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Mendeleev Commun., 2016, **26**, 413–414
Mendeleev Communications

Reactivity of electrogenerated thiocyanogen in the thiocyanation of pyrazolo[1,5-*a*]pyrimidines

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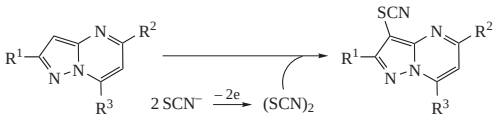
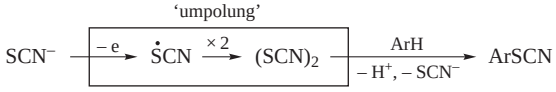
DOI: 10.1016/j.mencom.2016.09.016

Selective thiocyanation (yield 70–90%) at the 3-position of pyrazolo[1,5-*a*]pyrimidines was performed with thiocyanogen electrochemically generated *in situ* from NH_4SCN in MeCN on a Pt anode. For substrates with higher oxidation potential addition of Lewis acids was necessary.



R^1 = Alk; R^2, R^3 = Alk, Ar, NH_2, CF_3

The concept of electro-induced processes of hydrogen nucleophilic substitution in arenes, the S_N^H(An) reaction (where An is the anode), was formulated in reviews.[1,2] Based on the ideas developed by Ingold,[3] electrothiocyanation was considered among these processes.[4] It occurs through generation of thiocyanogen, $(SCN)_2$, due to polarity inversion ('umpolung')[5] in the original thiocyanate ion according to Scheme 1.



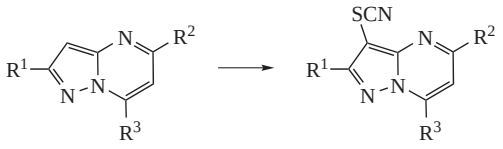
Scheme 1

The interest in the synthesis of thiocyanation products stems from the broad spectrum of their pharmacological activity, *e.g.* antitumor,[6] antiparasitic,[7] antifungal,[8,9] *etc*. On the other hand, the electrochemical method[10] is the simplest and most convenient one for synthesizing 'dirhodane' (known as thiocyanogen[11]) where the anode is used as a 'green' oxidizing agent, since the chemical methods of thiocyanogen synthesis usually involve the use of a considerable excess of inorganic or organic oxidants that are often toxic (see the review[12]). Each of these reasons stimulated the search for new objects for electrothiocyanation. Furthermore, identification of factors that affect the process efficiency was obviously of interest.

In the previous study,[4] we addressed the electrothiocyanation of derivatives of nitrogen-containing five-membered heterocycles (pyrazoles, pyrroles, *etc*.) to give target products with antifungal activity.[9] In continuation of these studies, we tried to perform the electrothiocyanation of functionally-substituted pyrazolo[1,5-*a*]-pyrimidine systems (condensation products of pyrazoles with 1,3-diketones), which by themselves may be pharmacologically active,[13,14] and to study the regularities of these processes.

The electrothiocyanation of bicycles **1a–e** during NH_4SCN oxidation was carried out in MeCN with 0.1 M $NaClO_4$ as a supporting electrolyte in an undivided cell with Pt electrodes (Scheme 2, Table 1). These processes were implemented under controlled potential electrolysis (CPE).† Based on cyclic voltammetry (CV) data, this potential corresponded to the thiocyanate ion → thiocyanogen oxidation peak (0.70 V *vs*. SCE). Regardless of the known[15] liability of thiocyanogen to polymerization, which requires the use of rather low temperatures (–20 to 5 °C),[16] it has been shown[4] that electrothiocyanation in MeCN can be successfully performed even at room temperatures (20–25 °C). The present study confirmed this conclusion. The process carried out in accordance with Scheme 1 occurred at 3-position of the pyrazole ring with sufficiently high yield (79–87%) of the target products **2a–e** (see Table 1).

