in **2** has a significant activating influence on the C–H bonds at C-10 in **2** (the position where a developing radical or carbocation would be stabilized by the cyclopropyl group) and a deactivating effect on the C–H bonds at C-1 and C-5 in **2** (the positions where a developing radical or carbocation would be inductively destabilized by the cyclopropyl group).¹¹ However, all of the available evidence shows that the mechanism for the oxidation of hydrocarbons by dioxirane closely resembles the “oxenoid” mechanism that has been suggested for the insertion of ozone into alkane C–H bonds.¹² Consistent with this proposal, no rearranged products are observed in the reaction of dimethyldioxirane with **2**.

It is interesting that the oxidation of Binor-S (**21**) with dimethyldioxirane follows a different reaction pathway. Although treatment of **21** under the standard GoAgg^{III} conditions proceeds only with 10% conversion of **21** to give ketone **22** in 8% yield,¹³ this reaction shows that the methylene positions in **21** are activated. However, treatment of **21** with dimethyldioxirane provides alcohol **23** in 98% yield.¹⁴ Further oxidation of **23** with additional dimethyldioxirane affords diol **24** in 75% yield.¹⁴ Thus, in contrast to the behavior of **2**, oxidation of **21** with



dimethyldioxirane does not lead to any attack at the methylene positions α to the cyclopropyl groups.

Experimental Section

Dry Ozonation of 2,4-Didehydroadamantane. A solution of **2** (255 mg, 1.9 mmol) in pentane (20 mL) was mixed with silica gel (30 g of Merck Kieselgel 60 which had been dried under vacuum), and the solvent was evaporated carefully at reduced pressure and room temperature with a rotary evaporator. The resulting free-flowing powder was allowed to spin for an additional 2 h. This material was transferred to a tightly closed gas-washing bottle that was immersed in a liquid N₂/acetone bath which was maintained at -78 °C. The bottle was connected to an ozone generator and a stream of O₂ was passed through the sample for 90 min at a rate of 4 L/min. At that time, the ozone generator was turned on (105 V, 6 psi) and a mixture of O₃ and O₂ was passed through the sample for 100 min at a rate of 3 L/min. The cooling bath was removed then, and the reaction vessel was allowed to warm slowly to room temperature. The silica gel was transferred to a chromatography column, and it was eluted sequentially with pentane (150 mL) and methanol until no more material eluted from the column. Distillation of the solvent from the pentane eluent at atmospheric pressure provided no residue. Evaporation of the solvent from the methanol eluent at reduced pressure gave 489 mg of a foamy solid. Analysis of this material by ¹³C NMR spectroscopy showed that it was composed of a complex mixture of products that contained formyl and carboxyl functional groups.

A solution of this material in acetone (25 mL) was treated with Jones reagent (2 mL at ca. 2.7 M in H₂CrO₄, 5.4 mmol) for 4 h at room temperature. The excess oxidant was destroyed by the addition of 2-propanol. The solution was diluted with H₂O (10 mL) and extracted with ether (4 × 25 mL). The combined ether extracts then were extracted with 1 N aqueous NaOH (4 × 25 mL). This solution was acidified to pH 2 with concentrated aqueous HCl and then saturated with NaCl. The resulting solution was extracted with ether (4 × 25 mL), and the combined extracts were dried over anhydrous MgSO₄. Evaporation of the solvent at reduced pressure provided 300 mg (69% yield) of (*cis,cis*-3,5-dicarboxycyclohexyl)ethanoic acid (**7**) which was crystallized from acetone/hexanes: mp 240–241 °C; ¹³C NMR in acetone-*d*₆ δ 176.2 (CO₂H at C-3 and C-5), 173.6 (CH₂CO₂H), 42.7 (C-3 and C-5), 41.5 (CH₂-CO₂H), 35.4 (C-2 and C-6), 34.3 (C-1), 31.9 (C-4); ¹H NMR in acetone-*d*₆ δ 10–8 (very broad s, 3 H), 2.48 (tt, *J* = 12.4 and 3.4 Hz, 2 H), 2.30 (d, *J* = 6.9 Hz, 2 H), 2.25 (dm, *J* ≈ 12 Hz, 1 H), 2.10 [dm, *J* ≈ 12 Hz, 2 H (overlaps with solvent signals)], 2.02–1.84 (broad m, 1 H), 1.45 (q, *J* =

(10) Yurchenko, A. G.; Isaev, S. D.; Novoselov, E. F. *Zh. Org. Khim.* 1984, 20, 222.

