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Double electrooxidative C–H functionalization of (het)arenes with thiocyanate and 4-nitropyrazolate ions

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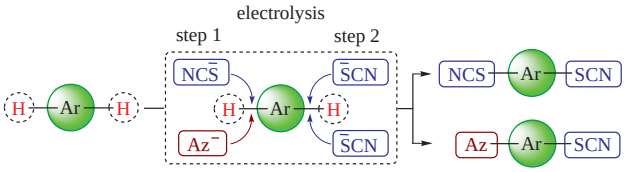
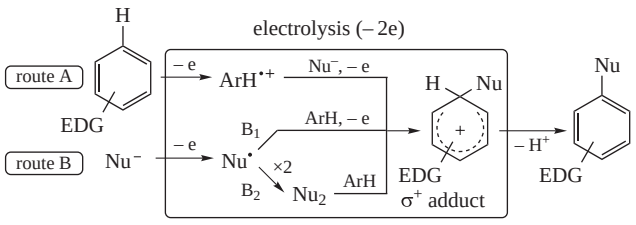
The double anodic C–H functionalization of *N*-methyl-1*H*-pyrrole and *N*,*N*-dimethylaniline using both thiocyanate and 4-nitro-1*H*-pyrazolate ions as nucleophiles has been accomplished for the first time. The mild reaction conditions and considerable pharmacological activity of the target products make such C–S and C–N coupling strategy to be highly attractive for further applications.



The functionalization of arenes is a key to their structural diversity opening the road to a wide range of useful substances. At present, C–H bond functionalization based on metal complex catalysis[1] or 'metal-free' chemical oxidation[2] has become a popular tool for modification of arenes. 'Anodic substitution' reactions described in the middle of the last century[3] represent electrooxidative C–H functionalization of arenes when anode serves as a 'green' oxidizing agent[4–8] thus allowing for direct formation of C–C and C–Het bonds. This method deprives the use of organohalogen substrates, complex and often expensive catalysts, whereas the electron transfer in controlled potential electrolysis (CPE) successfully replaces the empirical selection of unrecyclable chemical oxidants.

Our analysis[4,9] revealed the general regularities of such processes (Scheme 1) for the cases when arene would oxidize easier than nucleophile (Nu) (route A) and when Nu would oxidize easier than arene (route B). Based on this knowledge, we have systematically investigated the possibilities of anodic C–H functionalization of (het)arenes, in particular, scarcely explored C–H azolation and thiocyanation. Some of the thus obtained[9–11] functionalized (het)arenes exhibited noticeable pharmacological activity.[12,13]

It may be expected that the pharmacological activity for (het)arenes with two pharmacophore groups will be higher than that for mono-equipped ones. For example, the antifungal activity of 2,5-dithiocyanato-1*H*-pyrrole against the *Candida albicans* is 65 times higher than that of 2-thiocyanato-1*H*-pyrrole.[12,13] It prompted to study the double anodic C–H functionalization of some (het)arenes aiming to access hybrid[14] structures. In this work, electrooxidative C–H functionalization of *N*-methylpyrrole and *N*,*N*-dimethylaniline with the same Nu (thiocyanate ions) or different Nu (thiocyanate and azolate ions) were chosen as model processes.



Scheme 1 EDG stands for electron donating group.

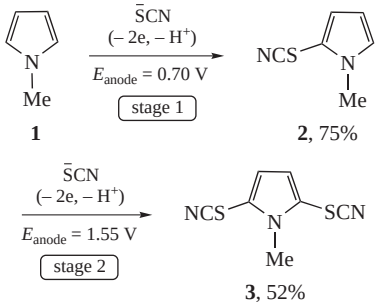
At the first stage, a thiocyanate ion/*N*-methylpyrrole **1** mixture was electrolyzed at the oxidation potential of thiocyanate ion ($E_{anode} = E_p^{ox} = 0.70$ V).† We have found earlier[9,10] that

† ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 on a Bruker Avance 300 instrument (300.13 MHz for ^{1}H and 75.48 MHz for ^{13}C). CV studies were carried out in a temperature-controlled (25 °C) cell (V = 10 ml) using a P30JM potentiostat (Elins, scan rate 0.1 V s^{-1}). A platinum disc 1.7 mm in diameter in a Teflon casing was used as the working electrode. SCE separated from the solution by a salt bridge (filled with the supporting electrolyte A (0.1 M $NaClO_4$ in MeCN) or B (0.1 M $NaClO_4$ in MeCN–MeOH, 4:1) was used as the reference electrode. A patinum plate (S = 3 cm^2) was used as the counter electrode. Electrolysis was carried out in two stages under nitrogen atmosphere using the same potentiostat in a glass temperature-controlled cell (V = 50 ml) with a Pt anode (S = 16 cm^2) and Pt cathode (S = 10 cm^2). 1-Methyl-1*H*-pyrrole **1**, *N*,*N*-dimethylaniline **6**, 4-nitropyrazole, MeCN for HPLC, MeOH, toluene, light petroleum, NH_4SCN, $NaClO_4$, Na_2SO_4 and Silica gel 0.035–0.070 mm, 60 Å for column chromatography (Acros Organics) were used as purchased. Sodium 4-nitro-1*H*-pyrazolate was prepared using a reported procedure.[11] NMR data for compounds **2**–**4** were close to those reported previously.[9,11–13]

*Electrosynthesis of 2,5-dithiocyanato-1*H*-pyrrole* **3**.

