Synthesis of 2-Substituted 8-Azabicyclo[3.2.1]octan-3-ones in Aqueous NaOH Solution of Low Concentration

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The tropane class of alkaloids has continued to elicit the unabated interests among organic chemists because of their pharmacological significance, and a great deal of efforts has been focused on the stereochemical synthetic methodologies.[1-4] Cocaine, a notorious member of this alkaloidal family, is found in erythroxylon coca, indigenous to the higher elevations of peru. The natives of this region, descendants of the Incas, still chew the coca leaf for its stimulatory properties. In particular, a series of tropans showed anticonvulsant activity against pentylenetetrazol-induced convulsions in mice and antiarrhythmic activity in rabbit previously treated with ouabain.[5-8]

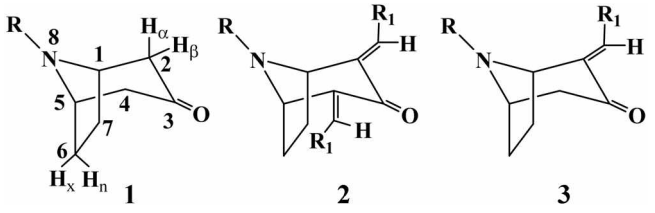
As a part of ongoing research[9] for the pharmacologically interesting tropane compounds, herein we report a new synthetic conditions of corresponding 2-substituted 8-azabicyclo[3.2.1]octan-3-one, **3**, by aldol condensation from 8-substituted 8-azabicyclo[3.2.1]octan-3-one, **1**. We already reported a synthesis of 2,4-disubstituted 8-azabicyclo[3.2.1]-octan-3-one, **2**, derived from the reaction of *N*-substituted 8-azabicyclo[3.2.1]octan-3-one, **1**, with aldehydes (R_1CHO) in the presence of ethanol and aqueous 5 *N* NaOH.[10] We also reported the synthesis of di-(*N*-tropinonyl)alkanes from the reaction of phenylenediamines (or diaminoalkanes) with 2,5-dimethoxytetrahydrofuran and acetonedicarboxylic acid.[11]

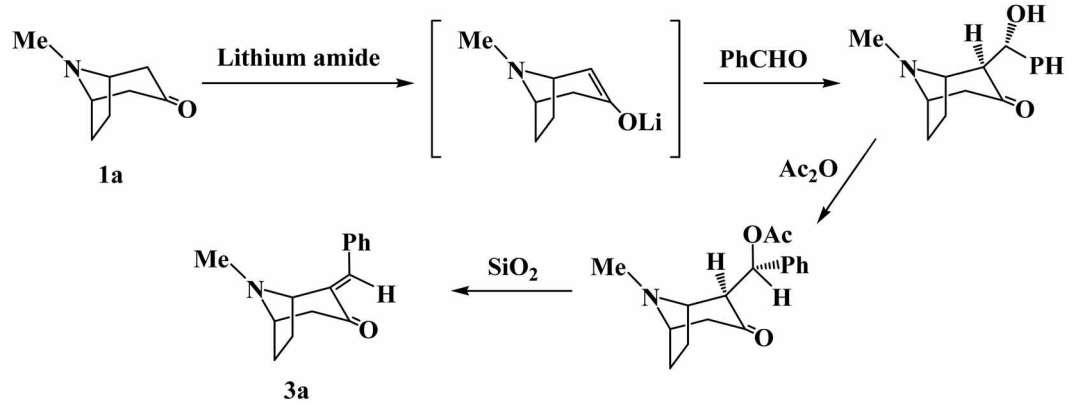
Then our attempt to prepare 2-substituted 8-azabicyclo-[3.2.1]octan-3-one, **3**, from 8-substituted 8-azabicyclo-[3.2.1]octan-3-one, **1**, was unsuccessful, under various reaction conditions: sodium hydride, sodium methoxide, or butyl lithium.[10]

But M. Majewski and R. Lazny[12] reported that their synthesized compound, 2-benzylidene-8-methyl-8-azabicyclo[3.2.1]octan-3-one was done through three-step treatment of chiral lithium amide, Ac_2O, and SiO_2 (Scheme 1). In brief, as their synthetic method had three-step reactions and three times work-ups, it was so complicated. Recently, Peter A. Crooks *et al.*[13] reported two-step synthesis by treatment of lithium diisopropylamide or lithium bis(trimethylsilyl)-amide.

