Delocalized Nitrogen Carbanions in $S_{RN}1$ Reactions

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Received July 21, 1995[⊗]

$S_{RN}1$ reactions can be performed with nitrogen carbanions as nucleophiles, and generally the reaction leads to a mixture of isomers. In the case of the pyrrolyl anion, position 2 is about four times more reactive than position 3. When the ortho positions of pyrrole are substituted by alkyl groups, the reactivity of position 2 increases while that of position 3 decreases. With *tert*-butyl groups as the substituents, no reaction at position 2 is observed. With the indolyl anion as the nucleophile, no substitution at position 2 or at the phenyl ring is observed, and only one product corresponding to monosubstitution at position 3 is obtained. Imidazolyl anions react preferentially at position 4 (5), and substitution of position 2 by a methyl group makes the coupling regioselective.

Introduction

After the discovery of the $S_{RN}1$ reaction by Bunnett in the 1970s while reacting aryl iodides with amide ions under a chemical activation by potassium in liquid ammonia,[1a] the reaction has been extended to various nucleophiles[1b] under photochemical[1c] or electrochemical inducement.[1d] The use of nitrogen carbanions has long been restricted to amides,[1b,2] phenyl amides,[1b] and naphthyl amides.[3] More recently, the reactivity of delocalized nitrogen carbanions such as imidazolyl anions has been evidenced in photostimulated $S_{RN}1$ reactions of benzyl chlorides[4] and electroinduced $S_{RN}1$ reactions of perfluoroalkyl iodides.[5]

Here we describe the synthesis of arylpyrroles, -indoles, and -imidazoles by a one-step electrochemically induced $S_{RN}1$ reaction in liquid ammonia starting from a nitrogen heterocyclic anion and an aromatic chloride activated by an electron-withdrawing group (cyano, sulfonyl) or by a heteroatom (nitrogen in a pyridyl or a quinolinyl ring). This reaction was first described with pyrrolyl and indolyl anions,[6] and we have extended its scope to other pyrrolyl anions and to different imidazolyl anions. The investigated heterocycles are the following: pyrrole, 2,5-dimethylpyrrole, 2,5-di-*tert*-butylpyrrole, indole, imidazole, 2-methylimidazole, and 4(5)-methylimidazole.

Direct alkylations of pyrroles, indoles, and imidazoles are well-known reactions, while, to our knowledge, chemical arylations of these heterocycles have only been mentioned in the case of indoles.[7] Alkylation of the pyrrolyl anion leads to mixtures of isomers corresponding to the coupling of the alkyl moiety at the different positions of the ring (the nitrogen and the carbons in positions 2 and 3); the relative proportions of the different isomers depend on the cation present in the medium, the solvent, and the alkylation reagent.[8] Electrophilic alkylation reagents react mainly at position 2 of pyrrole,[9] 3 of indole,[10] and 4(5) of imidazole.[11]

Multistep chemical arylations of nitrogen heterocycles are well documented in the literature. The most commonly used routes are syntheses in which one of the last steps is the formation of the pyrrole ring by a cyclization reaction.[12–15] Among the other routes, some are worth mentioning: (i) the synthesis of 2-arylpyrroles by isomerization of *N*-phenylpyrrole,[16a] from organometallic salts,[16b] or by a Gomberg reaction;[16c] (ii) the synthesis of 3-arylpyrroles by a Diels-Alder reaction[16d] or by a coupling reaction catalyzed by palladium;[16e,f] (iii) the synthesis of 3-arylindoles from Grignard reagents[16g,h] or by indirect arylation;[16i] and (iv) the synthesis of 4-arylimidazoles from *N*-(aminomethyl)benzamide[16j] or (2-(naphthylthio)methylformamide[16k] or by cycloaddition of a *N*-trisilylimine with a lithium reagent.[16l]

[⊗] Abstract published in *Advance ACS Abstracts,* November 1, 1995.

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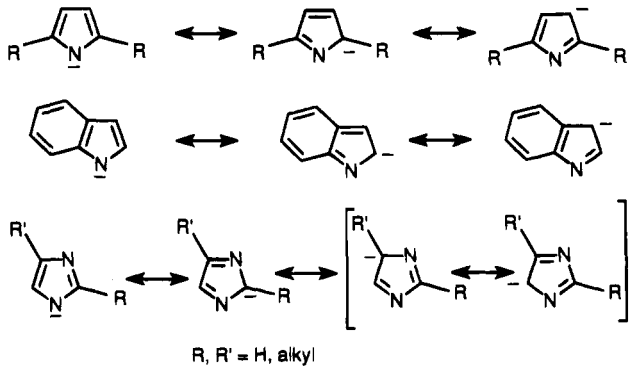
Results and Discussion

1. Principle of the Reaction. Delocalized Nitrogen Carbanions in $S_{RN}1$ Reactions. Arylpyrroles, -indoles, and -imidazoles were obtained via an electrochemically induced $S_{RN}1$ reaction in liquid ammonia, starting from an aromatic chloride and nitrogen heterocyclic anions. The latter were obtained in situ by deprotonation of the acidic form by potassium *tert*-butoxide.

The reactivity of nitrogen heterocyclic anions under $S_{RN}1$ conditions is due to the ambident character of such anions in which the negative charge can be delocalized at the different positions of the heterocycle:



R, R' = H, alkyl

When the negative charge is located at a carbon atom, the nucleophile possesses a soft character and therefore $S_{RN}1$ reactions can occur at that position, while when it is located at the nitrogen atom, the hard character of the nucleophile involved impedes the occurrence of the reaction at that position. The same behavior has already been mentioned with phenoxides.[17]

Mechanism of the Reaction with 2,5-Dimethylpyrrole. The mechanism of the reaction is illustrated in Figure 1 in the case of a pyrrole α-disubstituted by two methyl groups (R = CH_3). It combines a classical $S_{RN}1$ loop (reactions 1−3) and a deprotonation reaction (4). The loop is induced by the reduction of the starting aromatic chloride ArCl by the reduced form of a redox mediator, whose use is to minimize the main secondary reaction which is the two-electron reduction of the aromatic chloride.

