Supporting Information for

An Efficient Method for the Synthesis of Unsymmetrical 2,2'-Bis(pyrrolyl)alkanes.

Marie Laure Murat-Onana, Christophe Berini, Frédéric Minassian*, Nadia Pelloux-Léon*, and Jean-Noël Denis.

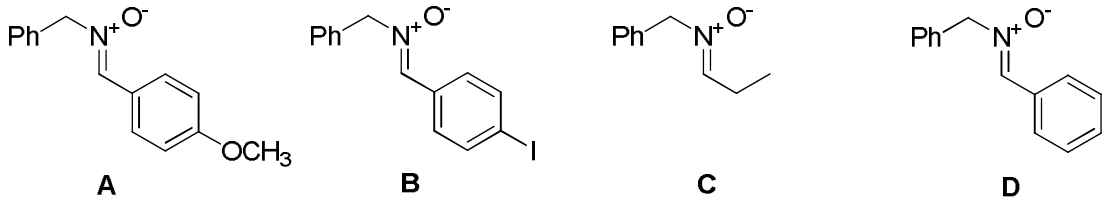
Département de Chimie Moléculaire (SERCO), UMR-5250, ICMG FR-2607, Université Joseph Fourier, CNRS, BP-53, 38041 Grenoble cedex 9, France;

E-mail: Frederic.Minassian@ujf-grenoble.fr, Nadia.Pelloux-Leon@ujf-grenoble.fr

Fax: +33-4-7663-5983; Tel: +33-4-7651-4908.

Table of contents

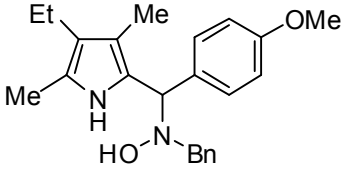
Nitrones **A**, **B**, **C** were prepared using Dondoni[1] procedure for the preparation of *N*-benzylnitrones. Nitrone **D** was prepared using the Murahashi[2] method by oxidation of *N*,*N*-dibenzylamine.



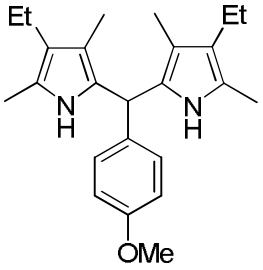
A **B** **C** **D**

Typical procedure for the synthesis of *N*-benzylhydroxylamines.

Freshly distilled acetyl chloride (1 equiv) was added dropwise to anhydrous methanol at 0 °C and the mixture was stirred for 15 min. The appropriate nitrone (1.2 or 2 equiv) was added and the mixture was cooled at −78 °C before the addition of the pyrrole derivate (1 equiv). The media was then warmed to the appropriate temperature and stirred for the appropriate time. The mixture was treated with saturated aqueous $NaHCO_3$ solution and allowed to warm to room temperature. The pH value was then 8-9. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated. The obtained *N*-benzylhydroxylamine was purified by flash chromatography on silica gel pretreated with 3% of triethylamine (v/v).

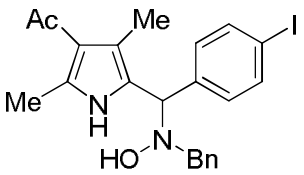


***N*-Benzyl-*N*-((4-ethyl-3,5-dimethyl-1*H*-pyrrol-2-yl)(4-methoxyphenyl)methyl)hydroxylamine 1c**. Prepared according to the above general procedure from nitrone **A** (588 mg, 2.44 mmol) in 12 mL of MeOH, acetyl chloride (96 mg, 1.22 mmol) and 2,4-dimethyl-3-ethylpyrrole **2c** (150 mg, 1.22 mmol). The mixture was stirred at −78 °C for 1 hour. Purification (eluent: pentane/EtOAc, 7/3 to 4/6) afforded *N*-benzylhydroxylamine **1c** (280 mg, 0.77 mmol, 63%) as a brown foam and the symmetrical 2,2'-bis(pyrrolyl)alkane **1ca** as a yellow foam (60 mg, 0.16 mmol, 27%); mp 60-61 °C; ν_{max}/cm^{-1} 3450 (br, NH), 3405, 2960, 2925; 2865, 1605, 1510, 1450, 1241 and 1180; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.07 (3H, t, J = 7.5 Hz, CH_3), 1.94 (3H, s, CH_3), 2.15 (3H, s, CH_3), 2.39 (2H, q, J = 7.5 Hz, CH_2), 3.78-3.84 (4H, m, OCH_3 and 1H of CH_2Ph), 3.89 (1H, d, J = 13.5 Hz, 1H of CH_2Ph), 4.59 (1H, br s, OH), 4.95 (1H, s, CHN), 6.86 (2H, d, J = 8.8 Hz, $2H_{Ar}$), 7.24-7.35 (7H, m, $7H_{Ar}$), 7.93 (1H, br s, NH); δ_C (75 MHz; $CDCl_3$) 9.4 (CH_3), 11.4 (CH_3), 15.9 (CH_3), 17.8 (CH_2), 55.4 (OCH_3), 61.4 (CH_2Ph), 65.5 (CHN), 113.9 ($2CH_{Ar}$), 120.1 (C_{Pyr}), 122.5 (C_{Pyr}), 127.2 (CH_{Ar}), 128.3 ($2CH_{Ar}$), 128.9 ($2CH_{Ar}$), 129.3 ($2CH_{Ar}$), 134.2 (C_{Ar}), 138.5 (C_{Ar}), 158.7 (C-OCH_3); MS (ESI^+) *m/z* 242 ($[MH–C_8H_{13}N]^+$, 100); Elemental analysis, cald (%) for $C_{23}H_{28}N_2O_2$: C, 75.80; H, 7.75; N, 7.69. Found: C, 76.11; H, 7.94; N, 7.45.

