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New data on heteroarene thiocyanation by anodic oxidation of NH₄SCN. The processes of electroinduced nucleophilic aromatic substitution of hydrogen

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ABSTRACT

Potentiostatic (galvanostatic) electrolysis of NH₄SCN in an undivided cell under mild conditions (25 °C, Pt anode, MeCN) was employed to perform the anodic thiocyanation of nitrogen-containing heterocycles with yields up to 95%. The regularities of the process are discussed, which show that it can be considered as electroinduced nucleophilic aromatic substitution of hydrogen.

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Methodology for introducing C—C and C—X (X=O, N, S, etc.) bonds on the basis of direct nucleophilic substitution of hydrogen in arenes $(S_{\rm H}^{\rm H}{\rm Ar})^{1,2}$ has been developed extensively. The process represents an attractive version of $S_{\rm N}{\rm Ar}$ reactions and, in a number of cases, a practical alternative to the well-known³ arene functionalization based on metal complex catalysis.

The key intermediate of S^H_AAr reactions is the $\sigma_{\rm H}$ adduct, the aromatization of which formally corresponds to hydride ion elimination. Among approaches to implementing such reactions (Scheme 1) are addition–oxidation reactions, S^H_H(AO),² where organohalogen compounds were not used. However, they are characterized by a few limitations. The most difficult here is the empiric selection of an external oxidant that would selectively oxidize $\sigma_{\rm H}$ adducts rather than Nu⁻, which is normally readily oxidizable.^{1,4} An excellent alternative is an electrochemical version of S^H_H(AO) reactions based on the selective electrooxidation of chemically generated $\sigma_{\rm H}$ adducts.^{5,6}

On the other hand, a comparison of chemical and anodic (electrochemical) substitution processes in arenes allowed the conclusion⁷ that the latter should be considered as another versatile type of S^N_H reaction denoted as S^N_H(An), where An is the anode. These reactions (Scheme 2) proceed via the generation of σ^+_H rather than σ^-_H adducts, therefore the substituted hydrogen was easily

eliminated as a proton. From an analysis of the characteristics of $S_N^H(An)$ reactions two basic pathways of such processes differing in their mechanism, stood out:⁷ with the participation of Nu⁻ (I) being harder to oxidize than arenes, and (II) being more readily oxidizable than arenes.

According to Ingold's classification,⁸ processes **I** and **II** (Scheme 2), irrespective of the mechanism, should be regarded as nucleophilic substitution since, in the ongoing formation of a new bond, the substituting reagent donating its electrons behaves as a nucleophile. Anodic substitution reactions have been discussed from this standpoint.^{7,9}

Previously (see Ref. 10 and literature cited therein), we performed $S_N^H(An)$ processes occurring via path I for the azolation of arenes. This research examined the thiocyanation of arenes proceeding by path IIb, through the well-known¹¹ electrogeneration of thiocyanogen, (SCN)₂. The electrochemical method where the anode was used as a 'green' oxidizing agent was the most feasible and expedient way to prepare thiocyanogen¹² because chemical methods typically employ toxic inorganic or organic oxidants in excess amounts.¹³

$$\operatorname{Ar}\mathbf{H} + \mathbf{N}\mathbf{u}^{-} \xleftarrow{} [\operatorname{Ar}\mathbf{H}\mathbf{N}\mathbf{u}]^{-} \xrightarrow{[O]} \operatorname{Ar}\mathbf{N}\mathbf{u}$$
$$\sigma_{\overline{H}} \operatorname{adduct} \xrightarrow{[-H^{-}]} \operatorname{Ar}\mathbf{N}\mathbf{u}$$

Scheme 1.







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Scheme 2.



Scheme 3.

Interest in thiocyanation products is connected with their wide range of biological activity such as antifungal,^{14–16} antitumor,¹⁷ antiparasitic,¹⁸ etc. Furthermore, they are useful precursors for the synthesis of sulfur-containing organic compounds (thiols, sulfides, thiazoles, oxathiolanes, etc.).¹¹

Electrochemical thiocyanation of aromatic substrates is mostly limited to phenol and aniline derivatives,¹² and only in recent years has the scope been extended to methoxybenzenes^{19,20} and indoles.^{15,21} The electrolysis was typically performed in the presence of Brønsted acids, which formed a complex with thiocyanogen having better electrophilic properties, and, as a rule, at rather low temperatures²⁰ (–20 to 5 °C), due to the propensity of thiocyanogen to undergo polymerization.²² Hence the search for milder conditions for the realization of S^H_N(An) thiocyanation processes and elucidation of the factors influencing their efficiency are of interest.

