COMMUNICATIONS

An Improved Synthesis of 1,4-Disubstituted Adamantanes

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Substitution of adamantane on both a bridge and a bridgehead carbon is rather troublesome. A few methods for the preparation of 1,4-disubstituted adamantanes have been reported but the procedures are elaborate, the yields are relatively low, and the products are often contaminated with isomers (mainly 1,3- and 2,6-disubstituted adamantanes). Thus, disproportionation of adamantan-2-ol in 70 % sulfuric acid gave a 40 % yield of 1,4-disubstituted adamantanes[1]. A 45–50 % yield of 5-hydroxyadamantan-2-one was obtained from the reaction of adamantane with 20 % oleum[2]. Microbiological hydroxylation of 1-acetamidoadamantane gave 1-acetamido-4-hydroxyadamantane in 45 % yield[3]. Bromination of adamantanone under vigorous conditions has been reported[4] to give a 90 % yield of fairly pure 5-bromoadamantan-2-one[4]; however, this reaction proved to depend critically on the quality of the aluminum bromide catalyst used[5].

The present paper describes the oxidation of adamantanone (1) with 100 % nitric acid, leading to the almost exclusive formation of 5-hydroxyadamantan-2-one (2). The reaction is preferentially carried out at room temperature where optimum results (in terms of conversion and yield) are obtained. At higher temperatures, the reaction proceeds much faster and the conversion of 1 is quantitative; however, the yield of 2 is lower, probably due to overoxidation to highly water-soluble di- and trihydroxyketones.

The smooth reaction of adamantanone with nitric acid is surprising, since adamantanone is fairly inert towards several other strong oxidizing agents, e.g., fuming sulfuric acid, chlorosulfonic acid, and chromic acid in acetic acid or in dilute sulfuric acid. Furthermore, the reported bromination of adamantanone occurred only under vigorous conditions (large excess of aluminum bromide, no solvent, elevated temperature, reaction time: 10 days).

In analogy to other bridgehead substitution reactions of adamantane[6], the preferred introduction of a hydroxy group at a tertiary carbon suggests an ionic attack of the adamantane nucleus by the nitric acid. In the case of a radical process, 1,2-, 2,4-, and 2,6-substituted adamantanes should also be formed in appreciable amounts, due to the proposed less discriminative abstraction of tertiary and secondary hydrogens by radicals[7]. In the present experiments, only a few percent of adamantane-2,6-dione could be detected (G.L.C.) in the product. This dione may, however, also be formed by an ionic mechanism, since the

H-atoms at C-6 are considered to be inductively only little influenced by an electron-withdrawing substituent at C-2 (in the present case, a protonated carbonyl oxygen which deactivates the molecule[2]).

Adamantane itself is also readily oxidized by 100 % nitric acid, yielding adamantan-1-ol, 1-adamantyl nitrate, and 1-nitroadamantane; adamantanone or 5-hydroxyadamantan-2-one are not formed under these conditions, indicating that the 1,2-hydride shift of the adamantyl cation, which is rapid in conc. sulfuric acid, probably is very slow in nitric acid[8].

The oxidation of adamantanone with nitric acid provides a useful method for the preparation of various 1,4-disubstituted adamantanes, since the oxidation product (2) is a versatile starting material for the synthesis of other adamantane derivatives. A few examples are summarized in the following Scheme and are described in the experimental section.
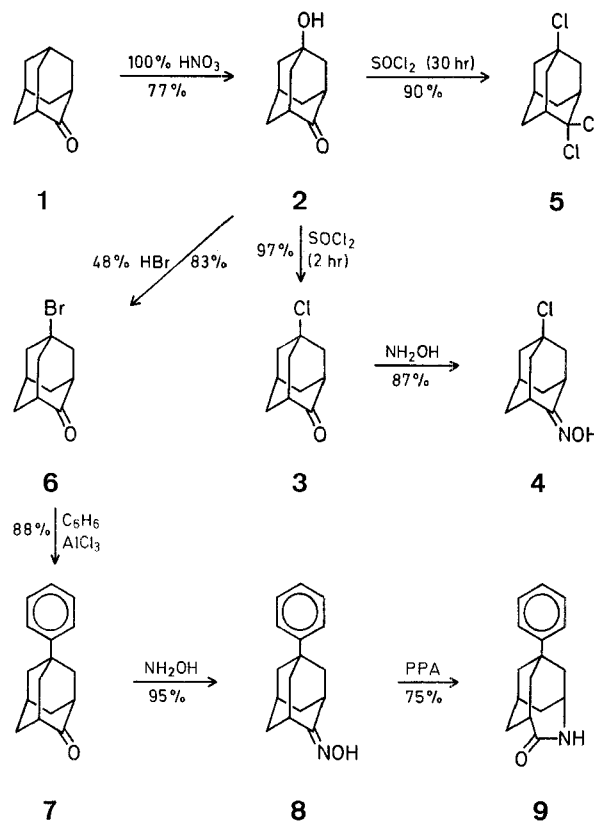
5-Hydroxyadamantan-2-one (2):

