A Convenient Synthesis of 2-Aminomethylpyrroles

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A high yielding route to simple 2-aminomethyl-1-arylpyrroles **5** from 1-arylpyrroles **1** is described. 2-Aminomethyl-1-(2-cyanophenyl)pyrrole was cyclised to a novel pyrrolo[1,2-α][1,4]benzodiazepine.

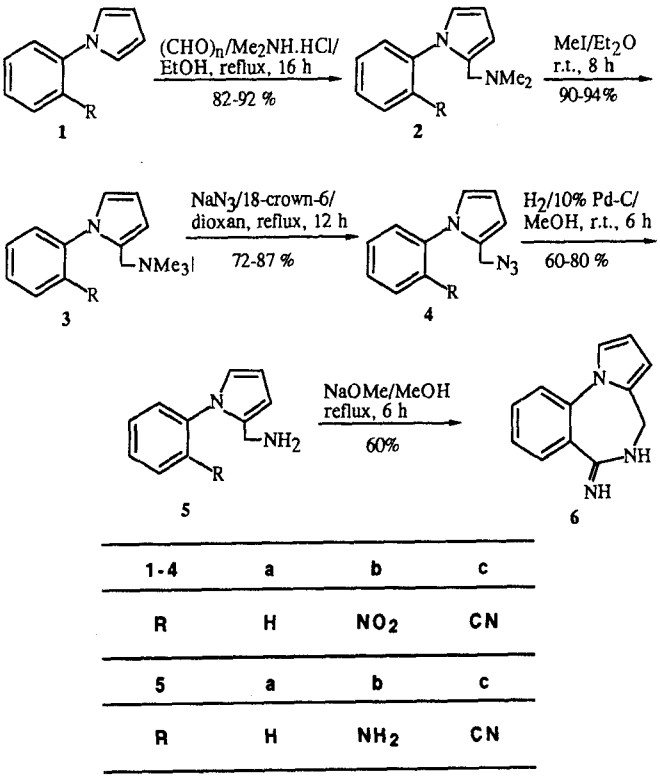
During the course of our investigations aimed at synthesising novel tricyclic compounds derived from 1-arylpyrroles,[1] we became interested in preparing 2-aminomethyl-1-arylpyrroles **5**. Obvious routes to these compounds would be via reduction of carbaldoximes,[2] ethanolysis of phthalimido derivatives[3] or by reductive amination of aldehydes.[4] In our hands, however, the application of these and several other literature methods,[5–8] failed to provide a satisfactory route to **5**. For example, hydrogenation of 1-phenylpyrrole-2-carbaldoxime over 10% palladium on carbon or platinum dioxide for 20 hours gave a mixture of starting material with only 20% of compound **5a**, which explains why 1-(2-nitrophenyl)pyrrole-2-carbaldoxime[9] cyclises to pyrrolo[1,2-α]quinoxaline[10] under similar conditions.

The Mannich reaction provides a very convenient method of introducing a dialkylaminomethyl group into the 2-position of a pyrrole ring. The dialkylamino group can then be displaced by a variety of nucleophiles,[11–13] including ammonia.[14] A suprising omission in this respect is the azide anion, since reduction of the resulting azide would provide ready access to the 2-aminomethylpyrroles. This route has been used for the conversion of phenols to *o*-hydroxybenzylamines.[15] However, alternative conditions have had to be devised to apply this route to pyrroles.

Following the above strategy, treatment of 1-arylpyrroles **1** with paraformaldehyde and dimethylamine hydrochloride in refluxing ethanol afforded the corresponding Mannich bases **2** as viscous oils. The quaternary salts **3** were obtained by stirring the Mannich bases **2** with an excess of methyl iodide in dry diethyl ether at room temperature. The introduction of the azido group was accomplished by the displacement of trimethylamine from the quaternary salts **3** using sodium azide in boiling dry dioxane and a catalytic amount of 18-crown-6. The resulting 1-aryl-2-azidomethylpyrroles **4** were stable, low melting solids. The aminomethyl derivatives **5** were obtained by reduction of the azido derivative **4** with hydrogen in the presence of 10% palladium on charcoal. Attempts to convert azido to amino by using the Staudinger reaction to convert the azides to an iminophosphorane followed by hydrolysis[16] were unsuccessful.

A simple illustration of the synthetic potential of these compounds is provided by the intramolecular cyclisation of the aminonitrile **5c** into the novel pyrrolo[1,2-α][1,4]-benzodiazepine **6** by refluxing in a methanolic solution of sodium methoxide.

We have thus developed a simple and efficient synthetic route to 2-aminomethyl-1-arylpyrroles which have been employed in the synthesis of a novel pyrrolo[1,2-α][1,4]-benzodiazepine.