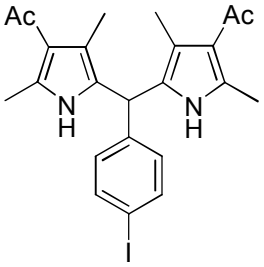


3-Ethyl-5-((4-ethyl-5-methyl-1*H*-pyrrol-2-yl)(4-methoxyphenyl)methyl)-2,4-dimethyl-1*H*-pyrrole 1ca; mp 88-89 °C; ν_{max}/cm^{-1} 3444 (br, NH), 3401, 2960, 2920, 2850, 1690, 1506, 1250 and 1033; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.05 (6H, t, J = 7.5 Hz, $2CH_3$), 1.77 (6H, s, $2CH_3$), 2.09 (6H, s, $2CH_3$), 2.36 (4H, q, J = 7.5 Hz, $2CH_2$), 3.79 (3H, s, OCH_3), 5.37 (1H, s, CH), 6.83 (2H, d, J = 8.8 Hz, $2H_{Ar}$), 7.01 (2H, br s, 2NH), 7.07 (2H, d, J = 8.8 Hz, $2H_{Ar.}$). δ_C (75 MHz; $CDCl_3$) 9.3 ($2CH_3$), 11.2 ($2CH_3$), 15.8 ($2CH_3$), 17.9 ($2CH_2$), 40.1 (CH), 55.3 (OCH_3), 113.6 (C), 114.0 ($2CH_{Ar}$), 120.7 (2C), 121.3 (2C), 125.4 (2C), 129.5 ($2CH_{Ar}$), 134.8 (2C), 158.2 (C). MS (ESI^+) *m/z* 387 ($[M+Na]^+$, 100); HRMS (ESI^-) $C_{24}H_{31}N_2O$ ($[M–H]^-$) requires 363.2430 found 363.2429.

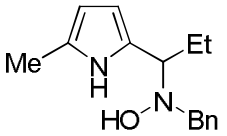
[1] A. Dondoni, S. Franco, F. L. Merchan, P. Merino and T. Tejero, *Synth. Commun.*, 1994, **24**, 2357.
[2] S.-I. Murahashi, H. Mitsui, T. Shiota, T. Tsuda and S. Watanabe, *J. Org. Chem.*, 1990, **55**, 1736.