Adamantanone[8] (12.0 g, 80 mmol) was added with stirring to 100 % nitric acid (100 ml) cooled in an ice-water bath. The temperature of the mixture during the addition was 13–15°. The adamantanone dissolved instantaneously and the color of the mixture turned orange-brown. The mixture was allowed to stand at room temperature for 70 hr and was then heated at 60° for

90 min. Most of the nitrogen dioxide evaporated. Nitric acid was distilled off under reduced pressure on the steam bath. The residual light yellow oil (17.75 g) solidified upon cooling (HNO$_3$-adduct of the hydroxyketone[10]). Water (40 ml) and 96 % sulfuric acid (15 ml) were added. The resultant clear yellow solution was heated on the steam bath in a hood (nitrous fumes!) for 1 hr. The solution was then cooled and extracted with a 2:1 mixture of petroleum ether (b.p. 40–60°) and ether (2 × 50 ml) to remove unreacted adamantanone (0.70 g). The acid layer was neutralized with 30 % aqueous sodium hydroxide and, while still warm, extracted with chloroform (3 × 50 ml). The extracts were washed with saturated sodium chloride solution (25 ml), combined, and concentrated in vacuo. The crude product (10.75 g) was dissolved in dichloromethane (15–20 ml), and petroleum ether (b.p. 40–60°) was added until no more precipitate was formed. The solid material was isolated by filtration and dried; yield: 9.65 g (77 %, based on converted adamantanone); m.p. 315–318°. G.L.C. analysis indicated the presence of 3 % of adamantane-2,6-dione. Recrystallization from carbon tetrachloride gave pure 2, which was identical with an authentic sample[1]; m.p. 319–321°.

5-Chloro-2-oximinoadamantane (4):

5-Chloroadamantan-2-one[1] (3; 5.3 g, 28.7 mmol), obtained from 2 (4.9 g, 29.5 mmol) and thionyl chloride, was dissolved in ethanol (40 ml). A solution of hydroxylamine hydrochloride (5.0 g, 72 mmol) in 2 N aqueous sodium hydroxide (30 ml) was added, the mixture was heated on a steam bath for 1 hr, and was then concentrated in vacuo to a volume of 20 ml. Upon addition of water (20 ml), the oxime 4 separated as a waxy solid. The product was isolated by filtration, washed with water and with petroleum ether (b.p. 40–60°), and dried; yield: 5.0 g (87 %); m.p. 131–133°.

1,4,4-Trichloroadamantane (5):

5-Hydroxyadamantan-2-one (2; 5.0 g, 30 mmol) was refluxed with thionyl chloride (40 ml) for 30 hr. The excess thionyl chloride was removed in vacuo and the solid residue recrystallized from methanol; yield: 5.78 g; m.p. 153–154°. Upon concentration of the mother liquor, a second crop (0.72 g) was obtained; m.p. 150–153°; total yield: 90 %.

5-Phenyladamantan-2-one (7):

5-Bromoadamantan-2-one[1] (6; 14.2 g, 62 mmol), obtained from 2 (12.3 g, 74 mmol) and 48 % hydrobromic acid, was dissolved in benzene (100 ml). Aluminum bromide (25 g, 94 mmol) was gradually added and the mixture was refluxed for 1 hr. It was then poured on ice, the benzene layer was separated, the aqueous layer was extracted with dichloromethane, the organic layers were combined, washed with water, dried with sodium sulfate, and evaporated to dryness. The resultant light brown oil solidified on cooling (14.1 g). The product was recrystallized from petroleum ether (b.p. 60–80°); yield: 10.1 g; m.p. 65–67°. Concentration of the mother liquor afforded a second crop (2.2 g); m.p. 61–64°; total yield: 88 %.

2-Oximino-5-phenyladamantane (8):

5-Phenyladamantan-2-one (7; 12.2 g, 54 mmol) was dissolved in hot ethanol. To the hot solution was added a solution of hydroxylamine hydrochloride (8.7 g, 1.25 mol) in 2 N aqueous sodium hydroxide (50 ml). The oxime began to crystallize immediately. The mixture was heated on the steam bath for 1 hr. It was then concentrated in vacuo to a volume of ~ 40 ml, diluted with water (40 ml), and filtered. The solid on the filter was washed with water and with ethanol and was recrystallized from ethanol; yield: 11.6 g; m.p. 176–179°. Concentration of the mother liquor afforded a second crop (0.8 g); m.p. 175–178°; total yield: 95 %.

5-Oxo-1-phenyl-4-azatricyclo[4.3.1.1^{3,8}]undecane (9):

2-Oximino-5-phenyladamantane (8; 1.2 g) was added with stirring to polyphosphoric acid (16.0 g, 85% P$_2$O$_5$) at 130° over a period of 10 min. The oxime gradually dissolved while the mixture became light brown. The mixture was stirred at 125–130° for 30 min and was then poured into a mixture of 25 % aqueous

ammonia (25 ml) and water (50 ml). The acid dissolved at a temperature of ~ 60° with stirring (cooling), leaving the lactam as a colorless precipitate. The product was isolated by filtration, washed with water, and dried; yield: 0.9 g (75 %); m.p. 196–199°.

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