Stereoselective synthesis of spiro derivatives of 2,4-dimethyl-2,3,4,4a,5,6-hexahydro-6*H*-benzo[*c*]quinolizine

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The reactions of 2-(3,5-dimethylpiperidino)benzaldehyde with Meldrum´s acid and cyclohexane-1,3-dione occur as a tandem of the Knoevenagel condensation and cyclization promoted by the *tert*-amino effect. The cyclization yields only one isomer with the axial hydrogen atoms in positions 4 and 4a of the benzoquinolizine ring.

Key words: *tert*-amino effect, cyclization, nitrogen-containing heterocycles, spiroheterocycles.

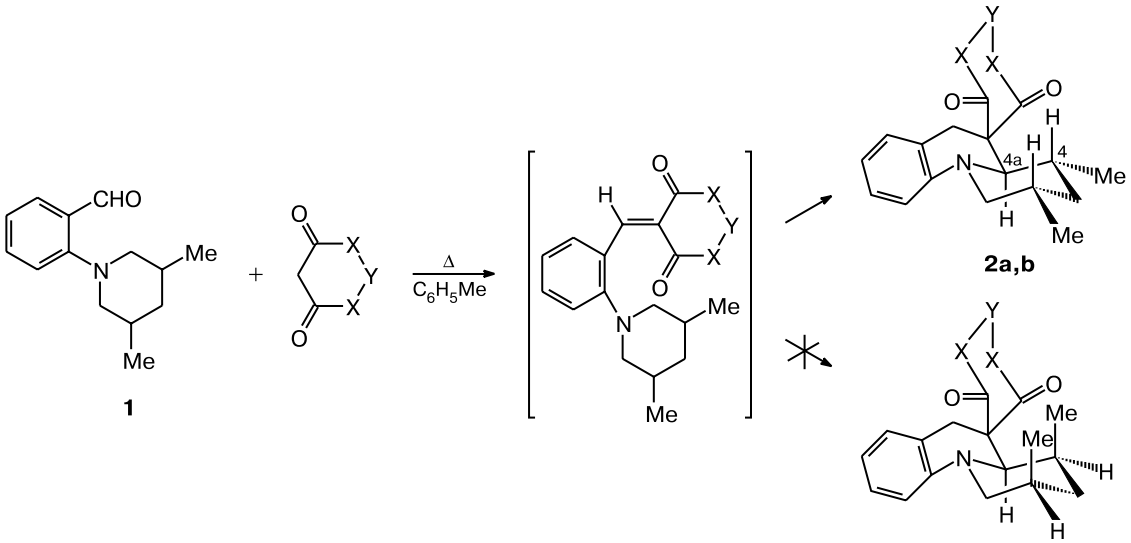
Earlier,[1—3] we proposed a one-step method for the synthesis of spiro compounds involving a tandem[4] of the Knoevenagel condensation of 2-dialkylaminobenzaldehyde with cyclic methylene-reactive compounds and the *tert*-amino effect cyclization.[5—7] When the dialkylamino group contains substituents, two different diastereomers can be formed.[5] In the present work, we reported stereoselective reactions of 2-(3,5-dimethylpiperidino)benzaldehyde (**1**) with Meldrum´s acid and cyclohexane-1,3-dione (Scheme 1) that afford spiro compounds **2** (2,4-dimethyl-2,3,4,4a,5,6-hexahydro-6*H*-benzo[*c*]quinolizine derivatives) as only one isomer with the axial hydrogen atoms in positions 4 and 4a of the benzoquinolizine ring. The formation of that isomer is obvious from the spin-spin coupling constant J = 9.7—9.8 Hz in the ^{1}H NMR spectra of the compounds obtained.

Thus, we discovered that the *tert*-amino effect cyclization is stereoselective when the C_β atom of the dialkylamino group bears a substituent.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 instrument (400 (^{1}H) and 100 MHz (^{13}C)) in DMSO-d_6 with Me_4Si as the internal standard. Mass spectra were recorded on a MAT11 spectrometer (EI, 70 eV). The course

Scheme 1



2: X = Y = CH_2 (**a**); X = O, Y = CMe_2 (**b**)

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 6, pp. 1492—1494, June, 2005.

1066-5285/05/5406-1537 © 2005 Springer Science+Business Media, Inc.

of the reactions was monitored and the purity of the compounds obtained was checked by TLC on DC-Plastikfolien Kieselgel 60 F 254 plates in CH_2Cl_2—hexane (15 : 1) and AcOEt—hexane (1 : 2). 3,5-Dimethylpiperidine and 2-fluorobenzaldehyde of the Acros Co. were used.

