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REGIOSPECIFIC RING ENLARGEMENT OF 2-NORADAMANTANONE TO 4- OR TO 5-PROTOADAMANTANONE. APPLICATION TO THE SYNTHESIS OF ADAMANTANE-1-^{13}C.

Malvina Fărcaşiu, Dan Fărcaşiu, Joel Slutsky, and Paul von Ragué Schleyer*

Department of Chemistry, Princeton University, Princeton, New Jersey 08540

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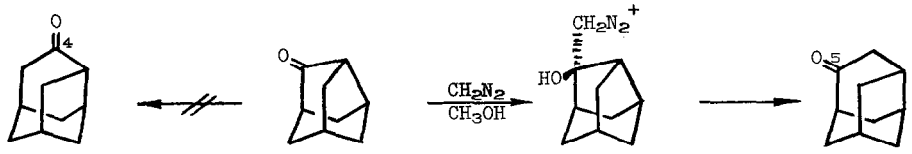
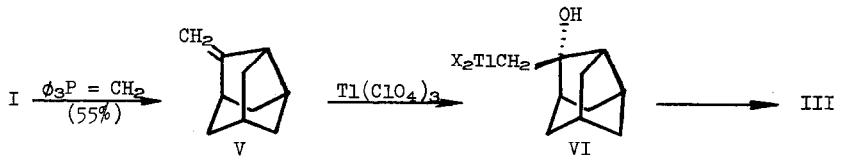
We have developed an efficient synthesis of bridgehead carbon-labelled adamantane starting from 2-noradamantanone (I).[1] Two of the three steps involved are mechanistically revealing.

The preferential attack of I by nucleophiles from the equatorial direction (exo side) is well established.[1] We have utilized this stereoselectivity to achieve regioselective ring expansion of I either to 5-protoadamantanone (II)[2] or to 4-protoadamantanone (III).[3] Thus, treatment of I[1] with diazomethane in methanol[4] gave II[2,5] in 90-96% yield and 95% purity with no detectable amount (glc)[6] of 4-ketone, III. This is the best method available for the synthesis of 5-protoadamantanone (II).[7]

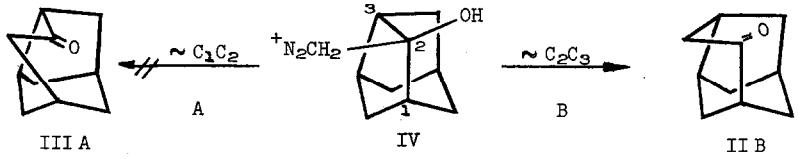


III I IV II

Since diazomethane should add from the less hindered exo side of I,[1,8] the rearrangement step should take place from IV, with the cationoidic methylene group ($-CH_2N_2^+$) equatorial. If this interpretation is correct, a reaction involving a cationoidic methylene group in an axial position should lead to a different product. It has been shown previously that thallic oxidation of exocyclic double bonds proceeds via an intermediate tertiary alcohol[9] resulting from the attack of water from the less hindered side of the molecule.[10] Therefore, the rearrangement step in the thallic oxidation of 2-methylenenoradamantane (V)[11] should take place from 2-thallomethyl-2-enoradamantanol (VI). As expected on this basis, a ca 60% yield of 4-protoadamantanone (III)[12] was actually produced; no ketone II could be found (glc).[6]



The complete migrational selectivity from both IV and VI is probably due to the strong conformational preference of the C_3-C_4-C_5-C_6 bridge in the protoadamantanone products.[3] For example, migration of the C_1-C_2 in IV would lead to a transition state resembling ketone III in conformation A while C_2-C_3 bond migration would give II B similarly. (By analogy, VI should lead to II initially in conformation A or III in conformation B.) Force field calculations on protoadamantane indicate conformation A to be ca 6 kcal/mole higher in energy than B; analysis of the nmr spectra of a number of protoadamantane derivatives confirm the strong preference for conformation B.[3,13] Conformation B transition states should also be preferred; this rationalizes the formation of II from IV and III from VI.[14]



5-Protoadamantanone-4-^{13}C (II-4-^{13}C) was prepared similarly (90% yield) using N-methyl-^{13}C-N-nitroso p-toluenesulfonamide (24 atom % ^{13}C). This ketone was reduced to protoadamantane-4-^{13}C (VII) in 76% yield following the literature.[3] A 0.3 M solution of $AlBr_3$ in CS_2 was used to isomerize VII to adamantane-1-^{13}C (VIII) in 94% yield; the reaction was complete in 15 min. at room temperature. Since ^{13}C-nmr indicated that the excess ^{13}C-label was completely at the 1-position, the degenerate 4-protoadamantyl → 4-protoadamantyl rearrangement[3] (which would scramble the label) did not compete under these conditions with the conversion to adamantane. The implication of this result for the adamantane rearrangement mechanism[15] will be discussed elsewhere.