In order to synthesize 2-substituted 8-azabicyclo[3.2.1]-octan-3-one, **3**, simply and efficiently, we conducted research on the effect of aqueous NaOH concentration variations (1 *N*, 0.5 *N*, 0.1 *N*, 0.02 *N*, or 0.01 *N*). Yield comparison of compound **3e** according to concentration variation of aqueous NaOH solution is expressed in Table 1.

In case of higher concentrations over aqueous 0.01 *N* NaOH solution, the ratio of 2,4-disubstituted 8-azabicyclo-[3.2.1]octan-3-one, **2**, was produced somewhat higher than that of 2-substituted 8-azabicyclo[3.2.1]octan-3-one, **3**. Yield of 8-benzylidene-8-phenyl-8-azabicyclo[3.2.1]octan-





Scheme 1. Three-step synthetic process reported by M. Majewski and R. Lazny.

Table 1. Yield comparison of compound **3e** according to concentration variation of aqueous NaOH solution

Starting Material	Product	Reaction time (h)	Concentration of NaOH Solution	Yield* (%)
1e	**3e**	3	1 *N*	7
			0.5 *N*	12
			0.1 *N*	23
			0.02 *N*	58
			0.01 *N*	93

*GC yield

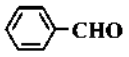
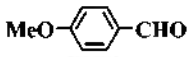
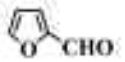
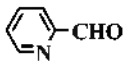
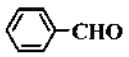
3-one, **3e**, obtained from the reaction of 8-phenyl-8-azabicyclo[3,2,1]octan-3-one, **1e**, and benzaldehyde in the presence of aqueous 0.01 *N* NaOH was shown most highly. The yield of 2-substituted 8-azabicyclo[3.2.1]octan-3-one, **3**, from high concentration of aqueous NaOH to aqueous 0.01 *N* NaOH became higher.

The structures and yields of the synthesized products (**3a-3e**) are summarized in Scheme 2 and Table 2.

A representative experimental procedure for the synthesis of 2-furan-2-ylmethylene-8-methyl-8-azabicyclo[3.2.1]-octan-3-one, **3c**, is as follows. A mixture of tropinone (1.39 g, 0.010 mol), ethanol (20 mL), and aqueous 0.01 *N* NaOH (2 mL) was stirred at 0 °C for 20 min. 2-Furaldehyde (1.44 g, 0.015 mol) was added by using a dropping funnel at 0 °C. The reaction mixture was stirred under N_2 at 0 °C for 3 h. After stirring for 3 h, a crude light brown solid was precipitated. The reaction mixture was diluted with water (10 mL) and neutralized with aqueous 0.01 *N* HCl (2 mL). The neutralized solution was extracted with dichloromethane (100 mL × 3). The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was chromatographed on a silica gel (*n*-hexane : ethyl acetate = 1 : 1, v/v) to yield **3c** (0.99 g, 45.6%) as a deep brown sticky oil.

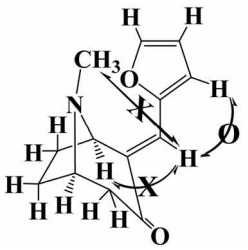
In the ^{1}H-NMR spectrum of **3c**, two doublets (J = 11 Hz) due to the two protons of C1,5 are appeared at δ4.82 (J = 6.6 Hz) and δ3.56 (J = 6.6 Hz). A single signal due to the vinyl proton is seen at δ7.25. The signals of the furanyl group are shown at δ 7.58, δ 6.70, and δ 6.49. The C-6 and C-7 methylene protons are seen at δ2.85 (ddd, J = 18.9 Hz, J = 5.7 Hz, J = 1.8 Hz), δ 2.34, δ 2.01, and δ 1.78. Mass spectrum showed a molecular ion peak at m/z 217 (18%) corresponding to the molecular formula $C_{13}H_{15}NO_2$.

