

Synthesis of Adamantane Derivatives. 37.¹ A Convenient and Efficient Synthesis of 1-Azidoadamantane and Related Bridgehead Azides, and Some of Their Reactions

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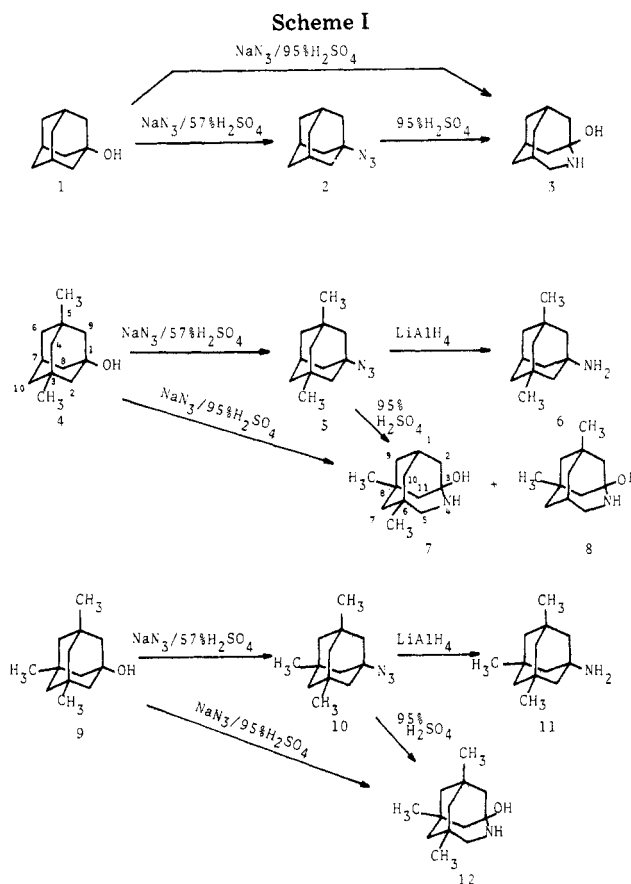
Several bridgehead azides such as 1-adamantyl (2), 3,5-dimethyl-1-adamantyl (5), 3,5,7-trimethyl-1-adamantyl (10), 1-bicyclo[3.3.1]nonyl (14), and 3-homoadamantyl azide (18) were prepared in high yields from the corresponding bridgehead alcohols on treatment with sodium azide in 57% H₂SO₄-CHCl₃. Azides 2, 5, and 10 were decomposed in 95% H₂SO₄ to afford the rearranged products, 4-azahomoadamantan-3-ol derivatives 3, 7, 8, and 12, which were also obtained from the corresponding bridgehead alcohols on treatment with sodium azide in 95% H₂SO₄. Azides 5, 10, 14, and 18 were converted to the corresponding bridgehead amines 6, 11, 15, and 19.

Organic azides are well known as an excellent synthetic starting material, however, synthetic studies by using bridgehead azides seem to be quite limited;² this might be due to the lack of a facile and efficient method for introduction of the azide group at bridgehead positions. For example, 1-azidoadamantane (2) has been prepared previously via a direct substitution method of 1-bromoadamantane with sodium azide in dimethyl sulfoxide by us³ or via a diazo-transfer method to 1-aminoadamantane by Quast and Eckert,⁴ but the former method gives only a moderate yield of 2 and the latter method requires vigorous anhydrous conditions and longer reaction times. The direct substitution method was considerably improved recently by Miller⁵ by using zinc chloride as the catalyst, but the reaction is quite slow. This paper deals with a convenient and efficient synthesis of 2 and related bridgehead azides as well as some of their reactions.

