Electrosynthesis of Arylpyrroles and -indoles Under $S_{RN}1$ Conditions

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Arylpyrroles and -indoles are electrosynthesized via a $S_{RN}1$ type reaction. With pyrrolyl anion, the reaction leads mainly to α-substitution, but β-substitution and disubstitution are also observed. With indolyl anion, the main product corresponds to β-substitution. In both cases, the yield of the main product is higher than 50%.

Synthetic methods for pyrroles can be classified into two categories depending on the type of precursor (cyclic or acyclic) used.[1,2] The methods under cyclic precursors include ring substitutions and reactions in which a preexisting ring other than a pyrrole is transformed into a pyrrole. Methods using acyclic precursors are ring-closure reactions.

β-Substituted pyrroles are interesting compounds since they can be used as starting products in the synthesis of substituted porphyrins and polypyrroles; β-arylpyrroles are especially interesting because of the charge transfer properties of the aromatic ring. Electrophilic reagents generally attack pyrrole at the *N*- and α-positions.[2-5] β-Products can nevertheless be obtained (i) by group migration to β-position[4] or (ii) when the synthesis is β-directed by the presence of an α- or a *N*-substituent[4] or (iii) by palladium-catalyzed coupling of pyrrolyl anion with aromatic halides.[6,7]

Although pyrrolyl anion was reported not to react under $S_{RN}1$ conditions,[8] we have performed the electrosynthesis of β-arylpyrroles by a $S_{RN}1$ reaction using the anion of 2,5-dimethylpyrrole as nucleophile.[9]

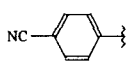
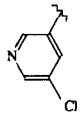
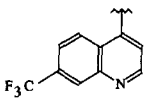
Substitution with indole generally leads to the coupling at the β-position of the heterocycle[10] either with alkyl[11] or aryl substituents.[12] α-[5] and *N*-substitutions[11,13] are also reported. Indolyl anion is not mentioned in the literature as nucleophilic under $S_{RN}1$ conditions.

Here, we describe the synthesis of new α- and β-arylpyrroles and β-arylindoles via an electrochemically induced $S_{RN}1$ reaction in liquid ammonia, starting from an aromatic chloride and the anions of pyrrole or indole. The latter were obtained in situ by deprotonation of the acidic form with potassium *tert*-butoxide. The reaction was performed under classical conditions for electrochemically induced $S_{RN}1$ reactions.[14-16] The electrochemical cell, whose design is simple, is of classical use in liquid ammonia and is easy to bring into operation.[17]

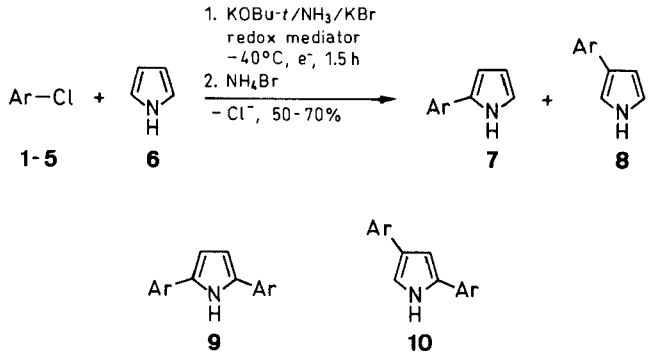
The charge consumed during electrolysis corresponded to the reduction of the starting aromatic chloride (ArX); in all cases, it was about 1F or less per mole of consumed ArX, which was in good agreement with the yields obtained. The rate constants of the coupling reaction have been determined in some cases by redox catalysis using previously described methods.[18]

With pyrrolyl anion, the reaction led mainly to the α-substituted product. β-Substituted products have been isolated in all cases with yields between 6 and 15% (Table 1). Disubstituted products have also been obtained. In the case of 4-chlorobenzonitrile, both α,α'- and α,β'-disubstituted products have been isolated in 7% yield. In the case of 3,5-dichloropyridine, disubstitution products have been detected by GC/MS but no attempts were made to isolate them.