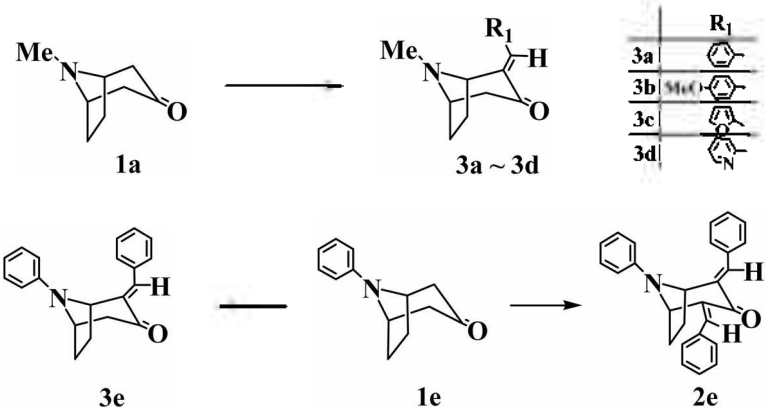
Table 2. Reaction condition and yield of 2-substituted 8-azabicyclo[3.2.1]octan-3-ones

Starting material	Aldehydes	Product	Reaction time (h)	Yield* (%)
1a		**3a**	4	68.0
		**3b**	8	71.7
		**3c**	3	45.6
		**3d**	5	79.0
1e		**3e**	3	90.0

*Isolated yield

From these observations, here we propose **3c** as the structure of this product. Structures of all other products were confirmed by the same manner as **3c**. The structural analysis of **3** in a similar way for **2**[10] provided only 2***E*** geometry. The stereochemical assignment of the double bond (C-2) of **3c** was supported by selective NOE experiments. A selective NOE spectrum showed an enhancement in the magnitude of the signal at δ6.67 (furanyl $H_{3\beta}$) when the signal at δ7.58 (vinyl H) was irradiated. But the signals for one proton of C1 (δ4.86) and three protons of methyl group (δ 2.47) were not affected thoroughly. Therefore, these selective NOE experiments of **3c** indicate 2***E*** geometry.





Scheme 2. Structure of the synthesized 2-substituted 8-azabicyclo[3.2.1]octane-3-ones, **3**.

In conclusion, in order to synthesize 2-substituted 8-azabicyclo[3.2.1]octan-3-one, **3**, we conducted research on the effect of aqueous NaOH concentration variations without catalysts such as lithium amide and LDA.

Experimental Section

Melting point was determined on an electrothermal capillary melting point apparatus and uncorrected. TLC was performed on glass plates coated with silicon oxide (silica gel $60F_{254}$) and compounds were visualized using a UV lamp. ^{1}H NMR and ^{13}C NMR spectra were obtained with Bruker AC 200 (200 MHz) and Varian Gemini (200 or 300 MHz) spectrometers. Mass spectra were measured with HP 5890 GC/Mass (70 eV, EI). The organic solvents and chemicals were obtained from commercial products and purified by the appropriate methods before use.