The key species of the process Ar•, obtained by the reductive cleavage of $ArCl^{\bullet -}$ (reaction 1), couples with the pyrrolyl anion (reaction 2) to give two coupling products anion radicals: one ($\mathbf{II}^{\bullet -}$) at position 2 of the heterocycle (reaction 2,2, rate constant $k_{2,2}$) and the other ($\mathbf{III}^{\bullet -}$) at position 3 of the heterocycle (reaction 2,3, rate constant $k_{2,3}$); no coupling product at the nitrogen is obtained. The two anion radicals in turn reduce the starting aromatic chloride (reaction 3) to give two imines: one which is stable (**II**) and does not react further and the other (**III**) which possesses a labile proton and is further deprotonated by a base present in the medium (the starting pyrrolyl anion for example) to give the pyrrolyl anion of the monosubstituted product (reaction 4) which can then be protonated by a strong acid (NH_4Br). The anion radical $ArCl^{\bullet -}$ is regenerated by reaction 3.

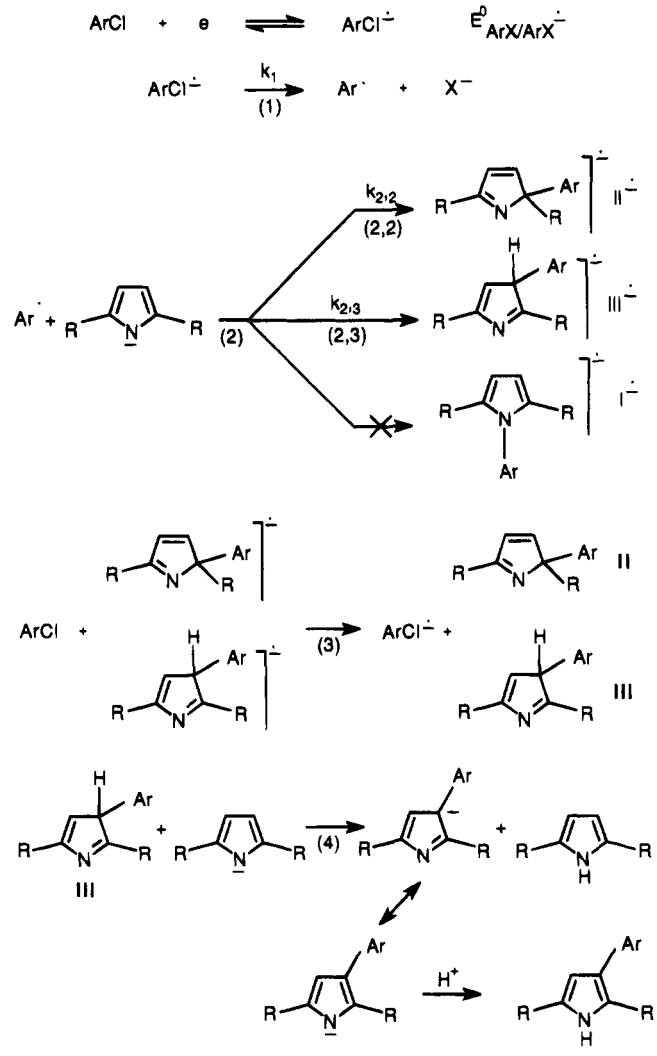


Figure 1. Sequence of reactions involved with a pyrrole α-disubstituted by two methyl groups (R = CH_3) as nucleophile under $S_{RN}1$ conditions. ArCl = aromatic chloride.

Extension to Other Nitrogen Heterocycles. The mechanism proposed for 2,5-dimethylpyrrole is also valid for pyrrole and 2,5-di-*tert*-butylpyrrole, except that (i) in the case of pyrrole (R = H) the imine (**II**) possesses a labile proton and consequently undergoes an aromatization in the same way as **III** and (ii) in the case of 2,5-di-*tert*-butylpyrrole (R = *tert*-butyl) coupling at position 2 is impossible due to the steric hindrance of the *tert*-butyl groups.

With indolyl and imidazolyl anions, the reaction follows a similar mechanism. Coupling occurs at position 3 of indole and at positions 2 and 4(5) of the imidazole ring. In the case of methylimidazoles, no coupling at positions already substituted by methyl groups was observed.

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The most reactive positions of nitrogen carbanions under $S_{RN}1$ conditions are therefore the same as those observed when performing chemical electrophilic substitution on pyrrole,[9] indole,[10] and imidazole.[11]

2. Reaction. The reaction was performed under classical conditions for preparative electrochemically induced $S_{RN}1$ reactions.[17c,d] The concentration of the nucleophile in the liquid ammonia solution ($T = -38$ °C) was equal to 0.19 M except in the case of 2,5-di-*tert*-butylpyrrole (0.08 M), which was not commercially available and had been prepared in a small amount. The electrolyses were carried out under intensiostatic conditions using a platinum or a stainless steel grid as the anode and a magnesium rod as the cathode. The current density was set to 0.5 A dm^{-2}.

The natures of the aromatic chlorides and products obtained are shown in Table 1 along with the product yields. The yields of the substituted products could be increased by decreasing the electrolysis current density.[17c] Yields of the reduction products ArH are not mentioned in this table; they were, in all cases, lower than 10%. The charge consumed during electrolysis corresponded to the reduction of the starting aromatic chloride; in all cases, it was less than 1 F per mole of consumed ArCl and in good agreement with the yields observed.