Stage 1. A solution of hetarene **1** (2 mmol) and NH_4SCN (8 mmol) in supporting electrolyte A (50 ml) was placed into the undivided cell. The electrolysis was performed at 25 °C and at E_{anode} = 0.70 V by passing 2 F (Q = 386 C) of electricity (for a one-electron oxidation of thiocyanate ion). After the solvent was distilled off *in vacuo*, the residue was extracted with Et_2O (4×15 ml). The combined extracts were dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. Column chromatography on SiO_2 using light petroleum–EtOAc as the eluent gave pure product **2**, which was used as initial arene at stage 2.

Stage 2. Preparation of initial reaction mixture, isolation and purification of product **3** were similar to stage 1 with the same quantities of reagents, but electrolysis was performed at E_{anode} = 1.55 V by passing 6 F (Q = 576 C) of electricity (for a two-electron oxidation of initial arene).

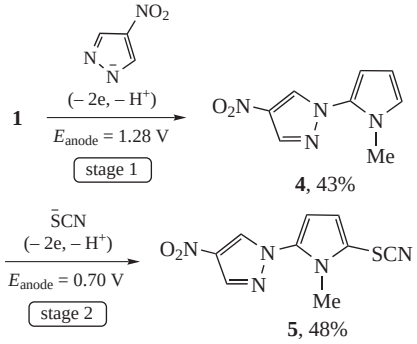


Scheme 2

electrogenerated $(SCN)_2$ was the true thiocyanating agent under such conditions, and the transformation proceeded according to route B_2 (see Scheme 1). After passing the theoretical amount of electricity ($Q = Q_t = 2$ F per mole for a one-electron oxidation of thiocyanate ion), the yield of monothiocyanate **2** (Scheme 2, stage 1) was 75% at full conversion of pyrrole **1** (E_p^{ox} = 1.30 V). However, further thiocyanation of isolated thiocyanate **2** (E_p^{ox} = 1.55 V) at E_{anode} = 0.70 V was ineffective (the yield of dithiocyanate **3** was less than 3%), apparently due to its low reactivity with respect to electrogenerated $(SCN)_2$. Previously, we observed[9,10] that thiocyanation efficiency decreased on growth of arene E_p^{ox}.

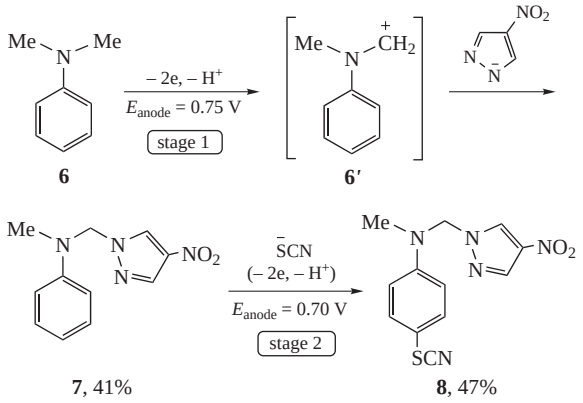
It is known,[15] however, that for 'easy oxidizable Nu/hard oxidizable arene' system the efficiency of the C–H functionalization may be improved under CPE at $E_{anode} = E_p^{ox}$ of arene (but not at E_p^{ox} of easily oxidizable Nu). Indeed (see Scheme 2, stage 2), CPE at the E_p^{ox} of monothiocyanate **2** (E_p^{ox} = 1.55 V) leads to dithiocyanate **3** in 52% yield. In this case, the transformation proceeds along the route A (see Scheme 1) *via* the interaction between the radical cation of arene **2** and the thiocyanate ion. This process is accompanied by some resinification which requires additional consumption of electricity ($Q/Q_t = 3$).

