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Review

Electrooxidation Is a Promising Approach to Functionalization of Pyrazole-Type Compounds

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Abstract: The review summarizes for the first time the poorly studied electrooxidative functionalization of pyrazole derivatives leading to the C–Cl, C–Br, C–I, C–S and N–N coupling products with applied properties. The introduction discusses some aspects of aromatic hydrogen substitution. Further, we mainly consider our works on effective synthesis of the corresponding halogeno, thiocyanato and azo compounds using cheap, affordable and environmentally promising electric currents.

Keywords: pyrazoles; pyrazolo[1,5-a]pyrimidines; aromatic substitution; electrooxidation; C–H halogenation; C–H thiocyanation; N–N coupling; cyclic voltammetry

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Citation: Lyalin, B.V.; Sigacheva, V.L.; Kudinova, A.S.; Neverov, S.V.; Kokorekin, V.A.; Petrosyan, V.A. Electrooxidation Is a Promising Approach to Functionalization of Pyrazole-Type Compounds. *Molecules* **2021**, *26*, 4749. https://doi.org/10.3390/molecules26164749

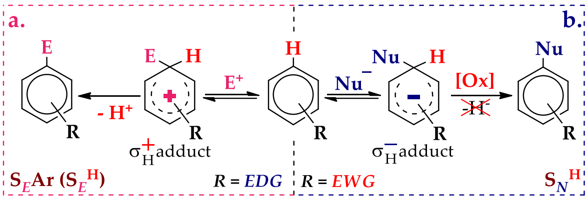
Academic Editors: Vera L. M. Silva and Artur M. S. Silva

Received: 30 June 2021
Accepted: 29 July 2021
Published: 5 August 2021

1. Introduction

The functionalization of arenes is the key to their diversity, opening the way to practically useful substances. At the beginning of the 21st century, C-H functionalization of arenes became a popular tool for the implementation of such processes [1], and the center for selective C-H functionalization (mainly based on metal complex catalysis) was organized in the USA [2,3]. At the same time, a more attractive metal-free C-H functionalization of arenes has existed for many years. Its development is discussed below, since the review is related to it.

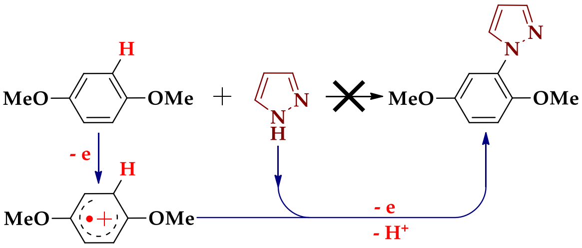
The first to consider is the electrophilic aromatic hydrogen substitution ($S_E{}^H$) [4]. It proceeds via the $\sigma_H{}^+$ adduct formation and proton elimination leading to the target product (Scheme 1a).



Scheme 1. Electrophilic (**a**) and nucleophilic (**b**) aromatic hydrogen substitution.

The nucleophilic aromatic hydrogen substitution ($S_N{}^H$, Scheme 1b) is problematic due to the difficulty of the hydride ion direct elimination from the $\sigma_H{}^-$ adduct. Nevertheless, in the mid-1970s, Chupakhin and Postovsky proposed an indirect way of obtaining the target product, the chemical oxidation of the $\sigma_H{}^-$ adduct [5]. To date, such processes have been extensively developed by Chupakhin and Charushin [6–9].

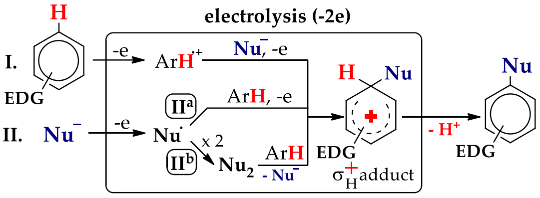
This review is devoted to electrooxidative functionalization of pyrazoles. Why is it so attractive? The answer is given by Seebach [10], who showed that the interaction of two near-polar co-reactants is provided by the polarity inversion of one of them. This is the essence of electrochemistry, where the electrode transformation of the substrate is accompanied by its polarity inversion. For example, 1,4-dimethoxybenzene (DMB) and pyrazole (Scheme 2) are two non-interacting nucleophiles, but polarity inversion of DMB by electrooxidation leads to the electrophilic radical cation that reacts with pyrazole. In the electrochemical literature, this C-H functionalization is called anodic substitution, which has been actively studied since the mid-1950s [11–20].



Scheme 2. Electrooxidative *N*-arylation of pyrazole by 1,4-dimethoxybenzene.

