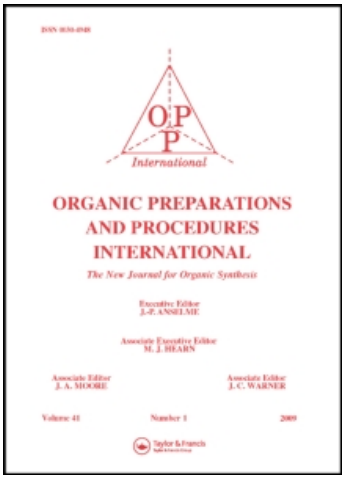


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# CONVENIENT PREPARATION OF 1-ADAMANTANOL FROM ADAMANTANE INDUCED BY A HYDRIDE TRANSFER

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## OPPI BRIEFS

# CONVENIENT PREPARATION OF 1-ADAMANTANOL FROM ADAMANTANE INDUCED BY A HYDRIDE TRANSFER

*Submitted by* (00/00/92)

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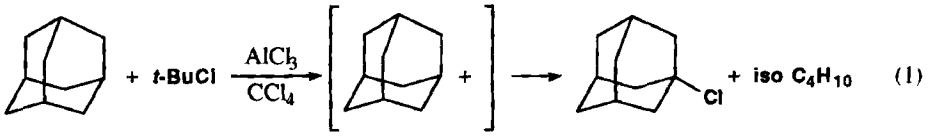
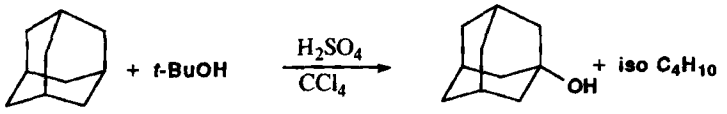
The selective activation (and functionalization) of alkanes is a topic of current interest[1] which combines the well-known lack of reactivity of hydrocarbons with recent progress in catalysis.[2] In the field of alkane functionalization, adamantane is a starting material of choice, owing to its symmetry, lipophilicity and multiple applications.[3] Among the functionalizations of adamantane, the oxidation to 1-adamantanol is one of the most useful.[4] Several methods have been described for transforming adamantane to 1-adamantanol. Worthy of note are the use of oxygen and ozone under different conditions,[5-10] of peroxydic reagents,[11-17] and more recently of the GIF-ORSAY system by BARTON.[18] However, many of these reactions give low yields or poor selectivity and require the use of complex catalytic systems or of hazardous reagents.

Under super acidic conditions ($SbCl_5$ + $FSO_3H$), the adamantyl cation derived from the isomerization of *endo*-trimethylenenorbornane,[19] was reported to be hydrolyzed to adamantanol. In a different study, using a Lewis acid ($AlCl_3$) and *t*-BuCl, we have been able to prepare 1-chloroadamantane, with high yield and selectivity, according to Eq. 1.[20]




(1)

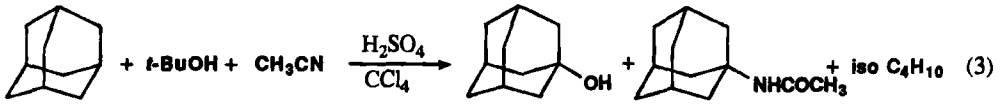
We therefore expected that 1-adamantanol could be obtained easily according to the same type of reaction.




(2)

The results of reaction 2 are reported in the Table. Entry 1 indicates that the reaction fails

when a simple extrapolation from Eq. 1 is made. Entry 2 corresponds to results of the Ritter procedure[21] extended to adamantane (Eq. 3), that we were studying for preparing adamantylamides from adamantane.



(3)

When the ratio of reagents from entry 2 was used, we obtained 21% of 1-adamantanol besides 1-acetylaminoadamantane (1%). We anticipated that a change of the proportion of $CH_3CN$ would give a increased yield in 1-adamantanol. This is observed in entries 3-8 of the Table where an optimum in yield is reported in entry 3. Entry 9 indicates that $CCl_4$ (frequently used in reactions of adamantane), in which adamantane is soluble, should be prefered to hexane.[22,23]

**TABLE.** Preparation of Adamantanol from Adamantane in $CCl_4$ using *t*-Butanol and $H_2SO_4$ (Eq. 2)

| Entry | Co-solvent | Ratio[a] $CH_3CN$/AdH | % Yield of 1-Adamantanol[b] |
|---|---|---|---|
| 1 | none | 0.5 | 0 |
| 2 | $CH_3CN$ | 0.5 | 21 |
| 3 | $CH_3CN$ | 1.8 | 89 |
| 4 | $CH_3CN$ | 2 | 86 |
| 5 | $CH_3CN$ | 4 | 86 |
| 6 | $CH_3CN$ | 6 | 61 |
| 7 | $CH_3CN$ | 10 | 42 |
| 8 | $CH_3CN$ | 18 | 7 |
| 9[c] | $CH_3CN$ | 18 | < 2 |

a) Molar ratio (0.05 mole of adamantane being constant. b) GC result. c) Hexane is used in place of $CCl_4$.

No di- or polyhydroxylation of adamantane was detected (by GC-MS) under the reaction conditions described in experimental section. The regioselectivity of hydroxylation in favor of a tertiary carbon (giving 1-adamantanol) instead of a secondary carbon (giving 2-adamantanol) was complete (no 2-adamantanol was detected by GC-MS). Small amounts of Adamantyl *t*-butyl ether were detected (0-1% depending upon the entry) and 1-acetylaminoadamantane was also formed in small amounts: 1.5% in entry 3 where the maximum yield (89% by GC) of 1-adamantanol was obtained.