Results and Discussion

In view of the fact that secondary and tertiary aryl carbinols can be converted to the corresponding azides with hydrazoic acid in trichloroacetic acid⁶⁻⁸ and the relatively facile formation of 1-adamantylcarbenium ion under acidic conditions,⁹ we examined the reaction of 1-adamantanol (1) with in situ generated hydrazoic acid in various acid-chloroform mixtures. As shown in Table I, azide 2 was obtained in an excellent yield by using 57% H₂SO₄ as the acid and 3 h as the reaction time. However, azide 2 was not stable under the reaction conditions and was converted slowly to a rearranged product 3, as demonstrated by the data of a 15-h reaction (Table I). 2 was also converted to 3 exclusively on treatment with 95% H₂SO₄-CHCl₃ (Scheme I). The rearranged product 3 was identified as 3-hydroxy-4-azatricyclo[4.3.1.1^{3,8}]undecane (4-azahomoadamantan-3-ol) by comparison with an authentic sample.^{4,10} 3 was also obtained directly from 1 in 94% yield by using 95% H₂SO₄-CHCl₃ and sodium azide (1.25-fold excess to 1) (The Schmidt reaction). This provides a facile and efficient synthesis of 3. The reaction of 1 with sodium azide in other acid-CHCl₃ mixtures did not give satisfactory results, as summarized in Table I.

Application of this simple azide synthetic method to 1-hydroxy-3,5-dimethyladamantane (4) afforded azide 5 in 72% yield which was converted to known amine 6¹¹ on lithium aluminum hydride reduction. Azide 5 on treatment with 95% H₂SO₄-CHCl₃ afforded a 2:1 mixture of rearranged products 7 and 8, which was also obtained directly from 4 on treatment with sodium azide in 95% H₂SO₄-CHCl₃ in high yields (Scheme I). The major product 7 was isolated after repeated recrystallizations from aqueous methanol and was characterized as 6,8-dimethyl-4-azahomoadamantan-3-ol on the basis of analytical and spectral data. The IR spectrum (KBr)



exhibited strong bands at 3300 and 3170 cm⁻¹ (OH and NH) but no carbonyl absorption bands, and the NMR spectrum (CDCl₃) revealed characteristic signals at δ 3.47 (s, 1 H) and 3.25 (br s, 1 H) (both signals disappeared on shaking with D₂O and are assignable to OH and NH), 2.63 (s, 2 H, -CH₂N-), 2.3-0.9 (m, 11 H), 0.90 (s, 3 H, CH₃), and 0.80 (s, 3 H, CH₃), supporting the assigned structure 7. The IR spectrum of the mixture of 7 and 8 was quite similar to 7, and the NMR spectrum exhibited a characteristic doublet at δ 2.90 ($J = 4.0$ Hz, 0.75 H against 1.25 H of the signal at δ 2.63) and a singlet signal at δ 0.92 (2.3 H against 3.7 H of the two methyl singlets at δ 0.90 and 0.80) besides the signals due to 7, and hence the rearranged product was analyzed as 2:1 mixture of 7 and 8, 1,8-dimethyl-4-azahomoadamantan-3-ol. The results indicate that the methyl substituent at C₃ and C₅ in 5 or its protonated form revealed no effect on the migratory aptitude of C₁-C₂ and C₁-C₉ bonds compared to the C₁-C₈ bond because the bond migration occurred in a statistical ratio.

Table I. Reactions of 1 with NaN₃ in Various Acid-CHCl₃ Mixtures

Acid ^a	Mol ratio of NaN ₃ to 1	React. time, h ^b	Product, % ^c		Unreacted 1, % ^d
			2	3	
CCl ₃ COOH	1.5	20	1	0	99
CF ₃ COOH	1.5	20	0.3	40	59
CH ₃ SO ₃ H	1.5	20	2.4	65	0.8
30% H ₂ SO ₄	3.0	15	Trace	0	99
47.5% H ₂ SO ₄	3.0	15	68	22	Trace
57% H ₂ SO ₄	2.0	3	96	Trace	4
57% H ₂ SO ₄	2.0	15	67	27	4
95% H ₂ SO ₄	1.25	1	0	94	1.8