Synthesis of 2-benzylidene-8-methyl-8-azabicyclo[3.2.1]-octan-3-one, 3a: In the procedure described for the preparation of **3c**, benzaldehyde (1.6 g, 0.015 mol) gave a crude brown solid after 4 h stirring. The residue was chromatographed on a silica gel (*n*-hexane : ethyl acetate = 15 : 1, v/v) to yield **3a** (0.53 g, 68%) as a light brown oil. IR (KBr, cm^{-1}); 3095, 2965, 2905, 1723 (C=O). ^{1}H-NMR ($CDCl_3$); δ 7.51 (s, 1H, vinyl H), 7.26-7.46 (m, 5H, phenyl H), 4.29 (d, 1H, J = 6.8 Hz), 3.53 (t, 1H, J = 6.0 Hz), 2.87 (ddd, 1H, J = 18.6, 5.7, 1.8 Hz), 2.40 (s, 3H), 2.23-2.55 (m, 3H), 1.90 (m, 1H), 1.72 (m, 1H). ^{13}C-NMR ($CDCl_3$); δ 199.8, 140.0, 135.2, 134.6, 130.5, 129.2, 128.9, 61.3, 59.2, 45.0, 37.7, 29.8, 29.3. Mass, m/z (rel. intensity, %); 227 (15.7), 199 (99), 171 (75.9), 115 (31.5), 94 (100).

Synthesis of 2-(4-methoxybenzylidene)-8-methyl-8-azabicyclo[3.2.1]octan-3-one, 3b: In the procedure described for the preparation of **3c**, *p*-anisaldehyde (2.04 g, 0.015 mol) gave a crude brown solid after 8 h stirring. The residue was chromatographed on a silica gel (*n*-hexane : ethyl acetate = 20 : 1, v/v) to yield **3b** (1.84 g, 71.7%) as a light yellow oil. IR (KBr, cm^{-1}); 3035, 2920, 2909, 1695 (C=O). ^{1}H-NMR ($CDCl_3$); δ 7.53 (s, 1H, vinyl H), 7.30 (d, 2H, phenyl H), 6.90 (d, 2H, phenyl H), 4.33 (d,1H, J = 6.6 Hz), 3.82 (s, 3H), 3.55 (t, 1H, J = 6.1 Hz), 2.97 (ddd, 1H, J = 18.6, 5.7, 1.8 Hz), 2.40 (s, 3H, methyl H), 2.31-2.43 (m, 3H), 1.90 (m, 1H), 1.73 (m, 1H). ^{13}C-NMR ($CDCl_3$); δ 198.9, 160.2, 134.7, 132, 131.8, 131.5, 127.2, 114.1, 60.9, 58.5, 44.2, 35.3, 30.3, 28.9. Mass, m/z (rel. intensity, %); 257 (4.6), 229 (100), 201 (57.4), 94 (57.4), 82 (16.7).

Synthesis of 2-furan-2-ylmethylene-8-methyl-8-azabicyclo[3.2.1]octan-3-one 3c: The mixture of tropinone (1.39 g, 0.010 mol), ethanol (20 mL), and aqueous 0.01 *N* NaOH (2 mL) was stirred at 0 °C for 20 min. 2-Furaldehyde (1.44 g, 0.015 mol) was added by using a dropping funnel at 0 °C. The reaction mixture was stirred under N_2 at 0 °C for 3 h. After stirring for 3 h, a crude light brown solid was precipitated. The reaction mixture was diluted with water (10 mL) and neutralized with aqueous 0.01 *N* HCl (2 mL). The neutralized solution was extracted with dichloromethane (100 mL × 3). The residue was chromatographed on a silica gel (*n*-hexane : ethyl acetate = 1 : 1, v/v) to yield **3c** (0.99 g, 45.6%) as a deep brown sticky oil. IR (KBr, cm^{-1}); 3070, 2990, 1680 (C=O), 1610. ^{1}H-NMR ($CDCl_3$); δ 7.58 (d, 1H, J = 1.8 Hz, furanyl H), 7.25 (s, 1H, vinyl H), 6.70 (d, 1H, J = 3.3 Hz, furanyl H), 6.49 (dd, 1H, J = 3.3, 1.8 Hz furanyl H), 4.82 (d, 1H, J = 6.6 Hz), 3.56 (t, 1H, J = 6.6 Hz), 2.85 (ddd, 1H, J = 18.9, 5.7, 1.8 Hz), 2.34 (s, 3H), 2.01-2.28 (m, 3H), 1.78 (m, 1H), 1.70 (m, 1H). ^{13}C-NMR ($CDCl_3$); δ 198.7, 151.9, 145.6, 135.9, 121.3, 118.2, 112.8, 61.6, 58.8, 44.6, 37.5, 30.7, 29.1. Mass, m/z (rel. intensity, %); 217 (3.0), 189 (90.3), 161 (100), 132 (40.1), 94 (25.6).

