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Electrochemical thiocyanation of nitrogen-containing aromatic and heteroaromatic compounds

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ABSTRACT

An efficient and convenient anodic thiocyanation of nitrogen-containing (hetero)aromatic compounds is described under constant current conditions in the presence of ammonium thiocyanate in methanol at room temperature. We have examined the in situ thiocyanation of various aromatic compounds in the presence of electrochemically generated thiocyanogen at a graphite electrode (the anode) in an undivided cell.

From a synthetic point of view, aryl thiocyanates are a versatile and valuable class of organic compounds. The thiocyanato motif can be transformed into other sulfur-bearing functionalities which are precursors to dyes, drugs and biologically active natural products.[1,2] The thiocyanato function is a key intermediate for the synthesis of other heterocyclic compounds such as thiazoles and thiazinones,[3,4] which are important in agrochemicals.[5] In addition to the above-mentioned applicability of the thiocyanato motif, its combination with other substrates yields important chemicals. For example, the cross-coupling desulfurization of aryl thiocyanates is used as a cyanide-free method for the cyanation of aryl boronic acids into nitriles.[6]

Due to the wide versatility of the thiocyanate group in chemistry and biochemistry, various methods have been reported for the thiocyanation of aromatic systems. Examples include the use of iodine/NH_4SCN,[7] $Mn(OAc)_3/NH_4SCN$,[8] acidic Montmorillonite K-10,[9] $Zn(SCN)_2/Cl_2$,[10] aqueous $H_5IO_6/KSCN$,[11] $FeCl_3$,[12] ceric ammonium nitrate (CAN)[13] and trichloroisocyanuric acid (TCCA)/wet SiO_2.[14] However, some of these methods suffer from disadvantages including low yields (especially the thiocyanation of aromatic amines), strongly acidic or harsh oxidizing conditions, long reaction times and/or high temperatures and the use of expensive and toxic reagents.

Electrochemical organo-synthetic methods have received significant attention because of their benefit to the environment. In these procedures, electricity acts as a 'green' oxidative and reductive agent. Although electrochemical syntheses of various organic compounds have been reported in the literature,[15] electrothiocyanation has rarely been examined.[16] Recently, an expedient approach to anodic thiocyanation of aromatic compounds was reported,[17,18] in which the electrochemical step involved anodic oxidation of the thiocyanate anion to its radical, followed by dimerization to thiocyanogen $(SCN)_2$. Krishnan and Gurjar[19] also studied the anodic thiocyanation of aromatic amines and phenols by two-phase electrolysis (dichloromethane–acidic solution of ammonium thiocyanate). They reported that anodic oxidation of SCN^- gave trithiocyanate, $(SCN)_3^-$ in the aqueous phase, which was immediately extracted into the organic phase as the thiocyanating reagent $(SCN)_2$.

In continuation of our work on the electrosynthesis of organic compounds and the thiocyanation of nitrogen-containing aromatic and heteroaryl compounds in the presence of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)/NH_4SCN,[20,21] herein we report a mild and efficient procedure for the one-pot electrochemical thiocyanation of nitrogen-containing aromatic and heteroaromatic compounds using constant current electrolysis in an undivided cell, in the presence of NH_4SCN as both the thiocyanating reagent and the electrolyte, in methanol at room temperature (Scheme 1).[22,23]

Initial studies were performed using indole (**1a**). The cyclic voltammogram of indole (**1a**) in methanol showed an oxidation peak at about 1.1 V (vs Ag/AgCl) whereas SCN^- is oxidized at a potential of about 0.95 V. Accordingly, preliminary experiments were carried out under constant anodic current electrolysis on indole (**1a**) and ammonium thiocyanate solutions in methanol using a graphite

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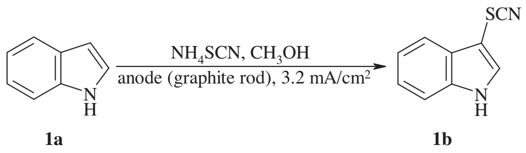
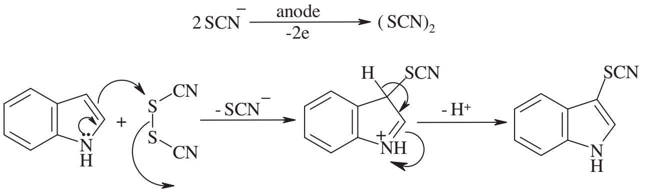


Scheme 1. Electro-thiocyanation of indole.



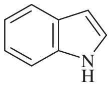
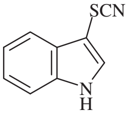
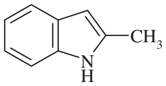
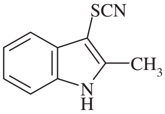
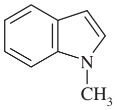
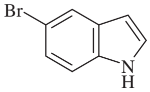
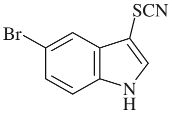
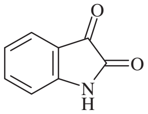
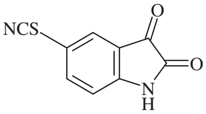
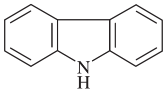
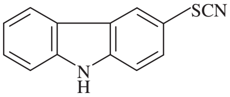
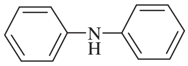
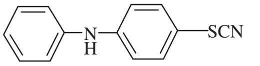
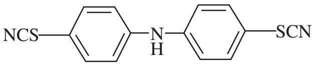
Scheme 2. A plausible mechanism for the anodic thiocyanation of indole.

