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Mendeleev Commun., 2012, **22**, 270–272
Mendeleev Communications

Electrochemical azolation of N-substituted pyrroles: a new case in S_N^H(An) reactions

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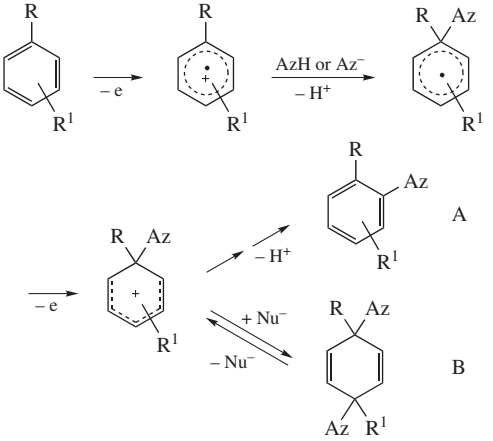
DOI: 10.1016/j.mencom.2012.09.015

Potentiostatic electrolysis (divided cell, anode compartment) of 1-methyl- and 1-phenylpyrroles in the presence of sodium 4-nitropyrazolate and sodium 3-nitropyrazolate in MeCN/MeOH gave the corresponding 2-(azol-1-yl)pyrroles in 20–43 % current and substance yields.

Anodic substitution is a well-known method for arene derivatization. The simplest nucleophiles (such as MeO^-, AcO^- and Hal^-) were generally used for this purpose;[1] however, studies were recently carried out on one-pot azolation of arenes to give ArAz as the products (where ArH stands for isomeric dimethoxybenzenes and Az represents pyrazole, triazole or tetrazole moieties).[2–5] The mechanism of this process is outlined in Scheme 1, according to which the formation of *ortho*-substitution products (A) is accompanied by the generation of *ipso*-bis-addition products (B) that can transform into compounds (A) during electrolysis.

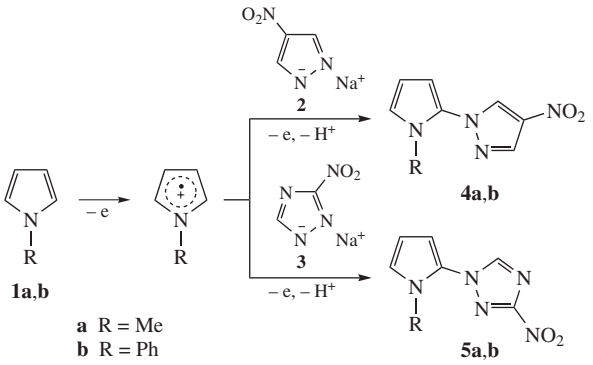


Scheme 1

N-Arylazole moiety is not uncommon in many bioactive compounds, *e.g.,* those possessing antifungal,[6] antidiabetic, antimicrobial[7] and (like *N*-arylpyrroles) anti-inflammatory activity.[8,9]

In continuation of our previous studies on the azolation of arenes, herein we performed a similar electrosynthesis of pyrrolylazoles using easily oxidizable pyrroles **1a**,**b** (Scheme 2) instead of benzene derivatives as the substrates. Only data on anodic cyanation[10] and methoxylation[11] of pyrroles have been reported up to date.

Electrolysis of pyrroles **1a**,**b** with sodium azolates **2**, **3** was carried out in the anode compartment of a divided cell in MeCN containing 20% MeOH (the latter ensured solubility of sodium azolates). According to cyclic voltammetry (CVA) data (Table 1), 1-R-pyrroles **1a**,**b** are oxidized irreversibly, and the heights of their first oxidation peaks are more than twice as much as the level of a one-electron process. This is apparently due to the



Scheme 2

liability of pyrroles to oxidative polymerization,[12] which imposes some limitations on electrolysis involving these compounds.

Pyrroles **1a**,**b** are oxidized more easily than azolate ions **2**, **3** (see Table 1), so electrolysis should be carried out at a controlled anode potential somewhat lower than 1.3 V in the case of compound **1a** and 1.5 V in the case of **1b** to diminish their intense polymerization. This mode was additionally justified by the fact that the target products were found to be oxidized at potentials close to those of the starting reactants. However, even in this case passivation of the anode occurred due to the formation of a poorly soluble film, so we had to interrupt current periodically (for ~3–5 s periods) to continue the process.

