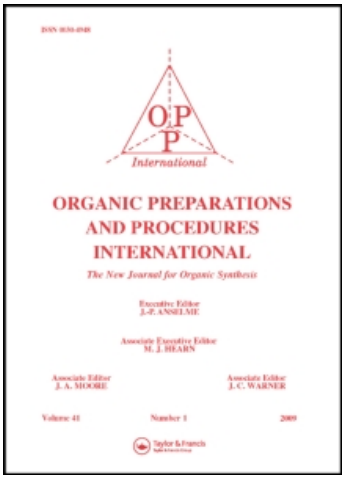


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# AN IMPROVED SYNTHESIS OF 2,3,4,6,7,8-HEXAHYDROQUINOLINES

Elmar Schuster[a]; Gerhard Jas[a]; Dieter Schumann[a]
[a] Institut für Organische Chemie, TU Berlin, Berlin, GERMANY

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# AN IMPROVED SYNTHESIS OF 2,3,4,6,7,8-HEXAHYDROQUINOLINES

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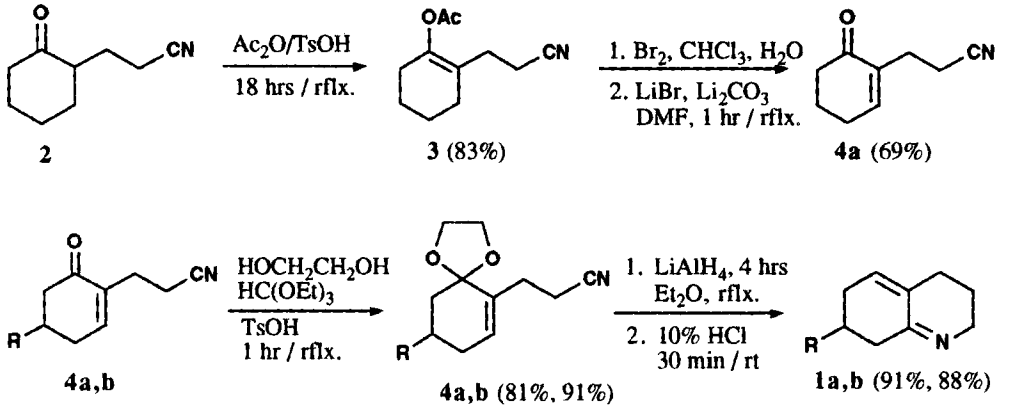
Elmar Schuster, Gerhard Jas and Dieter Schumann*

*Institut für Organische Chemie, TU Berlin*
*Straße des 17. Juni 135*
*W-1000 Berlin 12, GERMANY*

In the course of studies towards alkaloid synthesis, we needed large quantities of 2,3,4,6,7,8-hexahydroquinoline (**1a**) and 7-methyl-2,3,4,6,7,8-hexahydroquinoline (**1b**). There were only two methods[1,2] reported for the preparation of **1a**. Our synthesis is described in the Scheme below.




**Scheme** (1: R = H, b: R = $CH_3$)

Starting with the corresponding 2-(2-cyanoethyl)-2-cyclohexenones **4a** and **4b**, the hexahydroquinolines **1a** and **1b** were formed by ketalization,[3] reduction with lithium aluminum hydride and acidic hydrolysis. 2-(2-Cyanoethyl)-5-methyl-2-cyclohexenone (**4b**) was prepared in four steps in an overall yield of 45% according to a known procedure.[4] Compound **4a** was prepared in 2 steps (overall yield 83%) from the readily available 2-(2-cyanoethyl)cyclohexanone[5] (**2**) by regioselective enol acylation[6] followed by bromination-dehydrobromination.[7]

In conclusion, an improved synthetic route to 2,3,4,6,7,8-hexahydroquinolines (**1a**) (overall yield 42%) and **1b** (overall yield 36%) has been developed. The current procedure allows easy scale-up of each step.

## EXPERIMENTAL SECTION

$^1$H NMR spectra were recorded on a Bruker WM 400 (400 MHz) or a Varian EM 390 (90MHz) spectrometer. $^{13}$C NMR spectra were recorded on a Bruker WM 270 (67.5 MHz) spectrometer. Spectra were determined in deuteriochloroform solutions with tetramethylsilane as internal standard. *J*-Values are given in Hz. Mass spectra were recorded on a Varian MAT 711 or MAT 44S spectrometer with

relative intensity in parenthesis. IR spectra were recorded on a Beckman IR 9 spectrometer and are reported in $cm^{-1}$. DMF was distilled over $CaH_2$ under nitrogen; acetic anhydride and triethyl orthoformiate were distilled over $P_4O_{10}$ under nitrogen; diethyl ether was distilled over sodium benzophenone ketyl under argon; ethylene glycol was distilled over sodium under nitrogen. The resulting hexahydroquinolines should be stored under inert gas in a freezer.

**1-Acetoxy-2-(2-cyanoethyl)cyclohexene (3)**.- A solution of 2-(2-cyanoethyl)cyclohexanone (**2**)[5] (79.4 g, 0.52 mol) and TsOH (2.5 g) in acetic anhydride (500 mL, 5.3 mol) was refluxed for 18 hrs. Then the solvent was evaporated and the residue was poured into a saturated aqueous $NaHCO_3$ solution (150 mL). The aqueous phase was extracted with ether (3x50 mL). After washing of the combined organic phases with $H_2O$ and brine and drying ($MgSO_4$) the solvent was evaporated. Distillation in high vacuum gave **3** as a colorless liquid (82.6 g, 83%), bp. 91° (0.01 mmHg). $^1H$ NMR (400 MHz): δ 2.35 (m, 2H), 2.25 (m, 2H), 2.12 (s, 3H), 2.08 (m, 4H), 1.72-1.58 (m, 4H). MS (70 eV) m/z: 193 ($M^+$,3), 151 (24), 111(100), 55 (41).