Some products have already been described in previous papers.[6] New products are described in the Experimental Section. Some of them are presumed products since they have not been isolated but only detected and identified by GC/MS or NMR.

Electrosyntheses with Pyrrole. The reaction leads to a mixture of two monosubstituted products at positions 2 (yields between 50 and 70%, cf. (**1-5**)**a**) and 3 (yields between 3 and 15%, cf. (**1-5**)**b**) and two disubstituted products at positions 2,5 and 2,4 (yields in **1c** or **1d**: 7%). In the case of 2,5-dichloropyridine, which possesses two leaving groups, only one chlorine atom was involved in the $S_{RN}1$ process, which means that, in the competition between mono- and disubstitutuion of aromatic dichlorides, pyrrole behaves as an electron-donating substituent when attached to the aromatic moiety and belongs to the same family as 2,5-di-*tert*-butylphenoxide, acetone enolate, or ethyl cyanoacetate anions.[18]

When using 4-chloropyridine, 2,5-dichloropyridine, and 4-chloroquinoline (Table 1, lines 2, 3 and 4) as starting chlorides, two disubstituted products were detected by GC/MS but not isolated; they were supposed to have the same developed formula as **1c** and **1d**. In the case of 4-chloro-7-(trifluoromethyl)quinoline (Table 1, line 5), disubstituted products have not been detected, which is certainly due to the high molecular mass of these compounds.

In the case of 4-chlorobenzonitrile, upon changing the nature of the cation present in the medium (i.e., upon changing the supporting electrolyte), the relative proportions of the monosubstituted products did not change significantly. The yield in **1a** varied from 56% with K^+ to 60% with Na^+ and to 54% for Li^+, whereas the yield in **1b** remained equal to 7%.

Electrosyntheses with α-Disubstituted Pyrroles. When the α positions of pyrrole are substituted by methyl groups, two monosubstituted products at positions 2 and 3 and one disubstituted product at positions 3 and 4 are obtained. In the case of 4-chlorobenzonitrile, imine **6a** obtained by coupling at position 2 was isolated, while, for the other aromatic chlorides, the imines were only detected by GC/MS and the yields estimated assuming that the response coefficients of the imines were identical to those of the monosubstituted products at position 3. Coupling at a position substituted by methyl groups has already been mentioned with naphthoxides[19] and phenoxides.[17d]

Substitution by the methyl groups makes the yields in monosubstituted product at position 2 decrease (from about 60% for (**1-5**)**a** to about 20% for (**6-9**)**a**) because of the steric hindrance of the substituents, and the yields in monosubstitution at position 3 increase (from about 10% for (**1-5**)**b** to 40% for (**6-9**)**b**) because of the electron-donating character of the methyl groups that enhances the nucleophilicity of the anion. Position 3 therefore becomes more reactive than position 2.

Disubstituted products (**6-8**)**c** were not isolated and purified correctly in order to allow an accurate determination of their yields, which are about 5%. They can only be obtained from the monosubstituted products at position 3 since the imines cannot be deprotonated and therefore cannot undergo a second substitution. The structure of the disubstituted product was clarified in the case of 4-chlorophenyl phenyl sulfone: the ^1H NMR spectrum of **9c** corresponds to disubstitution at positions 3 and 4. The positions of the disubstitution of compounds (**6-8**)**c** obtained with the other aromatic chlorides were assumed to be the same.

When the α substituents are *tert*-butyl groups, only two products are obtained: the monosubstituted product at position 3 (yields 30% for **10b** and 60% for **11b**) and the disubstituted product at positions 3 and 4 (yields 25% for **10c** and 13% for **11c**). The high steric hindrance of the *tert*-butyl groups impedes substitution at position 2 while, the reactivity of position 3 is higher than that observed with 2,5-dimethylpyrrole because of the higher electron-donating character of *tert*-butyl groups compared to that of methyl groups. Disubstituted products were obtained in high yields since the concentration of the nucleophile during the experiments was lower than in standard conditions (0.08 M instead of 0.19 M). The yield of the disubstituted product **11c** is lower than that of **10c** due to the steric hindrance of the cyano group located α to the bond between the pyrrole and phenyl rings in the monosubstituted product **11b**.

Electrosyntheses with Indoles and Imidazoles. No disubstituted products were detected with indolyl and imidazolyl anions. The yields of the monosubstituted products are lower with indolyl and imidazolyl anions than the total yields observed with pyrrolyl anions, which means that these anions are less reactive than pyrrolyl anions since the aromatic chlorides used were unchanged.

The indolyl anion leads to one monosubstituted product at position 3 with a 60% yield in the cases of 4-chlorobenzonitrile and 4-chloropyridine (cf. **12** and **13**).

Imidazolyl anions have been studied with 4-chlorobenzonitrile as aromatic chloride. The imidazolyl anion itself is the least reactive and leads to a mixture of two monosubstituted products **14a** and **14b**, which were obtained in such small amounts that they could not be isolated; by analogy with the products obtained with

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(19) Beugelmans R.; Bois-Choussy M.; Tang T. *Tetrahedron Lett.* **1988**, *29*, 1705.

