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for the Preparation
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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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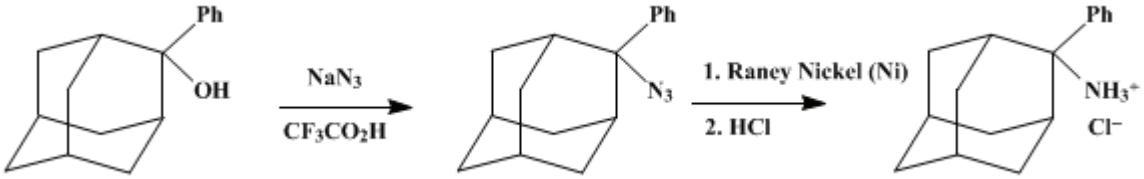
2-PHENYL-2-ADAMANTANAMINE HYDROCHLORIDE

[Tricyclo[3.3.1.1^{3,7}]decan-2-amine, 2-phenyl, hydrochloride]



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Checked by Carl R. Johnson and Debra L. Monticciolo.

1. Procedure

Caution! The reaction should be carried out in a good hood.

A. *2-Azido-2-phenyladamantane*. A 500-mL, three-necked, round-bottomed flask equipped with a mechanical stirrer, a pressure-equalizing dropping funnel, and a thermometer is charged with 125 mL of chloroform and 13 g (0.2 mol) of sodium azide. The mixture is cooled with an ice–salt bath to −5°C to 0°C, and 37.5 mL (0.5 mol) of trifluoroacetic acid is added, followed after 5–10 min with 22.8 g (0.1 mol) of 2-phenyl-2-adamantanol (Note 1). The resulting slurry is stirred for 4 hr at 0°C and then allowed to reach room temperature overnight. The mixture is cautiously neutralized with a slight excess of 12–15% aqueous ammonia solution and transferred to a separatory funnel. The chloroform layer is separated, and the aqueous solution is extracted with 50 mL of chloroform. The combined organic extracts are washed with 50 mL of water, separated, and dried over magnesium sulfate. The solvent is removed in a rotary evaporator. The oily residue solidifies on cooling. The yield is 23.6–24.8 g (93–98%), mp 42–45°C. Recrystallization of a sample from 2-propanol raises the melting point to 47–48°C (Note 2).

B. *2-Phenyl-2-adamantanamine hydrochloride*. A solution of 24 g (0.095 mol) of the crude 2-azido-2-phenyladamantane in 75 mL of 2-propanol is placed in a 1-L beaker fitted with a mechanical stirrer, and heated in a water bath that can be removed quickly. Wet, active Raney nickel (Note 3) and (Note 4) is added in portions at 60–70°C with stirring until the evolution of nitrogen ceases (Note 5). The mixture is heated for an additional 10 min, filtered through a Büchner funnel, and washed with 75 mL of 2-propanol in such a manner that the catalyst is always covered with liquid (Note 6). The filtrate is concentrated in a rotary evaporator under reduced pressure. The crude residue is dissolved in 75 mL of toluene and treated with 22 mL of concentrated hydrochloric acid while stirring. The 2-phenyl-2-adamantanamine hydrochloride is collected, triturated with 50 mL of warm acetone, filtered again, and air-dried. The yield is 22.5–24.0 g (90–96%), and the product melts at 293–296°C (closed capillary) (Note 7) and (Note 8).

2. Notes

1. 2-Phenyl-2-adamantanol[2] is prepared by adding 25 g (0.167 mol) of 2-adamantanone (Note 3) in several portions to phenylmagnesium bromide, obtained from 40 g of bromobenzene and 6.5 g of magnesium turnings in 200 mL of diethyl ether. The solution is stirred for 1 hr and worked up with aqueous ammonium chloride. The organic layer is separated, dried over magnesium sulfate, concentrated, and the oily residue is crystallized from petroleum ether. The yield is 25.5 g (67%) of crystals melting at 77–78°C. The crude oily residue may be used in the next step without purification.
2. The product is characterized by IR (CCl_4) cm^{-1}: 2075; ^{1}H NMR (CCl_4) δ: 1.72 and 2.40 (s, 14 H), 7.20 (s, 5 H).
3. 2-Adamantanone was obtained from Aldrich Chemical Company, Inc. Active Raney nickel catalyst