As we found earlier,^{15,19} this process appeared feasible in acetonitrile as the medium, even at room temperature (a similar conclusion was recently made for the electrothiocyanation of nitrogen-containing arenes in MeOH²¹). In the present research, we continued our investigations on the thiocyanation of some pyrazole, pyrrole, and isoxazole derivatives, which have not been studied in such processes before. For comparison, the range of sub-strates under study was widened by using indole derivatives and aniline, the anodic thiocyanation of which had been described under other conditions.^{20,21} The electrolysis was carried out in an undivided cell with Pt electrodes in acetonitrile at a controlled

potential (CPE), which, as evidenced by cyclic voltammetry (CV) data, corresponded to the oxidation peak of the thiocyanate ion (0.70 V vs SCE).^{23,24}

In accordance with Scheme 2, path **IIb**, the mechanism of the electrochemical thiocyanation included the following steps (Scheme 3): (i) thiocyanate ion electrooxidation, (ii) thiocyanogen formation, and competing steps (iii) polymerization and (iv) reaction with the arene.

The mechanism (Scheme 3) was confirmed by CV studies. For example, Figure 1a shows the CV curve **A** for NH₄SCN. The oneelectron peak of the SCN⁻ anion oxidation-1 ($E_p^{ox} = 0.70 \text{ V}$)-was non-reversible owing to the formation of (SCN)₂ fixed by its reduction peak **2** (E_p^{red} = 0.38 V). There was a one-electron peak **3** $(E_p^{ox} = 1.30 \text{ V})$ on the CV curve **B** of indole oxidation and peak **4** $(E_p^{ox} = 1.67 \text{ V})$ corresponds to further electrooxidation of indole. The equimolar amount of indole added to the solution that contained SCN⁻ led to the disappearance of peak **2** (curve **C**), which was indicative of the complete consumption of (SCN)₂ in stage iv of the mechanism shown in Scheme 3. Simultaneously, peaks 3 and **4** became lower and peak **4**′of the target product oxidation $(E_p^{ox} = 1.47 \text{ V})$ appeared. A similar peak was present in the CV curve **D** for 3-thiocyanato-1*H*-indole, which was isolated after electrolysis of an NH₄SCN/indole mixture (3:1). Figure 1b shows the CV curve evolution during such electrolysis (after removing NH₄SCN for more precise representation of the indole and target product peaks).

Generally, it follows from the CVA data that the rate of polymerization of thiocyanogen under the experimental conditions (stage iii, Scheme 3) was lower than the rate of its reaction with the arenes under study (stage iv). Qualitative evidence of this was evident from the yellowish flakes of polythiocyanogen^{12,22} and the intensity of their formation during the course of electrolysis increased if the yield of the target products was low.

Preliminary tests showed that at CPE (T = 20-25 °C) the best yield of arylthiocyanates was obtained when NH₄SCN was used as the starting reagent and NaClO₄ as the supporting electrolyte. Other salts (NaSCN, KSCN), the absence of NaClO₄ or its replacement with NH₄ClO₄ (Bu₄NClO₄) as well as an increase in the electrolysis temperature led to a significant reduction in the yield.

Table 1 summarizes the CPE results under the optimized conditions and, for comparison, the results of the galvanostatic electrolysis (GE) at a current density of 2.50 mA/cm², which was regarded as being optimum based on preliminary test results. Passing of 2.1 F per mol of arene in the course of CPE, and 2.5 F during GE, provided full conversion of the starting arenes.



Figure 1. (a) Cyclic voltammograms: NH₄SCN (2×10^{-3} M)–A, indole (2×10^{-3} M)–B, mixture of NH₄SCN/indole (1:1)–C, 3-thiocyanato-1*H*-indole (2×10^{-3} M)–D; (b) Evolution of CV curves during electrolysis of a mixture of NH₄SCN/indole (6×10^{-3} M/ 2×10^{-3} M) after removing NH₄SCN. Before electrolysis–B', after passing of 1 F–C', after passing of 2.1 F–D'. (Pt electrode, 0.1 M NaClO₄ in MeCN. Scan rate 0.20 V/s, $T = 25 \pm 1$ °C).

Table 1

Electrochemical thiocyanation of arenes and heteroarenes^a



^a Pt anode, 0.1 M NaClO₄ in MeCN (50 ml), NH₄SCN (6 mmol), arene **1a–9a** (2 mmol). $E_{an} = 0.70$ V versus SCE, Q = 2.1 F/mol (CPE) or *j* = 2.50 mA/cm², Q = 2.5 F/mol (GE).

