Intramolecular Cyclization of 1-benzyl-2-(nitromethylene)pyrrolidines in Triflic Acid

Bamba FANTE ^{1,*}, Yaya SORO ², Mawa KONE ¹, Sorho SIAKA ² and Jean-Marie COUSTARD³

¹*Laboratoire de Chimie Organique Structurale, Université Félix Houphouët-Boigny, 22 BP 582 Abidjan 22, Côte d'Ivoire*

²*Laboratoire des Procédés Industriels de Synthèse, de l'Environnement et des Energies Nouvelles, Institut National Polytechnique Félix Houphouët-Boigny, BP 991 Yamoussoukro, Côte d'Ivoire*

³*Laboratoire IC2MP-UMR 7285 CNRS, 40, Avenue du Recteur Pineau. F-86022 Poitiers Cedex. France*

Supporting informations

Experimental Section

General Remarks: Melting points were determined with a Büchi Melting point B545 apparatus using capillary tubes (temperature rate 2°C/min) and were not corrected. A Bruker DPX 300 spectrometer, equipped with a low temperature probe, was used for ¹H, ¹⁹F and ¹³C-NMR spectra that were recorded at 300.13, 282.37 and 75.47 MHz, respectively. NMR spectra of cations were recorded in neat triflic acid at low temperature in the presence of CD₃OD contained in a sealed capillary tube placed inside the NMR tube. NMR spectra of starting compounds and products were recorded at room temperature and chemical shifts reported relative to Me₄Si or CFC₃ for fluorine. The reproducibility of ¹³C NMR shift was about ±0.05 ppm, depending on cell and concentration. Chemical assignments were made using DEPT 135, 2D and usual chemical shift assignments rules. Electron-impact ionization (70 eV) mass spectra were obtained with a Finnigan Incos 500 Instrument. High Resolution Mass Spectrometry was performed by the “Faculty of Sciences-University of Picardie / Jules Verne, France”. Column chromatography was

* Tel: (225) 02 12 99 09 ; Fax (225) 22 48 70 43 & E-mail: fante_bamba1@yahoo.fr

carried out on flash silica gel (20 to 45 μm particle size). Triflic acid was purchased from Acros. No attempt was made to optimize the yields.

(E)-1-benzyl-2-(nitromethylene)pyrrolidine (**2a**)

Typical procedure: 1-benzylpyrrolidin-2-one (4.63 g, 26.46 mmol) and dimethylsulfate (2.60 mL, 27.40 mmol) were heated at 80 °C for 15 h under nitrogen atmosphere. The reaction mixture was then cooled at 50/60 °C and a solution of sodium ethoxide (0.742 g of sodium in ethanol (14.0 mL) was added dropwise. The resulting mixture was stirred under nitrogen for 4h at 50/60°C. Then nitromethane dried over CaCl_2 (3 mL, 55.0 mmol), was added and the resulting solution was refluxed for 10 min. After cooling, the solvent was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 , filtered and the solvent evaporated *in vacuo*.. The resulting oil was purified by column chromatography on silica gel ($\text{CH}_2\text{Cl}_2/\text{AcOEt}$, 99/1). Further crystallization from CH_2Cl_2 /petroleum ether afforded compound **2a** as white crystals (0.424 g, 28%).

Mp 94.9 °C (CH_2Cl_2 /petroleum ether).

^1H NMR (300 MHz, CDCl_3): δ = 2.10 (m, 2H, $\text{CH}_2\text{-CH}_2\text{-CH}_2$), 3.56 (m, 4H, $\text{CH}_2\text{-CH}_2\text{-CH}_2$), 4.40 (s, 2H, $\text{CH}_2\text{-Ph}$), 6.86 (s, 1H, $=\text{CH-NO}_2$), 7.08 (d, J = 7.3 Hz, 2H, *o*-H), 7.37 (m, 3H, *p*-H, *m*-H).

