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Working with Hazardous Chemicals

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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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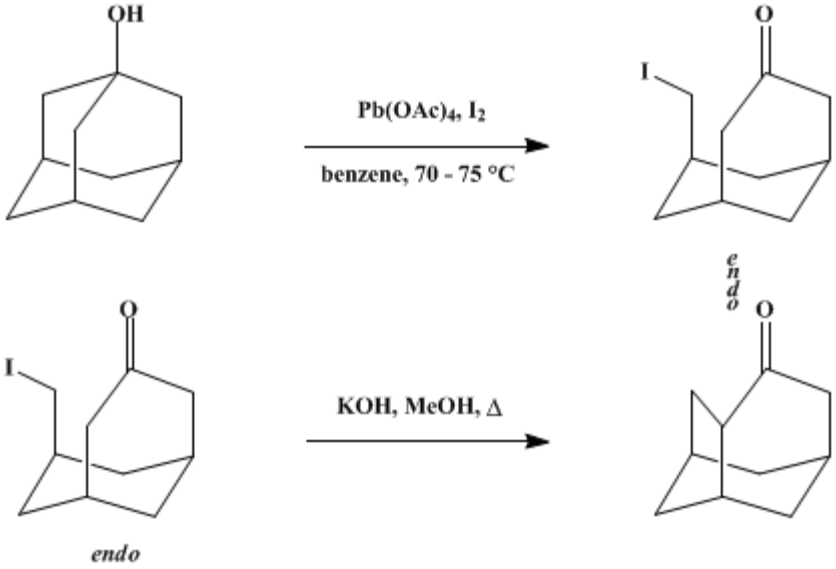
REARRANGEMENT OF BRIDGEHEAD ALCOHOLS TO POLYCYCLIC KETONES BY FRAGMENTATION-CYCLIZATION: 4-PROTOADAMANTANONE (TRICYCLO-[4.3.1.$0^{3,8}$]DECAN-4-ONE)

[2,5-Methano-1*H*-inden-7(4*H*)-one, hexahydro]



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1. Procedure

Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedure involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. endo-7-*Iodomethylbicyclo*[3.3.1]*nonan*-3-*one*. A 2-l., three-necked, round-bottomed flask equipped with an efficient mechanical stirrer and a reflux condenser is charged with 600 ml. of dry benzene (Note 1). The flask is immersed in a water bath, stirring is initiated, and 58.3 g. (0.132 mole) of lead tetraäcetate (Note 2), 37.4 g. (0.147 mole) of iodine, and 10.0 g. (0.0654 mole) of 1-adamantanol (Note 3) are added (Note 4). The bath temperature is gradually raised to 80° over a 20-minute period, then allowed to cool to 70–75°. Stirring is continued for 2 hours at 70–75° (Note 5) and for an additional hour with the mixture is cooled to room temperature. The inorganic salts are filtered and carefully washed with five 50-ml. portions of diethyl ether. The benzene filtrate and ether washings are combined in a 2-l. separatory funnel and shaken with 500 ml. of saturated aqueous sodium bisulfite (Note 6) until the dark red color disappears. The layers are *not* separated. If the color reappears within 10–15 minutes, the mixture is shaken again until colorless. This procedure is repeated as many times as necessary. The layers are then separated, and the organic layer is washed with 500 ml. of water and 250 ml. of saturated aqueous sodium hydrogen carbonate. The benzene–ether solution is dried over anhydrous magnesium sulfate for 1 hour and concentrated in a 500-ml., round-bottomed flask with a rotary evaporator (Note 7). The resulting crude, oily iodo ketone weighs 14–16 g. (Note 8) and is used immediately in Part B.

B. 4-*Protoadamantanone*. The flask containing the crude iodo ketone is equipped with a magnetic

stirring bar and a reflux condenser. A solution of 7 g. (0.1 mole) of potassium hydroxide in 150 ml. of methanol is added, and the mixture is stirred and heated at reflux for 3 hours. The contents of the flask are allowed to cool to room temperature and poured into 300 ml. of ice water. The resulting mixture is extracted with five 100-ml. portions of ether. The combined extracts are dried over anhydrous magnesium sulfate and evaporated under reduced pressure, leaving 8.6–9.1 g. of a yellow solid (Note 9). A solution of this crude product in 3 ml. of chloroform is allowed to percolate onto a chromatography column packed with 200 g. of activity III, neutral alumina in pentane (Note 10). The column is eluted first with 100 ml. of pentane, then with 500 ml. of 3:7 (v/v) ether–pentane, as 25-ml. fractions are collected and analyzed by GC (Note 11). Those fractions containing product whose purity is judged to be 98% or greater are combined and evaporated, affording 7.0–8.1 g. (71–82% based on 1-adamantanol) of 4-protoadamantanone as a colorless or pale-yellow solid, m.p. 202–204° (Note 12).