2-(3,5-Dimethylpiperidino)benzaldehyde (1). 3,5-Dimethylpiperidine (1.30 mL, 9.88 mmol) and potassium carbonate (1.38 g, 9.88 mmol) were added to a solution of 2-fluorobenzaldehyde (1.0 mL, 9.49 mmol) in DMF (8.0 mL). The reaction mixture was refluxed in a glycerol bath at 150 °C for 20 h. After the reaction was completed (monitoring by TLC), the mixture was cooled to room temperature and water (75 mL) was added. The product was extracted with ethyl acetate (3×60 mL). The combined organic extract was washed with a solution of ammonium chloride, the organic layer was dried over Na_2SO_4, and the solvent was removed *in vacuo*. The yield of compound **1** was 1.48 g (72%), m.p. 150 °C. Found (%): N, 6.39. $C_{14}H_{19}NO$. Calculated (%): N, 6.45. ^{1}H NMR, δ: 0.87 (d, 6 H, 2 Me, J = 6.4 Hz); 1.80—2.20 (m, 3 H, 3 CH); 2.40 (dd, 2 H, 2 CH, J = 11.3 Hz, J = 15.2 Hz); 2.67—2.78 (m, 1 H, CH); 3.10 (dm, 2 H, 2 CH, J = 15.2 Hz); 7.05 (dd, 1 H, H arom., J = 8.2 Hz, J = 7.2 Hz); 7.10 (d, 1 H, H arom., J = 7.2 Hz); 7.49 (dd, 1 H, H arom., J = 7.7 Hz, J = 8.2 Hz); 7.65 (d, 1 H, H arom., J = 7.7 Hz); 10.16 (s, 1 H, CHO). MS, m/z (I_{rel} (%)): 217 $[M]^{\bullet+}$ (100).

2,4-Dimethyl-2,3,4,4a,5,6-hexahydro-6*H*-spiro[benzo[*c*]quinolizine-5,2′-cyclohexane]-1′,3′-dione (2a). Cyclohexane-1,3-dione (0.26 g, 2.3 mmol) was added to a solution of benzaldehyde **1** (0.49 g, 2.3 mmol) in toluene (20 mL). The reaction mixture was refluxed for 3 h. After the reaction was completed (monitoring by TLC), the mixture was cooled to room temperature and concentrated *in vacuo* and the residue was triturated with ethanol. The yield of compound **2a** was 0.61 g (85%), m.p. 190 °C. Found (%): N, 4.55. $C_{20}H_{25}NO_2$. Calculated (%): N, 4.50. ^{1}H NMR, δ: 0.70 (d, 3 H, Me, J = 6.4 Hz); 0.83 (d, 3 H, Me, J = 6.7 Hz); 1.00—1.90 (m, 5 H, 5 CH); 2.11—2.23 (m, 1 H, CH); 2.26, 2.47 (both dm, 1 H each, 2 CH, J = 13.0 Hz); 2.69 (dd, 1 H, H(1), J = 14.3 Hz, J = 11.5 Hz); 2.84, 2.90 (AB system, 2 H, C(6)H_2, J = 17.0 Hz); 3.22—3.40 (m, 2 H, 2 CHCO); 3.84 (dm, 1 H, H(1), J = 14.3 Hz); 4.17 (d, 1 H, H(4a), J = 9.7 Hz); 6.60 (dd, 1 H, H arom., J = 7.3 Hz, J = 7.0 Hz); 6.67 (d, 1 H, H arom., J = 7.9 Hz); 6.93 (dd, 1 H, H arom., J = 7.9 Hz, J = 7.0 Hz); 7.02 (d, 1 H, H arom., J = 7.3 Hz). MS, m/z (I_{rel} (%)): 311 $[M]^{\bullet+}$ (100).

2,4,2′,2′-Tetramethyl-2,3,4,4a,5,6-hexahydro-6*H*-spiro[benzo[*c*]quinolizine-5,5′-[1,3]dioxane]-4′,6′-dione (2b) was obtained analogously from Meldrum′s acid (0.33 g, 2.3 mmol). The yield of compound **2b** was 0.63 (80%), m.p. 150 °C. Found (%): N, 4.00. $C_{20}H_{25}NO_4$. Calculated (%): N, 4.08. ^{1}H NMR, δ: 0.80 (d, 3 H, Me, J = 6.7 Hz); 0.92 (d, 3 H, Me, J = 6.1 Hz); 1.55—1.95 (m, 10 H, 4 CH + 2 Me); 2.67 (dd, 1 H, H(1), J = 13.5 Hz, J = 11.0 Hz); 3.08, 3.19 (AB system, 2 H, C(6)H_2, J = 14.9 Hz); 3.58 (d, 1 H, H(4a), J = 9.8 Hz); 3.90 (dm, 1 H, H(1), J = 13.5 Hz); 6.52 (dd, 1 H, H arom., J = 7.3 Hz, J = 8.0 Hz); 6.69 (d, 1 H, H arom., J = 8.0 Hz); 6.89 (d, 1 H, H arom., J = 7.3 Hz); 7.03 (dd, 1 H, H arom., J_1 = J_2 = 7.3 Hz). MS, m/z (I_{rel} (%)): 343 $[M]^{\bullet+}$ (100).

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Received November 30, 2004