The regularities of the processes studied (see Scheme 2) are similar to those previously reported for the azolation of arenes[2–5] and cyanation of pyrroles.[10] In particular, it was noted in those studies that functionalization of NH-azoles predominantly occurs at 1-position, whereas that of 1-methyl- and 1-phenylpyrroles occurs regioselectively at 2-position. For this reason, we assumed a similar regioselectivity in our case.

Thus, a series of experiments carried out in 0.1 M $NaClO_4$ as the supporting electrolyte with consumption of 2 F of electricity

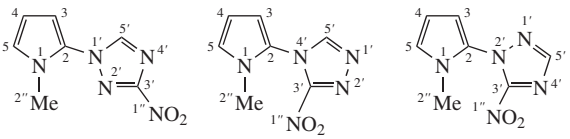
Table 1 Oxidation peak potentials (*versus* SCE) of starting reactants and electrolysis products.

Pyrrole	E_p^{ox}/V	Sodium azolate	E_p^{ox}/V	Product	E_p^{ox}/V
1a	1.30	**2**	1.65	**4a**	1.45
				4b	1.60
1b	1.50	**3**	1.95	**5a**	1.60
				5b	1.70

per mol of a pyrrole resulted in products **4a**,**b** and **5a**,**b** in both current and substance yields of 43, 28, 20 and 28%, respectively.† It can be assumed that the process was favoured by the fact that, according to reported data,[12] dimerization of the intermediate cation radicals is the slowest step in the formation of polypyrrole in MeCN medium.

The structure of the target products was based on ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry and elemental analysis data.‡ Additionally, ^{14}N NMR spectra and two-dimensional correlation spectra using NOESY, HSQC and HMBC sequences were obtained for compound **5a**, along with calculated ^{13}C and ^{14}N NMR spectra obtained using PRIRODA software.[13] The data obtained allowed us to make exact signal assignments and conclusions on the process regioselectivity.

Pyrrole functionalization at 2-position (Figure 1) is confirmed by cross peaks of methyl group 2″-protons with pyrrole carbon



5a **5′a** **5″a**

Figure 1 Possible isomers of compound **5a**.

atoms C^2 and C^5 in the 2D HMBC{^{1}H-^{13}C} NMR spectrum and agrees with the cross peaks of the C^{3}H and C$^{2''}$H$_3$ protons with the C$^{5'}$H proton in the 2D NOESY{^{1}H-^{1}H} NMR spectrum. The presence of the latter two cross peaks makes it possible to rule out the formation of the **5″a** isomer. However, these data do not allow one to choose between compounds **5a** and **5′a**. To determine the most likely isomer, we performed theoretical calculations[13] of ^{13}C and ^{14}N spectra for structures **5a** and **5′a** and then compared the results with the experimental spectra. The square roots of the mean sum of squares of differences between the experimental and calculated chemical shifts ($\Delta\delta$) and the correlation coefficients R [from the linear regression equation $Y(X) = A + BX$] served as the comparison criteria (Table 2).

As one can see from Table 2, both calculated ^{13}C NMR spectra for structures **5a** and **5′a** are quite similar both to the experimental spectrum and to each other. The differences are insignificant and do not allow us to choose the isomer structure.

Unlike the experimental ^{13}C NMR spectrum where all the signals are assigned with certainty, only the narrowest signal of the azole N$^{1''}$O$_2$ group at δ 28.67 in the ^{14}N spectrum could be assigned unambiguously. The rest of the experimental and calculated signals were matched in the series of increasing chemical

† Attempted use of sodium peroxydisulfate as the oxidant (instead of anodic oxidation) in the most cases afforded lower yields of the products.