electrode as the anode. Initially, the effects of various reaction parameters on the typical anodic thiocyanation of indole were examined. Based on our previous studies,[20,21] four different organic solvents (methanol, ethanol, *n*-hexane and chloroform) were investigated in the preliminary experiments and methanol proved to be the most effective for the thiocyanation process. Current densities from 0.6 to 4 mA/cm^2 were examined and the highest yield (95%) of thiocyanated product was obtained at 3.2 mA/cm^2. Electrolysis at higher current densities was not possible since indole also underwent simultaneous oxidation with thiocyanate and the colour of the solution changed to brown due to the electropolymerization of indole.[24] On investigating the effect of the salt/indole ratio on the reaction yield, surprisingly we found that the yield increased on increasing the salt/indole ratio and reached a maximum (about 85%) at a ratio of higher than 1:2. However, in almost all the previously reported work on the anodic thiocyanation of organic compounds, the amount of the organic substrate was relative to the thiocyanate salt. Although we could not find any reasonable explanation for the excess of salt in comparison to the substrate, we used a ratio of indole:NH$_4$SCN of 1:5 in which NH$_4$SCN participated as both the supporting electrolyte and the thiocyanating agent during the reaction.

Next, using the optimized conditions (substrate/NH$_4$SCN mole ratio of 1:5 in methanol with a constant current density of 3.2 mA/cm^2), we thiocyanated various nitrogen-containing heterocycles (Table 1). The total charge involved during each electrochemical process was calculated from the duration of electrolysis at a constant current density of 3.2 mA/cm^2 (Table 1). Under these conditions, it was found that the one-pot anodic oxidation of thiocyanate was very effective for the thiocyanation of various heterocyclic compounds.

According to Table 1, indole (**1a**) and its electron-donating 1-methyl and 2-methyl derivatives **2a** and **3a** underwent thiocyanation at their 3-position in high yields. The electron-withdrawing

Table 1
Constant current electrochemical thiocyanation of nitrogen-containing heterocycles

Entry	Substrate	Product[a]	Yield[b] (%)	Charge (F/mol)	Time (min)	Mp (°C)
1	 **1a**	 **1b**	95	1.5	25	105–106[12]
2	 **2a**	 **2b**	96	2.0	30	99–101[12]
3	 **3a**	 **3b**	92	2.0	30	83–84[8]
4	 **4a**	 **4b**	90	2.5	40	127–129[8]
5	 **5a**	 **5b**	75	3.7	60	201–202[12]
6	 **6a**	 **6b**	55	5.6	90	80–81[9]
7	 **7a**	 **7b**	60	3.7	60	62–64[13]
		 **7c**	10			110–111[13]

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[a] The products were identified from their spectral data and by comparison with authentic samples.

[b] Isolated yields.

5-bromoindole (**4a**) produced the corresponding 3-thiocyanato-5-bromoindole (**4b**) in a longer time compared to indole. Isatin (**5a**) gave 5-thiocyanatoisatin (**5b**) in 75% yield within 60 min. In comparison to most of the organic procedures reported, the electrochemical isatin thiocyanation is more successful (entry 5). To investigate the efficacy of this method we examined carbazole (**6a**) as another example of a nitrogen-containing aromatic substrate, and the corresponding 3-thiocyanatocarbazole (**6b**) was obtained in 55% yield. Electrochemical thiocyanation of diphenylamine (**7a**) generated 4-thiocyanatodiphenylamine (**7b**) and 4,4′-dithiocyanatodiphenylamine (**7c**) in a 6:1 ratio.

A plausible mechanism for this reaction is proposed in Scheme 2. It has been postulated that SCN^- is oxidized via a one-electron oxidation process to a radical, which undergoes dimerization at the electrode surface to form thiocyanogen. Then the electrogenerated nascent thiocyanogen, $(SCN)_2$ reacts with the substrate to produce the product. In our literature survey, we found that substrates that were sparingly soluble in water and which had oxidation potentials close to that of SCN^-, could undergo in situ thiocyanation.[25] Comparing our system with this claim partially substantiates our proposed mechanism.

In conclusion, the use of electrochemical thiocyanation has advantages in comparison with conventional chemistry. These include: (i) in situ generation of the thiocyanating reagent, (ii) the avoidance of using a supporting electrolyte, (iii) a one-pot reaction affording excellent yields under mild conditions, (iv) the avoidance of polluting or hazardous chemicals and toxic reagents and (v) involves an easy work-up procedure.

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22. *Typical procedure for the electro-synthesis of* ***2a:*** 30 ml MeOH solution of indole (**1a**) (1 mmol, 0.117 g) and ammonium thiocyanate (5 mmol, 0.34 g) in an undivided cell fitted with a graphite rod as the cathode and an assembly of three graphite rods (8 mm diameter and 4 cm length) as the anode, was subjected to electrolysis at a constant current at room temperature. A magnetic stirrer was employed during the electrolysis. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was evaporated and the resulting crude product was purified by preparative thin-layer chromatography on silica gel (eluent: *n*-hexane–EtOAc, 9:1) to afford 3-thiocyanatoindole (**2a**) (0.165 g, 95%). Mp 105–106 °C.[12] IR (KBr, cm^{-1}): 3334 (NH), 2150 (SCN), 735 (N–H), 635 (C–S). ^1H NMR (500 MHz, $CDCl_3$): 7.42–7.29 (m, 4H), 7.81 (d, 1H, *J* = 8.72 Hz), 8.90 (br s, 1H, NH). EI-MS *m*/*z* (%): 174 [M^+] (100), 148 [M^+−CN] (63), 116 [M^+−SCN] (28).
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