Note that chemical (electrophilic and nucleophilic) substitution and electrochemical (anodic) substitution in arenes have been being developed in parallel and independently of each other for a long time. In addition, the role of anodic substitution among the corresponding chemical processes was unconsidered.

Only recently we have introduced the concept of anodic substitution as an electrochemical aromatic substitution of hydrogen [21,22]. Such reactions were designated as S_N^H An (An is anode), since the key stage is anodic oxidation of the substrate. For electron-rich arenes, the processes proceed along two main routes (Scheme 3), depending on the ease of oxidation of nucleophile vs. arene [21]. Route I (arene oxidizes easier than Nu^-) proceeds via the interaction between Nu^- and the arene radical cation. Route II (Nu^- oxidizes easier than arene) proceeds via the formation of $Nu^•$, which either interacts with the arenes homolytically (route II^a) or forms a dimer that interacts with the arene as an electrophile (route II^b).



Scheme 3. Main routes of S_N^H An processes: **I** ($E_p{}^{ox}{}_{Ar} < E_p{}^{ox}{}_{Nu^-}$) or **II** ($E_p{}^{ox}{}_{Nu^-} < E_p{}^{ox}{}_{Ar}$).

In general, the multitude of S_N^H (An) processes, where hydrogen is displaced with a nucleophile, are electrooxidative C-H functionalizations (C–H An) and can be described by Scheme 4. Such strategy opens up the direct method of C–H functionalization of arenes with the C–C and C–Het coupling realization. The latter is especially shown in the examples of electrooxidative C–H halogenation and thiocyanation of pyrazole derivatives (Sections 2 and 3). A special place is occupied by the N–N coupling of amino pyrazoles via the N–H functionalization (Section 4), since its patterns are somehow similar to those described above, but not sufficiently studied.

Scheme 4. General scheme of the electrooxidative C-H functionalization (C–H An).

Such processes are attractive for green chemistry [23,24] because they use cheap, affordable and environmentally promising electric current instead of chemical oxidants (often toxic, unrecyclable and used in excess) and complex catalysts (sometimes expensive and toxic). In addition, the varying anode potential eliminates the difficulties of an empirical search for suitable chemical oxidants, while Pt, a frequently used electrode material [25], can be replaced by more attractive ones, e.g., glassy carbon, or ruthenium–titanium oxide (for more information on electrode materials see [25–27]).

Since the review is devoted to the poorly studied electrochemical functionalization of pyrazole derivatives, Sections 2–4 mainly summarize the investigations of the review's authors.

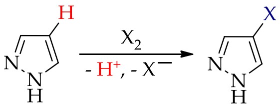
2. Electrooxidative C–H Halogenation of Pyrazole and Its Substituted Derivatives

Halogenated pyrazoles are widely used in organic synthesis; in particular, iodo and bromo pyrazoles are the key reagents in transition metal-catalyzed cross-coupling [28]. Moreover, they are important precursors of drugs, such as antihepatitis, anti-Alzheimer, antiparkinsonian and anti-schizophrenic drugs (chloro-pyrazoles) [29–31], antiglaucoma drugs (bromo-pyrazoles) [32] and antiatherosclerotic, antimalarial, anti-inflammatory and immunocorrective drugs (iodo-pyrazoles) [33–38]. At the same time, chloro- and iodo-pyrazoles are used for preparation of antidiabetic drugs [39,40], bromo- and iodo-pyrazoles—of anticancer [41–44] and antimicrobial [45,46] agents, and chloro- and bromo-pyrazoles—of agrochemicals [47–51].

The active use of halogeno-pyrazoles has stimulated interest in their efficient and ecologically attractive synthesis, including electrosynthesis (see Introduction). At the same time, the electrochemical halogenation of pyrazoles has practically not been studied before us, but it was preceded by chemical halogenation, the aspects of which are briefly given below.

2.1. Chemical Halogenation of Pyrazoles

The processes (Scheme 5) are usually carried out by the interaction of pyrazoles and halogens (or halogenating reagents), and they occur first at position 4 and only then at other positions [28].



Scheme 5. Chemical halogenation of pyrazoles (X = Cl, Br, I).

2.1.1. Chlorination

The most common is the interaction of pyrazoles and Cl_2. It was used to convert the pyrazole and its alkyl derivatives into the 4-chloro pyrazoles (yields 40–85%, at 0–40 °C, in CH_2Cl_2 or CCl_4). Under severe conditions (at 80–100 °C, in AcOH) dichloropyrazoles and the chloro products of the alkyl groups were also formed [52,53]. At the same time, the corresponding 4-chloro derivatives were obtained by the reaction of 3,5-dimethyl-1*H*-pyrazole (and its *N*-substituted derivatives) with *N*-chlorosuccinimide (yield 95–98%, at 20–25 °C, in CCl_4 or H_2O) [54,55].