‡ The ^{1}H and ^{13}C NMR spectra of the products in $CDCl_3$ were obtained on Bruker Avance-300 (300.13 MHz for ^{1}H and 75.48 MHz for ^{13}C) and Bruker DRX-500 (500.13 MHz for ^{1}H, 125.76 MHz for ^{13}C and 36.14 MHz for ^{14}N) instruments. Mass spectra were recorded using a Finnigan MAT INCOS 50 instrument. Voltammetric studies were carried out by the cyclic voltammetry method in a temperature controlled (25 °C) 10 ml cell, using a PI-50-1.1 potentiostat. A platinum wire 1 mm in diameter in a Teflon casing was used as the working electrode. A saturated calomel electrode separated with a salt bridge containing the supporting electrolyte (0.1 M Bu_4NClO_4 in MeCN–MeOH, 4:1) from the solution being studied was used as the reference electrode; the same was used as the counter electrode.

Quantum chemical calculations were carried out using the PRIRODA program[13] within DFT density functional with functional PBE on 3z basis, both for geometry optimizations and for calculation of chemical shifts in GIAO (Gauge Including Atomic Orbital) approximation. The initial molecule geometry was pre-optimized by molecular mechanics methods using the MarvinSketch program (version 5.2.6, 2009-10-19).[17]

3-Nitro-1,2,4-triazole was obtained using a reported procedure.[18] 1-Methylpyrrole (**1a**), 1-phenylpyrrole (**1b**), 4-nitropyrazole, MeCN, MeOH, $NaClO_4$ and Silica gel 0.035–0.070 mm, 60 Å for column chromatography (Acros Organics) were used as purchased.

Sodium 4-nitropyrazolate **2**. Sodium metal (2.3 g, 0.1 g-atom) was dissolved under argon in anhydrous methanol (100 ml). 4-Nitropyrazole (11.3 g, 0.1 mol) was added and, after stirring for 8 h under argon, the solvent was distilled off *in vacuo*. The resulting salt was dried for 6 h at 2 Torr at 50 °C. The product was obtained in quantitative yield.

Sodium 3-nitro-1,2,4-triazolate **3**. The same technique was applied to 3-nitro-1,2,4-triazole (11.4 g, 0.1 mol).

General electrolysis procedure. Electrolysis was carried out in a stream of argon using a 0.1 M $NaClO_4$ solution in a MeCN–MeOH (4:1) mixture as the supporting electrolyte, in a temperature-controlled (30 °C) glass cell (50 ml) with a tracing-paper diaphragm and a cylindrical Pt anode (25 cm^2) and cathode (10 cm^2), a B5-49 DC source and a coulometer designed at the Institute of Organic Chemistry of the Russian Academy of Sciences. The potential of the anode was monitored by an AKTAKOM ABM-4551 multimeter. Saturated calomel electrode was used as the reference electrode.

The supporting electrolyte (40 ml) containing 2 mmol of pyrrole (**1a**,**b**) and 4 mmol of sodium azolate (**2**, **3**) was placed in the anode cell compartment and the supporting electrolyte (10 ml) was placed in the cathode compartment. Electrolysis was carried out at a controlled potential of 1.28 V in the case of compound **1a** and 1.48 V in the case of **1b** with periodical current interruptions (for ~3–5 s). Upon passing 2 F of electricity (for a two-electron process), the electrolysis was discontinued, the solvent was distilled off *in vacuo* from the anolyte, water (25 ml) was added and the mixture was extracted with benzene (3×20 ml). The benzene extract was dried with anhydrous $MgSO_4$ and concentrated *in vacuo*. Subsequent purification was carried out by column chromatography using light petroleum–ethyl acetate as the eluent, followed by reprecipitation from a benzene–light petroleum mixture.

1-(1-Methylpyrrol-2-yl)-4-nitropyrazole **4a**. Yellowish crystals, mp 59–61 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ: 3.57 (s, 3H, C$^{2''}$H$_3$), 6.15 (dd, 1H, C^{4}H, $J_{4\text{-}3}$ 3.9 Hz, $J_{4\text{-}5}$ 2.9 Hz), 6.25 (dd, 1H, C^{3}H, $J_{3\text{-}4}$ 3.9 Hz, $J_{3\text{-}5}$ 1.9 Hz), 6.66 (dd, 1H, C^{5}H, $J_{5\text{-}4}$ 2.9 Hz, $J_{5\text{-}3}$ 1.9 Hz), 8.27 (s, 1H, C$^{5'}$H), 8.32 (s, 1H, C$^{3'}$H). ^{13}C NMR (75.48 MHz, $CDCl_3$) δ: 33.72 (NMe), 104.86 (C^{3}H), 107.14 (C^{4}H), 122.43 (C^{5}H), 127.24 (C^2), 131.06 (C$^{5'}$H), 136.40 (C$^{4'}$), 136.87 (C$^{3'}$H). MS, *m/z*: 192 (M$^+$). Found (%): C, 50.23; H, 4.45; N, 28.87. Calc. for $C_8H_8N_4O_2$ (%): C, 50.0; H, 4.20; N, 29.15.