It follows from the E_p^{ox} values from Table 1 (the potentials of irreversible oxidation peaks of pyrazolo[1,5-*a*]pyrimidine systems) that bicycles **1a–c** containing electron-donating groups in the pyrimidine ring undergo oxidation more easily than bicycles **1d**,**e** with electron-withdrawing groups in the pyrimidine ring. Thus,



1a–e **2a–e**

a $R^1 = R^2 = Me$, $R^3 = NH_2$
b $R^1 = R^2 = R^3 = Me$
c R^1 = cyclopropyl, $R^2 = R^3 = Me$
d $R^1 = Me$, R^2 = 2-thienyl, $R^3 = CF_3$
e $R^1 = Me$, $R^2 = Ph$, $R^3 = CF_3$

Scheme 2

† ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 instrument (300.13 MHz for ^1H and 75.47 MHz for ^{13}C). HRMS spectra were recorded on a Bruker micrOTOF II instrument. 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 Pt wire 1 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 (0.1 M $NaClO_4$ in MeCN) was used as the reference electrode. A Pt plate (S = 3 cm^2) was used as the counter electrode.

The following compounds were synthesized as described: 2-methylpyrazolo[1,5-*a*]pyrimidin-7-amine[18] **1a**, 2-methyl-5-(thiophen-2-yl)-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine[19] **1d**, 2-methyl-5-phenyl-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine[19] **1e**. 2,5,7-Trimethylpyrazolo[1,5-*a*]-pyrimidine **1b** and 2-cyclopropyl-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine **1c** were prepared as follows. 3-Methyl- or 3-cyclopropyl-1*H*-pyrazol-5-amine (0.012 mol) was dissolved in water (5 ml). Concentrated HCl (3 ml) and a solution of pentane-2,4-dione (5 ml, 0.01 mol) in EtOH were added (if the mixture became turbid, more EtOH was added to obtain a clear solution). The solution was stirred for 24 h, then EtOH was distilled off *in vacuo* and 0.1 M aq. NaOH was added. The crystals that precipitated were washed with water to pH ~7 and dried in air. The yield of products **1b**,**c** amounted to 60%.

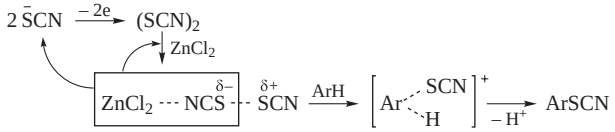
Table 1 The oxidation peaks (E_p^{ox}) of compounds **1a**–**e** and the yields of their thiocyanation products **2a**–**e** in electrooxidation of NH_4SCN in the presence of **1a**–**e** (Pt anode, E = 0.7 V *vs.* SCE, 0.1 M $NaClO_4$, MeCN).

Reactant **1**	E_p^{ox}/V	Product	Yield (%)
1a	1.20	**2a**	79
1b	1.50	**2b**	87
1c	1.50	**2c**	82
1d	1.85	**2d**	71[a]
1e	1.88	**2e**	69[a]

[a] In the presence of $ZnCl_2$, in its absence the yield was 0%.

the nature of the substituent in the pyrimidine ring of the bicycle determines to a considerable extent the increase in E_p^{ox} values on transition from bicycle **1a** to bicycle **1e**. Note (see Table 1) that the yield of thiocyanation products of the pyrazolo[1,5-*a*]pyrimidine systems changed in reverse order. It was rather high (up to 87%) in case of bicycles **1a**–**c** but decreased to zero in the case of bicyclic structures **1d**,**e**.The latter had E_p^{ox} values more positive than 1.8 V and did not undergo electrothiocyanation at all under the conditions of the experiment.

It is interesting[4] that the yield of thiocyanation products of indoles and pyrroles also decreased with an increase in their E_p^{ox} values, while attempts at thiocyanation of 2-methylfuran, furan, and thiophene failed (E_p^{ox} = 1.7, 2.0, and 2.15 V, respectively). It can therefore be concluded that the efficiency of using electrogenerated thiocyanogen in the thiocyanation of arenes is limited by the E_p^{ox} value of an arene. We assumed, however,[4] that this limitation that reflects the reactivity of thiocyanogen itself can be mitigated to some extent by addition of electrophilic catalysts. In fact, the yield of products **2d** and **2e** rose from 0 to almost 70% on addition of $ZnCl_2$ to the reaction system. In this case, the process mechanism can be described by Scheme 3.