Synthesis of 8-methyl-2-pyridin-2-ylmethylene-8-azabicyclo[3.2.1]octan-3-one, 3d: In the procedure described for the preparation of **3c**, 2-pyridinecarboxaldehyde (1.6 g, 0.015 mol) gave a crude brown solid after 5 h stirring. The residue was chromatographed on a silica gel (*n*-hexane : ethyl acetate = 10 : 1, v/v) to yield **3d** (1.79 g, 79%) as a light yellow sticky oil. IR (KBr, cm^{-1}); 3090, 2968, 2905, 1695 (C=O). ^{1}H-NMR ($CDCl_3$); δ 8.63 (d, 1H, pyridinyl H), 7.62 (s, 1H, vinyl H), 7.21 (m, 3H, pyridinyl 3H), 4.19 (d, 1H, J = 6.7 Hz), 3.48 (t, 1H, J = 6.0 Hz), 2.85 (ddd, 1H, J = 18.6, 5.7, 1.8 Hz), 2.40 (s, 3H, methyl H), 2.34-2.49 (m, 3H), 1.92 (m, 1H), 1.74 (m, 1H). ^{13}C-NMR ($CDCl_3$); δ 200.8, 154.5, 149.5, 148.9, 136.1, 130.6, 127.0, 122.6, 60.8, 58.9, 45.5, 37.6, 29.7, 28.7. Mass, m/z (rel. intensity, %); 228 (18.5), 200 (39.4), 185 (48.1), 172 (100), 159 (27.8).

Synthesis of 8-benzylidene-8-phenyl-8-azabicyclo[3.2.1]-octan-3-one, 3e: The mixture of 8-phenyl-8-azabicyclo-[3,2,1]octan-3-one (2.02 g, 0.010 mol), ethanol (10 mL), and aqueous 0.01 *N* NaOH (2 mL) was stirred at 0 °C for 20 min. Benzaldehyde (1.6 g, 0.015 mol) was added by using a dropping funnel at 0 °C. The reaction mixture was stirred under N_2 at 0 °C for 3 h. After stirring for 3 h, a crude light brown solid was precipitated. The reaction mixture was diluted with water (10 mL) and neutralized with aqueous 0.01 *N* HCl (2 mL). The neutralized solution was extracted with dichloromethane (100 mL × 3). The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was chromatographed on a silica gel (*n*-hexane : ethyl acetate = 10 : 1, v/v) to yield **3e** (2.60 g, 90%) as a light yellow solid. mp; 165-166 °C. IR (KBr, cm^{-1}); 3070, 2990, 1680 (C=O), 1610, 1460. ^{1}H-NMR ($CDCl_3$); δ 7.79 (s, 1H, vinyl H), 7.51-7.40 (m, 10H, aromatic H), 5.24 (t, 1H, J = 6.7 Hz), 3.47 (t, 1H, J = 6.0 Hz), 2.71-2.75 (m, 2H), 2.23-2.30 (dd, 2H, J = 9.0, 6.0 Hz), 1.63 (m, 2H). ^{13}C-NMR ($CDCl_3$); δ 188.3, 145.6, 139.1, 137.3, 135.5, 130.5, 130.2, 129.5, 129.4, 129.1, 119.0, 116.4, 56.6, 30.5. Mass, m/z (rel. intensity, %); 293 (73), 221 (100), 145 (89), 136 (56), 77 (32).

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