1-(1-Phenylpyrrol-2-yl)-4-nitropyrazole **4b**. Yellowish crystals, mp 102–104 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ: 6.36 (dd, 1H, C^{4}H, $J_{4\text{-}3}$ 3.8 Hz, $J_{4\text{-}5}$ 3.2 Hz), 6.51 (dd, 1H, C^{3}H, $J_{3\text{-}4}$ 3.8 Hz, $J_{3\text{-}5}$ 1.9 Hz), 6.93 (dd, 1H, C^{5}H, $J_{5\text{-}4}$ 3.1 Hz, $J_{5\text{-}3}$ 1.9 Hz), 7.09–7.17 (m, 2H, Ph), 7.30–7.45 (m, 3H, Ph), 8.12 (s, 1H, C$^{5'}$H), 8.14 (s, 1H, C$^{3'}$H). ^{13}C NMR (75.48 MHz, $CDCl_3$) δ: 107.58 (C^{3}H), 108.41 (C^{4}H), 122.41 (C^{5}H), 124.66 (2CH, Ph), 126.91 (C^2), 128.03 (CH, Ph), 129.52 (2CH, Ph), 131.58 (C$^{5'}$H), 136.39 (C$^{4'}$), 136.51 (C$^{3'}$H), 137.53 (C, Ph). MS, *m/z*: 254 (M$^+$). Found (%): C, 61.15; H, 4.23; N, 21.89. Calc. for $C_{13}H_{10}N_4O_2$ (%): C, 61.41; H, 3.96; N, 22.04.

1-(1-Methylpyrrol-2-yl)-3-nitro-1,2,4-triazole **5a**. Yellowish crystals, mp 105–107 °C. ^{1}H NMR (500.13 MHz, $CDCl_3$) δ: 3.60 (s, 3H, C$^{2''}$H$_3$), 6.20 (dd, 1H, C^{4}H, $J_{4\text{-}3}$ 3.9 Hz, $J_{4\text{-}5}$ 3.1 Hz), 6.37 (dd, 1H, C^{3}H, $J_{3\text{-}4}$ 3.9 Hz, $J_{3\text{-}5}$ 1.9 Hz), 6.74 (dd, 1H, C^{5}H, $J_{5\text{-}4}$ 2.9 Hz, $J_{5\text{-}3}$ 2.0 Hz), 8.34 (s, 1H, C$^{5'}$H). ^{13}C NMR (125.76 MHz, $CDCl_3$) δ: 33.81 (C$^{2''}$H$_3$), 106.43 (C^{3}H), 107.58 (C^{4}H), 123.12 (C^2), 123.61 (C^{5}H), 146.81 (C$^{5'}$H), 163.43 (C$^{3'}$). ^{14}N NMR (36.14 MHz, $CDCl_3$) δ: –235.53 (br. s, 1N, N^1), –163.76 (br. s, 1N, N$^{1'}$), –135.03 (br. s, 1N, N$^{4'}$), –82.29 (br. s, 1N, N$^{2'}$), –28.67 (s, 1N, NO_2). MS, *m/z*: 193 (M$^+$). Found (%): C, 43.64; H, 3.87; N, 36.42. Calc. for $C_7H_7N_5O_2$ (%): C, 43.53; H, 3.65; N, 36.26.