Table 1. Arylpyrrole, -indole, and -imidazole Synthesis by an Electrochemically Induced $S_{RN}1$ Reaction of Aromatic Chlorides and Nitrogen Carbanions in Liquid Ammonia at −38 °C[a]

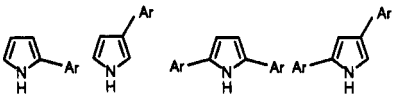
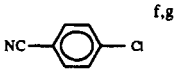
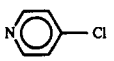
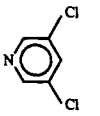
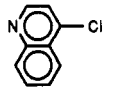
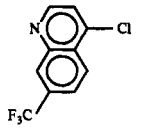
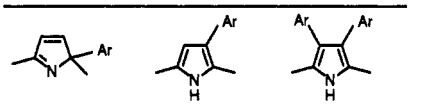
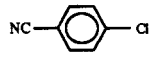
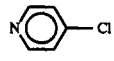
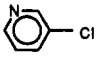
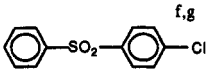
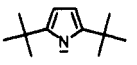
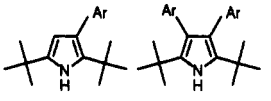
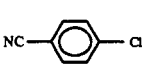
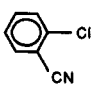
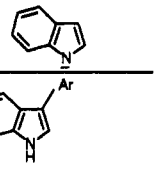
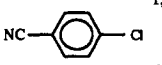
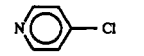
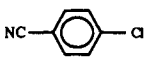
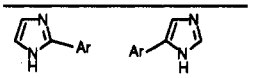
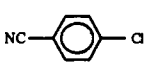
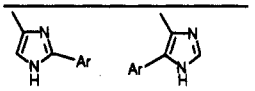
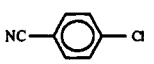
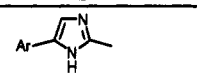
ArCl	Products	[b]	[c] k_2 ($M^{-1}.s^{-1}$)	[d] $k_{2,2}$ ($M^{-1}.s^{-1}$)	[e] $k_{2,3}$ ($M^{-1}.s^{-1}$)
					
					
 [f,g]	**1a** 52% **1b** 7% (3%) **1c** 7% **1d** 7%	[k]	6 10^9 [n]	5 10^9	1 10^9
 [f,h]	**2a** 60% (63%) **2b** (3%) **2c** **2d**	[k] [l]	10^9 [m]	[p]	[p]
 [f,g]	**3a** 67% (70%) **3b** 8% (10%) **3c** **3d**	[k] [l]	3 10^9 [o]	[p]	[p]
 [i,j]	**4a** 53% (68%) **4b** 8% (13%) **4c** **4d**	[k] [l]	2 10^9 [n]	[p]	[p]
 [i,j]	**5a** 65% **5b** 14%	[k] [m]			
					
					
 [f,g]	**6a** 20% (34%) **6b** 40% **6c** ~5%	[q] [l]	8 10^9 [n]	4 10^9	4 10^9
 [f,h]	**7a** (25%) **7b** 40% **7c** ~5%	[q] [l]	6 10^9 [o]	2 10^9	4 10^9
 [f,h]	**8a** (25%) **8b** 40% **8c** ~5%	[q] [l]	5 10^9 [o]	2 10^9	3 10^9
 [f,g]	**9a** (11%) **9b** 40% **9c** ~5%	[q] [m]	1.5 10^9 [r]	2.5 10^8	1 10^9
					[s]
					
 [i,g]	**10b** 30% **10c** 25%		7 10^9 [o]	0	7 10^9
 [i,g]	**11b** 60% **11c** 13%		9 10^9 [n]	0	9 10^9

Table I (Continued)

ArCl	Products	b	c k_2 ($M^{-1}.s^{-1}$)	d $k_{2,2}$ ($M^{-1}.s^{-1}$)	t $k_{2,5}$ ($M^{-1}.s^{-1}$)
					
 f,g	**12** 60%	k	3 10^9 o	0	3 10^9
 f,h	**13** 60%	k	10^9 o	0	10^9
					
 i,g	 **14a** **14b** (14b/14a = 4)[u]		6 10^8 o	1 10^8	5 10^8
					
 i,g	 **15a** 10% **15b** 40%		3 10^9 o	6 10^8	2.5 10^9
					
 i,g	 **16** 40%		10^9 o	0	10^9

[a] Electrolysis performed at -38°C in 80 mL of liquid ammonia, 5 mmol of ArX, 15 mmol of nitrated carbanion and 2 mmol of mediator. Galvanostatic conditions. [b] successively: in bold characters symbol of the product, then yield in isolated product with respect to the consumed aromatic chloride (conversion about 90%) and in brackets yield in product determined by GC/MS. [c] k_2 Global coupling rate constant of the reaction $Ar^\circ + Nu^- \rightarrow ArNu^{\circ-}$. [d] $k_{2,2}$: Coupling rate constant at position 2. [e] $k_{2,3}$: Coupling rate constant at position 3. [f] Cathode: Platinum (10 cm^2, 1024 mesh per cm^2). [g] Mediator: 4,4'-dipyridyl. [h] Mediator: 2,4'-dipyridyl. [i] Cathode: Stainless steel (10 cm^2, 156 mesh per cm^2). [j] Mediator: quinoxaline. [k] Ref 6b. [l] Disubstituted product detected by GC/MS. [m] The absence of detected disubstituted products could be due to their high molecular mass. [n] Determined by the comparative method; reference nucleophiles and aryl radicals: 2-mercaptopyridine for 4-cyanophenyl; diethylphosphite for 2-cyanophenyl and 4-quinolinyl. [o] Determined by the perturbed redox catalysis method. [p] Local rates constants could not be determined accurately since the yields in disubstituted products were not known precisely. [q] Ref 6a. [r] Determined from the yields in substituted products. [s] : 6.3 mmol of nucleophile instead of 15 mmol. [t] $k_{2,5}$: Coupling rate constant at position 5. [u] Products not isolated; the ratio of the yields of the two isomers was determined by GC/MS assuming the equality of their response coefficients.

4(5)- and 2-methylimidazoles, the two isomers are believed to correspond to the coupling at the two α positions of the ring, **14b** being the most abundant of the two. Assuming the equality of the response coefficients of **14a** and **14b** in GC/MS, the ratio of their yields was estimated to be about 4.

