Effect of "anomalous" electrochemical halogenation of pyrazoles and its reasons

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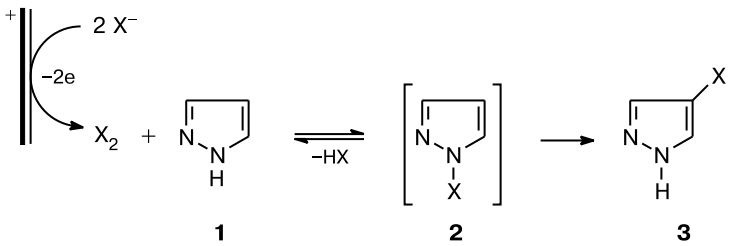
We have previously[1—3] found that the nature of halogen determines, to a noticeable extent, the yield of target products in the electrochemical halogenation of pyrazoles in aqueous solutions of alkaline metal halides. It is known[4] that pyrazole halogenation proceeds *via* the mechanism of electrophilic aromatic substitution, and the reactivity of halogen in these reaction decreases in the series Cl > Br > I. This is consistent with the results of chlorination and iodination of pyrazoles[3]; however, the data on bromination[2] sharply fall out of the regularity. For instance, in spite of the lower reactivity of Br_2 compared to Cl_2, the yield of target products and conversion of azole in the bromination[2] are substantially higher than those for chlorination.[1]

Based on the data[5] indicating that the halogenation of pyrazoles **1** (Scheme 1) proceeds through the formation of halogen derivative **2** followed by its rearrangement to *C*-halogen derivative **3**, we assumed that the reason for the anomalous bromination is a higher (compared to chlorination) rate of rearrangement **2** → **3** for this process. To check this hypothesis, we synthesized 1-chloro-4-nitropyrazole[6] and 1-bromo-4-nitropyrazole[7] following earlier described procedures and studied their transformation under the conditions (aqueous solution of $NaHCO_3$, 20—25 °C) close to those of electrochemical halogenation. The consumption of *N*-halopyrazoles was monitored by iodometric titration.[8] We showed that on stirring with an AcOH-acidified aqueous solution of KI these compounds evolved I_2, which can be titrated off with a 0.1 *M* solution of $Na_2S_2O_3$. It turned out that for 3 h of stirring the conversion of the *N*-chloroderivative was only 6%, whereas for the *N*-bromoderivative it attained 40%, which agrees with our hypothesis. In order to establish the transformation products of 1-bromo-4-nitropyrazole, the reaction was carried out for 72 h until completion (the conversion of the *N*-bromoderivative was 94%). As a result, the formation of 3,5-dibromo-4-nitropyrazole (^{13}C NMR) and 4-nitropyrazole (^1H NMR) was found. The presence of earlier undescribed 3(5)-bromo-4-nitropyrazole in the reaction mixture was proved by high-resolution mass spectrometry.

Taking into account that 3,5-dibromo-4-nitropyrazole gives no characteristic signals in the ^1H NMR spectrum and with the purpose to estimate the molar ratio of the products, the obtained reaction mixture was methylated at the N atom of the pyrazole ring and then analyzed by ^1H NMR. It turned out that the molar ratio of 3,5-dibromo-1-methyl-4-nitropyrazole, 1-methyl-4-nitropyrazole, and a mixture of 3-bromo-1-methyl-4-nitropyrazole and 5-bromo-1-methyl-4-nitropyrazole was 1.0 : 1.0 : 2.14.

As we found for the first time, during the bromination of pyrazoles the intramolecular N—C rearrangement occurs with a higher rate than during chlorination, which was observed in different yields of the target products. Note that the lower rate of the N—C tranfer of halogen atom for pyrazole chlorination allows one to perform secondary processes leading to the formation of 4,4′-dichloro-1,3′(5′)-bipyrazole along with the target 4-chloropyrazole.[1]

Scheme 1



X = Cl, Br

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The starting 4-nitropyrazole was synthesized according to an earlier described procedure.[9] Pyrazoles obtained by methylation were identified by comparing their ^{1}H NMR spectra with the literature data.[10,11]

Identification of the N—C rearrangement products of 1-bromo-4-nitropyrazole and estimation of their ratio. A suspension of 1-bromo-4-nitropyrazole (0.05 mol) in an aqueous solution of $NaHCO_3$ (30 mL, 0.01 mol) was stirred for 72 h, acidified with concentrated HCl (to pH 2—3), and extracted with Et_2O (2×20 mL). After the solvent was distilled off, a solid (1.26 g) was obtained containing 3,5-dibromo-4-nitropyrazole (identified by ^{13}C NMR comparing with the spectrum of authentical 3,5-dibromo-4-nitropyrazole synthesized by a known procedure[12]), 4-nitropyrazole (identified by ^{1}H NMR), and 3(5)-bromo-4-nitropyrazole (identified by high-resolution mass spectrometry: calculated $C_3H_2BrN_3O_2$, M – **2** 189.9247; found ESI (–) 189.9259).

Dimethyl sulfate (1.5 mL, 0.0159 mol) and K_2CO_3 (3.3 g, 0.24 mol) were added to a solution of a mixture of products (0.88 g) in MeCN (40 mL). The reaction mixture was refluxed for 24 h and then cooled. The precipitate that formed was filtered off and washed with MeCN, concentrated aqueous NH_3 (2.6 mL) was added, and the mixture was stirred for 20 min (binding of dimethyl sulfate excess). The resulting solution was evaporated to dryness, and a solid residue was washed with H_2O (2×10 mL) and dried in air, and the product was obtained in a yield of 0.24 g. Target substances (0.51 g) were additionally isolated from the mother liquor by extraction with EtOAc (3×20 mL).

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