2.1.2. Bromination

The reaction of alkyl-substituted pyrazoles and their carboxylic acids with Br_2 (at 20–25 °C) proceeded in yields of 75–96% in non-aqueous media (CH_2Cl_2, $CHCl_3$ or CCl_4) [45,56–58], or 50–75% in water [59,60]. The NaOH additives (which binds with HBr formed) allows bromination of low-reactive pyrazole-3-carboxylic acid in the yield of 90% [61]. A number of 4-bromopyrazoles were also obtained by the reaction of 3,5-dimethyl-1*H*-pyrazole (and its *N*-substituted derivatives) with *N*-bromosuccinimide (yields 90–99%, at 20–25 °C, in CCl_4 or H_2O) [55].

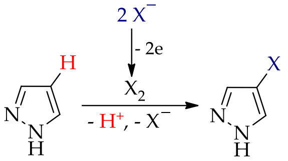
2.1.3. Iodination

Good results in the iodination of pyrazoles with donor substituents were obtained using the I_2–NaI–K_2CO_3 system (yields 75–90% at 20–25 °C in aq. EtOH) [62–64]. A solution of N-iodosuccinimide in acidic media (50% aq. H_2SO_4, CF_3SO_3H, CF_3COOH, AcOH) was also efficient for the iodination [44,62,65]. Finally, the iodination of practically any pyrazoles proceeded efficiently and without toxic waste using the I_2–HIO_3 system in AcOH–CCl_4 [66,67].

In general, the above methods are quite effective, but not ecologically attractive enough due to the frequent use of halogens in their pure form or waste of other halogenating agents (e.g., succinimide). Such problems can be solved using electrochemical methods—C–H An halogenation.

2.2. *C-H An Halogenation of Pyrazoles*

The halogenation (Scheme 6) usually proceeds [26] via the electrogeneration of a halogen followed by its interaction with pyrazole (cf. Scheme 3, route II^b).

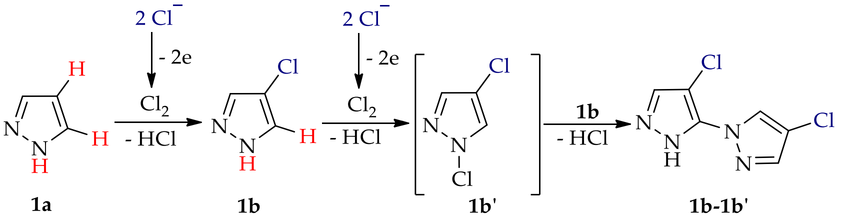


Scheme 6. C–H An halogenation of pyrazoles (X = Cl, Br, I).

Such processes are mainly carried out under mild conditions in an anodic compartment of a divided cell on a Pt-anode under galvanostatic electrolysis with alkali metal halides in H_2O or in H_2O–$CHCl_3$. A series of *N–H* and *N–Alk* pyrazoles, including those with donor (acceptor) substituents, were objects of study (Tables 1–3).

2.2.1. Chlorination

C–H An chlorination of pyrazole **1a** (Table 1, entry 1) led to 4-chloropyrazole **1b** (yield 46%) and to by-product **1b′** (yield 8%) in H_2O–$CHCl_3$ at the theoretical amount of electricity passed (Q/Q_t = 1). Apparently, the product **1b** undergoes chlorination to 1,4-dichloropyrazole **1b′** (Scheme 7), followed by C–N dehydrogenative cross-coupling to by-product **1b-1b′**.

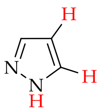
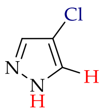
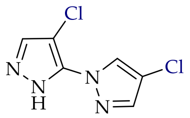
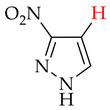
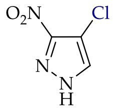
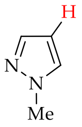
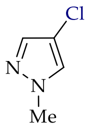
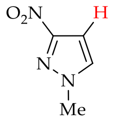
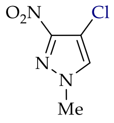
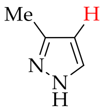
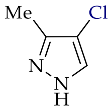
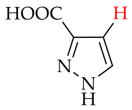
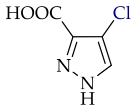
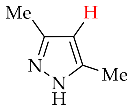
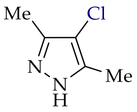
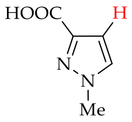
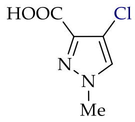
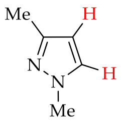
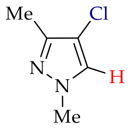
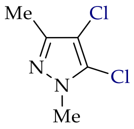
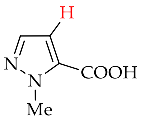
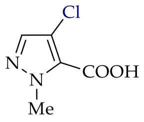
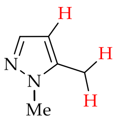
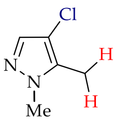
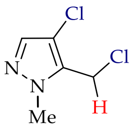
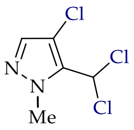
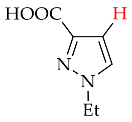
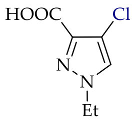
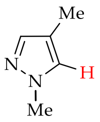
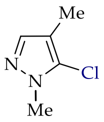
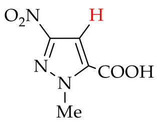
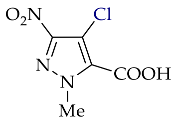