Methylimidazole anions are more reactive than the imidazole anion owing to the electron-donating character of the methyl group. Coupling at positions already substituted by a methyl group was not observed. From the yields obtained in monosubstituted products at positions 2 or 4(5) with either imidazole or 4(5)-methylimidazole, it appears that position 4(5) is about four times more reactive than position 2 (compare the yields of **14a** and **14b**, **15a** and **15b**). When the methyl substituent is located at position 2, the reaction becomes regioselective and gives one product (**16**).

3. Rate Constants of the Coupling Reaction. Global and Local Rate Constants. The rate constants of the coupling reaction have been determined by previously described electrochemical methods, such as the comparative and the redox catalysis methods.[20] The global rate constants k_2 determined by these methods depend on the different rate constants involved, which correspond to monosubstitution (at positions 2 and 3 for pyrroles, 3 for indole, and 2 and 4 for imidazoles) and

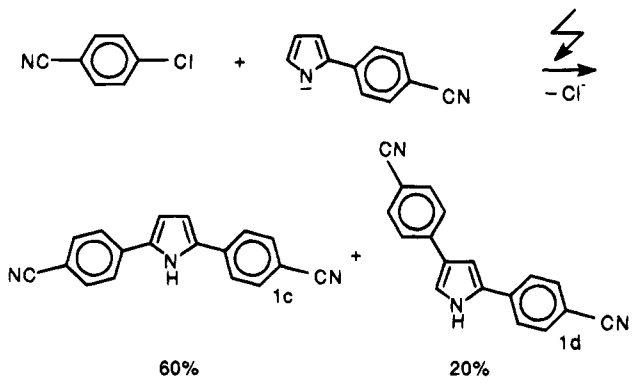
(20) (a) Amatore, C.; Chaussard, J.; Pinson, J.; Savéant, J. M.; Thiébault, A. *J. Am. Chem. Soc.* **1979**, *101*, 6012. (b) Amatore, C.; Oturan, M. A.; Pinson, J.; Savéant, J. M.; Thiébault, A. *J. Am. Chem. Soc.* **1984**, *106*, 6318. (c) Amatore, C.; Oturan, M. A.; Pinson, J.; Savéant, J. M.; Thiébault, A. *J. Am. Chem. Soc.* **1985**, *107*, 3451. (d) Amatore, C.; Combellas, C.; Oturan, M. A.; Pinson, J.; Robveille, S.; Savéant, J. M.; Thiébault, A. *J. Am. Chem. Soc.* **1985**, *107*, 4846. (e) Amatore, C.; Combellas, C.; Robveille, S.; Savéant, J. M.; Thiébault, A. *J. Am. Chem. Soc.* **1986**, *108*, 4754.

disubstitution (at positions 2 and 3 for pyrrole)

$$k_2 = \underbrace{\sum_i k_{2,i}}_{\text{monosubstitution}} + \underbrace{\sum_{ij} k'_{2,ij}[I^-]/[Nu^-]}_{\text{disubstitution}}$$

with $k_{2,i}$ equal to the local rate constant of monosubstitution at position i, I the monosubstituted product at position i, and $k'_{2,ij}$ the local rate constant of disubstitution at position j consecutive to monosubstitution at position i.

With 4-Chlorobenzonitrile and the Anion of Pyrrole. In the case of 4-chlorobenzonitrile and the anion of pyrrole, the measured rate constant k_2 has been determined by the comparative method using 2-mercaptopyridine as a reference ($k_2 = 6 \times 10^9$ $M^{-1}\cdot s^{-1}$). In order to evaluate the different local rate constants, we have reacted the anion of monosubstituted product **1a** with 4-chlorobenzonitrile under the same $S_{RN}1$ conditions:



The rate constant of this second substitution has been determined by perturbed redox catalysis using 4,4'-bipyridine as mediator ($k'_{2,2} = 8 \times 10^8$ $M^{-1}\cdot s^{-1}$). From the yields obtained for the disubstituted products, the local rate constants at positions 2 and 3 could easily be deduced (respectively, $k'_{2,2,5} = 6 \times 10^8$ $M^{-1}\cdot s^{-1}$ and $k'_{2,2,4} = 2 \times 10^8$ $M^{-1}\cdot s^{-1}$). The rate constant of this second substitution (and also by analogy that of the second substitution involving the monosubstituted product at position 3) is about 10 times lower than the global rate constant which takes into account all the substitution reactions (6×10^9 $M^{-1}\cdot s^{-1}$). Since, in addition, the ratio $[I^-]/[Nu^-]$ is lower than 0.1—because of (i) the concentrations used ($[ArCl]/[Nu^-] \sim 0.2$) and (ii) the values of the yields for the monosubstituted product (about 60%)— the term relative to disubstitution can be neglected when compared to that relative to monosubstitution. In the case of pyrrole and 4-chlorobenzonitrile, we have also deduced from the different yields obtained that the amount of substitution at position 2 was equal to 70%, while the amount of substitution at position 3 was equal to 18%,[21] which means that position 2 is about four times more reactive than position 3 ($k_{2,2}/k_{2,3} = 4$, $k_{2,2} = 4.8$ ($\sim$5) $\times 10^9$ $M^{-1}\cdot s^{-1}$, $k_{2,3} = 1.2$ ($\sim$1) $\times 10^9$ $M^{-1}\cdot s^{-1}$). This law should be general for pyrrole since the yields in the two monosubstituted products are about the same for each of the five aromatic chlorides investigated.