*Anal.* Calcd. for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.28; H, 7.65; N, 7.41

**2-(2-Cyanoethyl)cyclohexenone (4a)**.- To a vigorously stirred suspension of $CaCO_3$ (22.0 g, 0.22 mol) in $H_2O$ (75 mL) and $CHCl_3$ (75 mL) were added at the same time a solution of **3** (38.7 g, 0.2 mol) in $CHCl_3$ (150 mL) and a solution of bromine (10.2 mL, 0.2 mol) in $CCl_4$ with cooling (0°). After stirring for 1 hr at 0°, the mixture was filtered and the organic layer was separated. The aqueous phase was extracted with $CHCl_3$, and the combined organic phase was dried ($MgSO_4$) and concentrated at room temperature under reduced pressure. The residue was poured under nitrogen to a boiling suspension of dry LiBr (35.9 g, 0.41 mol) and dry $LiCO_3$ (35.9 g, 0.49 mol) in DMF (200 mL). After refluxing for 1 hr the mixture was allowed to cool to room temperature, poured into ice water (500 mL) and brought to pH 4 by carefully adding conc. HCl. The water layer was extracted with $CH_2Cl_2$. The combined organic layer was washed with $H_2O$, saturated aqueous $NaHCO_3$ solution and brine, dried ($Na_2SO_4$), concentrated under reduced pressure and distilled to yield **4** (19.3 g, 69%) as a slightly yellow liquid, bp. 92° (0.04 mmHg). IR ($CCl_4$): 2250, 1690 $^1H$ NMR (400 MHz): δ 6.90 (br t, 1H, $J$ = 4.5), 2.51-2.42 (m, 4H), 2.42-2.34 (m, 4H), 1.97 (tt, 1H, $J$ = 7; 7). MS (70 eV) m/z: 149 ($M^+$, 28), 148 (24), 121 (30), 81 (90), 53 (100).

*Anal.* Calcd. for $C_9H_{11}NO$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.61; H, 7.59; N, 9.50

**2-(2-Cyanoethyl)-2-cyclohexenone Ethylene Ketal (5a)**.- A solution of **4a** (39.0 g, 0.26 mol), ethylene glycol (14.6 mL, 0.26 mol) and TsOH (1g) in triethyl orthoformiate (80 mL) was refluxed for 1 hr under nitrogen. Then $Na_2CO_3$ was added. Solid compounds were filtered off, the solvent was evaporated and the residue was distilled to furnish **5a** (40.8 g, 81%) as a slightly yellow oil, bp. 82° (0.01 mmHg). $^1H$ NMR (400 MHz): δ 6.59 (m, 1H), 3.96 (m, 4H), 2.49 (*br* t, 2H, $J$ = 7), 2.33 (t, 2H, $J$ = 7), 2.04 (m, 2H), 1.70 (m, 4H). MS (70 eV) m/z: 193 ($M^+$,1), 165 (38), 125(100).

*Anal.* Calcd. for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.57; H, 7.71; N, 7.43

**2-(2-Cyanoethyl)-5-methyl-2-cyclohexenone Ethylene Ketal (5b)**.- The synthesis of **5b** was performed as described for **5a** with the exception that **4b**[4] (26.9 g, 0.16 mol) was reacted with

ethylene glycol (8.9 mL, 0.16 mol), TsOH (1g) and triethyl orthoformate (70 mL). Purification afforded **5b** (30.3 g, 91%) as a slightly yellow oil, bp. 85° (0.01 mmHg). $^1$H NMR (90 MHz): δ 5.8 (dd, 1H, $J$ = 4; 2), 3.9 (m, 4H), 1.8 (m, 2H), 1.4-1.1 (m, 3H), 1.0 (d, 3H, $J$ = 6). MS (70 eV) m/z: 207 ($M^+$,1), 165 (36), 125 (100).

*Anal.* Calcd. for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.74; H, 8.41; N, 6.53

**2,3,4,6,7,8-Hexahydroquinoline (1a).**- A solution of **5a** (9.7 g, 50 mmol) in $Et_2O$ (50 mL) was added dropwise to a cold (0°) suspension of $LiAlH_4$ (1.9 g, 50 mmol) in $Et_2O$ (75 mL) under nitrogen. The mixture was refluxed for 2 hrs and quenched with saturated aqueous $Na_2SO_4$ solution at 0°. The precipitate was filtered off and thoroughly washed with $Et_2O$. The resulting mixture was acidified with 10% HCl (pH 3) and stirred for an additional 30 min under nitrogen at room temperature. The layers were separated, the aqueous phase was brought to pH 10 with 10% NaOH and was extracted with $Et_2O$ (4x25 mL). The combined organic extract was washed with brine, dried ($Na_2SO_4$), concentrated under reduced pressure and distilled to furnish **1a** (6.2 g, 91%) as a slightly yellow liquid, bp. 35° (0.01 mmHg). The spectroscopic data are identical with those already published.[2]

**7-Methyl-2,3,4,6,7,8-hexahydroquinoline (1b).**- This compound was prepared according to the synthesis of **1a** with the exception that a solution of **5b** (5.2 g, 25 mmol) in $Et_2O$ (50 mL) was reacted with $LiAlH_4$ (1.2 g, 32 mmol) in $Et_2O$ (70 mL). Purification gave **1b** (3.3g, 88%) as a slightly yellow liquid, bp. 45° (0.01mmHg), spectroscopic data identical with those already published.[2]



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