2. Notes

1. Solvent grade benzene was dried over sodium wire prior to use. If the benzene is wet, a considerable amount of starting 1-adamantanol remains unreacted owing to hydrolysis of lead tetraäcetate.
2. Lead tetraäcetate, both purchased from Fluka AG, Buchs, Switzerland, and prepared according to a literature procedure,[2] was used by the submitters without any noticeable difference. Lead tetraäcetate was dried prior to use for at least 12 hours over potassium hydroxide and phosphorus pentoxide in an evacuated desiccator (12 mm.), protected from direct light. If well protected from moisture, lead tetraäcetate can be kept for weeks. However, after exposure to moisture in the air it usually turns brown due to hydrolysis to lead hydroxide. The reactivity of such lead tetraäcetate is diminished somewhat, but it can still be used. If it has turned black, the reagent should be recrystallized from glacial acetic acid and dried prior to use, as described above.
3. 1-Adamantanol is available from the following three suppliers: Aldrich Chemical Company, Inc.; Fluka AG, Buchs, Switzerland; E. Merck, Darmstadt, Germany. It may also be prepared from adamantane by bromination to 1-bromoadamantane and hydrolysis.[3] Adamantane is sold by the same three suppliers.
4. The resulting solution is dark red in color.
5. The temperature of the bath should be *carefully* maintained in this range. At temperatures below 70° the reaction is much slower and increased amounts of unreacted 1-adamantanol will contaminate the product. At temperatures above 75° the amount of tar in the product is increased.
6. Other reducing agents such as sodium thiosulfate or sodium metabisulfite may be used as well.
7. Most of the solvent was evaporated with a bath temperature of 40–50°. The last 40–50 ml. was removed without heating. *endo*-7-Iodomethylbicyclo[3.3.1]nonan-3-one should be handled as quickly as possible, since this iodo ketone is thermally unstable. In the absence of solvent, decomposition may be rapid even at room temperature.
8. The crude iodo ketone usually contains up to 10% benzene, which does not interfere with the cyclization step (Part B). Complete removal of the benzene takes time, during which a considerable proportion of the iodo ketone may decompose.
9. A GC analysis on the crude product was carried out by the submitters using a 1.5 m. × 3.2 mm. column packed with 10% diethylene glycol succinate supported on 60/80 mesh Chromosorb W and heated at 140°. The chromatogram showed peaks for product, 1–3% unreacted 1-adamantanol, and a total of 1–2% of several other minor by-products.
10. Activity III alumina is prepared by adding 6% (w/w) of water to neutral alumina of activity grade I. The submitters used a 50 × 3 cm. glass column for the chromatography.
11. The conditions for GC are given in Note 9. The product was found mainly in fractions 2–20 by the submitters. The first 25-ml. fraction contained considerable amounts of by-products, while fractions 21 and higher contained 1-adamantanol. The checkers collected 10-ml. fractions with an automatic fraction collector.
12. Recrystallization from aqueous methanol raised the melting point to 207–210° (lit.,[4] m.p. 210–212°). The product obtained by the checkers was analytically pure. Analysis calculated for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 80.19; H, 9.31. The spectral characteristics of 4-protoadamantanone are as follows: IR (KBr) cm.$^{-1}$: 2920, 2860, 1710 (C=O), 1322, 1235; ^{1}H NMR ($CDCl_3$), δ (multiplicity, number of protons): 1.0–2.0 (m, *ca.* 7H), 2.0–3.0 (m, *ca.* 7H); ^{13}C NMR ($CDCl_3$) δ (assignment): 216.2 (*C*=O), 51.1 (*C*H), 45.0 (CH_2), 41.4 (CH_2), 38.2 (CH_2), 37.3 (CH_2 and *C*H), 37.2 (*C*H), 34.9 (CH_2), 29.6 (*C*H); mass spectrum *m/e* (relative intensity): 150 (M^+, 100), 95 (63), 93 (23), 81 (24), 80 (40), 79 (46), 67

(30), 66 (40).