Scheme 3

Thus, our study has revealed the principal possibility of electrochemical thiocyanation of pyrazolo[1,5-*a*]pyrimidine systems. The efficiency of the process is dependent on the oxidation potential of the substrate and can be regulated by Lewis acid additives. The reactions in question play an important role in organic transformations and preparation of hybrid/molecular systems.[17]

This work was supported by the Russian Science Foundation (grant no. 14-50-00126).

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Received: 14th April 2016; Com. 16/4910

Electrosynthesis (general procedure). A 0.1 M solution of $NaClO_4$ in MeCN (50 ml) containing NH_4SCN (0.003 mol) and reactant **1a**–**e** (0.001 mol) was placed in a glass temperature-controlled (25 °C) cell (V = 60 ml) equipped with coaxial cylindrical Pt-electrodes (S_{anode} = 26 cm^2, $S_{cathode}$ = 10 cm^2). In the case of **1d**,**e** (see Table 1), $ZnCl_2$ (0.0015 mol) was also added. The electrolysis was carried out by passing 2–4 F of electricity (based on 1 F per 1 mol NH_4SCN) with vigorous stirring in a stream of nitrogen at a potential of 0.70 V *vs.* SCE until the starting **1** was fully consumed (TLC and CV monitoring). After the reaction was completed, the solvent was distilled off *in vacuo*, water (20 ml) was added, and the mixture was extracted with EtOAc (4 × 25 ml). The extracts were combined, dried with anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography on SiO_2 (light petroleum–EtOAc, with increasing fraction of the latter from 5 to 100 vol%, as the eluent) gave pure thiocyanates **2a**–**e**.

2-Methyl-3-thiocyanatopyrazolo[1,5-a]pyrimidin-7-amine **2a**: yellowish solid, mp > 180 °C (decomp.). ^{1}H NMR (DMSO-d_6) δ: 2.52 (merge with DMSO, s, 3H, 2-Me), 6.26 (d, 1H, C^{6}H, $J_{6,5}$ 5.4 Hz), 8.11 (br. s, 2H, 7-NH$_2$), 8.20 (d, 1H, C^{5}H, $J_{5,6}$ 5.4 Hz). ^{13}C NMR, δ: 12.50 (2-Me), 80.96 (C^3), 90.48 (C^{6}H), 111.92 (3-SCN), 148.37 (C^2), 150.17 (C^{5a}), 151.32 (C^{5}H), 156.17 (C^7). HRMS (ESI), *m*/*z*: 206.0498 (calc. for $C_8H_7N_5S$, *m*/*z*: 206.0495 [M + H]$^+$).

2,5,7-Trimethyl-3-thiocyanatopyrazolo[1,5-a]pyrimidine **2b**: white solid, mp 143–144 °C. ^{1}H NMR ($CDCl_3$) δ: 2.62 (s, 3H, 5-Me), 2.63 (s, 3H, 2-Me), 2.72 (s, 3H, 7-Me), 6.69 (s, 1H, C^{6}H). ^{13}C NMR, δ: 13.04 (2-Me), 16.83 (7-Me), 24.89 (5-Me), 84.11 (C^3), 110.11 (C^{6}H), 111.18 (3-SCN), 146.28 (C^7), 149.72 (C^2), 157.86 (C^5), 161.92 (C^{5a}). HRMS (ESI), *m*/*z*: 219.0707 (calc. for $C_{10}H_{10}N_4S$, *m*/*z*: 219.0699 [M + H]$^+$).