1-4	a	b	c
R	H	NO_2	CN

5	a	b	c
R	H	NH_2	CN

Et_2O, dioxane and THF were dried and distilled from sodium. Silica gel (230–400 mesh) for flash chromatography was used throughout for product purification. Melting points were determined with a Büchi 510 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 257 spectrometer. ^1H NMR spectra were measured at 90 MHz on a Varian EM 390 or at 250 MHz on a Bruker WM 250 spectrometer. Mass spectra were obtained with a JEOL JMS-AX505W machine. Elemental analyses were performed by the European Environmental Research Institute of Ioannina on a Perkin-Elmer 2400 element analyser.

1-Aryl-2-dimethylaminomethylpyrroles 2; General Procedure:
A stirred mixture of 1-arylpyrrole **1** (30 mmol), paraformaldehyde (3.0 g) and dimethylamine hydrochloride (4.28 g, 52 mmol) in abs. EtOH (120 mL) was heated under reflux for 16 h. The solvent was evaporated in vacuo and to the remaining oil, water (80 mL) was added. The resulting solution was basified with 1 N NaOH (pH = 8–9) and extracted with CH_2Cl_2 (3 × 35 mL), the organic extracts combined, and dried (Na_2SO_4). The solvent was evaporated and the residual material chromatographed on a flash column using EtOAc/petroleum ether (bp 40–60°C) (1:1) and then EtOAc as eluents, to afford the pure products **2** as oils (Table).

1-Aryl-2-dimethylaminomethylpyrrole Methiodides 3; General Procedure:
To a solution of the pyrrole **2** (20 mmol) in dry Et_2O (80 mL) under argon, MeI (3.73 mL, 60 mmol) was added and the mixture stirred at 20–24°C for 8 h. The suspension was filtered off and washed with dry Et_2O to give the pure salts **3** (Table).

1-Aryl-2-azidomethylpyrroles 4; General Procedure:
A mixture of quaternary salt **3** (13 mmol), NaN_3 (1.7 g, 26 mmol), a few crystals of 18-crown-6 and dry dioxane (120 mL) was refluxed

Table Pyrroles **2–5** Prepared

Product	Yield (%)	mp (°C) or bp	MS (70 eV) *m/z* (%)	IR (Nujol or neat) ν (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, *J* (Hz)
2a	92	oil[17]	201 ($M^+ + 1$, 100), 156 (79)	3055, 2968, 2945, 2860, 2820, 2780, 1610	2.18 [s, 6H, $N(CH_3)_2$], 3.27 (s, 2H, CH_2), 6.19–6.34 (m, 2H, H-3, H-4), 6.88 (dd, 1H, H-5), 7.24–7.70 (m, $5H_{arom}$)
2b[a]	82	164–166/14	246 ($M^+ + 1$, 100), 201 (75)	3100, 2950, 2870, 2830, 2780, 1618	1.97 [s, 6H, $N(CH_3)_2$], 3.09 (s, 2H, CH_2), 6.17 (dd, 1H, H-4), 6.24 (dd, 1H, H-3), 6.71 (dd, 1H, H-5), 7.49–8.00 (m, $4H_{arom}$)
2c[a]	90	110–112/10	226 ($M^+ + 1$, 100), 181 (81)	3100, 3060, 2980, 2940, 2860, 2820, 2780, 2230, 1605	2.05 [s, 6H, $N(CH_3)_2$], 3.25 (s, 2H, CH_2), 6.24–6.30 (m, 2H, H-3, H-4), 6.84 (dd, 1H, H-5), 7.43–7.76 (m, $5H_{arom}$)
3a[b]	90	155–157	298 ($M^+ - 44$, 100), 156 (8), 143 (100)	3095, 3045, 1600	2.77 [s, 9H, $N(CH_3)_3I$], 4.59 (s, 2H, CH_2), 6.37 (dd, 1H, H-4), 6.68 (dd, 1H, H-3), 7.16 (dd, 1H, H-5), 7.43–7.61 (m, $5H_{arom}$)[c]
3b[b]	94	> 245 dec	201 ($M^+ - 186$, 55), 168 (12), 154 (35) 51 (100)	3070, 1600	2.89 [s, 9H, $N(CH_3)_3I$], 4.37 (d, 1H, $J = 14.4$, CH_2), 4.60 (d, 1H, $J = 14.4$, CH_2), 6.38 (dd, 1H, H-4), 6.70 (dd, 1H, H-3), 7.07 (dd, 1H, H-5), 7.08–8.25 (m, $4H_{arom}$)[c]
3c[b]	92	> 232–235 dec	181 ($M^+ - 186$, 100), 128 (8), 58.1 (33)	3060, 2235, 1600	2.84 [s, 9H, $N(CH_3)_3I$], 4.53 (s, 2H, CH_2), 6.46 (dd, 1H, H-4), 6.76 (dd, 1H, H-3), 7.25 (dd, 1H, H-5), 7.70–8.11 J = (m, $4H_{arom}$)[c]
4a[a]	80	105–107/12	199 ($M^+ + 1$, 14), 169, (39), 156 (100)	3060, 2960, 2930, 2860, 2110, 1600	4.21 (s, 2H, CH_2), 6.27 (dd, 1H, H-4), 6.38 (dd, 1H, H-3), 6.88 (dd, 1H, H-5), 7.34–7.49 (m, $5H_{arom}$)
4b[b]	87	53–55	243 (M^+, 18), 201 (100), 187 (26), 171 (70), 154 (90), 143 (60)	3040, 2210, 1600	4.11 (s, 2H, CH_2), 6.29 (dd, 1H, H-4), 6.39 (dd, 1H, H-3), 6.72 (dd, 1H, H-5), 7.52–8.01 (m, $4H_{arom}$)
4c[a]	72	35–36	224 ($M^+ + 1$, 27), 196 (84), 181 (100)	3100, 2230, 2110, 1600	4.18 (s, 2H, CH_2), 6.34 (dd, 1H, H-4), 6.44 (dd, 1H, H-3), 6.91 (dd, 1H, H-5), 7.51–7.81 (m, $4H_{arom}$)
5a[a]	80	97–99/18	172 (M^+, 75), 156 (100), 144 (29)	3370, 3280, 3110, 3060, 2930, 2860, 1600	2.09 (s, 2H, NH_2), 3.79 (s, 2H, CH_2), 6.22 (m, 2H, H-3, H-4), 6.78 (dd, 1H, H-5), 7.34–7.48 (m, $5H_{arom}$)
5b[a]	78	79–81/10	187 (M^+, 26), 169 (100), 140 (12)	3440, 3360, 3320, 3190, 3100, 2930, 2860, 1600	2.51 (br s, 4H, $2 \times NH_2$), 3.59 (s, 2H, CH_2), 6.20 (dd, 1H, H-4), 6.25 (dd, 1H, H-3), 6.63 (dd, 1H, H-5), 6.77–7.26 (m, $4H_{arom}$)
5c[a]	60	127–129/10	196 ($M^+ - 1$, 100), 183 (84), 169 (28), 154 (40)	3370, 3300, 3100, 3070, 2940, 2850, 2230, 1600	3.75 (s, 2H, CH_2), 4.76 (br s, 2H, NH_2), 6.12 (dd, 1H, H-4), 6.28 (dd, 1H, H-3), 7.02 (dd, 1H, H-5), 7.27–7.81 (m, $4H_{arom}$)

