Synthesis of 1,2,3,4,5,6,7,8-Octahydroacridine via Condensation of Cyclohexanone with Formaldehyde

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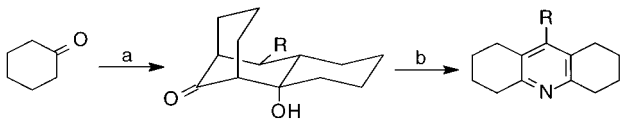
Received November 27, 2000

Introduction

Several hydrogen-bonding receptors and polydentate ligands have been synthesized from 1,2,3,4,5,6,7,8-octahydroacridine (**1**)[1] and from 9-substituted 1,2,3,4,5,6,7,8-octahydroacridines.[2] Because **1** is a valuable starting material of limited commercial availability, we have undertaken its large scale synthesis. Of the many methods for the preparation of **1**,[3] the two-step process outlined in Scheme 1 was chosen on the basis of the successful large scale synthesis of 9-butyl-1,2,3,4,5,6,7,8-octahydroacridine (**2**).[4] Currently, the most efficient methods for the synthesis of **1** require three steps (51−71% overall)[3b,d,k] and involve the low melting intermediate, 2,2′-methylenebiscyclohexanone (**5**) (Scheme 2). This compound and its high-melting isomer, 2-hydroxytricyclo-

Scheme 1

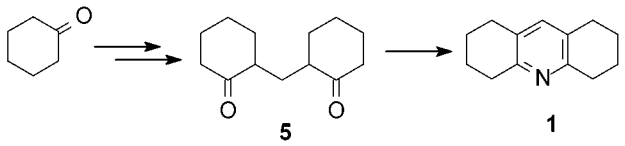


3 R = H
4 R = Butyl

1 R = H
2 R = Butyl

a) R = H: $(CH_2O)_n$, KOH, MeOH; R = butyl: C_4H_8CHO, KOH, EtOH.
b) $Cu(OAc)_2$, NH_4OAc, AcOH.

Scheme 2



5 **1**

[7.3.1.$0^{2,7}$]tridecan-13-one (**3**), have also been the subject of several synthetic[5] and stereochemical[6] studies. Reported herein are the optimization of the synthesis of **3**, its conversion to **1**, and the structure of a new hexacyclic compound encountered along the way.

Results and Discussion

The formation of **3** begins with aldol condensation between cyclohexanone and formaldehyde and elimination of water to form 2-methylenecyclohexanone. Michael addition of cyclohexanone enolate gives 2,2′-methylenebiscyclohexanone (**5**) as a mixture of meso and *d*,*l* isomers. Finally, intramolecular aldol condensation provides compound **3**. The configuration of **3** was assigned as shown in Scheme 1, on the basis of the NMR and crystallographic data published for the 8-methyl derivative.[6f]

Any stereoisomer of **5** or **3** could be used in the preparation of **1**, as retro-aldol reaction occurs under the conditions for the formation of **1**. Our goal was to develop a reproducible protocol for the preparation and isolation of **5** or **3** on a large scale, with reasonable purity and yield, using variations of known procedures.[5] When the condensation was performed with aqueous formaldehyde,[5c] vacuum distillation (bp 139−148 °C, 0.7 mm) gave a stereoisomeric mixture of 1,5-diketones (**5**) in low yield (<20%).

The patented procedure of Becke and Wick[5b] for the synthesis of **5** involves the addition of a basic methanolic solution of paraformaldehyde to a solution of cyclohexanone in methanol. By this method we were able to obtain only the desired product **3** as a white solid (mp 166−168 °C, lit.[5c] 166−168 °C), again in poor yield (20−50%). It was noticed that a higher-melting side product (mp 200−202 °C) was also formed under these conditions.

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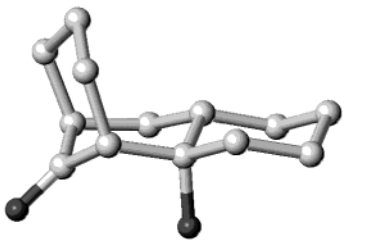
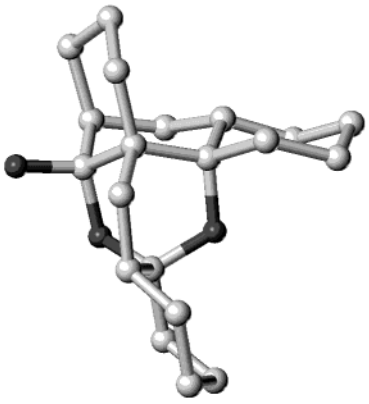
10.1021/jo005746u CCC: $20.00
Published on Web 01/17/2001



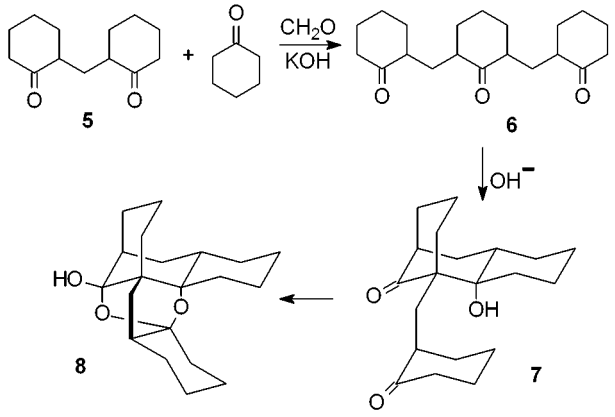
3



8

Figure 1. Crystallographically determined configurations of **3** and **8**.