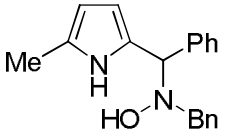
***N*-Benzyl-*N*-((4-ethyl-3,5-dimethyl-1*H*-pyrrol-2-yl)(4-iodophenyl)methyl)hydroxylamine 1f**. To anhydrous CH_2Cl_2 (2 mL) at –40 °C was added nitrone **B** (122 mg, 0.36 mmol) followed by the addition of HCl (90 µL, 2.0 N in Et_2O, 0.18 mmol) and 3-acetyl-2,4-dimethylpyrrole **2b** (25 mg, 0.18 mmol). The mixture was stirred at –40 °C for 24 hours and then treated with a saturated aqueous $NaHCO_3$ solution. The pH value was 8-9. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated. The crude product was purified by flash chromatography on silica gel (eluent: pentane/EtOAc, 1/1 to 1/4) to afford *N*-benzylhydroxylamine **1f** (45 mg, 95 µmol, 52%) as a white solid and a mixture of the symmetrical bispyrrolylalkane and BnNHOH. The latter mixture was washed twice with aqueous HCl 0.1N to afford the symmetrical 2,2'-bis(pyrrolyl)alkane **1fa** as a pink powder (4 mg, 8 µmol, 9%); mp 99-100 °C; ν_{max}/cm^{-1} 3409 (br, NH), 3323, 3028, 2938, 2869, 1615 (CO), 1484, 1439, 1406, 1251 and 1009; δ_H (400 MHz; $CDCl_3$; Me_4Si) 2.15 (3H, s, CH_3), 2.44 (3H, s, CH_3), 2.51 (3H, s, CH_3), 3.89 (2H, q, AB_q, J_{AB} = 13.2 Hz, CH_2Ph), 4.98 (2H, s, CHN and OH), 7.06 (2H, d, J = 8 Hz, $2H_{Ar}$), 7.29-7.35 (5H, m, $5H_{Ar}$), 7.63 (2H, d, J = 8 Hz, $2H_{Ar}$), 8.70 (1H, br s, NH); δ_C (75 MHz; $CDCl_3$) 12.0 (CH_3), 15.6 (CH_3), 31.16 (CH_3), 61.8 (CH_2), 63.2 (CHN), 92.8 (C-I), 120.3 (C), 121.15 (C), 123.4 (C), 127.7 (CH_{Ar}), 128.6 ($2CH_{Ar}$), 129.3 ($2CH_{Ar}$), 129.4 ($2CH_{Ar}$), 135.2 (C), 137.4 (C), 137.7 ($2CH_{Ar}$), 140.7 (C), 195.5 (CO); MS (ESI^+) *m/z* 971 ($[2M+Na]^+$, 50), 497 ($[M+Na]^+$, 50); Elemental Analysis, cald (%) for $C_{22}H_{23}IN_2O_2$: C, 55.71; H, 4.89; N, 5.91. Found: C, 55.61; H, 4.80; N, 5.78.



1-(5-((4-acetyl-3,5-dimethyl-1*H*-pyrrol-2-yl)(4-iodophenyl)methyl)-2-methyl-1*H*-pyrrol-3-yl)ethanone 1fa; mp 160-161 °C; ν_{max}/cm^{-1} 3436 (br, NH), 3280, 2960, 2924, 2850, 1623 (CO), 1475, 1453, 1406 and 1002; δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.11 (6H, s, $2CH_3$), 2.33 (6H, s, $2CH_3$), 2.37 (6H, s, $2CH_3$), 5.49 (1H, s, CH), 6.80 (2H, d, J = 8.4 Hz, $2H_{Ar}$), 7.57 (2H, d, J = 8.4 Hz, $2H_{Ar}$), 8.54 (2H, br s, 2NH); δ_C (75 MHz; $CDCl_3$) 12.0 ($2CH_3$), 15.3 ($2CH_3$), 31.0 ($2CH_3$), 38.1 (CH), 92.6 (C-I), 117.0 (C), 121.8 (C), 125.6 (2C), 130.3 ($2CH_{Ar}$), 134.8 (2C), 137.9 ($2CH_{Ar}$), 140.7 (C), 196.1 (2CO); MS (ESI^+) *m/z* 511 ($[M+Na]^+$, 23), 489 ($[M+H]^+$, 77); HRMS (ESI^+) $C_{23}H_{25}O_2N_2INa$ ($[M+Na]^+$) requires 511.0852 found 511.0852.