^{13}C NMR (75 MHz, CDCl_3): δ = 20.85 ($\text{CH}_2\text{-C=}$), 35.04 ($\text{CH}_2\text{-CH}_2\text{-CH}_2$), 51.37 ($\text{CH}_2\text{-Ph}$), 54.56 ($\text{N-CH}_2\text{-CH}_2$), 109.88 ($=\text{CH-NO}_2$), 127.60 ($2 \times \text{ar-CH}$), 128.68 (ar-CH), 129.54 ($2 \times \text{ar-CH}$), 134.24 (*ipso*-C), 164.72 ($>\text{C=CH-}$; C-2).

HRMS (ESI): m/z $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}_2\text{Na}$: 218.0953; found: 241.0959.

(E)-1-(4-Methylbenzyl)-2-(nitromethylene)pyrrolidine (**2b**)

From 1-(4-methylbenzyl)pyrrolidin-2-one (5 g, 26.45 mmol), **2b** was obtained as white crystals (1.98 g, 32 %).

Mp 98.5 °C (CH₂Cl₂/petroleum ether).

¹H NMR (300 MHz, CDCl₃): δ = 2.08 (m, 2H, CH₂-CH₂-CH₂), 2.35 (s, 3H, CH₃), 3.54 (m, 4H, CH₂-CH₂-CH₂), 4.35 (s, 2H, CH₂-Ph), 6.87 (s, 1H, vinylic-H), 7.06 (d, *J* 7.8 Hz, 2H), 7.17 (d, *J* 7.8 Hz, 2H).

¹³C NMR (75 MHz, CDCl₃): δ = 20.78 (CH₂-CH₂-CH₂), 21.52 (CH₃), 35.09 (CH₂-C=), 51.15 (CH₂-Ph), 54.47 (N-CH₂-CH₂), 109.76 (=CH-NO₂), 127.70 (2 × ar-CH), 130.15 (2 × ar-CH), 131.22 (*ipso*-C), 138.50 (C-Me), 164.70 (>C=CH-NO₂).

HRMS (ESI): *m/z* [M+Na]⁺ calcd for C₁₃H₁₆N₂O₂Na: 255.1109; found 255.1120.

(E)-1-(4-Methoxybenzyl)-2-(nitromethylene)pyrrolidine (**2c**)

From 1-(4-methoxybenzyl)pyrrolidin-2-one (5.42 g, 26.4 mmol), **2c** was obtained as white powder (1.44 g, 22%).

Mp 128.5 °C (CH₂Cl₂/petroleum ether).

¹H NMR (300 MHz, CDCl₃): δ = 2.07 (q, *J* 7.6 Hz, 2H, CH₂-CH₂-CH₂), 3.53 (m, 4H, CH₂-CH₂-CH₂), 3.81 (s, 3H, OCH₃), 4.33 (s, 2H, CH₂-Ph), 6.89 (d, 2H, *J* 8.5 Hz, ar-H); 6.90 (s, 1H, vinylic H); 7.12 (d, *J* 8.4 Hz, 2H, ar-H).

¹³C NMR (75 MHz, CDCl₃): δ = 20.75 (CH₂-CH₂-CH₂); 35.09 (CH₂-C=); 50.89 (CH₂-Ph); 54.23 (N-CH₂-CH₂); 55.73 (OCH₃); 109.79 (=CH-NO₂); 114.87 (2 × ar-CH); 126.19 (*ipso*-C); 129.20 (2 × ar-CH); 159.95 (≥C-OMe); 164.53 (>C=CH-NO₂).

HRMS (ESI): *m/z* [M+Na]⁺ calcd for C₁₃H₁₆N₂O₃Na: 271.1058; found 271.1071.

(E)-1-(4-fluorobenzyl)-2-(nitromethylene)pyrrolidine (**2d**)

From 1-(4-fluorobenzyl)pyrrolidin-2-one (5.10 g, 26.4 mmol). **2d** was obtained as white crystals (1.50 g, 24%).