Scheme 3



This side product (**8**)[7] was separated from **3** by fractional crystallization, and on the basis of GC/MS and microanalytical data, the molecular formula was determined to be $C_{20}H_{30}O_3$. Crystals of both **3** and **8** were then grown, and their respective structures were determined by X-ray crystallography (Figure 1). The structures confirmed the stereochemical assignment of **3** and identified **8** as 9,22-dioxahexacyclo[15.3.1.1.^{8,21}0.^{3,8}0.^{1,10}0^{10,15}]docosan-21-ol.

Hexacyclic product **8** is apparently formed from diketone **5** via intermediates **6** and **7**, as shown in Scheme 3. Reaction of **5** with formaldehyde and cyclohexanone (or with 2-methylenecyclohexanone) would give triketone **6**, which would cyclize to **7** by analogy with the conversion of **5** to **3**. Tandem ketalization/hemiketalization of **7** to **8** could occur under the reaction conditions or upon work-up. Neither **6** or **7** have been isolated, but TLC analysis of the crude product shows many products, of which only the most easily isolated and crystallized have been identified.

Higher-melting **8** interferes with purification of **2** by crystallization, so reaction conditions were varied in order to limit its production. The most favorable conditions involved adding a basic methanol solution of paraformaldehyde to cyclohexanone at 80 °C over 4−6 h, depending on the scale of the reaction. After the addition was complete, the cloudy yellow solution was held at 80 °C under reflux for 1 h and cooled slightly, and excess cyclohexanone was removed by vacuum distillation. If the solution was heated under reflux for longer than 1 h, the percentage of **8** increased.

The removal of cyclohexanone was necessary in order to obtain the product in one clean crop. Also, if the addition time was much shorter, an oily, yellow crude product was obtained with a much lower melting range, most likely due to the presence of the intermediate **5**. With the above modifications, the crude yield of **3** was increased to 64% with only a trace of **8** present by TLC. The crude product was recrystallized from methanol, yielding a white crystalline solid (mp 162−172 °C). By GC/MS this product was not completely pure; it contained several compounds all with molecular weight 208, and no **8** was detected. This mixture was used to prepare 1,2,3,4,5,6,7,8-octahydroacridine (**1**), in 99% yield. From this result, it was apparent that the recrystallized sample of **3** contained a mixture of isomers (including possibly **5**, on the basis of the depressed melting point).

A reproducible method has been developed for the preparation of keto-alcohol **3** and its subsequent conversion to 1,2,3,4,5,6,7,8-octahydroacridine on a scale of almost 200 g with 50% overall yield. The advantage of this preparation lies in the small number of synthetic steps and the ease of isolation and purification of intermediate **3**.

Experimental Section

All procedures were carried out under nitrogen and using a magnetic stirrer, unless otherwise indicated. Melting points were determined in open glass capillaries on a Mel-Temp apparatus and are uncorrected. Elemental analysis was performed by Supersun Technology Analytical Laboratory, Stony Brook, NY. IR data are given in cm^{-1}. ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ with 0.05% TMS at 300 and 75 MHz, respectively. Chemical shift values are referenced to TMS (δ 0.0, ^{1}H) or $CDCl_3$ (δ 77.0, ^{13}C). Organic reagents were purchased from Aldrich Chemical Co. or Fisher Scientific and used as obtained, unless otherwise indicated. All solid products were dried under vacuum (0.1−0.5 mm) at room temperature or at 78 °C.

2-Hydroxytricyclo[7.3.1.0^{2,7}]tridecan-13-one (3). Cyclohexanone (1 L, 9.6 mol) was heated to 80 °C and stirred as a solution of sodium hydroxide (2.9 g, 72 mmol) and paraformaldehyde (54 g, 1.8 mol) in 300 mL of methanol was added over 4.5 h. The cloudy yellow solution was heated under reflux for an additional 1 h, and the excess cyclohexanone was removed by vacuum distillation (0.2−0.5 mm), which resulted in a cloudy viscous residue. After the residue was cooled to 0 °C for 24 h, the oily solid was triturated with ethyl acetate (500 mL), and the resulting white solid was collected by vacuum filtration, yielding 239 g (64%). Recrystallization from methanol yielded 197 g (53%) of a white crystalline solid, mp 162−172 °C (lit.[5d] 166−168 °C): ^{1}H NMR ($CDCl_3$) δ 1.30−2.24 (m, 19 H), 2.46 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 20.3, 20.6, 26.0, 27.8, 29.4, 34.8, 36.4, 36.6, 39.0, 46.6, 59.3, 78.2, 219.6; IR (KBr) 3408 (br.), 2979, 2921, 2849, 1706, 1451, 1415, 1284, 1246, 1142, 1104, 1046, 974, 955, 871, 617; MS (EI) *m*/*z* 208 (M, 31), 112 (25), 111 (41), 98 (100).