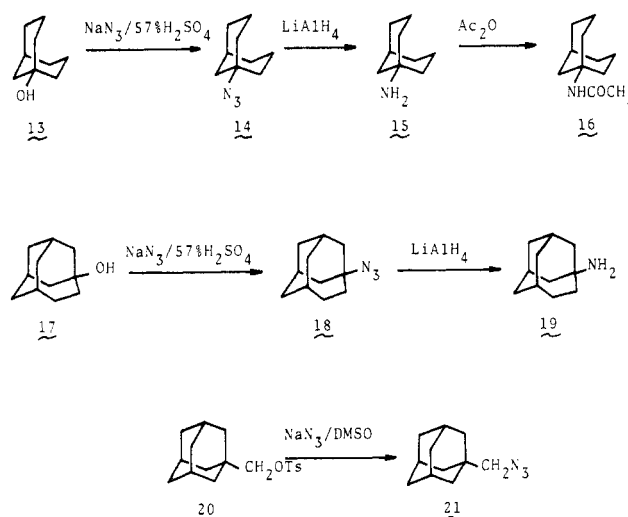
^a A 1:1 (v/v) mixture of the acid and CHCl₃ was used. ^b Sodium azide was added little by little during 0.5 h to a stirred and ice-cooled mixture of 1 and acid-CHCl₃, and the stirring was continued at 20–25 °C. The reaction time involves the addition time of NaN₃. ^c Isolated yield of the crude product. ^d GLC analysis of the crude product.

Similarly, 3,5,7-trimethyl-1-adamantyl azide (10) was prepared from 9 in 76% yield and was converted to the corresponding amine 11 which was identified with an authentic sample.¹² The acid-catalyzed decomposition of 10 afforded 1,6,8-trimethyl-4-azahomoadamantan-3-ol (12) in high yield, which was also obtained from 9 and sodium azide in 95% H₂SO₄ (Scheme I).

Other bridgehead azides such as 14 and 18 were also obtained in good yields (Scheme II). 1-Azidobicyclo[3.3.1]nonane (14) was obtained from the corresponding bridgehead alcohol 13¹³ in 70% yield on treatment with sodium azide in 57% H₂SO₄-CHCl₃. Lithium aluminum hydride reduction of 14 gave the corresponding amine 15 which was acetylated to the known acetylamino derivative 16.¹⁴

3-Homoadamantyl azide (18) was obtained in 73% yield from 3-homoadamantanol (17) under the similar conditions. Lithium aluminum hydride reduction of 18 gave 3-homoadamantylamine 19.¹⁵ The skeletal integrity of 18 was evidenced by the spectral data (Table II) and also by comparison with 1-adamantylcarbinyl azide (21) which was prepared from the carbinyl tosylate 20 on treatment with sodium azide in dimethyl sulfoxide (Scheme II). All of these results are summarized in Schemes I and II, and Tables I and II.

Although several improved procedures for the synthesis of bridgehead azides have been developed recently,^{5,16} the present procedure by using sodium azide in 57% H₂SO₄-CHCl₃ may be one of the most simple and efficient methods. However, it should be noted that this method can not be applicable to less-reactive bridgehead alcohols such as non-

Scheme II

radamantan-1-ol, since the corresponding bridgehead carbonium ion can not be generated under the reaction conditions (57% H₂SO₄).¹⁷

Experimental Section¹⁸

General Procedure for Synthesis of Bridgehead Azides from the Corresponding Alcohol. To an ice-cooled and stirred mixture of an appropriate bridgehead alcohol (10 mmol) in 57% H₂SO₄ (10 mL) and CHCl₃ (10 mL) was added little by little solid sodium azide (1.30 g, 20 mmol) (or an appropriate amount depending on the substrate, see Table II) during 0.5 h, and the resulting mixture was stirred for 2–27 h at 20–25 °C (Tables I and II). The mixture was poured onto ice-water and extracted with methylene chloride (four 10 mL portions). The combined extracts were washed with 5% NaHCO₃ (10 mL) and water (5 mL) and dried (Na₂SO₄). Removal of the solvent under reduced pressure (water aspirator) gave the corresponding azides. The solid azides 2 and 18 were purified by recrystallization from aqueous methanol and sublimation. The oily azides 5, 10, and 14 were purified on a silica gel column eluting with *n*-hexane-methylene chloride or by Kugelrohr distillation. The acidic aqueous layer was basified with ice-50% NaOH and extracted with CHCl₃ (five 10 mL portions). The combined extracts were dried (Na₂SO₄) and evaporated to dryness to afford rearranged products such as 3 in various amounts depending on the reaction conditions.