Scheme 7. C-H An chlorination of pyrazole **1a**.

The need for $CHCl_3$ (as an extractant of target product) should be noted, since its absence decreased the yield of product **1b** to 34% and increased the yield of by-product **1b-1b′** to 15%. Pyrazoles **2a–7a** (entries 2–7), gave the monochlorinated products **2b–7b** with different yields (8–71%) depending on the position of Me groups. Di- and trichloroproducts were obtained in entries 5 and 6.

Pyrazoles with acceptor groups (NO_2 or COOH) were chlorinated without $CHCl_3$ additives: the yields of the target products **8b–14b** were 41–93% (entries 8–14). Only pyrazole **14a**, containing both NO_2 and COOH groups, was the least reactive. Therefore, the electrochemical method for the synthesis of 4-chloropyrazolcarboxylic acids [68] is noticeably superior to the corresponding chemical one [69].

Table 1. C-H An chlorination of pyrazoles (Az-H) [1].

Entry	Az-H, Az-Cl and other Products (Yield, %) [70,71]				Entry	Az-H, Az-Cl (Yield, %) [68,70,71]	
1	 **1a**	 **1b** (46 [2])	 **1b-1b′** (8 [2])		8	 **8a**	 **8b** (41 [2])
2	 **2a**		 **2b** (71 [3])		9	 **9a**	 **9b** (64 [3])
3	 **3a**		 **3b** (34 [2])		10	 **10a**	 **10b** (92 [3])
4	 **4a**		 **4b** (70 [3])		11	 **11a**	 **11b** (69 [3])
5	 **5a**	 **5b** (15 [2])	 **5b′** (35 [2])		12	 **12a**	 **12b** (93 [3])
6	 **6a**	 **6b** (47 [2])	 **6b′** (13 [2])	 **6b″** (4)[2]	13	 **13a**	 **13b** (84 [3])
7	 **7a**		 **7b** (8 [2])		14	 **14a**	 **14b** (4 [2])

[1] Electrolysis in 100 mL of 4 M solution of NaCl in H_2O–$CHCl_3$ (entries 1–7), H_2O (entries 8–14), 15 °C, pyrazole (12.5–50 mmol), divided cell, Pt anode, Cu cathode, galvanostatic electrolysis (j_{anode} = 100 mA·cm^{-2}), Q_t = 2412–9650 C, Q/Q_t = 1–2; [2] the yield was calculated from the ^{1}H NMR spectroscopic data for the isolated mixture of products with unreacted pyrazoles; [3] the yield was determined for the isolated product.

Table 2. C-H An bromination of pyrazoles (Az-H) [1].

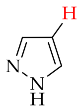
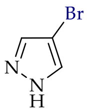
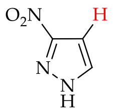
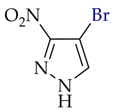
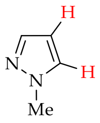
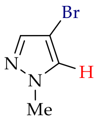
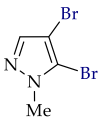
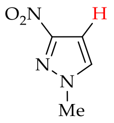
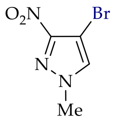
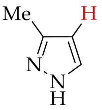
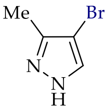
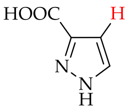
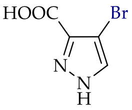
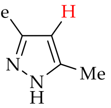
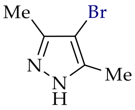
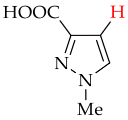
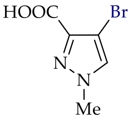
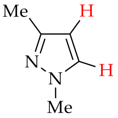
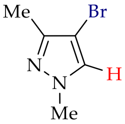
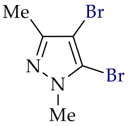
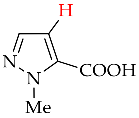
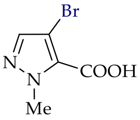
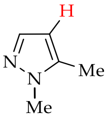
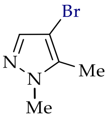
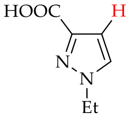
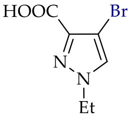
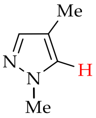
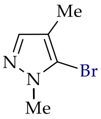
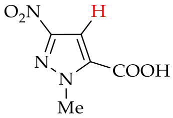
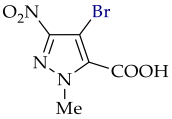
Entry	Az-H, Az-Br and Other Products (Yield, %) [71,72]			Entry	Az-H, Az-Br (Yield, %) [71,72]	
1	 **1a**		 **1c** (70 [2])	8	 **8a**	 **8c** (89 [2])
2	 **2a**	 **2c** (76 [3])	 **2c′** (5 [3])	9	 **9a**	 **9c** (15 [3])