(7) A product of formula $C_{19}H_{28}O_3$ (mp 193 °C) was obtained in 22% yield by Plesek and Munk,[5a] exclusively by reaction of cyclohexanone with aqueous formaldehyde in the presence of methanolic potassium hydroxide.

Anal. Calcd for $C_{13}H_{20}O_2$ (208.30): C, 74.96; H, 9.68. Found: C, 74.96; H, 10.06.

9,22-Dioxahexacyclo[15.3.1.1^{8,21}.0^{3,8}.0^{1,10}.0^{10,15}]docasan-21-ol (8). The following procedure gave the highest isolated yield of **8**. A solution of NaOH (0.48 g, 12 mmol) and paraformaldehyde (9.0 g, 0.3 mol) in ethanol (11 mL) was added to cyclohexanone (60 mL, 0.58 mol) at 60−70 °C over 6 h. Once the addition was complete, the cloudy suspension was maintained at 60−70 °C for an additional 30 h. After the mixture cooled to 0 °C, the resulting viscous oil was triturated with hexanes, and the white solid was collected by vacuum filtration and dried, yielding 9.5 g (15%), mp 185−202 °C. Recrystallization from methanol provided pure **8**, mp 200−202 °C: ^{1}H NMR ($CDCl_3$) δ 1.1−2.1 (m); ^{13}C NMR ($CDCl_3$) δ 21.1, 21.2, 23.0, 25.5, 26.1, 27.7, 28.5, 28.6, 29.0, 31.4, 31.9, 33.7, 35.4, 37.6, 39.4, 39.6, 40.9, 78.8, 96.0, 98.1; IR (KBr) 3389 (br.), 2935, 2848, 1460, 1443, 1360, 1259, 1153, 1072, 1022, 983, 943, 640; MS (EI) *m*/*z* 300 (M − H_2O, 100), 282 (25), 239 (39), 211 (18), 202 (24), 173 (21). Anal. Calcd for $C_{20}H_{30}O_3$ (318.45): C, 75.43; H, 9.50. Found: C, 75.56; H, 9.69.

1,2,3,4,5,6,7,8-Octahydroacridine (1). A mixture of cupric acetate monohydrate (391 g, 1.9 mol), ammonium acetate (88.5 g, 1.2 mol), and acetic acid (950 mL) was heated under reflux for 15 min. The reaction mixture was then cooled below reflux, and 197 g (0.95 mol) of **3** was added. The reaction mixture was stirred and heated under reflux for 3 h and then cooled to 0 °C for 3 h. The precipitated cuprous acetate was removed by vacuum filtration and washed with anhydrous diethyl ether (200 mL). Concentrated aqueous ammonium hydroxide (ca. 2 L) was then added slowly to the combined filtrates, while cooling with ice (final pH 10−11). The resulting mixture was then separated, and the aqueous layer was extracted with ether (3 × 800 mL). The combined ether layers were washed with 20% aqueous ammonium hydroxide (800 mL) followed by saturated aqueous NaCl (800 mL). The dried (Na_2SO_4) ether solution was concentrated under vacuum, and the resulting solid was dried, yielding 176 g (99%) of a light brown solid, mp 62−67 °C. Polar impurities were removed by filtration of a solution of **1** in a minimum volume of CH_2Cl_2 through a pad of neutral alumina (ca. 300 g), which was washed with three times the original volume of CH_2Cl_2. Evaporation of the CH_2Cl_2 under reduced pressure provided 162 g (91%) of a light tan solid, mp 66−68 °C (lit.[3d] 71 °C): ^{1}H NMR ($CDCl_3$) δ 1.78 (quint, J = 6 Hz, 4 H), 1.86 (quint, J = 6 Hz, 4 H), 2.69 (t, J = 6 Hz, 4 H), 2.85 (t, J = 7 Hz, 4 H), 7.04 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 22.9, 23.4, 28.4, 32.3, 129.2, 137.4, 154.1.

Acknowledgment. This research was supported by the National Institutes of Health (PHS Grant GM R01-32937). The authors would like to thank Joseph C. Depczynski for his contribution to this project.

Supporting Information Available: X-ray data for compounds **3** and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO005746U