3-Hydroxy-4-azatricyclo[4.3.1.1^{3,5}]undecane (3). To an ice-cooled and stirred mixture of 95% H₂SO₄ (8 mL) and chloroform (8 mL) was added 1-hydroxyadamantane (1) (0.76 g, 5.0 mmol) in one portion and then solid sodium azide (0.41 g, 6.3 mmol) little by little during 0.5 h. After the stirring was continued for a further 0.5 h at 20–25 °C, the mixture was poured onto ice-water (ca. 20 mL), and the aqueous layer was separated from the chloroform layer, washed with methylene chloride (two 10-mL portions), and basified with ice-50% NaOH, and extracted with chloroform (seven 10-mL portions). The

Table II. Synthesis of Bridgehead Azides 5, 10, 14 and 18, and Their Physical Data^{a,b}

Alcohol	Mol ratio of NaN ₃ to alcohol	React. time, h ^c	Azide (yield, %)	n _D (mp, °C)	IR, ^d cm ⁻¹	NMR chemical shift, ^e δ
4	3.0	2.0	5 (72)	1.5038 (27)	2100	2.4–2.0 (m, 2 H), 1.8–1.0 (m, 12 H), 0.89 (s, 6 H)
9	3.0	24.0	10 (76)	1.5045 (15)	2090	1.35 (s, 6 H), 1.10 (s, 6 H), 0.89 (s, 9 H)
13	4.3	2.0	14 (70)	1.5092 (20)	2100	2.2 (br s, 1 H), 2.1–1.1 (m, 14 H)
17	4.0	27.0	18 (73)	97–98	2100	2.7–1.2 (m)

^a Solid NaN₃ was added to a stirred and ice-cooled mixture of alcohol and 57% H₂SO₄-CHCl₃ (1:1, v/v, ratio) during 0.3–0.5 h, and the mixture was stirred at 20–25 °C. ^b Satisfactory elemental analytical data were reported for all compounds listed in the table. ^c The reaction time involves the addition time of NaN₃. ^d Neat film for oily azides and KBr for solid azides. ^e In CDCl₃.

combined extracts were dried (Na_2SO_4) and evaporated to afford **3** as colorless crystals (0.785 g, 94.0%) which the IR spectrum was superimposable with an authentic sample.¹⁰ One recrystallization from methanol afforded **3** of mp 163–165 °C (lit.¹⁰ 164–165 °C) (0.668 g, 85.0%).

Azide **2** (50 mg, 0.28 mmol) was stirred in 95% H_2SO_4 (1 mL) and CHCl_3 (1 mL) for 1 h at 20–25 °C and the usual workup as above afforded **3** (38 mg, 81%).

1-Amino-3,5-dimethyladamantane (6). A mixture of azide **5** (62 mg, 0.30 mmol) and lithium aluminum hydride (38 mg, 1.0 mmol) in anhydrous ether (2 mL) was stirred for 12 h at room temperature and refluxed for 1 h. The cooled reaction mixture was treated with water, and the mixture was extracted with ether (ten 2-mL portions). The combined extracts were dried (Na_2SO_4) and saturated with dry hydrogen chloride gas to precipitate the hydrochloride of the amine **6** (40 mg, 61.4%), mp >300 °C, which the IR spectrum was superimposable with an authentic sample, mp >300 °C, which was prepared by hydrolysis of 1-acetylamino-3,5-dimethyladamantane.¹¹