In principle, obvious modifications of the syntheses described here could be used to prepare a variety of 1- and 2-carbon labelled adamantane derivatives.[16] Particularly useful intermediates would be 4-protoadamantanone-5-^{13}C and 4-protoadamantene-4- or 5-^{13}C.[2,17]

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2. (a) H.W. Whitlock, Jr., and M.W. Siefken, J. Amer. Chem. Soc., 90, 4929 (1968); (b) J. Boyd and K.H. Overton, Chem. Commun., 211 (1971).
3. D. Lenoir, R.E. Hall and P.v.R. Schleyer, J. Amer. Chem. Soc., 96, 2138 (1974) and literature cited therein.
4. The procedure for the synthesis of 4-homoadamantanone (R.M. Black and G.B. Gill, J. Chem. Soc. (C), 671 (1970)) was modified: To a stirred solution of I (1g) and KOH (4g) in water (3 ml) and methanol (10 ml), N-methyl-N-nitroso-p-toluenesulfonamide (3g) in methanol (45 ml) was added over a 6 hr. period at 0°. Stirring was continued for another 15 hrs. at room temperature before work-up to give 1.00-1.06g of crude product.
5. After recrystallization from pentane (m.p. 222-227°), II was identical (nmr, ir, glc) with authentic material.[2b,e]
6. The glc analyses were performed in the laboratory of Prof. K.H. Overton on a 50 m x 0.5 mm capillary column, coated with Carbowax 1540. Isomeric detectability limits were substantially less than 1%.
7. Other methods either start from dehydroadamantanone,[2a] the synthesis of which (although recently improved by R.K. Murray, Jr. and K.A. Babiak, Tetrahedron Letters, 319 (1974)) is rather tedious, or give II in a difficult to separate mixture with III [2b] or with adamantanone (K.H. Overton, personal communication).
8. This expectation was based on the reaction of diazomethane with 2-norbornanone, see M.A. McKinney and P.P. Patel, J. Org. Chem., 38, 4059 (1973) and refs. cited therein.

9. (a) P. Abley, J.E. Byrd, and J. Halpern, J. Amer. Chem. Soc., 95, 2591 (1973); (b) For general references see A. McKillop and E.C. Taylor, Chem. Brit., 4 (1973).

10. D. Fărcaşiu, P.v.R. Schleyer, and D.B. Ledlie, J. Org. Chem., 38, 3455 (1973).

11. This new compound was prepared in 55% yield by the Wittig reaction of I in DMSO (R. Greenwald, M. Chaykovsky, and E.J. Corey, J. Org. Chem., 28, 1128 (1963), as modified in reference 10) as a white, volatile solid, m. 46-7° (sealed tube), nmr (CCl_4) δ = 1.60 to 1.85 (complex, 12 H) and 4.53 (d of broadened signals, Δ δ 13 cps. 2H), M = 134.109231 (by mass spectrometry), calcd. M = 134.109545. An attempt to prepare the same compound by acid dehydration of 2-methyl-2-a-noradamantanol[1] gave a complex mixture with no $=CH_2$ group shown in the NMR spectrum.

12. A side product (ca 15% yield) was not isolated pure but was tentatively identified as 2-methyl-2-e-noradamantanol by the ir (ν_{OH} = 3300-3600 cm^{-1}) and nmr (singlet for the angular methyl group at δ 1.43 ppm in CCl_4) (cf. ref. 10).

13. J. Boyd and K.H. Overton, J. Chem. Soc., Perkin I, 2533 (1972).

14. Similar arguments have been used to explain the (lower) regioselectivity of ring expansion reactions in other systems.[8]

15. See E.M. Engler, M. Fărcaşiu, A. Sevin, J.M. Cense and P.v.R. Schleyer, J. Amer. Chem. Soc., 95, 5769 (1973).

16. For other preparations of carbon-labeled adamantanes, see: Z. Majerski, P.v.R. Schleyer and A.P. Wolf, J. Amer. Chem. Soc., 92, 5731 (1970); Z. Majerski, S.H. Liggero and P.v.R. Schleyer, Chem. Commun., 1506 (1970); Z. Majerski, A.P. Wolf and P.v.R. Schleyer, J. Labelled Compounds, 6, 179 (1970); S.H. Liggero, Z. Majerski and P.v.R. Schleyer, A.P. Wolf and C.S. Redvanly, H. Wynberg, J.A. Boerma and J. Strating, J. Labelled Compounds 7, 3 (1971).

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