Table 1. Electrosynthesis of Pyrroles **7** and **8**

Ar-Cl (Ar)		Mediator	α-Substituted Product	Yield[a] (%)	β-Substituted Product	Yield[a] (%)
	**(1)**	4,4'-bipyridyl	**7a**	52	**8a**	7
	**(2)**	2,4'-bipyridyl	**7b**	60	**8b**	3[b]
	**(3)**	4,4'-bipyridyl	**7c**	67	**8c**	6
	**(4)**	Quinoxaline	**7d**	53	**8d**	8
	**(5)**	Quinoxaline	**7e**	65	**8e**	14

[a] Yield of isolated product.
[b] Yield determined by GC.



In the case of indolyl anion, the reaction led mainly to the β-substituted product (Table 2).

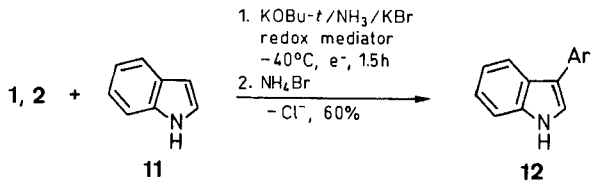


Table 2. Electrosynthesis of Substituted Indoles **12**

Ar-Cl	Mediator	Product	Yield[a] (%)
4-CNC_6H_4Cl **(1)**	4,4'-bipyridyl	**12a** (Ar = 4-CNC_6H_4)	60
4-Chloro-pyridine **(2)**	2,4'-bipyridyl	**12b** (Ar = 4-chloropyridyl)	60

[a] Yield of isolated product.

The main positions of coupling with pyrrolyl or indolyl anions under $S_{RN}1$ conditions are therefore the same as those reported for the electrophilic substitutions of pyrrole and indole.[2-4,10-12] In a preliminary experiment we had also used pyrrolyl anion under the same conditions.[9] The existence of new species was checked by GC but the coupling products were not isolated, which led to a wrong identification and less precise yields.

The rate constants of the coupling reactions are about one order of magnitude lower than those obtained under similar conditions with thiophenoxide, acetone enolate or the anion of diethyl phosphite.[19] Nevertheless, α-products (pyrrole) and β-products (indole) are obtained by this one-step process with appreciable yields.

All the reagents were purchased from Aldrich and used without further purification. The electrochemical cell is described in Ref. 17. Melting points were measured with a hot stage microscope. ^1H, ^{13}C NMR spectra were recorded on a Bruker spectrometer operating at 300 MHz and 75.5 MHz respectively. TMS was used as internal standard for ^1H and ^{13}C spectra. Some mass spectra were recorded on a Nermag R-10-10B instrument under electronic impact at 70 eV. The others were recorded on a Hewlett-Packard 5971 GC equipped with a mass selective detector. Combustion analyses were performed by the Service de microanalyse de l'Université Pierre et Marie Curie, Paris; C ± 0.36, H ± 0.11, N ± 0.11.

Arylpyrroles and -indoles 7, 8, 12; General Procedure:
The reaction was carried out in an undivided electrochemical cell without any separator containing liquid ammonia (80 mL) and KBr (42 mmol, 5 g) as supporting electrolyte. The cell was equipped with four entries corresponding to: (i) auxiliary and working electrodes. The anode (auxiliary electrode) was a sacrificial Mg rod surrounded by a cylindrical shaped cathode (working electrode). The distance between the two electrodes was about 1 cm; (ii) the inlet for the reactants; (iii) a N_2 inlet; and (iv) a separate reference compartment (reference system Ag/Ag^+, $[Ag^+] = 10^{-1}$ M) which was suppressed if no cyclic voltammograms were wanted. The aromatic chloride (3 mmol), pyrrole or indole (15 mmol, 1.01 g or 1.76 g respectively), KOBu-*t* (15 mmol, 1.68 g) and a redox mediator (2 mmol) were successively introduced into the cell. A constant current density of 0.5 $A.dm^{-2}$ was imposed between a platinum grid **(7a–c, 8a–c, 9, 10, 12a, b)** or a stainless steel grid **(7d, e, 8d, e)** and a Mg rod, till the disappearance of the starting aromatic chloride. When the reaction was over, the bases present in the medium were neutralized by NH_4Br (20 mmol, 1.96 g). After evaporation of ammonia, the organic products were extracted with CH_2Cl_2. The substitution products were separated by flash chromatography over *silica* gel (300 g of silica gel 60, 70–230 mesh, Merck) using different eluents (pentane, CH_2Cl_2, Et_2O, EtOAc, MeOH). Most of the products were recrystallized from heptane except in the case of **8a** (heptane/$CHCl_3$ 80:20) and **12b** (toluene).