3-Hydroxy-6,8-dimethyl-(7) and 3-Hydroxy-1,8-dimethyl-4-azatricyclo[4.3.1.1^{3,8}]undecane (8). To an ice-cooled and stirred mixture of 1-hydroxy-3,5-dimethyladamantane (**4**) (1.08 g, 6.0 mmol), CHCl_3 (8 mL), was added solid sodium azide (0.65 g, 10 mmol) during 0.5 h, and the stirring was continued for a further 3 h at 20–25 °C. The mixture was poured onto ice-water and the chloroform layer was separated. The aqueous layer was basified with ice–50% NaOH and extracted with chloroform (seven 10-mL portions), and the combined extracts were dried (Na_2SO_4). Removal of the solvent gave crude rearranged products which were recrystallized from aqueous methanol to afford a 2:1 mixture of **7** and **8** (1.08 g, 92%); mp 78–88 °C; IR (KBr) 3300, 3170, 1455, and 1050 cm^{-1} ; NMR see the text.

Anal. Calcd for $\text{C}_{12}\text{H}_{21}\text{ON}$: C, 73.79; H, 10.84; N, 7.17. Found: C, 73.79; H, 10.58; N, 7.20.

Recrystallization of the mixture five times from aqueous methanol afforded pure **7** (105 mg, 9%); mp 105–107 °C; IR (KBr) 3300, 3170, 1456, and 1050 cm^{-1} ; NMR see the text.

Anal. Calcd for $\text{C}_{12}\text{H}_{21}\text{ON}$: C, 73.79; H, 10.84; N, 7.17. Found: C, 73.76; H, 10.60; N, 7.19.

Azide **5** (19 mg, 0.093 mmol) was decomposed in 95% H_2SO_4 (0.5 mL) and CHCl_3 (0.5 mL) for 0.5 h at 20 °C, and workup as above gave also a 2:1 mixture of **7** and **8** (15 mg, 82.6%).

1-Amino-3,5,7-trimethyladamantane (11). A mixture of azide **10** (170 mg, 0.78 mmol) and lithium aluminum hydride (170 mg, 4.5 mmol) in anhydrous ether (15 mL) was refluxed for 6 h, and the usual workup afforded amine **11** as the hydrochloride (150 mg, 90%), mp >300 °C, which the IR spectrum was superimposable with an authentic sample, mp >300 °C.¹²

1,6,8-Trimethyl-3-hydroxy-4-azahomoadamantane (12). To an ice-cooled and stirred mixture of the alcohol **9** (389 mg, 2.00 mmol) in 95% H_2SO_4 (6 mL) and CHCl_3 (6 mL) was added sodium azide (260 mg, 4.0 mmol). After the stirring was continued for 1 h, the mixture was poured onto ice-water and workup as above afforded the rearranged product **12** as colorless crystals after recrystallization from methanol (345 mg, 82.4%); mp 153–154 °C; IR (KBr) 3300, 3130, 1455, 1040 cm^{-1} ; NMR (CDCl_3) δ 3.6–2.7 (br m, 2 H, disappeared on shaking with D_2O), 2.65 (s, 2 H, CH_2N^-), 1.75–1.1 (m, 10 H, other ring protons), 0.92 (s, 6 H, two CH_3 at C_1 and C_8), and 0.98 (s, 3 H, $\text{C}_6\text{-CH}_3$).

Anal. Calcd for $\text{C}_{13}\text{H}_{23}\text{ON}$: C, 74.59; H, 11.08; N, 6.69. Found: C, 74.64; H, 10.80; N, 6.92.

Azide **10** (52 mg, 0.24 mmol) was decomposed in 95% H_2SO_4 (2 mL) and CHCl_3 (2 mL) for 0.5 h at 20–25 °C. Workup as above afforded the rearranged product **12** as colorless crystals (42 mg, 84.7%).

1-Aminobicyclo[3.3.1]nonane (15). A mixture of azide **14** (48 mg, 0.29 mmol) and lithium aluminum hydride (100 mg, 2.6 mmol) in anhydrous ether (10 mL) was refluxed for 5 h. The usual workup and treatment of the crude product with dry hydrogen chloride gas afforded the hydrochloride of the amine **15** as colorless solids (50 mg, 98%); mp >300 °C; IR (KBr) 3300–2400, 1600, 1510, and 1375 cm^{-1} ; NMR (CDCl_3) δ 8.25 (br s, 3 H, disappeared on shaking with D_2O) and 2.8–1.3 (m, 15 H).