General Case. The neglect of disubstitution compared to monosubstitution has also been made with the other aromatic chlorides and the other pyrroles. Therefore, in the following, we will assume that for all the nitrogen carbanions investigated:

$$k_2 = \sum_i k_{2,i}$$

As we have shown with pyrrole and 4-chlorobenzonitrile, when disubstitution occurs, it is not necessary to estimate the rate constants involved in disubstitution in order to determine the local rate constants of monosubstitution, but the yields of all the products obtained have to be known. With the other aromatic chlorides and pyrrole, the calculations of the local rate constants were not possible because the yields of the disubstituted products have not been estimated (Table 1, lines 2-5). In the case of 2,5-dimethylpyrrole, the local rate constants were calculated, assuming that the yields of the disubstituted products were about 5% (rough estimation). With 2,5-di-*tert*-butylpyrrole, indole and 2-methylimidazole, the local rate constants at position 2 are zero since no substitution products at this position were obtained.

The different rate constants are shown in Table 1. Pyrrolyl anions are more reactive than the indolyl anion, which is itself more reactive than imidazolyl anions. The values obtained with pyrrolyl anions are of the same order of magnitude as with 2,5-di-*tert*-butylphenoxide[17c] and a little lower than those observed with classical $S_{RN}1$ nucleophiles (acetone enolate, thiophenoxide, diethyl phosphite),[20c] which are close to the diffusion limit rate constant ($k_d = 3 \times 10^{10}$ $M^{-1}\cdot s^{-1}$ in liquid ammonia at −38 °C). The reactivities of the transcient aryl radicals follow the same order as with 2,5-di-*tert*-butylphenoxide: 2-cyanophenyl > 4-cyanophenyl ~ 3-pyridyl > 4-pyridyl.[17c]

Influence of Substitution on the Rate Constants. The effect of the electronic character of the substituents (donating or withdrawing) on the reactivity of the nitrogen carbanions can be deduced from the values of the rate constants.

When the α positions of pyrrole are substituted by methyl groups, the global rate constants, k_2, and local rate constants at position 3, $k_{2,3}$, increase due to the electron-donating character of the methyl group, while the local rate constants at position 2, $k_{2,2}$, decrease because of the steric hindrance of the methyl group (compare lines **1** and **6** for 4-chlorobenzonitrile and lines **2** and **7** for 4-chloropyridine). This phenomenon is enhanced with *tert*-butyl groups instead of methyl groups (cf. Table 1, lines 1, 6, and 10 for 4-chlorobenzonitrile) and no substitution at position 2 is observed; this is in agreement with the increase of both the electron donating character and the steric hindrance of *tert*-butyl groups compared to methyl groups. The same tendancy is observed when substituting imidazole by methyl groups (cf. Table 1, lines 14, 15, and 16); in this case substitution at positions already substituted by methyl groups does not occur, which can be explained by the lower reactivity of imidazoles compared to pyrroles. The effect is all the more accentuated as the radical involved is the least reactive in $S_{RN}1$ reactions due to the levelling effect of the diffusion rate constant which is about 1 order of magnitude higher than the rate constants in question:

(21) The yield of substitution at position 2 in percent is equal to: 52 (2-substituted product) + 2 × 7 (2,5-disubstituted product) + 2 × 7 × 20/80 (2,4-disubstituted product obtained with the anion of the 2-substituted product as nucleophile) = 69.5. The yield of substitution at position 3 in percent is equal to: 7 (3-substituted product) + 2 × 7 × 60/80 (2,4-disubstituted product obtained with the anion of the 3-substituted product as nucleophile) = 17.5.

the increase of reactivity is greater for the 4-pyridyl radical than for the 4-cyanophenyl radical (compare (i) lines 1 and 6 with (ii) lines 2 and 7 of Table 1).

When using 2,5-bis(2-thienyl)pyrrolyl anion as the nucleophile in the presence of 4-chlorobenzonitrile, only one product corresponding to a coupling at position 3 of pyrrole was obtained; the reactivity of the nucleophile is about the same as that of 2,5-dimethylpyrrole ($k_{2,3} = 4 \times 10^9$ $M^{-1}\cdot s^{-1}$), but in this case, no substitution at positions already substituted by the thienyl groups, nor at the thienyl moiety, is possible. In $S_{RN}1$ reactions, the electronic character of the thienyl substituent is therefore about the same as that of a methyl group.

The unfavorable effect of electron-withdrawing substituents on the reactivity of nitrogen nucleophiles has been shown by the measurement of the coupling rate constants of 2-(4-cyanophenyl)pyrrolyl anion with 4-cyanophenyl radical, which are all lower than the corresponding constants with pyrrole (8×10^8 $M^{-1}\cdot s^{-1}$ measured by perturbed redox catalysis instead of 6×10^9 $M^{-1}\cdot s^{-1}$ for the k_2; 6×10^8 $M^{-1}\cdot s^{-1}$ instead of 5×10^9 $M^{-1}\cdot s^{-1}$ for the rate constants at position 2, $k_{2,2}$, and 2×10^8 $M^{-1}\cdot s^{-1}$ instead of 10^9 $M^{-1}\cdot s^{-1}$ for the rate constants at position 3, $k_{2,3}$).

Conclusion

$S_{RN}1$ reactions can be performed with nitrogen carbanions as nucleophiles, and the reaction leads generally to a mixture of isomers. In the case of the pyrrolyl anion, two monosubstituted and two disubstituted products are obtained. Position 2 of the pyrrole ring is about four times more reactive than position 3 whatever the nature of the associated counter cation, and the main product corresponds to monosubstitution at that position. When the α positions of pyrrole are substituted by alkyl groups, the reactivity of position 2 decreases while that of position 3 increases. With *tert*-butyl groups as the substituents, no reaction at position 2 is observed. Substitution of pyrrole by electron-withdrawing groups such as cyanophenyl makes reactivities of both positions 2 and 3 decrease.