Products **7a–e, 8a,c,d, 12a,b** were fully characterized. Products **8b,d, 9, 10** could not be completely characterized since they were obtained in too small amounts to be properly purified.

7a; eluent: pentane/EtOAc (70:30); mp 137 °C.

^1H NMR (300 MHz, acetone-d_6): δ = 6.23–6.27 (m, 1H), 6.73–6.78 (m, 1H), 6.97–7.01 (m, 1H), 7.70, 7.79 (AA'BB', *J* = 9 Hz, 4H), 10.77 (br s, H).

^{13}C NMR (75 MHz, acetone-d_6): δ = 108.8 (C), 109.3 (CH), 110.9 (CH), 119.6 (CN), 122.0 (CH), 124.4 (2CH), 130.7 (C), 133.4 (2CH), 138.1.

MS (EI): *m/z* = 168 (M^+), 141, 140, 129, 115, 114, 113, 112, 102, 88, 84.

7b; eluent: EtOAc/MeOH (90:10); mp 172 °C.

^1H NMR (300 MHz, acetone-d_6): δ = 6.22–6.26 (m, 1H), 6.79–6.83 (m, 1H), 6.98–7.02 (m, 1H), 7.55, 8.48 (AA'BB', *J* = 6 Hz, 4H), 10.97 (br s, 1H).

^{13}C NMR (75 MHz, acetone-d_6): δ = 109.3, (CH), 110.8 (CH), 118.2 (2CH), 122.0 (CH), 129.7 (C), 140.5 (C), 150.9 (2CH).

MS (EI) *m/z* = 144 (M^+), 117, 116, 90, 89, 63.

7c; eluent: pentane/EtOAc (70:30); mp 162 °C.

^1H NMR (300 MHz, acetone-d_6): δ = 6.59–6.63 (m, 1H), 6.90–6.95 (m, 1H), 7.41–7.47 (m, 1H), 8.01 (t, *J* = 2 Hz, 1H), 8.33 (d, *J* = 2 Hz, 1H), 8.82 (d, *J* = 2 Hz, 1H), 10.78 (br, s, 1H).

^{13}C NMR (75 MHz, acetone-d_6): δ = 108.9 (CH), 110.8 (CH), 121.8 (CH), 127.7 (C), 130.2 (CH), 131.3 (C), 132.6 (C), 144.0 (CH), 145.4 (CH).

GC/MS: *m/z* = 180, 179, 178 (M^+), 151, 143, 116, 89.

7d; eluent: Et_2O; mp 160 °C.

^1H NMR (300 MHz, acetone-d_6): δ = 6.35–6.42 (m, 1H), 6.69–6.75 (m, 1H), 7.11–7.17 (m, 1H), 7.50 (d, *J* = 5 Hz, 1H), 7.60 (dt, ABCD, J_{CA} = 1 Hz, $J_{C,B} = J_{C,D}$ = 8 Hz, 1H), 7.75 (dt, ABCD, $J_{B,A} = J_{B,C}$ = 8 Hz, $J_{B,D}$ = 1 Hz, 1H), 8.07 (dd, BCD, $J_{D,B}$ = 1 Hz, $J_{D,C}$ = 8 Hz), 8.48 (dd, ABC, $J_{A,B}$ = 8 Hz, $J_{A,C}$ = 1 Hz, 1H), 8.84 (d, *J* = 5 Hz, 1H), 10.84 (br s, 1H).