^b The first oxidation peak based on CVA.²³

^c Isolated products. Identified by ¹H and ¹³C NMR spectroscopy and elemental analysis.

^d Yield based on the amount of initial arene under CPE (GE) conditions.

The process proceeded regioselectively and with good product yields in all experiments. In the cases of indole derivatives **1a**, **2a**, and aniline **9a**, the obtained yield was comparable²⁰ or higher¹⁹ than the thiocyanation product yields under other conditions. In addition, the efficiency of thiocyanogen participation in such reactions was limited by the potential of the first peak arene oxidation (E_p^{ox}). The product yields of the thiocyanation of indoles **1a**, **2a**, and **3a**, and those of pyrroles **4a** and **5a**, dropped as their E_p^{ox} increased (Table 1, entries 1–3, 4, and 5), and attempts to thiocyanate

2-methylfuran, furan, and thiophene (E_p^{ox} = 1.7, 2.0 and 2.15 V, respectively) failed. However this limitation, which reflects the reactivity of thiocyanogen, can be eliminated, to a greater or lesser extent, with the addition of electrophilic catalysts.¹⁹

At the same time, the thiocyanation efficiency also diminished in the cases of arenes **7a** and **8a** with $E_p^{\text{ox}} < 1.1$ V (entries 7 and 8) being close to E_p^{ox} of the thiocyanate ion (0.7 V). The reason for this being that the process occurs via another mechanism (different from that shown in Scheme 3), where thiocyanogen could act as the oxidant of the arene. However, this issue requires further investigation.

In conclusion, the examined thiocyanation of aromatic systems of different structures occurs *via* the S_N^H (An) process that proceeds regioselectively under mild conditions (T = 20-25 °C) affording high yields of the products. The antifungal activity of target products **1b–9b** (Table 1)^{15,16} made the synthesis of these structures attractive.

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Supplementary data

Supplementary data (containing spectral data of **1b–9b**) associated with this article can be found, in the online version, at http:// dx.doi.org/10.1016/j.tetlet.2014.06.028. These data include MOL files and InChiKeys of the most important compounds described in this article.

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- 23. The voltammetry studies were performed at a potential scan rate of 0.20 V/s in a thermostated (25 °C) cell (V = 10 ml). A potentiostat (PI-50-1.1) controlled by LabView software was used. A working electrode—Pt wire Ø 1 mm with a Teflon insulating holder, reference electrode—SCE separated from the working

solution by a salt bridge with the supporting electrolyte (0.1 M NaClO₄ in MeCN), counter electrode–Pt wire, was employed. The evolution of CV curves during electrolysis of the NH₄SCN/indole mixture were recorded after removing the NH₄SCN by the extraction procedure (see Ref.²⁴), before electrolysis, after passing 1 and 2.1 F of electricity.

24. Typical procedure as an example of the electrosynthesis of **1a**: A 0.1 M NaClO₄ solution (50 ml) in MeCN containing NH₄SCN (6 mmol, 0.46 g) and indole (**1a**) (2 mmol, 0.24 g) was placed in a glass cell with coaxally positioned Pt electrodes (S_{an} = 26 cm², S_{cat} = 10 cm²). The electrolysis was performed at E = 0.70 V vs SCE (CPE) or at j = 2.5 mA/cm² (GE). After passing of 2.1 F of electricity in CPE (or 2.5 F in GE) calculated on the basis of 1 F/NH₄SCN mol, the

electrolysis was terminated and the MeCN was distilled off. H₂O (10 ml) was added and the residue was extracted with CH₂Cl₂ (4 × 25 ml). The extracts were combined, dried over anhydrous Na₂SO₄, filtered and the solvent was distilled off. The residue was purified by column chromatography on silica gel (eluent–a mix of light petroleum and EtOAc with a buildup of the volume fraction of the latter from 5% to 20%) to afford pure 3-thiocyanato-1*H*-indole (**1b**) [0.295 g (0.285 g), 85% (82%)]: Mp 74–76 °C.¹⁶ ¹H NMR (300.13 MHz, CDCl₃): δ 8.90 (br s, 1H, NH), 7.80 (d, 1H, CH, *J* = 8.8 Hz), 7.56–7.15 (m, 4H, C₆H₄). ¹³C NMR (75.48 MHz, CDCl₃): δ 136.09, 131.11, 127.69, 123.89, 121.92, 112.20, 118.71, 112.17, 92.02. Anal. calcd for C₉H₆N₂S C, 62.05; H, 3.47; N, 16.08. Found: C, 62.32; H, 3.54; N, 15.82.