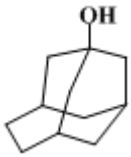
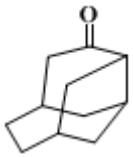
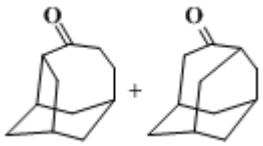
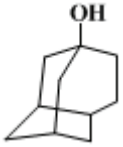
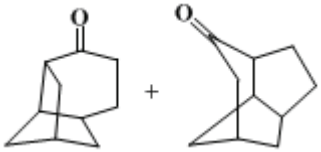
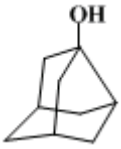
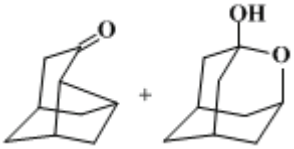
3. Discussion

4-Protoadamantanone is a versatile intermediate for the synthesis of not only protoadamantane derivatives,[5,6,7] but also 1,2- and 2,4-disubstituted adamantanes,[8,9,10] 2-substituted noradamantanes,[11] and 4(5)-substituted 4-homoprotoadamantanes.[12]

4-Protoadamantanone has been prepared by the nitrous acid deamination of 2-amino-1-adamantanol (77%),[5] by aprotic diazotization of *endo*-7-aminomethylbicyclo[3.3.1]nonan-3-one in benzene with an equivalent amount of acetic acid (67%),[13] and by thermolysis of 1-adamantyl hypohalites followed by base-promoted cyclization of the resulting halo ketones (32–37%),[4,14,15] In spite of low and erratic yields, the last reaction sequence has provided the most convenient route to the protoadamantanes, since the other two approaches require lengthy syntheses of the starting materials.

The procedure described here is a modification of one involving the thermal fragmentation of 1-adamantyl hypoiodite and cyclization of the resulting iodo ketone.[4,14,16] With this procedure, 4-protoadamantanone is obtained from 1-adamantanol with consistent yields in the range of 71 to 82% and a purity greater than 98%. This method is also applicable to the preparation of other polycyclic ketones from the related bridgehead alcohols with α-bridges of zero, one, or two carbon atoms (see Table I).

TABLE I
REARRANGED POLYCYCLIC KETONES PREPARED BY FRAGMENTATION AND RECYCLIZATION OF BRIDGEHEAD ALCOHOLS

Alcohol	Product(s)	Ratio	Yield (%)	Reference
		—	74	16
		2:3	78	17
		1:1	69	18
		2:1[a]	30	18

[a] The base-catalyzed cyclization was carried out in aqueous 70% dioxane at reflux.

With unsymmetrical bridgehead alcohols the structure of the product depends on the regioselectivity of both the fragmentation and intramolecular alkylation reactions. The position of the bond cleavage in the fragmentation step appears to be controlled by the relative thermodynamic stability of the keto free radical intermediates which subsequently react with iodine to produce the iodo ketones. In most cases

this can be approximated simply by combination of the relative strain energies of the corresponding hydrocarbons and the relative stabilities of the free radical centers. The course of the cyclization is controlled by the balance of at least three factors: preferential enolization toward one α-methylene group, the size of the smallest ring to be formed, and the relative degree of distortion of the preferred collinear arrangement of the two enolate α-carbon atoms and the carbon-leaving group bond.

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

sodium metabisulfite

4-Protoadamantanone

4-PROTOADAMANTANONE (TRICYCLO-[4.3.1.$0^{3,8}$]DECAN-4-ONE

2-l. separatory funnel

acetic acid (64-19-7)

Benzene (71-43-2)

methanol (67-56-1)

ether,
diethyl ether (60-29-7)

chloroform (67-66-3)

sodium hydrogen carbonate (144-55-8)

lead hydroxide

sodium thiosulfate (7772-98-7)

nitrous acid (7782-77-6)

sodium bisulfite (7631-90-5)

iodine (7553-56-2)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

Pentane (109-66-0)

magnesium sulfate (7487-88-9)

dioxane (123-91-1)

Adamantane (281-23-2)

1-Adamantanol (768-95-6)

1-bromoadamantane (768-90-1)

2,5-Methano-1H-inden-7(4H)-one, hexahydro (27567-85-7)

2-amino-1-adamantanol

1-adamantyl (19740-18-2)

1-adamantyl hypoiodite

iodo ketone

phosphorus pentoxide (1314-56-3)

endo-7-Iodomethylbicyclo[3.3.1]nonan-3-one (29817-49-0)

endo-7-aminomethylbicyclo[3.3.1]nonan-3-one

lead tetraacetate (546-67-8)