Scheme 3 outlines preparation of thiocyanatopyrrolylazole **5**, which involves the initial anodic C–H azolation of pyrrole **1** followed by isolation of *N*-pyrrolylazole **4** and its subsequent C–H thiocyanation.‡ To this end, the 4-nitropyrazolate-ion/pyrrole **1** mixture is subjected to CPE (see Scheme 3, stage 1) at oxidation potential of pyrrole **1** of 1.28 V. Earlier[11] it was shown that the mechanism of the process under these conditions can also be described by route A (see Scheme 1). The yield of pyrrolylazole **4** is 43% at full conversion of pyrrole **1** ($Q/Q_t = 1$). Subsequent C–H thiocyanation of isolated *N*-pyrrolylazole **4** proceeds along route B_2 (see Scheme 1) with $Q/Q_t = 2$ and leads to thiocyanatopyrrolylazole **5** in 48% yield. The increased consumption of electricity is apparently related to a lower reactivity of pyrrolylazole **4** (E_p^{ox} = 1.45 V) with respect to $(SCN)_2$. However, its reactivity is still greater than that of thiocyanate **2** (E_p^{ox} = 1.55 V).



Scheme 3

Scheme 4 shows the C–H azolation and thiocyanation of *N*,*N*-dimethylaniline **6**. Unlike *N*-methylpyrrole **1**, C–H azolation of substrate **6** proceeds though selectively but at the Me group (apparently *via* intermediate **6′**) without affecting the aromatic



Scheme 4

*1-Methyl-2,5-dithiocyanato-1*H*-pyrrole* **3**. White solid, mp 117–119 °C. ^{1}H NMR ($CDCl_3$) δ: 3.90 (s, 3H, 1-Me), 6.74 (s, 2H, C^3H, C^4H). ^{13}C NMR ($CDCl_3$) δ: 32.9 (1-Me), 108.5 (2-SCN, 5-SCN), 113.9 (C^2, C^5), 120.9 (C^3, C^4). Found (%): C, 43.37; H, 2.78; N, 20.86. Calc. for $C_7H_5N_3S_2$ (%): C, 43.06; H, 2.58; N, 21.02.

‡ *Electrosynthesis of compounds* **5** *and* **8**.

Stage 1. A solution of arene **1** or **6** (2 mmol) and sodium 4-nitro-1*H*-pyrazolate (4 mmol) in supporting electrolyte B (42 ml) was placed into the anodic compartment of cell with a tracing-paper diaphragm. The supporting electrolyte B (8 ml) was placed into the cathodic compartment. Electrolysis was performed at 30 °C and at E_{anode} = 1.28 (arene **1**) or 0.75 V (arene **6**) by passing 2 (arene **1**) or 3 F (arene **6**) of electricity (for a two-electron oxidation of initial arene) with periodical current interruptions (for ~3–5 s).

Stage 2. The thiocyanation of arenes **4** and **7** was performed as for arene **1** (stage 1) in anodic compartment by passing 4 and 3 F of electricity, respectively. Products **4**, **5**, **7** and **8** were isolated as described above. Compounds **4** and **5** were purified by column chromatography (see above), whereas **7** and **8** by reprecipitating from toluene–light petroleum mixture.

*1-(1-Methyl-5-thiocyanato-1*H*-pyrrol-2-yl)-4-nitro-1*H*-pyrazole* **5**. Yellowish solid, mp 115–117 °C. ^{1}H NMR ($CDCl_3$) δ: 3.74 (s, 3H, 1′-Me, 1-C_4H_4N), 6.37 (d, 1H, $C^{4'}$H, 1-C_4H_4N, $J_{4',3'}$ 3.6 Hz), 6.74 (d, 1H, $C^{3'}$H, 1-C_4H_4N, $J_{3',4'}$ 3.6 Hz), 8.32 (s, 1H, C^5H), 8.39 (s, 1H, C^3H). ^{13}C NMR ($CDCl_3$) δ: 32.6 (1′-Me, 1-C_4H_4N), 106.9 ($C^{3'}$H, 1-C_4H_4N), 108.9 (5′-SCN, 1-C_4H_4N), 109.6 ($C^{5'}$, 1-C_4H_4N), 120.4 ($C^{4'}$H, 1-C_4H_4N), 131.8 (C_5H), 132.9 (C^2), 137.7 (C^4), 138.2 (C^3H). Found (%): C, 43.20; H, 2.95; N, 28.16. Calc. for $C_9H_7N_5O_2S$ (%): C, 43.37; H, 2.83; N, 28.10.