Table 2. *Cont.*

Entry	Az-H, Az-Br and Other Products (Yield, %) [71,72]			Entry	Az-H, Az-Br (Yield, %) [71,72]	
3	 **3a**		 **3c** (66 [3])	10	 **10a**	 **10c** (68 [3])
4	 **4a**		 **4c** (94 [2])	11	 **11a**	 **11c** (78 [2])
5	 **5a**	 **5c** (55 [3])	 **5c′** (26 [3])	12	 **12a**	 **12c** (84 [2])
6	 **6a**		 **6c** (88 [2])	13	 **13a**	 **13c** (84 [2])
7	 **7a**		 **7c** (0 [5])	14	 **14a**	 **14c** (0 [3])

[1] Electrolysis in 100 mL of 1 M solution of NaBr in H_2O–$CHCl_3$ (entries 1–7), H_2O (entries 8–14), 30 °C, pyrazole (12.5–50 mmol), divided cell, Pt anode, Cu cathode, galvanostatic electrolysis (j_{anode} = 30 mA·cm^{-2}), Q = Q_t = 2412–9650 C; [2] the yield was determined for the isolated product; [3] the yield was calculated from the ^{1}H NMR spectroscopic data for the isolated mixture of products with (or) unreacted pyrazoles; [5] unpublished data.

Table 3. C-H (An) iodination of pyrazoles (Az-H).

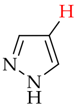
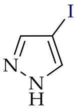
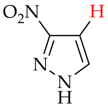
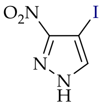
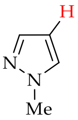
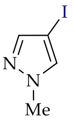
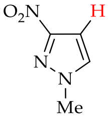
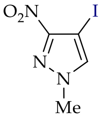
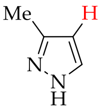
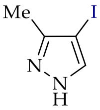
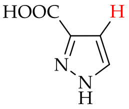
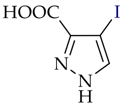
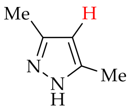
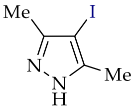
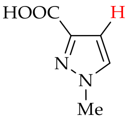
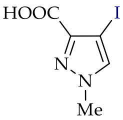
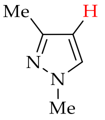
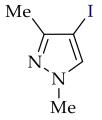
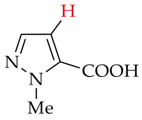
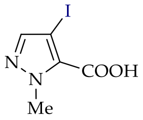
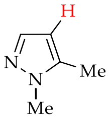
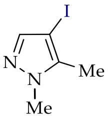
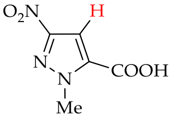
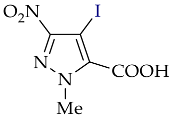
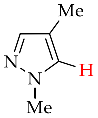
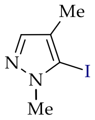
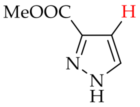
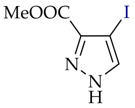
Entry	Az-H, Az-I (Yield, %) [73,74]		Entry	Az-H, Az-I (Yield, %) [73,74]	
1	 **1a**	 **1d** (57 [1,3], 93 [2,3])	8	 **8a**	 **8d** (2 [1,4], 82 [2,3])
2	 **2a**	 **2d** (5 [1,4], 79 [2,3])	9	 **9a**	 **9d** (0 [1,4])
3	 **3a**	 **3d** (71 [1,3])	10	 **10a**	 **10d** (30 [1,4], 86 [2,3])
4	 **4a**	 **4d** (86 [1,3], 93 [2,3])	11	 **11a**	 **11d** (0 [1,4], 74 [2,3])