With the indolyl anion as the nucleophile, no substitution at position 2 or at the phenyl ring is observed and only one product corresponding to monosubstitution at position 3 is obtained. Imidazolyl anions react preferentially at position 4 (5), and substitution of position 2 by a methyl group makes the coupling regioselective.

Further work could be achieved in the field of polypyrroles and porphyrins. To reach such an objective, new 2,5-disubstituted pyrroles should be synthesized. The α protecting groups should (i) be big enough to make the coupling regioselective at position 3, (ii) possess an electron-donating character in order to increase the reactivity of position 3, and (iii) be labile enough to be easily eliminated from the coupling products. *tert*-Butyl groups satisfy the first two requirements, and we have deduced from our first investigations that the third one could be met once the N position of pyrrole has been blocked (for instance, by an alkyl group).

Experimental Section

All the reagents were purchased from Aldrich and used without further purification. 2,5-Di-*tert*-butylpyrrole was prepared according to a previously described procedure.[22] The electrochemical cell used with liquid ammonia is described in ref 23. Melting points were measured with a hot stage microscope. ^1H and ^{13}C NMR spectra were recorded on a Bruker spectrometer operating at 300 MHz and 75.5 MHz, respectively. The mass spectra were recorded on a Hewlett-Packard 5971 gas chromatograph equipped with a mass selective detector. Combustion analyses were performed by the "Service de microanalyse de l'Université Pierre et Marie Curie", Paris.

All the experiments, cyclic voltammetry as well as preparative electrolyses, were run in an undivided cell filled with 80 mL of liquid ammonia, and potassium bromide 0.1 M (30 mmol, 3.6 g) was used as supporting electrolyte. The temperature was maintained at −38 °C with a cryocooler (Bioblock scientific). The reference electrode was a Ag/Ag^+ (0.01 M) electrode.[24] The working electrode was either a gold disc (ϕ = 0.5 mm) for cyclic voltammetry and a platinum or a stainless steel grid (10 cm^2, 1024 mesh per cm^2 for platinum and 156 mesh per cm^2 for stainless steel) for preparative-scale electrolysis. A platinum wire worked as auxilliary electrode for CV, whereas a sacrificial magnesium anode was used in preparative experiments.

In the cyclic voltammetry experiments, a solid-state amplifier potentiostat with positive feedback resistance compensation was used together with a function generator (Tacussel TPPRT), a storage oscilloscope (Nicolet), and an X−Y recorder (Sefram TGM 164). For kinetic measurements, the mediators and substrates concentrations varied from 2×10^{-3} to 2×10^{-2} M and the sweep rates from 0.1 to 0.5 $V\cdot s^{-1}$. A stabilized power supply (Sodilec) was used for the preparative experiments.

Electrosynthesis of Aromatic Chlorides with Nitrogen Heterocycles except 2,5-Di-*tert*-butylpyrrole. The mediator (2 mmol), the aromatic chloride (3 mmol), the nitrogen heterocycle (15 mmol), and potassium *tert*-butoxide (15 mmol, 1.684 g) were successively introduced into the electrochemical cell. The reaction was carried out in the presence of an additional base, potassium hydroxide (1 mmol) prepared in situ by deprotonation of water by potassium *tert*-butoxide. The electrodes were then introduced into the cell, and the electrolysis was performed under controlled current (i = 0.5 A dm^{-2}). It was stopped when there was no more aromatic chloride in the solution (checked by HPLC). After ammonia evaporation, the products were extracted by dichloromethane. The substitution products were separated by flash chromatography over silica (300 g of silica gel 60, 70−230 mesh, Merck) using different eluents (pentane, dichloromethane, diethyl ether, ethyl acetate, methanol). The products were recrystallized from *n*-heptane except **15b** which was recrystallized from a mixture of *n*-heptane/ethanol (80/20, v/v) and **16** which was dissolved in ethyl acetate instead of dichloromethane and recrystallized from *n*-pentane.

Electrosynthesis of Aromatic Chlorides with 2,5-Di-*tert*-butylpyrrole. The synthesis of 2,5-di-*tert*-butylpyrrole is described in ref 22.

The conditions are identical to those described for the other nitrogen heterocycles, except that the amount of nucleophile and potassium *tert*-butoxide was smaller (6.3 mmol instead of 15 mmol) because 2,5-di-*tert*-butylpyrrole was not synthesized in a large amount.

Description of the Products. Some products are described in the references indicated in Table 1. Description of the new ones is given below. In some cases, the products have not been fully characterized but only detected by GC/MS.

2,5-Bis(4-pyridinyl)pyrrole (2c): MS (CPV coupling), m/z = 223 (M + 2), 196, 145, 118, 106, 91, 78.

2,4-Bis(4-pyridinyl)pyrrole (2d): MS (CPV coupling), m/z = 223 (M + 2), 196, 147, 118, 105, 91, 78.

2,5-Bis(5-chloro-3-pyridinyl)pyrrole (3c): MS (CPV coupling), m/z = 291 (M $^{35}Cl_1$, $^{37}Cl_2$), 289 (M $^{35}Cl_1$, $^{35}Cl_2$).

(22) (a) Ramasseul, A. R.; Rassat A. *Bull. Soc. Chim. Fr.* **1963**, 2214. (b) Ajello, T.; Gusmano, S. *Gazzetta* **1939**, *69*, 207. (c) Ramasseul, A. R.; Rassat, A. *J. Chem. Soc., Chem. Commun.* **1964**, 453.

(23) Combellas C., Lu Y., Thiébault A. *J. Appl. Electrochem.* **1993**, *23*, 841.

(24) Herlem M. *Bull. Soc. Chim. Fr.* **1967**, 1687.

