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Use of Pyrrole Anions as Nucleophiles in Electrochemically Induced $S_{RN}1$ Reactions

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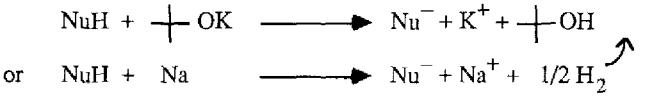
Key Words: liquid ammonia; $S_{RN}1$; electrosynthesis; substituted pyrroles.

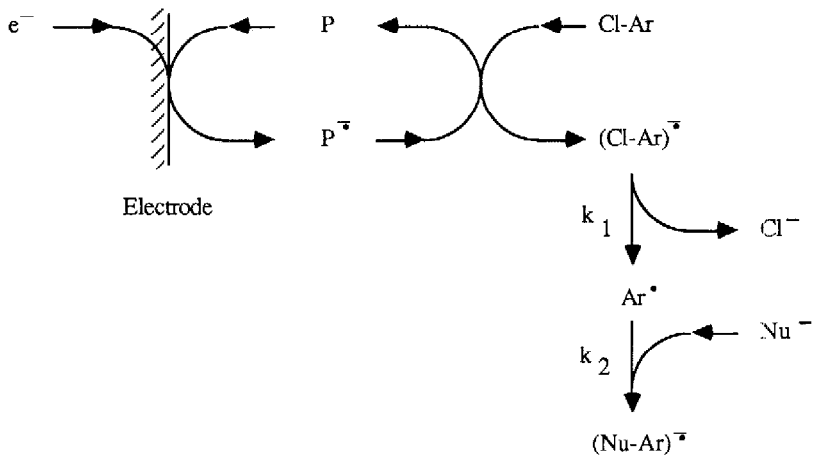
Abstract: *The reactivity of different aryl radicals towards anions of pyrroles is examined under $S_{RN}1$ conditions. The coupling rate constants are determined by cyclic voltammetry. The corresponding electrolyses are performed using a redox mediator.*

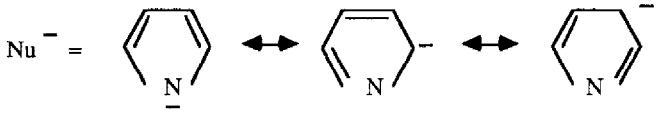
$S_{RN}1$ reactions with nucleophiles such as aliphatic carbanions, phosphorus or sulfur anions are a well-known process.[1,2] Recently the use of aromatic nucleophiles such as phenoxides in $S_{RN}1$ type reactions using electrochemical inducement was investigated; it led to a new synthetic route to unsymmetrical biaryls.[3,4] We have tried to extend the scope of this reaction to nitrogenated heteroaromatic nucleophiles. The reactions first studied are those involving the anions of pyrrole and 2,5-dimethyl pyrrole. They are carried out in liquid ammonia. The nucleophiles Nu^- are prepared in situ either by deprotonation (by means of potassium tert-butoxide or potassium hydroxide) or by alkaline reduction of the acidic form NuH:



In both cases, the formation of Nu^- is selective; no secondary reaction (such as Birch type hydrogenation of the heterocycle) is observed.

The aryl radical Ar$^\cdot$ is generated indirectly by reductive cleavage of the corresponding chlorohalide ArX, using a redox mediator M. The role of the mediator is to control and to minimize the most important secondary reaction, which is the reduction of Ar$^\cdot$. The reaction can be represented by the following scheme:



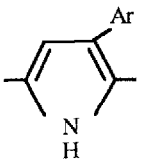


The electrolyses are performed in a single compartment cell containing 80ml liquid ammonia at −40°C and equipped with a magnesium soluble anode and a platinum grid as the cathode. We use generally 3g of KBr (supporting electrolyte), 5 mmoles of aromatic halide, 15 mmoles of nucleophile, 1 mmole of mediator. The electrolyses are carried out at a constant current density of 0,3 A/dm^2.

Once the reaction is over, the solution is acidified by ammonium bromide; after ammonia evaporation, the solid residue is extracted with dichloromethane. The reaction products are separated by flash chromatography.

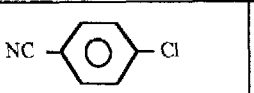
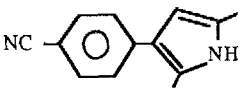
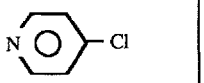
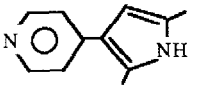
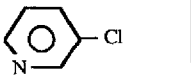
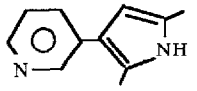
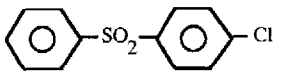
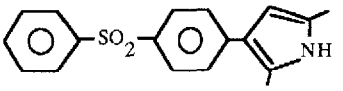
The rate constants k_2 of the coupling reaction were determined by redox catalysis, according to previously described methods.[2]

With 2,5-dimethyl pyrrole, only the reaction products corresponding to a coupling in the meta position to the nitrogen atom could be isolated in moderate yields:



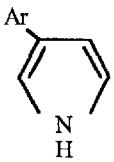
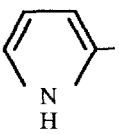
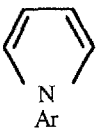
The results of the electrolyses and the values of the rate constants k_2 are presented in Table 1.