[a] Satisfactory HRMS values obtained: $m/z \pm 0.0015$.
[b] Satisfactory microanalyses obtained: C ± 0.23, H ± 0.30, N ± 0.31 %.
[c] In DMSO-d_6.

with stirring under argon for 12 h. After cooling the NaI was filtered off and the filtrate was evaporated under reduced pressure at 30 °C. The residual material was chromatographed on a flash column using EtOAc/petroleum ether (bp 40–60 °C) (1:4) as eluent to give the pure products **4** (Table).

2-Aminomethyl-1-arylpyrroles 5; General Procedure:
To a solution of azide **4** (13 mmol) in abs. MeOH (80 mL), 10 % Pd on C (0.3 g) was added and the mixture was hydrogenated at r.t. and 4 atm for 6 h. The catalyst was removed by filtration over Hyflo and the solvent evaporated in vacuo at 35 °C. The residual material was chromatographed on a flash column using EtOAc and then MeOH/Et_3N (10:0.5) as eluents, to yield the pure oils **5** (Table).

4,5-Dihydro-6-iminopyrrolo[1,2-*a*][1,4]benzodiazepine (6):
Sodium (0.23 g, 10 mmol) was dissolved in dry MeOH (25 mL) and pyrrole **5c** (1 g, 5 mmol) was added. The mixture was refluxed with stirring for 6 h. The solvent was evaporated and to the residue water (20 mL) was added and extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were dried (Na_2SO_4) and the solvent evaporated to dryness. The residue was crystallised from isopropyl alcohol to give **6** (0.6 g, 60 %), mp 197–198 °C.

$C_{12}H_{11}N_3$	calc.	C 73.07	H 5.62	N 21.31
(197.2)	found	72.83	5.81	21.63

IR (Nujol): ν = 3475, 3305, 1645 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 3.42 (br s, 1H, NH), 3.71 (d, 1H, J_{gem} = 13 Hz, H-4a), 4.12 (br s, 1H, NH), 4.23 (d, 1H, J_{gem} = 13 Hz, H-4b), 6.00 (dd, 1H, H-2), 6.19 (dd, 1H, H-3), 7.19 (dd, 1H, H-1), 7.33–7.76 (m, $4H_{arom}$).

MS (CI): *m/z* (%) = 197 (M^+, 94), 196 ($M^+ - 1$, 100), 181 (56), 169 (62).

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