Mp 108 °C (CH₂Cl₂/petroleum ether).

¹H NMR (300 MHz, CDCl₃): δ = 2.09 (q, *J* 7.6 Hz, 2H, CH₂-CH₂-CH₂), 3.53 (t, *J* 7.6 Hz, 4H, CH₂-CH₂-CH₂), 4.37 (s, 2H, CH₂-Ph), 6.83 (s, 1H, vinylic-H), 7.06 (t, *J* 8.7 Hz, 2ar-H, *o*-F), 7.16 (t, *J* 5.3 Hz, 2 ar-H, *m*-F).

¹³C NMR (75 MHz, CDCl₃): δ = 20.82 (CH₂-CH₂-CH₂), 35.01 (CH₂-C=), 50.65 (CH₂-Ph), 54.45 (N-CH₂-CH₂), 109.85 (=CH-NO₂), 116.45 (d, ²*J*_{CF} 21.4 Hz, 2 × ar-C), 129.50 (d, ³*J*_{CF} 8.2 Hz, 2 × ar-C), 130.17 (⁴*J*_{CF} 3.3 Hz, *Ips*o-C), 162.85 (d, ¹*J*_{CF} 247 Hz, *Ips*o-F), 164.65 (>C=CH-NO₂).

HRMS (ESI): *m/z* [M+Na]⁺ calcd for C₁₂H₁₃FN₂O₂Na: 259.0858; found 259.0852.

2,3-Dihydro-1H-pyrrolo[1,2-b]isoquinolin-4-ium trifluoromethanesulfonate (**5a**).

Typical procedure: (*E*)-1-benzyl-2-(nitromethylene)pyrrolidine **2a** (218 mg, 1 mmol) was dissolved in triflic acid (5 mL, 56.2 mmol) at 2 °C under nitrogen atmosphere. The reaction was monitored by TLC (CH₂Cl₂/MeOH, 97/3). After the disappearance of the starting compound, the acidic solution was poured into 50 mL of a mixture of CH₂Cl₂/MeOH (90:10) at -60 to -40 °C and let to warm. When the temperature was close to 0°C, brine (10 mL) and anhydrous Na₂CO₃ (6 g) were added. The extraction was carried out promptly with CH₂Cl₂/MeOH, 95/5 (4 × 20 mL). The organic phase was dried over MgSO₄ and the solvent evaporated under reduced pressure. The crude product was purified by column chromatography using CH₂Cl₂/MeOH, 95/5 as eluent, followed by precipitation from a mixture of dichloromethane/petroleum ether, to yield **5a** (124 mg, 39%) as white powder.

Mp 73-4 °C (CH₂Cl₂/petroleum ether).

¹H NMR (300 MHz, acetone-d₆): δ = 2.66 (m, 2H, CH₂-CH₂-CH₂); 3.67 (t, *J* 7.5 Hz, 2H, CH₂-C=), 5.16 (t, *J* 7.4 Hz, 2H, CH₂-N); 7.98 (t, *J* 7.2 Hz, 1H, H-9); 8.18 (t, *J* 7.3 Hz, 1H, H-8); 8.26 (d, *J* 8.4 Hz, 1H, H-7); 8.47 (d, *J* 9.5 Hz, 1H, H-10); 8.49 (s, 1H, H-6); 10.02 (s, 1H, H-5).

¹³C NMR (75 MHz, CD₃COCD₃): δ = 23.90 (CH₂-CH₂-CH₂); 31.99 (CH₂-C=); 60.06 (CH₂-N); 122.61 (qd, *J*_{CF} 321.6 Hz, CF₃SO₃⁻); 122.60 (C-6); 128.25 (C-5a); 128.43 (C-7); 131.21 (C-9); 131.54 (C-10); 137.63 (C-8); 140.09 (C-9a); 147.62 (C-5); 150.16 (C-10a).