N-*Methyl*-N-*[(4-nitro-1*H*-pyrazol-1-yl)methyl]aniline* **7**. Yellow solid, mp 53–56 °C. ^{1}H NMR (DMSO-d_6) δ: 3.08 (s, 3H, NMe), 5.80 (s, 2H, NCH_2), 6.74 (tt, 1H, C^4H, $J_{4,3\,(4,5)}$ 7.3 Hz, $J_{4,2\,(4,6)}$ 1.0 Hz), 6.96 (dd, 2H, C^2H, C^6H, $J_{2,3\,(6,5)}$ 8.8 Hz, $J_{2,4\,(6,4)}$ 1.0 Hz), 7.19 (dd, 2H, C^3H, C^5H, $J_{3,2\,(5,6)}$ 8.8 Hz, $J_{3,4\,(5,4)}$ 7.3 Hz), 8.24 (s, 1H, $C^{3'}$H, 1-C_4H_4N), 8.90 (s, 1H, $C^{5'}$H, 1-C_4H_4N). ^{13}C NMR (DMSO-d_6) δ: 38.1 (NMe), 68.5 (NCH_2), 113.5 (C^2H, C^6H), 118.5 (C^4H), 128.8 ($C^{4'}$, 1-C_4H_4N), 129.1 (C^3H, C^5H), 129.9 ($C^{5'}$H, 1-C_4H_4N), 135.6 ($C^{3'}$H, 1-C_4H_4N), 146.7 (C^1). Found (%): C, 56.78; H, 5.20; N, 24.27. Calc. for $C_{11}H_{12}N_4O_2$ (%): C, 56.89; H, 5.21; N, 24.12.

N-*Methyl*-N-*[(4-nitro-1*H*-pyrazol-1-yl)methyl]-4-thiocyanatoaniline* **8**. Yellowish solid, mp 95–97 °C. ^{1}H NMR (DMSO-d_6) δ: 3.13 (s, 3H, NMe), 5.85 (s, 2H, NCH_2), 7.10 (d, 2H, C^2H, C^6H, $J_{2,3\,(6,5)}$ 8.8 Hz), 7.51 (d, 2H, C^3H, C^5H, $J_{3,2\,(5,6)}$ 8.8 Hz), 8.27 (s, 1H, $C^{3'}$H, 1-C_4H_4N), 8.58 (s, 1H, $C^{5'}$H, 1-C_4H_4N). ^{13}C NMR (DMSO-d_6) δ: 38.2 (NMe), 67.8 (NCH_2), 110.1 (4-SCN), 112.9 (C^4), 115.0 (C^2H, C^6H), 130.1 ($C^{5'}$H, 1-C_4H_4N), 133.8 (C^3H, C^5H), 134.7 ($C^{4'}$, 1-C_4H_4N), 136.0 ($C^{3'}$H, 1-C_4H_4N), 148.8 (C^1). Found (%): C, 49.64; H, 3.95; N, 24.26. Calc. for $C_{12}H_{11}N_5O_2S$ (%): C, 49.82; H, 3.83; N, 24.21.

Table 1 Comparative bioactivity of *N*-methyl-*N*-[(4-nitro-1*H*-pyrazol-1-yl)-methyl]aniline **7**, *N*,*N*-dimethyl-4-thiocyanatoaniline (4-$Me_2NC_6H_4SCN$) and *N*-methyl-*N*-[(4-nitro-1*H*-pyrazol-1-yl)methyl]-4-thiocyanatoaniline **8**.[a]

Pathogen	Minimal inhibitory concentration/μg ml^{-1}		
	7	4-$Me_2NC_6H_4SCN$	**8**
Aspergillus niger	>256	31.2[10]	0.5
Candida albicans	>256	31.2[10]	1.9
Staphylococcus aureus	>256	62.5[10]	62.5

[a] The preliminary bioassays of products against fungi and bacteria (*Aspergillus niger* 37a, *Candida albicans* CBS 8833, *Staphylococcus aureus* ATCC 29213) were performed in compliance with the CLSI guidelines.[12,17,18]

ring (see Scheme 4, stage 1) to afford *N*-(azolylmethyl)aniline **7** in 41% yield. The thiocyanation of isolated compound **7** (stage 2) occurs selectively at the *para*-position of the aromatic ring and gives the target product **8** in 47% yield.

Preliminary bioassays of obtained compounds, as expected, reveals the higher activity of bifunctional products as compared to monofunctional ones (Table 1). For example, the presence of an azole substituent in structure **8** leads to a sharp increase in antifungal activity relative to the previously described[12] activity of *N*,*N*-dimethyl-4-thiocyanatoaniline (for *Candida albicans* – by a factor of 16, and for *Aspergillus niger* – by a factor of 64). Such activity of compound **8** in terms of the minimal inhibitory concentration is comparable[16] with those of amphotericin B and itraconazole. In the meantime, the antibacterial activity (for *Staphylococcus aureus*) is the same and low for these structures, while azolylaniline **7** is inactive in all cases.

Ultimately, our studies on the double anodic C–H functionalization of (het)arenes reveals a new opportunity for the electrosynthesis of bifunctional compounds. The products with both thiocyanate and 4-nitro-1*H*-pyrazole moieties have been successfully obtained from *N*-methyl-1*H*-pyrrole and *N*,*N*-dimethylaniline with moderate yields at each stage. Such processes open up the prospects for obtaining new potential pharmaceuticals *via* direct C–S and C–N coupling using the anode as a 'green' oxidizing agent as well as make contribution to the methodology for construction of polyfunctional hybrid structures.

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