^{13}C NMR (75 MHz, acetone-d_6): δ = 110.6 (CH), 112.6 (CH), 119.7 (CH), 121.8 (CH), 126.4 (C), 126.8 (CH), 127.3 (CH), 128.5 (C), 129.9 (CH), 130.8 (CH), 140.0 (C), 150.2 (C), 150.9 (CH).

GC/MS: *m/z* = 194 (M^+), 166, 139.

7e; eluent: Et_2O/CH_2Cl_2: (50:50); mp 134 °C.

^1H NMR (300 MHz, acetone-*d*-6): δ = 6.37–6.48 (m, 1H), 6.71–6.83 (m, 1H), 7.15–7.22 (m, 1H), 7.64 (d, *J* = 4 Hz, 1H), 7.83 (d, *J* = 9 Hz, 1H), 8.37 (br s, 1H), 8.68 (d, *J* = 9 Hz, 1H), 8.95 (d, *J* = 4 Hz, 1H), 10.92 (br s, 1H).

GC/MS: *m/z* = 262 (M^+), 261, 193.

^{13}C NMR (75 MHz, acetone-d_6): δ = 111.0 (CH), 113.4 (CH),

115.0 (C), 121.3 (CH), 122.4 (q, $J = 4$ Hz, CH), 122.5 (CH), 125.2 (q, $J_{C,F} = 272$ Hz, C), 127.8 (C), 128.2 (q, $J = 4$ Hz, CH), 128.8 (CH), 131.0 (q, $J = 32$ Hz, C), 140.1 (C), 149.1 (C), 152.5 (CH).

8a; eluent: pentane/EtOAc (70:30); mp 197 °C.

^{1}H NMR (300 MHz, acetone-d_6): δ = 6.58–6.62 (m, 1H), 6.89–6.93 (m, 1H), 7.40–7.44 (m, 1H), 8.48, 8.62 (AA'BB', $J = 9$ Hz, 4H), 10.40 (br s, 1H).

^{13}C NMR (75 MHz, acetone-d_6): δ = 106.7 (CH), 108.4 (C), 117.7 (CH), 119.9 (CN), 120.7 (CH), 123.4 (C), 125.8 (2CH), 132.2 (2CH), 142.3 (C).

MS (EI): m/z = 168 (M^+), 141, 140, 128, 115, 114, 113, 112, 89, 88, 87, 86, 85, 84.

8b; GC/MS: m/z = 144, 117, 90.

8c; eluent: pentane/EtOAc (70:30); mp 174 °C.

^{1}H NMR (300 MHz, acetone-d_6): δ = 6.59–6.63 (m, 1H), 6.90–6.95 (m, 1H), 7.42–7.47 (m, 1H), 7.94 (t, $J = 2$ Hz, 1H), 8.29 (d, $J = 2$ Hz, 1H), 8.7 (d, $J = 2$ Hz, 1H), 10.47 (br s, 1H).

^{13}C NMR (75 MHz, acetone-d_6): δ = 106.6 (CH), 117.3 (CH), 120.1 (C), 120.6 (CH), 131.5 (CH), 132.5 (C), 134.7 (C), 145.0 (CH), 145.1 (CH).

MS (EI): m/z = 178 (M^+), 151. 116, 89, 63.

8d; eluent: Et_2O.

GC/MS: m/z = 194 (M), 166, 139.

8e; eluent: Et_2O/CH_2Cl_2 (50:50); mp 166 °C.

^{1}H NMR (300 MHz, acetone-d_6): δ = 6.56–6.64 (m, 1H), 7.02–7.12 (m, 1H), 7.33–7.42 (m, 1H), 7.60 (d, $J = 4$ Hz, 1H), 7.80 (d, $J = 9$ Hz, 1H), 8.38 (br s, 1H), 8.68 (d, $J = 9$ Hz, 1H), 8.93 (d, $J = 4$ Hz, 1H), 10.58 (br s, 1H).

GC/MS: m/z = 262 (M^+), 261, 235, 234, 193.