¹⁹F NMR (282 MHz, CD₃COCD₃): δ = -73.9 (CF₃SO₃⁻).

HRMS (EI): *m/z* [M-(CF₃SO₃⁻)] calcd for C₁₂H₁₂N: 170.0969; found 170.0961.

10-Amino-2,3-dihydro-1H-pyrrolo[1,2-b]isoquinolin-4-ium trifluoromethane sulfonate (**6a**).

From **2a** was obtained the second product **6a** (91 mg, 27%) as powder.

Mp 153-4 °C (CH₂Cl₂/petroleum ether).

¹H NMR (300 MHz, CD₃COCD₃): δ = 2.66 (m, 2H, CH₂-CH₂-CH₂); 3.67 (m, 2H, CH₂-C=); 5.16 (m, 2H, CH₂-N); 6.65 (broad s, 2H, NH₂); 7.92 (dt, *J* 7.2 Hz; 1.2 Hz, 1H, H-8); 8.05 (dt, *J* 7.0 Hz; 1.0 Hz, 1H, H-7); 8.28 (d, *J* 8.3 Hz, 1H, H-9); 8.48 (d, *J* 8.6 Hz, 1H, H-6); 9.17 (s, 1H, H-5).

¹³C NMR (75 MHz, CD₃COCD₃): δ = 22.99 (CH₂-CH₂-CH₂); 29.88 (CH₂-C=); 60.74 (CH₂-N⁺); 122.54 (qd, *J*_{CF} 321.6 Hz, CF₃SO₃⁻); 122.98 (≥CH, C-6); 127.21 (C-5a); 129.35 (C-9a); 130.63 (≥CH, C-9); 131.18 (≥CH, C-7); 131.58 (C-10a); 132.32 (bs. >N⁺=CH-; C-5); 134.49 (CH, C-8); 141.32 (C-NH₂).

¹⁹F NMR (282 MHz, CD₃COCD₃): δ = -74.1 (CF₃SO₃⁻).

HRMS (EI): *m/z* [M-(CF₃SO₃⁻)] calcd for C₁₂H₁₃N₂: 185.1074; found 185.1074.

8-Methyl-2,3-dihydro-1H-pyrrolo[1,2-b]isoquinolin-4-ium trifluoromethanesulfonate (**5b**).

From (*E*)-1-(4-Methylbenzyl)-2-(nitromethylene)pyrrolidine **2b** (232 mg, 1 mmol) was obtained **5b** (206 mg, 62%) as powder.

Mp 136.9 °C (CH₂Cl₂/petroleum ether).

¹H NMR (300 MHz, CDCl₃): δ = 2.58 (q, *J* 7.6 Hz, 2H, CH₂-CH₂-CH₂); 2.65 (s, 3H, CH₃); 3.55 (t, *J* 7.3 Hz, 2H, CH₂-C=); 5.07 (t, *J* 7.6 Hz, 2H, CH₂-N); 7.65-7.68 (cd, *J* 8.6 Hz, 1H, H-6); 7.79 (s, 1H, H-9); 8.02 (s, 1H, H-10); 8.26-8.29 (d, *J* 8.6 Hz, 1H, H-7); 9.92 (s, 1H, H-5).

¹³C NMR (75 MHz, CDCl₃): δ = 23.00 (CH₃ and CH₂-CH₂-CH₂); 31.17 (CH₂-C=); 58.65 (CH₂-N); 120.5 (qd, *J*_{CF} 320.5 Hz, CF₃SO₃⁻); 120.90 (C-6); 125.86 (C-5a); 126.25 (C-10); 130.21 (C-7); 133.16 (C-9); 139.37 (C-Me); 145.79 (C-5); 148.21 (C-9a); 149.01 (C-10a).

¹⁹F NMR (282 MHz, CD₃COCD₃): δ = -72.23 (CF₃SO₃⁻).