Table 1.
Results of the Electrolyses and Values of the Coupling Rate Constants.

ArX	Mediator	n [(a)]	Product		R [(b)]	k_2 [(c)]
	4,4'-bipyridine	0.20		I	40	8.10^9
	2,4 -bipyridine	0.31		II	40	5.10^9
	2,4 -bipyridine	0.31		III	35	6.10^9
	4,4'-bipyridine	0.38		IV	40	

(a) n: number of Faradays per mole of substrate
(b) R: isolated product yield (%)
(c) k_2 in $M^{-1}s^{-1}$

In the case of the pyrrole anions, the reaction leads to a mixture of three isomers:

 (≈ 80%),  (≈ 10%) and  (Ar = 4-cyanophenyl)

The rate constant of the coupling reaction is equal to $2.10^9 M^{-1}s^{-1}$.

$S_{RN}1$ reactions in liquid ammonia with anions of pyrroles as nucleophiles offer an interesting alternative for the synthesis of meta-substituted pyrroles, which are difficult to obtain by classical chemical means. Using the anions of indole, carbazole, imidazole, the same kind of behaviour is observed; research in this area is going on at present.

REFERENCES

1. R.A. Rossi, R.H. de Rossi, Aromatic Nucleophilic Substitution by the $S_{RN}1$ Mechanism, A.C.S. Monograph 178, American Chemical Society, Washington, DC (1983).
2. C. Amatore, M.A. Oturan, J. Pinson, J.M. Savéant and A. Thiébault, J. Am. Chem. Soc. 1985, 107, 3451.
3. N. Alam, C. Amatore, C. Combellas, J. Pinson, J.M. Savéant, A. Thiébault and J.N. Verpeaux, J.Org. Chem. 1988, 53, 1496.
4. N. Alam, C. Amatore, C. Combellas, A. Thiébault and J.N. Verpeaux, J.Org. Chem. 1990, 55, 6347.
5. Product analysis:

   I m.p. 175°C (decomposition); ^{1}H NMR (250 MHz, $CDCl_3$): 2.3 (s, 3H), 2.4 (s, 3H), 6.0 (m, 1H), 7.5_5 and 7.6 (AA'BB', J_{app}=9 Hz, 4H), 7.8 (s, 1 pyrrolic H); ^{13}C NMR (20MHz, DMSO D6) 12.4 (CH_3), 13.0 (CH_3), 105.1 (CH), 105.7 (C), 117.6 (C), 119.5 (CN), 124.6 (C), 125.8 (C), 126.2 (2CH), 132.2 (2CH), 142.4 (C); MS: m/z=196 (M), 195, 181, 153, 127, 98, 83.

   II m.p. 171°C (decomposition); ^{1}H NMR (90 MHz, $CDCl_3$): 2.2_5 (s, 3H), 2.4 (s, 3H), 6.0_5 (m, 1H), 7.3 and 8.5 (AA'BB', J_{app}=6 Hz, 4H), 9.0 (s, 1 pyrrolic H); ^{13}C NMR (20MHz, $CDCl_3$) 12.7 (CH_3), 13.2 (CH_3), 105.6 (CH), 117.8 (C), 121.4 (2CH), 125.2 (C), 125.8 (C), 145.2 (C), 149.3 (2CH); MS: m/z=172 (M), 171, 156, 130, 115, 102, 94, 86, 77.

   III m.p. 112°C (decomposition); ^{1}H NMR (90 MHz, $CDCl_3$): 2.2_5 (s, 3H), 2.4 (s, 3H), 6.0 (m, 1H), 7.1_5 (dd, 1H) 7.6 (dt, 1H), 8.3 (dd, 1H), 8.6 (d, 1H); ^{13}C NMR (20MHz, DMSO D6) 12.7 ($2CH_3$), 105.1 (CH), 115.9 (C), 123.3 (C), 123.6 (C), 125.8 (CH), 133.2 (CH), 133.4 (C), 145.2 (CH), 147.5 (CH); MS: m/z=172 (M), 171, 156, 130, 102, 97, 94, 86, 77.

   IV m.p. 182°C (decomposition); ^{1}H NMR (90 MHz, $CDCl_3$): 2.2 (s, 3H), 2.3 (s, 3H), 6.0 (m, 1H), 7.4 to 7.6 (m,5H), 7.8 to 8.0_5(m,5H); ^{13}C NMR (20MHz, DMSO D6) 9.7 (CH_3), 10.2 (CH_3), 102.4 (CH), 115.0 (C), 121.9 (C), 123.4 (C), 123.6 (2CH), 124.2 (2CH), 124.8 (2CH), 126.4 (2CH), 130.1 (C), 132.9 (C), 139.3 (C), 140.4 (C).

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