^{13}C NMR (75 MHz, acetone-d_6): δ = 109.9 (CH), 120.0 (CH), 120.4 (CH), 120.5 (C), 122.0 (q, $J = 3$ Hz, CH), 122.6 (CH), 125.3 (q, $J_{C,F} = 272$ Hz, C), 128.2 (q, $J = 4$ Hz, CH), 129.0 (CH), 129.3 (C), 130.8 (q, $J = 32$ Hz, C), 149.0 (C), 152.6 (CH).

9; Ar = 4-CNC_6H_4; eluent: CH_2Cl_2.

^{1}H NMR (300 MHz, acetone-d_6): δ = 6.92 (d, $J = 3$ Hz, 2H), 7.76, 7.96 (AA'BB', $J = 9$ Hz, 8H).

^{13}C NMR (75 MHz, acetone-d_6): δ = 109.9 (2C), 111.8 (2CH), 119.6 (2CN), 125.4 (4CH), 133.5 (4CH), 134.3 (2C), 137.3 (2C).

GC/MS: m/z = 270, 269 (M^+), 268.

10: Ar = 4-CNC_6H_4; eluent: CH_2Cl_2.

^{1}H NMR (300 MHz, acetone-d_6): δ = 6.45 (t, $J = 3$ Hz, 1H), 7.09 (t, $J = 3$ Hz, 1H), 7.49, 7.68 (AA'BB', $J = 9$ Hz, 4H), 7.54, 7.71 (AA'BB', $J = 9$ Hz, 4H), 10.81 (br s, 1H).

^{13}C NMR (75 MHz, acetone-d_6): δ = 110.0 (C), 110.6 (C), 111.9 (CH), 119.3 (CN), 119.5 (CN), 121.6 (CH), 123.0 (C), 128.1 (C), 128.8 (2CH), 129.8 (2CH), 133.0 (2CH), 133.2 (2CH), 138.2 (C), 142.6 (C).

GC/MS: m/z = 270, 269 (M^+), 268.

12a; eluent: Et,O/pentane (50:50); mp = 169 °C.
^{1}H NMR (75 MHz, acetone-d_6): δ = 7.18, 7.23 (2 dt, $J_1 = 7$ Hz, $J_2 = 1$ Hz, 2H), 7.54 (dd, $J_1 = 8$ Hz, $J_2 = 1$ Hz, 1H), 7.78, 7.93 (AA'BB', $J = 9$ Hz, 4H), 7.84 (d, $J = 8$ Hz, 1H), 7.98 (dd, $J_1 = 8$ Hz, $J_2 = 1$ Hz, H).

^{13}C NMR (75 MHz, acetone-d_6): δ = 108.9 (C), 112.9 (CH), 116.0 (C), 119.7 (CN), 119.9 (CH), 121.3 (CH), 123.0 (CH), 125.5 (CH), 125.9 (C), 127.7 (2CH), 133.3 (2CH), 138.3 (C), 142.0 (C).

MS (CI): m/z = 219, 218 (M^+), 190.

12b; eluent: EtOAc/MeOH (90:10); mp 217 °C.

^{1}H NMR (300 MHz, acetone-d_6): δ = 7.19, 7.23 (2 dt, $J_1 = 7$ Hz, $J_2 = 1.5$ Hz, 2H), 7.54 (dd, $J_1 = 7$ Hz, $J_2 = 1.5$ Hz, 1H), 7.71, 8.56 (AA'BB', $J = 6$ Hz, 4H), 7.93 (d, $J = 3$ Hz, 1H), 8.03 (dd, $J_1 = 7$ Hz, $J_2 = 1.5$ Hz, 1H).

^{13}C NMR (75 MHz, acetone-d_6): δ = 113.0 (CH), 114.9 (C), 120.2 (CH), 121.4 (CH), 121.7 (2CH), 123.1 (CH), 125.8 (CH), 126.1 (C), 138.5 (C), 144.4 (C), 151.0 (2CH).

GC/MS: m/z = 194 (M^+), 166, 139.

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