Table 3. *Cont.*

Entry	Az-H, Az-I (Yield, %) [73,74]		Entry	Az-H, Az-I (Yield, %) [73,74]	
5	 **5a**	 **5d** (35 [1,4])	12	 **12a**	 **12d** (0 [1,4], 78 [2,3])
6	 **6a**	 **6d** (42 [1,5])	13	 **14a**	 **14d** (0 [1,5], 79 [2,3])
7	 **7a**	 **7d** (0 [1,5])	14	 **15a**	 **15d** (40 [1,4])

[1] Electrolysis in 100 mL of 0.3 M solution of $NaNO_3$ in H_2O–$CHCl_3$, 30 °C, KI (10 mmol), pyrazole (10 mmol), $NaHCO_3$ (15 mmol), divided cell, Pt anode, Cu cathode, galvanostatic electrolysis (j_{anode} = 7.5 mA·cm^{-2}), Q = Q_t = 1930 C; [2] two-step process: 1. electrogeneration of KIO_3 in 1M aq. KOH, 70 °C, KI (30 mmol), $K_2Cr_2O_7$ (0.7 mmol), undivided cell, NiO(OH) anode, Ni cathode, galvanostatic electrolysis (j_{anode} = 200 mA·cm^{-2}), Q_t = 17370 C, Q/Q_t = 0.9–1.1; 2. pyrazole (45–150 mmol), KIO_3 (9–30 mmol), I_2 (18–60 mmol), H_2O–$CHCl_3$ (or H_2O–CCl_4), H_2SO_4 conc., temperature 50–66 °C, 0.5–14 h; [3] the yield was determined for the isolated product; [4] the yields were calculated from the ^{1}H NMR spectroscopic data for the isolated products with (or) unreacted pyrazoles; [5] unpublished data.

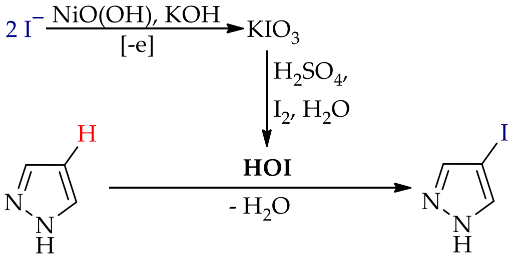
2.2.2. Bromination

Compared with chlorination, the C-H An bromination (Table 2) proceeded more effectively for pyrazole and its methyl derivatives (yields of products **1c**–**6c** 55–94%). In some cases, dibromo by-products (entries 2 and 5), low yield (entry 9), or the absence of any reactions (entries 7 and 14) were observed.

2.2.3. Iodination

C-H An iodination by weakly electrophilic I_2 (Table 3) was generally less effective than bromination [73]. Traces of the target products or no reaction were observed in half of the cases (entries 2, 7–9, 11–13). In other cases, the yields were 35–86% (for pyrazole and its methyl derivatives in entries 1, 3–6) and 30–40% (for nitro- and carboxypyrazoles in entries 10 and 14).

A much more effective iodinating agent was HOI, which can be obtained by the reaction of KIO_3 with KI (or I_2) and H_2SO_4 [75–79]. The original process [74] includes the electrogeneration of KIO_3 (on the NiO(OH) anode [80]), followed by the interaction of HOI generated in situ with the pyrazole (Scheme 8). As a result, the yields of target products increased to 74–93% (entries 1, 2, 4, 8, 10–12, 13).

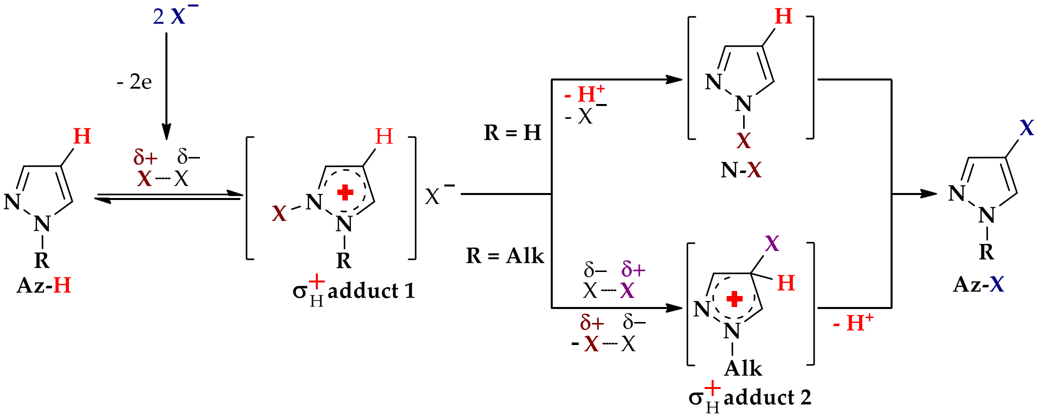


Scheme 8. C–H iodination of pyrazoles via HOI.