In all entries, the reaction was initiated by a hydride transfer between the *t*-butyl cation, derived from *t*-butanol and adamantane. This is true even in Entry 1, where no adamantanol is obtained; in this case the adamantyl cation is not hydrolyzed but reacts with isobutene (derived from *tert*-butyl cation) giving *iso*-butyladamantane. The reason why the adamantyl cation is not hydrolyzed (Entry 1) is not fully understood at the moment and we are studying further this mechanistic aspect to check whether this step is under chemical or physical control. However, the synthesis of 1-adamantanol from adamantane reported in entry 3 of the table (and described in the Experimental Section)

gives, to the best of our knowledge, one of the highest yield so far reported of crude isolated material, under facile conditions using simple reagents. In addition, the functionalization (between adamantane and *t*-butanol) induced by a hydride transfer can be extended to other reagents.[26] We are studying these possibilities further.

## EXPERIMENTAL SECTION

GC Analyses were carried out using a SHIMADZU GC 14 gas chromatograph equipped with a SHIMADZU C-RGA integrator, a flame ionization detector and a packed column with chromosorb WAP 80/100 and 3% OV 101(200 cm length, 2.2 mm section) operated between 120 and 280°C with a temperature gradient of 8°C/min and 2 bars pressure of dinitrogen. The melting point was determined on a Electrothermal 1A9100 digital melting point apparatus. $^1$H NMR spectra were recorded on a Bruker AW-60. $^{13}$C NMR spectra were recorded on a Bruker AM-100. IR were obtained with a Beckman Acculab 2.

**Procedure for the Hydroxylation of Adamantane.**- Into a 250 mL flask, fitted with a mechanical stirrer, dropping funnel and reflux condenser, were placed 6.812 g (0.05 mole) of adamantane, 50 mL of carbon tetrachloride and 70 mL of 98% sulfuric acid. A mixture of acetonitrile (0.09 mole, see Table)/*t*-butyl/alcohol (0.1 mole) was added dropwise to the solution at 40° and stirred for 4 hrs at that temperature. The reaction mixture was cooled in an ice-water bath and the two phases were separated. The aqueous phase was extracted with carbon tetrachloride and the organic extract was washed successively with 50 mL of saturated sodium hydrogen carbonate (10%), 50 mL of water and dried over sodium sulfate. The solvent was removed with a rotary evaporator at 50°, giving 6.56 g (86% crude yield) of white crystals which were sublimed and recrystallized from 1:1 (v/v) dichloromethane/hexane giving 4.25 g (56% yield) of 1-adamantanol (98.9% purity(by GC)) mp. 240.-242°, lit [17] mp 238-240°.

GC: solvent ($CCl_4$), 0.61min; adamantanol, 3.83min. $^1$H NMR ($CDCl_3$) (ppm): δ 1.73 (m); δ 2.17 (s).$^{13}$C NMR ($CDCl_3$) (ppm): δ 30.72 (CH); δ 36.12 ($CH_2$); δ 45.33 ($CH_2$); δ 68.17 (C-OH). IR 3291, 2917, 2849, 1453, 1353, 1300, 1118, 1102, 1088, 982, 926, 551 cm$^{-1}$. An authentic sample (purchased from Aldrich-Chimie) had similar mp (240-242°), $^1$NMR [27] and IR [28] data.

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## FORMATION OF A 1,2-DIHYDROPYRAZINE USING AN AMINO ACID AND D-GLUCOSE

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Pyrazines, the most important flavored compounds in food,[1] may have dihydropyrazines as precursors which are currently considered to be produced from complex interactions between amino acids and carbohydrates.[2] However, to our knowledge, such dihydropyrazines have never been isolated and identified due to their instability. A previous paper[3] reported that *antiaromatic* 1,4-dihydropyrazines can be synthesized only if the ring substituents are electron-deficient or hinder the conjugation of the 8p electron system by steric repulsion. Usually, the poorly stable 1,4-dihydropyrazines undergo a 1,3-sigmatropic rearrangement to form relatively stable 1,2-dihydropyrazines. In order to explore the pathway leading to the formation of pyrazines in the Maillard reaction, we undertook the synthesis of dihydropyrazines in which carbohydrate and amino acid moieties were combined.

3,5,6-Tri-O-methyl-D-glucose (**1**), ethyl glycine, *p*-toluidine and phenacyl bromide were chosen as starting materials in order to enhance the stability of reaction products. The D-glucose derivative **1**[4] and N-phenacyl-*p*-toluidine (**2**)[3] were prepared as reported previously. Reaction between **1** and **2** did not occur at room temperature and the decomposition of **1** became a serious problem with increasing reaction temperatures. Since Lewis acids[5] catalyze the condensation of aldehydes or ketones with secondary amines to form enamines, this led us to utilize zinc chloride ($ZnCl_2$). The reaction proceeded rapidly to give a 46% yield of N-phenacyl-N-*p*-tolyl-3,5,6-tri-O-methyl-D-glucofuranosylamine **3** (Method A). Structural elucidation was based on the interpretation of the physical data of its acetyl derivative **4**. In acidic medium, compound **3** underwent the Amadori rearrangement to provide its isomer **5**.