4-(1-Phenylpyrrol-2-yl)-3-nitro-1,2,4-triazole **5b**. Yellow oil. ^{1}H NMR (300.13 MHz, $CDCl_3$) δ: 6.34 (dd, 1H, C^{4}H, $J_{4\text{-}3}$ 3.8 Hz, $J_{4\text{-}5}$ 3.1 Hz), 6.57 (dd, 1H, C^{3}H, $J_{3\text{-}4}$ 3.9 Hz, $J_{3\text{-}5}$ 1.9 Hz), 6.95 (dd, 1H, C^{5}H, $J_{5\text{-}4}$ 3.1 Hz, $J_{5\text{-}3}$ 1.9 Hz), 7.09–7.24 (m, 2H, Ph), 7.31–7.40 (m, 3H, Ph), 8.12 (s, 1H, C^{5}H). ^{13}C NMR (75.48 MHz, $CDCl_3$) δ: 108.62 (C^{3}H), 108.95 (C^{4}H), 122.77 (C^2), 123.47 (C^{5}H), 125.01 (2CH, Ph), 128.47 (CH, Ph), 129.63 (2CH, Ph), 136.74 (C, Ph), 147.45 (C^{5}H), 162.80 (C$^{3'}$). MS, *m/z*: 255 (M$^+$). Found (%): C, 56.22; H, 3.82; N, 27.13. Calc. for $C_{12}H_9N_5O_2$ (%): C, 56.47; H, 3.55; N, 27.44.

Table 2 Comparison of experimental chemical shifts ^{13}C NMR (δ/ppm) for compound **5a** and calculated chemical shifts for structures **5a** and **5′a**.

Atom number	Experiment	Calculation	
	5a	**5a**	**5′a**
2″	33.81	37.82	35.90
3	106.43	109.96	114.22
4	107.58	112.80	112.64
2	123.12	131.68	124.87
5	123.61	127.89	126.42
5′	146.81	146.34	150.76
3′	163.43	173.46	165.93
$\Delta\delta$		5.95	4.20
R_C		0.997	0.999

Table 3 Comparison of experimental chemical shifts ^{14}N NMR (δ/ppm) for compound **5a** and calculated chemical shifts for structures **5a** and **5′a**.

Atom number	Experiment	Calculation	
	5a	**5a**	**5’a**
1	–235.53	–214.52	–207.73
1′	–163.76	–141.59	–195.55
4′	–135.03	–109.45	–25.89
2′	–82.29	–65.49	–13.26
1″	–28.67	–22.48	–27.66
$\Delta\delta$		19.53	60.76
R_N		0.998	0.827

shifts. One can see from Table 3 that a good agreement is observed between the experimental and calculated chemical shifts for isomer **5a** (unlike **5′a**); the correlation factor R_N is 0.998. Figure 2 clearly demonstrates the correspondence between the experimental and theoretical chemical shifts (R_{NC} = 0.999) in the ^{14}N and ^{13}C NMR spectra of compound **5′a**. The results obtained allow us to assign the signals in the experimental ^{14}N NMR spectrum of compound **5a** and to conclude that it is the most likely isomer.

In conclusion, these studies demonstrate a new example of nucleophilic substitution of a hydrogen atom (an S_N^H reaction[14]). Similar electrochemically induced processes that occur due to polarity reversal (Umpolung)[15] of the original substrate were recently considered in a review[16] and were named as S_N^H(An) reactions (where ‘An’ means ‘anode’).

This study was supported by the Russian Foundation for Basic Research (grant no. 12-03-00517a) and the Division of Chemistry and Materials Sciences of the Russian Academy of Sciences (programme no. 01 for fundamental research).

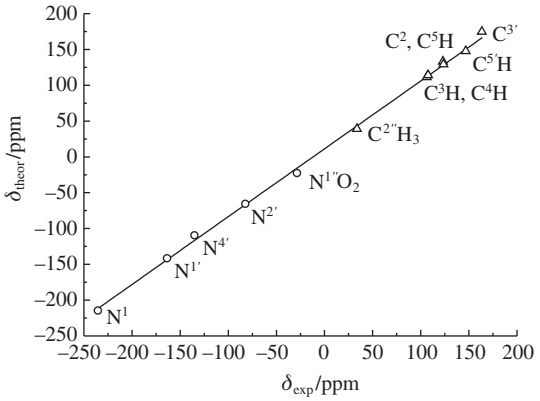


Figure 2 Correlation between the calculated and experimental chemical shifts in the ^{14}N and ^{13}C NMR spectra for **5a** (A = 11.980, B = 0.947, R = 0.999, n = 12).

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Received: 11th March 2012; Com. 12/3893