A new method for the synthesis of 3,7-diazabicyclo[3.3.1]nonanes

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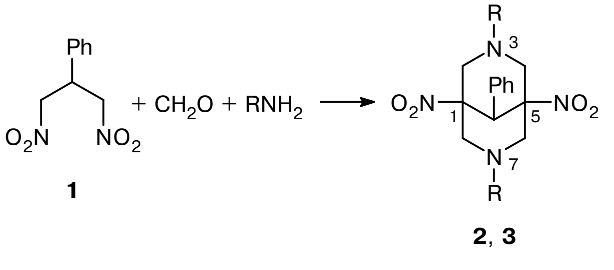
The 3,7-diazabicyclo[3.3.1]nonane fragment is a constituent[1,2] of a number of alkaloids and biologically active compounds with insecticide,[3] antiarrhythmic,[4] and antitumor properties.[5] Such compounds can be prepared in several ways, *e.g.*, by the Mannich reaction of aliphatic ketones,[6] piperidin-4-ones,[6] or nitromethane[7—9] with primary amines and formaldehyde.

We developed a convenient method for the one-step synthesis of 1,5-dinitro-3,7-diazabicyclo[3.3.1]nonanes from 1,3-dinitropropanes. Thus it was shown that 1,3-dinitro-2-phenylpropane (**1**) reacts with formalin and methylamine in a molar ratio of 1 : 7 : 9 in $CHCl_3$—EtOH at 10 °C to give 3,7-dimethyl-1,5-dinitro-9-phenyl-3,7-diazabicyclo[3.3.1]nonane (**2**) in 83% yield (Scheme 1).[10] Under these conditions, *i.e.*, where a considerable excess of both formaldehyde and the amine is used, virtually no 3,5-dinitropiperidine, a monocyclization product, is formed. The condensation of **1** with formaldehyde and 2-aminoethanol affords 3,7-bis(2-hydroxyethyl)-1,5-dinitro-3,7-diazabicyclo[3.3.1]nonane (**3**) in 75% yield. It should be noted that the condensation of primary mononitroalkanes with formaldehyde and primary amines is usually a complex reaction which gives not only nitroalkylamines but also nitrotetrahydrooxazines and nitrohexahydropyrimidines.[11,12]

Scheme 1



R = Me (**2**); CH_2CH_2OH (**3**)

Thus, the condensation of 1,3-dinitro-2-phenylpropane with formaldehyde and primary amines mostly gives rise to cyclic rather than oligomeric products and affords 3,7-diazabicyclo[3.3.1]nonane derivatives in high yields.

^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer (300.1 and 75.47 MHz, respectively) in $CDCl_3$ with Me_4Si as the internal standard. IR spectra were recorded on a Specord M-80 instrument (Vaseline oil). Mass spectra were recorded on an MKh-1300 spectrometer (ionizing voltage 70 eV).

General procedure. A mixture of 32% formalin (0.90 mL, ~10 mmol of CH_2O) and a 32% aqueous solution of methylamine (1.35 mL, ~13 mmol) or a mixture of 32% formalin (1.4 mL, ~15 mmol of CH_2O) and 2-aminoethanol (1.22 g, 20 mmol) was added to a solution of 1,3-dinitro-2-phenylpropane (**1**) (0.30 g, 1.4 mmol) in 15 mL of a $CHCl_3$—EtOH mixture (5 : 1) at 0—10 °C. The reaction mixture was stirred at 20 °C for 4 h, washed with water (3×5 mL), dried with anhydrous Na_2SO_4, and concentrated to dryness. The solid residue was recrystallized from EtOH.

3,7-Dimethyl-1,5-dinitro-9-phenyl-3,7-diazabicyclo[3.3.1]nonane (2), colorless crystals, yield 0.38 g (83%), m.p. 207—208 °C. Found (%): C, 56.72; H, 6.42; N, 17.73. $C_{15}H_{20}N_4O_4$. Calculated (%): C, 56.24; H 6.29; N, 17.49. ^1H NMR ($CDCl_3$), δ: 2.34 (s, 3 H, Me—N(3)); 2.49 (s, 3 H, Me—N(7)); 2.87 (d, 4 H, $H_eC(2)$, $H_eC(4)$, $H_aC(6)$, $H_aC(8)$, ^2J = 11.4 Hz); 3.10 (d, 2 H, $H_eC(6)$, $H_eC(8)$, ^2J = 11.4 Hz); 3.45 (d, 2 H, $H_aC(2)$, $H_aC(4)$, ^2J = 11.4 Hz); 4.44 (br.s, 1 H, H(9)); 7.05—7.35 (m, 5 H, Ph). ^{13}C NMR ($CDCl_3$), δ: 44.06 (q, Me—N(3)); 44.82 (q, Me—N(7)); 51.14 (d, C(9)); 54.69 (t, C(6) and C(8)); 64.62 (t, C(2) and C(4)); 88.07 (s, C(1) and C(5)); 128.54 (d, *o*-Ph); 128.79 (d, *m*-Ph); 130.61 (s, *i*-Ph); 131.56 (d, *p*-Ph). IR, ν/cm^{-1}: 704, 816, 1460 (Ph); 1544, 1376 (NO_2). MS, *m/z*: 320 $[M]^+$.

3,7-Bis(2-hydroxyethyl)-1,5-dinitro-9-phenyl-3,7-diazabicyclo[3.3.1]nonane (3), colorless crystals, yield 0.40 g (75%), m.p. 118 °C. Found (%): C, 53.83; H, 6.43; N, 15.72. $C_{17}H_{24}N_4O_6$. Calculated (%): C, 53.68; H, 6.36; N, 14.73. ^1H NMR ($CDCl_3$), δ: 2.76 (t, 2 H, $CH_2N(3)$, ^3J = 5.2 Hz); 3.02 (t, 2 H, $CH_2N(7)$, ^3J = 5.4 Hz); 3.35 (dd, 2 H, $H_aC(6)$, $H_aC(8)$, ^2J = 10.8 Hz, ^4J = 2.3 Hz); 3.44 (d, 2 H, $H_eC(6)$, $H_eC(8)$, ^2J = 10.8 Hz); 3.47 (d, 2 H, $H_eC(2)$, $H_eC(4)$, ^2J = 12.2 Hz); 3.68 (t, 2 H, CH_2O, ^3J = 5.2 Hz); 3.74 (dd, 2 H, $H_aC(2)$, $H_aC(4)$, ^2J = 12.2 Hz, ^4J = 2.3 Hz); 3.81 (t, 2 H, CH_2O, ^3J = 5.4 Hz); 4.33 (br.s, 3 H, H(9) and 2 OH); 7.10—7.34 (m, 5 H, Ph). ^{13}C NMR ($CDCl_3$), δ: 51.54 (t, C(6), C(8)); 54.29 (d, C(9)); 58.07 (t, $CH_2N(3)$); 58.14 (t, $CH_2N(7)$); 58.26 and 58.65 (both t, CH_2OH); 63.74 (t, C(2), C(4)); 86.98 (s, C(1), C(5)); 128.86 (d, *o*-Ph); 129.21 (d, *m*-Ph); 130.79 (s, *i*-Ph); 131.01 (d, *p*-Ph). IR, ν/cm^{-1}: 704, 815, 1460 (Ph); 1544, 1375 (NO_2). MS, *m/z*: 380 $[M]^+$.

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