(11) (a) Ree, B. R.; Martin, J. C. *J. Am. Chem. Soc.* 1970, 92, 1660. (b) Buss, V.; Gleiter, R.; Schleyer, P. v. R. *J. Am. Chem. Soc.* 1971, 93, 3927. (c) de Meijere, A.; Schallner, O.; Weitmeyer, C. *Angew. Chem., Int. Ed. Engl.* 1972, 11, 56. (d) Rhodes, Y. E.; DiFate, V. G. *J. Am. Chem. Soc.* 1972, 94, 7582. (e) Andersen, B.; Schallner, O.; de Meijere, A. *J. Am. Chem. Soc.* 1975, 97, 3521. (f) de Meijere, A.; Schallner, O.; Weitmeyer, C.; Spielmann, W. *Chem. Ber.* 1979, 112, 908. (g) Harris, J. M.; Moffatt, J. R.; Case, M. G.; Clarke, F. W.; Polley, J. S.; Morgan, T. K., Jr.; Ford, T. M.; Murray, R. K., Jr. *J. Org. Chem.* 1982, 47, 2740.

(12) Mello, R.; Fiorentino, M.; Fusco, C.; Curci, R. *J. Am. Chem. Soc.* 1989, 111, 6749.

(13) Barton, D. H. R.; Eaton, P. E.; Liu, W.-G. *Tetrahedron Lett.* 1991, 32, 6263.

(14) Pramod, K.; Eaton, P. E.; Gilardi, R.; Flippen-Anderson, J. L. *J. Org. Chem.* 1990, 55, 6105.

12.7 Hz, 1 H), 1.12 (q, $J = 12.5$ Hz, 2 H); IR (KBr pellet) 2935 (broad), 1705, 1424, 1292, 1206, 1182, 945 cm^{-1} ; HRMS calcd for $\text{C}_8\text{H}_{11}\text{O}_4$ (M- $\text{CH}_2\text{CO}_2\text{H}$) 171.0657, found 171.0651. Anal. Calcd for $\text{C}_{10}\text{H}_{14}\text{O}_6$: C, 52.18; H, 6.13. Found: C, 52.03; H, 6.15.

Oxidation of 2,4-Didehydroadamantane with Ruthenium Tetraoxide. Ruthenium dioxide hydrate (30 mg, 0.2 equiv) was added to a stirred mixture of **2** (134 mg, 1.0 mmol), NaIO_4 (650 mg, 3.3 equiv), CCl_4 (2.0 mL), CH_3CN (2.0 mL), and aqueous phosphate buffer (pH 7.2, 3.0 mL). The resulting dark mixture was stirred vigorously for 24 h at room temperature. It was diluted then with H_2O (10 mL) and extracted with CH_2Cl_2 (3×10 mL). The organic extracts were combined, washed with a mixture (10 mL) of saturated aqueous solutions of $\text{Na}_2\text{S}_2\text{O}_3$, NaHCO_3 , and NaCl (1:1:1), and dried over anhydrous Na_2SO_4 . Evaporation of the solvent at reduced pressure provided 66 mg of a white solid. Analysis of this material by quantitative ^{13}C NMR spectroscopy showed that it consisted of a mixture of **2** and **1** in a ratio of 75:25, respectively. Column chromatography of this material on TLC mesh silica gel with 75:25 pentane/ether as the eluent gave 36 mg of **2** followed by 9 mg of **1** (8% yield based on 73% conversion of **2**).

Oxidation of 2,4-Didehydroadamantane with Dimethyldioxirane. A solution of dimethyldioxirane in acetone (26 mL of 0.085 M, 2.2 mmol), prepared and

assayed according to the method of Adam,⁹ was added to a solution of **2** (132 mg, 1.0 mmol) in acetone (15 mL). The reaction mixture was protected from light, and it was stirred for 12 h at room temperature. This solution was concentrated by evaporation of most of the solvent at reduced pressure. The remaining material was diluted with CH_2Cl_2 and then dried over anhydrous MgSO_4 . Evaporation of the solvent at reduced pressure provided 152 mg of a waxy solid. Analysis of this material by quantitative ^{13}C NMR spectroscopy showed that it consisted of a mixture of unreacted **2**, ketone **1**, and 7-hydroxy-2,4-didehydroadamantane¹⁰ (**16**) in a ratio of 30:45:25, respectively. Column chromatography of this material on 60–200 mesh silica gel with 90:10 pentane/ether as the eluent gave 24 mg of **2** followed by 88 mg of a mixture of **1** and **16**. Careful column chromatography of this mixture of **1** and **16** on TLC mesh silica gel with 75:25 pentane/ether as the eluent provided 35 mg of **1** (29% yield based on 82% conversion of **2**), 8 mg of a fraction containing **1** and **16** in a ratio of 30:70, respectively, and 25 mg of **16** (21% yield based on 82% conversion of **2**) as a white solid: ^{13}C NMR δ 70.3 (C-7), 51.4 (C-9), 41.8 (C-6 and C-8), 37.2 (C-10), 35.8 (C-1 and C-5), 27.4 (C-3), 23.2 (C-2 and C-4); ^1H NMR δ 2.52 (bs, 2 H), 2.12–2.02 (complex m, 1 H), 1.80 (dd, $J = 2.5$ and 1.3 Hz, 2 H), 1.65–1.57 (m, 1 H), 1.52–1.28 (complex m, 8 H); HRMS calcd for $\text{C}_{10}\text{H}_{14}\text{O}$ 150.1045, found 150.1042.