2,4-Bis(5-chloro-3-pyridinyl)pyrrole (3d): MS (CPV coupling), m/z = 291 (M $^{35}Cl_1$, $^{37}Cl_2$), 289 (M $^{35}Cl_1$, $^{35}Cl_2$).

2,5-Bis(4-quinolinyl)pyrrole (4c): MS (CPV coupling), m/z = 321 (M), 207.

2,4-Bis(4-quinolinyl)pyrrole (4d): MS (CPV coupling), m/z = 321 (M), 207.

2,5-Dimethyl-2-(4-cyanophenyl)-*2H*-pyrrole (6a): MS (CPV coupling), m/z = 196 (M), 195, 181, 153, 127, 98, 83.

2,5-Dimethyl-3,4-bis(4-cyanophenyl)pyrrole (6c): MS (CPV coupling), m/z = 297 (M), 280, 253, 227, 195, 140.

2,5-Dimethyl-2-(4-pyridinyl)-*2H*-pyrrole (7a): MS (CPV coupling), m/z = 172 (M), 171, 156, 130, 115, 102, 94, 86, 77.

2,5-Dimethyl-3,4-bis(4-pyridinyl)pyrrole (7c): MS (CPV coupling), m/z = 249 (M).

2,5-Dimethyl-2-(3-pyridinyl)-*2H*-pyrrole (8a): MS (CPV coupling), m/z = 172 (M), 171, 156, 130, 115, 102, 97, 94, 86, 77.

2,5-Dimethyl-3,4-di(3-pyridinyl)pyrrole (8c): MS (CPV coupling), m/z = 249 (M), 233, 205, 171, 103.

2,5-Dimethyl-2-[4-(phenylsulfonyl)phenyl-*2H* pyrrole (9a): MS (CPV coupling), m/z = 313 (M + 2), 298, 285, 172, 144, 128, 119, 77.

2,5-Dimethyl-3,4-bis[4-(phenylsulphonyl)phenyl]pyrrole (9c): ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) = 2.38 (s, 6 H), 7.2–7.6 (m, 8 H), 7.6–8.1 (m, 10 H).

2,5-Di-*tert*-butyl-3-(4-cyanophenyl)pyrrole (10b): mp = 197 °C; MS (CPV coupling) m/z = 280 (M), 265. Anal. Calcd for $C_{19}H_{24}N_2$: C, 81.38; H, 8.63; N, 9.99. Found: C, 81.28; H, 8.55; N, 9.88.

2,5-Di-*tert*-butyl-3,4-bis(4-cyanophenyl)pyrrole (10c): mp > 300 °C; MS (CPV coupling) m/z = 381 (M), 366. Anal. Calcd for $C_{26}H_{27}N_3$: C, 81.84; H, 7.14; N, 11.02. Found: C, 81.42; H, 7.10; N, 10.79.

2,5-Di-*tert*-butyl-3-(2-cyanophenyl)pyrrole (11b): mp = 124 °C; MS (CPV coupling) m/z = 280 (M), 265. Anal. Calcd for $C_{19}H_{24}N_2$: C, 81.38; H, 8.63; N, 9.99. Found: C, 81.36; H, 8.69; N, 9.97.

2,5-Di-*tert*-butyl-3,4-bis(2-cyanophenyl)pyrrole (11c): mp = 238 °C; MS (CPV coupling) m/z = 381 (M), 366. Anal. Calcd for $C_{26}H_{27}N_3$: C, 81.84; H, 7.14; N, 11.02. Found: C, 81.81; H, 7.18; N, 10.98.

2-(4-Cyanophenyl)imidazole (14a): MS (CPV coupling) m/z = 169(M), 142, 115, 102.

4(5)-(4-Cyanophenyl)imidazole (14b): MS (CPV coupling) m/z = 169(M), 142, 115, 102.

2-(4-Cyanophenyl)-4(5)-methylimidazole (15a): MS (CPV coupling) m/z = 184, 183(M), 155, 128, 114, 102.

5(4)-(4-Cyanophenyl)-4(5)-methylimidazole (15b): mp = 215 °C; MS (CPV coupling) m/z = 184, 183 (M), 155, 128, 114, 102. Anal. Calcd for $C_{11}H_9N_3$: C, 72.10 H, 4.95; N, 22.95. Found: C, 72.09; H, 4.94; N, 22.92.

4(5)-(4-Cyanophenyl)-2-methylimidazole (16): mp = 238 °C. MS (CPV coupling) m/z = 184, 183 (M), 155, 128, 114, 102. Anal. Calcd for $C_{11}H_9N_3$: C, 72.10 H, 4.95; N, 22.95. Found: C, 71.42; H, 4.91; N, 22.99.

Acknowledgment. This work was supported by CNRS (UA 429). G. Bidan is gratefully acknowledged for the synthesis of 2,5-bis(2-thienyl)pyrrole.

Registry numbers provided by the author: 2,5-dimethylpyrrole, 625-84-3; pyrrole, 109-97-7; 2,5-di-*tert*-butylpyrrole, 3760-56-3; indole, 120-72-9; imidazole, 288-32-4; 2-methylimidazole, 693-98-1; 4-methylimidazole, 822-36-6; 4,4′-dipyridyl, 553-26-4; 2,4′-dipyridyl, 581-47-5; quinoxaline, 91-19-0; 4-chlorobenzonitrile, 623-03-0; 4-chloropyridine hydrochloride, 7379-35-3; 2,5-dichloropyridine, 16110-09-1; 4-chloroquinoline, 611-35-8; 4-chloro-7-(trifluoromethyl)quinoline, 346-55-4; 3-chloropyridine, 626-60-8; 4-chlorophenyl phenyl sulfone, 80-00-2; 2-chlorobenzonitrile, 873-32-5.

JO951340J