was obtained from W. R. Grace Company.
4. The amount of Raney nickel depends on its hydrogen content. Usually 25–35 g is sufficient.
5. A large vessel is required because of excessive frothing. The frothing may be controlled by adding a little cold 2-propanol, by removing the heating, or by stopping the stirrer.
6. *Caution! Dry catalyst is pyrophoric.*
7. The free 2-phenyl-2-adamantanamine may be liberated from the salt by adding a solution of ammonia or sodium hydroxide, extracting with toluene, concentrating, and distilling under reduced pressure; bp 120–122°C (0.15 mm); n_D^{17} 1.5850; ^{1}H NMR (CCl_4) δ: 1.30 (s, 2H, NH_2), 1.68 and 2.26 (br s, 14 H, adamantane protons), 7.1 (m, 5H, Ph).
8. Similarly, 2-butyl-2-adamantanamine hydrochloride, mp 300–305°C, is obtained from 2-butyl-2-adamantanol[3] in 30% yield.

3. Discussion

The present procedure is an example of preparation of tertiary phenylcarbinylamines, and is in many cases superior to methods based on the Ritter reaction,[4] and Hofmann[5] or Curtius degradation.[6] The availability of starting materials, fair yields of products, and the simplicity of operations (there is no need to isolate any intermediates or to use a hydrogenation apparatus) are the main advantages of this procedure. The azide synthesis is adapted from procedures described for the preparation of 1,1-diphenyl-2-azidoethane[7] and 1-phenyl-1-azidocyclohexane.[8] The azides are quite stable and could be distilled under reduced pressure. The amines and their substitution products are physiologically active agents.[4,9]

A number of compounds have been prepared by this method (the isolation of hydrochloride can be omitted), as listed in Table I.[10]

TABLE I
AMINES FROM TERTIARY ALCOHOLS

Alcohol	Azide[a] Bp (°C) (mm Hg)	Amine Bp (°C) (mm Hg)	Amine Yield (%)	Amine Starting Material
2-Phenyl-2-propyl	106 (22)	100 (22)	66	α-Methylstyrene
1-Phenylcyclo-pentyl	139–140 (38)	128–130 (20)	40	Cyclopentanone
1-Phenylcyclo-hexyl		115–120 (5)	38	Cyclohexanone
2-Methyl-1-phenyl-cyclohexyl	90–91 (0.25)	150–153 (23)	66	2-Methyl-1-phenyl-cyclohexanol
1-Phenylcyclo-heptyl	153–155 (23)	163–165 (25)	45	Cycloheptanone
2-Phenyl-2-norbornyl	150–155 (25)	163–165 (28)	51	2-Norbornanone

[a] The azides contain up to 15–20% of the corresponding phenylalkenes.

References and Notes

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

petroleum ether

amine

alcohol (64-17-5)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

magnesium turnings (7439-95-4)

Cyclohexanone (108-94-1)

nitrogen (7727-37-9)

Raney nickel (7440-02-0)

acetone (67-64-1)

toluene (108-88-3)

2-propanol (67-63-0)

bromobenzene (108-86-1)

Cyclopentanone (120-92-3)

Phenylmagnesium bromide (100-58-3)

sodium azide (26628-22-8)

magnesium sulfate (7487-88-9)

Cycloheptanone (502-42-1)

trifluoroacetic acid (76-05-1)

α-methylstyrene (98-83-9)

2-Norbornanone (497-38-1)

2-adamantanone (700-58-3)

2-Phenyl-2-adamantanamine hydrochloride,
Tricyclo[3.3.1.1^{3,7}]decan-2-amine, 2-phenyl, hydrochloride (73032-81-2)

2-phenyl-2-adamantanol (29480-18-0)

2-Azido-2-phenyladamantane (65218-96-4)

2-phenyl-2-adamantanamine

2-butyl-2-adamantanamine hydrochloride

2-butyl-2-adamantanol

1,1-diphenyl-2-azidoethane

1-phenyl-1-azidocyclohexane

2-Phenyl-2-propyl (16804-70-9)

1-Phenylcyclo-pentyl

1-Phenylcyclo-hexyl

2-Methyl-1-phenyl-cyclohexyl

2-Methyl-1-phenyl-cyclohexanol

1-Phenylcyclo-heptyl

2-Phenyl-2-norbornyl