2.3. *The Mechanistic Aspects of C–H (An) Halogenation of Pyrazoles*

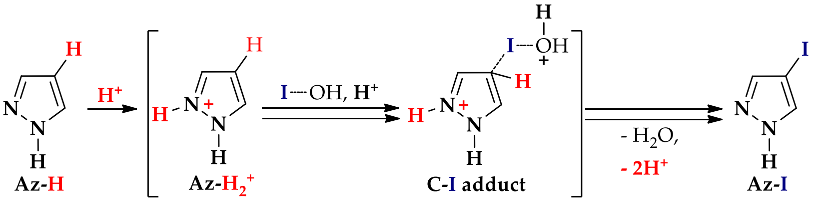
Since I$^-$, Br$^-$, and Cl$^-$ are commonly oxidized at lower anodic potentials than the studied pyrazoles, the process proceeds via the electrooxidation of Hal$^-$ to Hal_2

followed by interaction of the latter with arenes (see Scheme 3, route II^b and Scheme 6). The possible mechanism [26,71,79] (Scheme 9) includes the initial attack of the halogen on the N^2 of **Az–H** with the formation of **σ_H^+ adduct 1**. The latter, depending on the **R**, gives either **N–X** intermediate (R = H) or **σ_H^+ adduct 2** (R = Alk). Therefore, the target **Az–X** is formed either due to N–C rearrangement of **N–X** derivative or due to the deprotonation of **σ_H^+ adduct 2**.



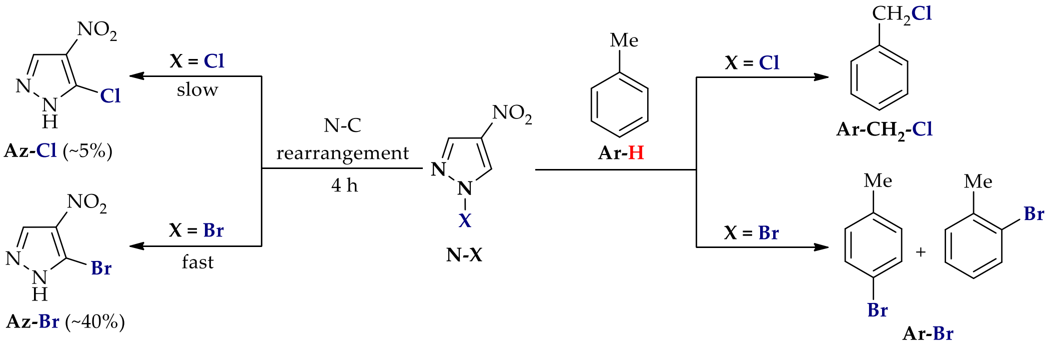
Scheme 9. C–H An halogenation of pyrazoles (possible mechanisms, X = Cl, Br, I).

Iodination by HOI proceeds similarly, but for highly basic N-unsubstituted pyrazole and its alkyl derivatives it most likely occurs (Scheme 10) via **C–I adduct** (the result of protonation of N^2 and HOI attack on C^4) [74,75,77–79].



Scheme 10. Iodination of highly basic pyrazoles by HOI.

Additional control experiments showed different properties of N–Cl and N–Br intermediates (Scheme 11). Therefore, the N–C rearrangement of the N–Cl derivative is significantly lower than that for the N–Br (cf. stages **N–X→Az–Cl** and **N–X→Az–Br**). At the same time, for the N–Cl bond, homolytic cleavage is observed, while for N–Br it is heterolytic (cf. stages **N–X→Ar–CH$_2$-Cl** and **N–X→Ar–Br**).



Scheme 11. Different behavior of N–Cl and N–Br intermediates (unpublished control experiments).

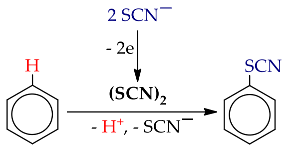
The above data not only reveal the essence of pyrazoles C-H An halogenation, but also explain the difference in its efficiency (e.g., the anomalously less efficient chlorination of N-unsubstituted pyrazoles compared to bromination (cf. entries 1, 3 and 4, Tables 1 and 2), and the formation of by-products (e.g., entries 1 and 6, Table 1).

Therefore, this Section describes the basic patterns of C–H An halogenation, and the efficient (up to 94% yield) gram-scale synthesis of a series of chloro-, bromo- and iodo-pyrazoles in aqueous or aqueous-organic media. The following Section reflects the main points on the related C-H An thiocyanation of pyrazole derivatives.