Anal. Calcd for $\text{C}_9\text{H}_{18}\text{NCl}$: C, 61.52; H, 10.33; N, 7.97. Found: C, 61.78; H, 10.10; N, 7.95.

The amine **15** hydrochloride (25 mg, 0.14 mmol) was acetylated with acetic anhydride (0.21 g, 2.0 mmol) in pyridine (2.5 mL) at 50 °C for 2 h and the usual workup, followed by recrystallization from *n*-hexane– CH_2Cl_2 , afforded the acetylamino derivative **16** as colorless crystals (22 mg, 86.7%), mp 87.5–88.5 °C (lit.¹⁴ mp 85–86 °C), which the IR and NMR spectra were superimposable with an authentic sample.¹⁴

3-Aminohomoadamantane (19). A mixture of azide **18** (90 mg, 0.47 mmol) and lithium aluminum hydride (90 mg, 2.4 mmol) in anhydrous ether (4 mL) was stirred for 15 h at room temperature. The usual workup and two sublimations afforded the amine **19** as colorless solids (62 mg, 79.8%), mp 193–195 °C (lit.¹⁵ mp 193–194 °C), which the IR and NMR spectra were superimposable with an authentic sample.¹⁵

1-Azidomethyladamantane (21). A mixture of 1-adamantylcarbinyl tosylate (**20**)¹⁹ (0.32 g, 1.0 mmol) and sodium azide (0.65 g, 10 mmol) in dimethyl sulfoxide (10 mL) was stirred at 60 °C for 1 week. The mixture was diluted with water (50 mL) and extracted with methylene chloride (three 10-mL portions). The combined extracts were washed with water and dried (Na_2SO_4). Removal of the solvent gave crude azide which was purified on a silica gel column eluting with *n*-hexane to afford azide **21** as an oil (50 mg, 26.1%); n_D^{25} 1.5205; IR (neat) 2100, 1455, 1275, 980, and 930 cm^{-1} ; NMR (CDCl_3) δ 2.91 (s, 2 H, CH_2N), 1.97 (br s, 3 H, bridgehead protons), and 1.8–1.35 (m, 12 H, ring methylene protons).

Anal. Calcd for $\text{C}_{11}\text{H}_{17}\text{N}_3$: C, 69.07; H, 8.96; N, 21.97. Found: C, 69.33; H, 8.84; N, 21.83.

Registry No.—**1**, 768-95-6; **2**, 24886-73-5; **3**, 55086-02-7; **4**, 707-37-9; **5**, 63534-29-2; **7**, 63534-30-5; **8**, 63534-31-6; **9**, 13987-76-3; **10**, 63534-32-7; **12**, 63534-33-8; **13**, 15158-56-2; **14**, 63534-34-9; **15** HCl, 19388-60-4; **17**, 14504-80-4; **18**, 63534-35-0; **20**, 795-63-1; **21**, 63534-36-1.

References and Notes

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- (17) In fact, 1-noradamantanol was recovered on treatment with NaN_3 (2.5 mol excess) in 57% $\text{H}_2\text{SO}_4\text{-CHCl}_3$ for 2 h, but the reaction in 95% $\text{H}_2\text{SO}_4\text{-CHCl}_3$ gave rearranged products which were not completely characterized yet. The alcohol **13** and **17** gave also rearranged products on treatment with NaN_3 in 95% $\text{H}_2\text{SO}_4\text{-CHCl}_3$ and these results will be reported in future publications.
- (18) Microanalyses were performed with a Perkin-Elmer 240 elemental analyzer. Melting points were determined with a Yanagimoto micromelting point apparatus (hot-stage type) and are uncorrected. IR spectra were obtained with a Jasco IRA-1 spectrometer. NMR spectra were taken with a Jeol C-60HL spectrometer using Me_4Si as internal standard.
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