2-Cyclopropyl-5,7-dimethyl-3-thiocyanatopyrazolo[1,5-a]pyrimidine **2c**: yellowish solid, mp 143–146 °C. ^{1}H NMR ($CDCl_3$) δ: 1.18 (m, 4H, 2-cyclopropyl, C$^{2'}$H$_2$, C$^{3'}$H$_2$), 2.34 (m, 1H, 2-cyclopropyl, C$^{1'}$H), 2.66 (s, 6H, 5-Me, 7-Me), 6.66 (s, 1H, C^{6}H). ^{13}C NMR, δ: 8.32 (2-cyclopropyl, C$^{1'}$H), 9.21 (2-cyclopropyl, C$^{2'}$H$_2$, C$^{3'}$H$_2$), 16.69 (7-Me), 24.82 (5-Me), 83.68 (C^3), 109.85 (C^{6}H), 111.52 (3-SCN), 146.34 (C^7), 149.83 (C^2), 161.50 (C^5), 162.51 (C^{5a}). HRMS (ESI), *m*/*z*: 245.0854 (calc. for $C_{12}H_{12}N_4S$, *m*/*z*: 245.0855 [M + H]$^+$).

2-Methyl-3-thiocyanato-5-(thiophen-2-yl)-7-(trifluoromethyl)pyrazolo-[1,5-a]pyrimidine **2d**: yellow solid, mp 182–185 °C. ^{1}H NMR ($CDCl_3$) δ: 2.69 (s, 3H, 2-Me), 7.21 (dd, 1H, 5-C$_4$H$_3$S, C$^{4'}$H, $J_{4',5'}$ 5.1 Hz, $J_{4',3'}$ 3.7 Hz), 7.56 (s, 1H, C^{6}H), 7.66 (dd, 1H, 5-C$_4$H$_3$S, C$^{5'}$H, $J_{5',4'}$ 5.1 Hz, $J_{5',3'}$ 1.1 Hz), 7.85 (dd, 1H, 5-C$_4$H$_3$S, C$^{3'}$H, $J_{3',4'}$ 3.7 Hz, $J_{3',5'}$ 1.1 Hz). ^{13}C NMR, δ: 13.23 (2-Me), 87.62 (C^3), 110.36 (3-SCN), 104.05 (q, C^{6}H, $^3J_{C,F}$ 4.1 Hz), 117.26 (q, 7-CF$_3$, $^1J_{C,F}$ 275.1 Hz), 128.95 (5-C$_4$H$_3$S, C$^{4'}$H), 129.86 (5-C$_4$H$_3$S, C$^{5'}$H), 132.98 (5-C$_4$H$_3$S, C$^{3'}$H), 134.60 (q, C^{7}H, $^2J_{C,F}$ 37.8 Hz), 141.21 (5-C$_4$H$_3$S, C$^{2'}$), 150.16 (C^{5a}), 153.38 (C^5), 159.79 (C^2). HRMS (ESI), *m*/*z*: 341.0138 (calc. for $C_{13}H_7F_3N_4S_2$, *m*/*z*: 341.0137 [M + H]$^+$).

2-Methyl-5-phenyl-3-thiocyanato-7-(trifluoromethyl)pyrazolo[1,5-a] pyrimidine **2e**: yellowish solid, mp 155–157 °C. ^{1}H NMR (DMSO-d_6) δ: 2.63 (s, 3H, 2-Me), 7.63 (m, 3H, 5-Ph, C$^{2'}$H, C$^{4'}$H, C$^{6'}$H), 8.28 (s, 1H, C^{6}H), 8.39 (m, 2H, 5-Ph, C$^{3'}$H, C$^{5'}$H). ^{13}C NMR, δ: 12.71 (2-Me), 91.62 (C^3), 106.11 (q, C^{6}H, $^3J_{C,F}$ 3.9 Hz), 111.18 (3-SCN), 117.38 (q, 7-CF$_3$, $^1J_{C,F}$ 274.9 Hz), 127.87 (5-Ph, C$^{2'}$H, C$^{6'}$H), 129.17 (5-Ph, C$^{3'}$H, C$^{5'}$H), 132.00 (5-Ph, C$^{4'}$H), 132.94 (q, C^{7}H, $^2J_{C,F}$ 37.2 Hz), 134.94 (5-Ph, C$^{1'}$), 149.53 (C^{5a}), 157.98 (C^5), 158.52 (C^2). HRMS (ESI), *m*/*z*: 335.0568 (calc. for $C_{15}H_9F_3N_4S$, *m*/*z*: 335.0573 [M + H]$^+$).