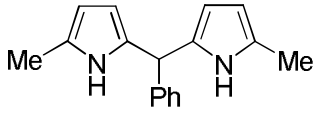


***N*-benzyl-*N*-(1-(5-methyl-1*H*-pyrrol-2-yl)propyl)hydroxylamine 1g**. Prepared according to the above general procedure from nitrone **C** (1.00 g, 6.13 mmol) in 25 ml of anhydrous MeOH, acetyl chloride (442 mg, 5.62 mmol) and 2-methylpyrrole **2a** (425 mg, 5.24 mmol). The mixture was stirred at –40 °C during 2.5 hours. Purification (eluent: CH_2Cl_2/EtOAc, 95/5) afforded *N*-benzylhydroxylamine **1g** (985 mg, 4.03 mmol, 77%) as a beige solid; mp 82-83 °C; ν_{max}/cm^{-1} 3444 (br, NH), 3219, 2967, 2863, 1579, 1493, 1450; δ_H (400 MHz; $CDCl_3$; Me_4Si) 0.82 (3H, t, J = 7.5Hz, CH_3), 1.66-1.73 (1H, m, 1H of CH_2), 1.87-1.79 (1H, m, 1H of CH_2), 2.36 (3H, s, CH_3), 3.45-3.48 (2H, m, CHN and 1H of CH_2Ph), 3.63 (1H, d, J = 13.5Hz, 1H of CH_2Ph), 5.77 (1H, br s, H_{Pyr}), 5.87-5.85 (1H, m, H_{Pyr}), 6.47 (1H, br s, OH), 7.21-7.29 (5H, m, $5H_{Ar}$), 8.26 (1H, br s, NH); δ_C (100 MHz; $CDCl_3$) 11.6 (CH_3), 13.3 (CH_3), 25.5 (CH_2), 64.1 (CH_2), 65.7 (CHN), 104.9 (CH_{Pyr}), 108.6 (CH_{Pyr}), 127.3 (CH_{Ar}), 127.7 (C), 128.3 (C), 128.3 ($2CH_{Ar}$), 129.8 ($2CH_{Ar}$), 138.1 (C); MS (ESI^+) *m/z* 122 ($[MH-C_8H_{13}N]^+$, 100); Elemental Analysis, cald (%) for $C_{15}H_{20}N_2O$: C, 73.74; H, 8.26; N, 11.47. Found: C, 73.71; H, 8.27; N, 11.29.



***N*-benzyl-*N*-((5-methyl-1*H*-pyrrol-2-yl)(phenyl)methyl)hydroxylamine 1h**. Prepared according to the above general procedure from nitrone **D** (170 mg, 0.80 mmol) in 2,5 ml of anhydrous MeOH, acetyl chloride (32 mg, 0.40 mmol) and 2-methylpyrrole **2a** (32 mg, 0.40 mmol). The mixture was stirred at –78 °C during 1.5 hour. Purification (eluent:

pentane/CH_2Cl_2, 20/80) afforded *N*-benzylhydroxylamine **1h** (38 mg, 0.13 mmol, 32%) as a yellow solid and the symmetrical 2,2'-bis(pyrrolyl)alkane **1ha** (10 mg, 40 μmol, 20%) as a yellow solid; mp 45-46 °C; ν_{max}/cm^{-1} 3516 (br, NH), 3431, 3024, 2920, 2902, 2850, 1488 and 1449; δ_H (400 MHz; $CDCl_3$; Me_4Si) 2.19 (3H, s, CH_3), 3.76 (2H, s, CH_2Ph), 4.71 (1H, br s, OH), 4.86 (1H, s, CHN), 5.76 (1H, br s, H_{Pyr}), 5.88-5.90 (1H, m, H_{Pyr}), 7.16-7.36 (10H, m, $10H_{Ar}$), 8.25 (1H, br s, NH); δ_C (75 MHz; $CDCl_3$) 13.3 (CH_3), 61.6 (CH_2), 68.4 (CHN), 105.5 (CH_{Pyr}), 109.8 (CH_{Pyr}), 127.3 ($2CH_{Ar}$), 127.4 ($2CH_{Ar}$), 128.3 ($2CH_{Ar}$), 128.4 ($2CH_{Ar}$), 129.3 ($2CH_{Ar}$), 138.3 (2C), 141.0 (2C); MS (ESI^+) *m/z* 170 ($[MH–C_8H_{13}N]^+$, 100); Elemental analysis, cald (%) for $C_{19}H_{20}N_2O$: C, 78.06; H, 6.90; N, 9.59. Found: C, 77.96; H, 7.01; N, 9.45.



5,5'-(Phenylmethylene)bis(2-methyl-1*H*-pyrrole) 1ha; ν_{max}/cm^{-1} 3427 (br, NH), 3362, 2915, 2850, 1592, 1440 and 1410; δ_H (400 MHz; $CDCl_3$; Me_4Si) 2.21 (6H, s, $2CH_3$), 5.36 (1H, s, CH), 5.75-5.77 (2H, m, $2H_{Pyr}$), 5.80 (2H, br s, $2H_{Pyr}$), 7.24-7.26 (3H, m, $3H_{Ar}$), 7.30-7.32 (2H, m, $2H_{Ar}$), 7.63 (2H, br s, 2NH). δ_C (100 MHz; $CDCl_3$) 13.1 ($2CH_3$), 44.2 (CH), 105.9 ($2CH_{Pyr}$), 107.3 ($2CH_{Pyr}$), 126.9 (CH_{Ar}), 127.3 ($2C_{Pyr}$), 128.5 ($2CH_{Ar}$), 128.6 ($2CH_{Ar}$), 131.3 ($2C_{Pyr}$), 142.5 (C_{Ar}); MS (DCI) *m/z* 251 ($[M+H]^+$, 100).