HRMS (EI): *m/z* [M-(CF₃SO₃⁻)] calcd for C₁₃H₁₄N: 184.1126; found 184.1133.

10-Amino-8-methyl-2,3-dihydro-1H-pyrrolo[1,2-b]isoquinolin-4-ium trifluoromethanesulfonate (**6b**).

From the reaction of (*E*)-1-(4-Methylbenzyl)-2-(nitromethylene) pyrrolidine **2b** (232 mg, 1 mmol) in triflic acid, **6b** (108 mg, 31%) was also isolated as powder.

Mp 67-8 °C (CH₂Cl₂/petroleum ether).

¹H NMR (300 MHz, CD₃COCD₃): δ = 2.65 (m, 5H, CH₃ and CH₂-); 3.47 (t, *J* 7.3 Hz, 2H, CH₂-C=); 5.06 (t, *J* 7.5 Hz, 2H, CH₂-N); 6.50 (broad s, 2H, NH₂); 7.75 (d, *J* 7.7 Hz, 1H, H-6); 8.17 (d, *J* 8.7 Hz, 1H, H-7); 8.27 (s, 1H, H-9); 9.05 (s, 1H, H-5).

^{13}C NMR (75 MHz, CD_3COCD_3): δ = 22.85 (CH_3); 23.02 (CH_2); 29.78 ($\text{CH}_2\text{-C=}$); 60.41 ($\text{CH}_2\text{-N}$); 121.98 (CH ; C-9); 122.33 (qd, J_{CF} 320.5 Hz, CF_3SO_3^-); 127.59 (C-5a); 128.69 (C-9a); 130.41 (CH ; C-7), 132.19 (CH ; C-5); 133.31 (CH ; C-6); 140.51 (Ipso-Me); 143.63 (C-10a); 146.13 (C-NH₂).

^{19}F NMR (282 MHz, acetone- d_6): δ = -74.3 (CF_3SO_3^-).

HRMS (EI): m/z [$\text{M}-(\text{CF}_3\text{SO}_3^-)$] calcd for $\text{C}_{13}\text{H}_{15}\text{N}_2$: 199.1235; found 199.1245.

5-Methoxy-2,3-dihydro-1H-pyrrolo[1,2-b]isoquinolin-4-ium trifluoromethanesulfonate (**5c**).

From (*E*)-1-(4-methoxybenzyl)-2-(nitromethylene)pyrrolidine **2c** (248 mg, 1 mmol), **5c** was obtained as powder (53 mg, 15%).

Mp 98-99 °C (CH_2Cl_2 /petroleum ether).

^1H NMR (300 MHz, CDCl_3): δ = 2.84 (q, J 7.3 Hz, 2H, $\text{CH}_2\text{-CH}_2\text{-CH}_2$), 3.44 (t, J 7.4 Hz, 2H, $\text{CH}_2\text{-C=}$), 4.22 (s, 3H, OCH_3), 4.64 (t, J 7.4 Hz, 2H, $\text{CH}_2\text{-N}$), 7.15-7.28 (m, 2H, H-7 and H-6), 8.27 (s, 1H, H-5), 8.62-8.64 (d, J 7.0 Hz, 1H, H-9), 8.65-8.68 (d, J 6.9 Hz, 1H, H-10).

^{13}C NMR (75 MHz, CDCl_3): δ = 24.52 ($\text{CH}_2\text{-CH}_2\text{-CH}_2\text{C-2}$), 27.20 ($\text{CH}_2\text{-C=}$), 50.31 ($\text{CH}_2\text{-N}$), 58.70 (OCH_3), 116.28 (C-9), 118.38 (C-7), 120.37 (C-5a), 120.80 (qd, J_{CF} 320.5 Hz, CF_3SO_3^-), 122.19 (C-5), 131.36 (C-9a), 145.98 (C-10a), 147.27 (C-10), 147.29 (C-6), 180.31 (C-OMe).

^{19}F NMR (282 MHz, CD_3COCD_3): δ = -75.1 (CF_3SO_3^-).

HRMS (EI): m/z [$\text{M}-(\text{CF}_3\text{SO}_3^-)$] calcd for $\text{C}_{13}\text{H}_{14}\text{NO}$: 200.1075; found 200.1069.

10-Amino-8-fluoro-2,3-dihydro-1H-pyrrolo[1,2-b]isoquinolin-4-ium trifluoromethanesulfonate (**6d**).

From (*E*)-1-(4-fluorobenzyl)-2-(nitromethylene)pyrrolidine **2d** (236 mg, 1 mmol). **6d** was obtained as powder (245 mg, 69%).

Mp 158-9 °C (CH₂Cl₂/petroleum ether).

¹H NMR (300 MHz, CD₃COCD₃): δ = 2.66 (m, 2H, CH₂-CH₂-CH₂), 3.51 (m, 2H, CH₂-C=), 5.11 (m, 2H, CH₂-N), 6.62 (broad s, 2H, NH₂), 7.74-7.81 (m, 1H, H-9), 8.20-8.25 (m, 1H, H-7), 8.40-8.47 (m, 1H, H-6), 9.23 (s, 1H, H-5).

¹³C NMR (75 MHz, CD₃COCD₃): δ = 23.01 (CH₂-CH₂-CH₂), 29.89 (CH₂-C=), 60.70 (CH₂-N⁺), 107.57 (d, ²J_{CF} 26 Hz, C-7), 121.62 (d, ²J_{CF} 24 Hz, C-9), 122.42 (qd, J_{CF} 321.1 Hz, CF₃SO₃⁻), 126.65 (C-5a), 129.01 (d, ³J_{CF} 9.33 Hz, C-9a), 131.67 (C-10a), 132.54 (C-5), 134.60 (d, ³J_{CF} 10.5 Hz, C-6), 140.77 (C-NH₂), 166.25 (d, ¹J_{CF} 255.8 Hz, C-F).

¹⁹F NMR (282 MHz, CD₃COCD₃): δ = -72.4 (CF₃SO₃⁻), -95.7 (CF).

HRMS (EI): m/z [M-(CF₃SO₃-)] calcd for C₁₂H₁₂FN₂: 203.0984; found 203.0975

Cation in triflic acid **12b**

¹H NMR (300 MHz, 298 K, CD₃OD): δ = 1.98 (t, *J* 7,5 Hz, 2H, H-2); 2,04 (s, 3H, CH₃); 2.92 (t, *J* 7,5 Hz, 2H, H-1); 4.26 (t, *J* 7,5 Hz, 2H, H-3); 7.16 (d, *J* 8,6 Hz, 1H, H-6); 7,27 (s, 1H, H-9); 7.45 (s, 1H, H-10); 7.47(d, *J* 8,6 Hz, 1H, H-7); 8.58 (s, 1H, H-5).

¹³C NMR (75 MHz, 298 K, CD₃OD): δ = 21,72 (CH₃); 22,71 C-2); 30,80 (C-1); 58,77 (C-3); 121,29 (C-6); 126,14 (C-5a); 126,29 (C-10); 129,32 (C-7); 133,75 (C-9); 140,21 (C-8); 144,12 (C-5); 148,66 (C-9a); 150,40 (C-10a).

2a

2b

2b

2b_DEPT135

2c

2d

2d

5a

5a (continued)

5b

5b (continued)

5c (triflate salt)

6a (triflate salt)

6a_13C & DEPT 135 (aromatic region) _ (triflate salt)

6b. NH₂ H/D exchange with D₂O

6b ¹³C and DEPT135 - (triflate salt)

6d (triflate salt)

6d ((triflate salt/continued)

DEPT135. Cations in triflic acid: **2b** transformed into cations in TfOH. Main cation: **12** (272 K)

Cations formed in triflic acid from protonation of **2b**