3. Electrooxidative C–H Thiocyanation of 5-Aminopyrazoles and Pyrazolo [1,5-a]pyrimidines

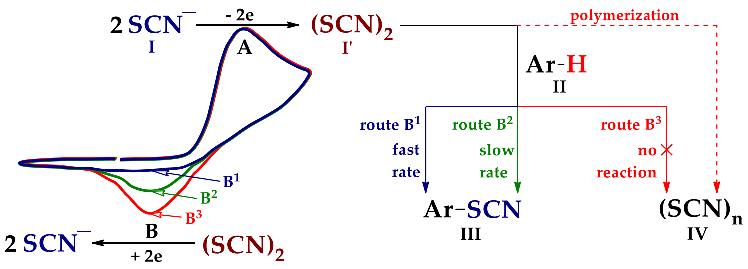
Thiocyanation of the C–H bond of arenes is an effective tool for C–S coupling [81–84]. The resulting aryl thiocyanates are valuable precursors of sulfur and nitrogen-containing compounds (thiols [85], (di)sulfides [86,87], dithiocarbamates [88], thiazoles [89], tetrazoles [90]), and are highly bioactive compounds (antifungal [91], antitumor [92], antiparasitic [93]). Recently synthesized thiocyanates of pyrazole derivatives also have sufficient antifungal [94] and antitumor [95] activity.

One of the key intermediates of C-H thiocyanation of arenes is the well-known [96,97] pseudohalogene thiocyanogen $(SCN)_2$. It is usually obtained in situ by chemical or electrochemical oxidation of the thiocyanate ion (Scheme 12).



Scheme 12. C–H thiocyanation of arenes via the thiocyanogen.

The chemical approach has been actively developed over the past 10–15 years, but it is often associated with the use of an excess of unrecyclable oxidants, which can sometimes be toxic, scalding or poorly available (e.g., Br_2 [98], I_2 [99], DEAD [100], HIO_3 [101], H_5IO_6 [102], I_2O_5 [103], H_2O_2 [102,104–107], $K_2S_2O_8$ [108,109], CAN [110], $Mn(OAc)_3$ [111], *p*-TSA [112], NCS [113], NBS [100], NIS [114], NTS [115], DDQ [116,117]). The electrochemical approach (see [22], Scheme 3, route II^b, and Scheme 13) is devoid of such disadvantages, but it is poorly studied in general [118–120]. For pyrazole derivatives, C–H An thiocyanation is studied for the first time in a series of works [22,121–126], which are reflected in this Section.



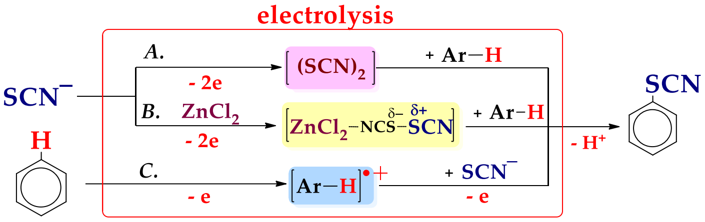
Scheme 13. C–H An thiocyanation of arenes (**II**) via the thiocyanogen (**I′**) and voltammetric test of the process efficiency.

3.1. C–H An Thiocyanation: General Patterns and Approaches

According to the above and developed [22,118–126] concepts, C–H An thiocyanation occurs during the anodic oxidation of the thiocyanate ion in the presence of arene, as a rule, via the thiocyanogen (Scheme 13, step **I**→**I′**). The latter either interacts with arene (step **I′** + **II**→**III**), or gives polythiocyanogen [127] (step **I′**→**IV**).

These processes were investigated by cyclic voltammetry (CV) [22,123,125,126]. Scheme 13 shows a typical CV curve of SCN$^-$. Peak **A** corresponds to the oxidation of thiocyanate ion **I** to thiocyanogen **I′**, which is detected on the reverse scan by its reduction peak **B** (**B**^{3}). If after the addition of arene **II**, peak **B** disappears (cf. peaks **B**^{1} and **B**^{3}) or decreases (cf. peaks **B**^{2} and **B**^{3}), then Ar–H **II** interacts with $(SCN)_2$, respectively, via the route **B**^{1} or **B**^{2} to form the target Ar–SCN **III**. If the peak **B** does not change, then Ar–H **II** does not react with $(SCN)_2$ (see peak B^3 and route B^3). In this case the main reaction product is polythiocyanogen **IV**.

Further, we proposed [122,123] the original system of approaches to the C–H An thiocyanation of arenes (Scheme 14) depending on the reactivity of arenes with respect to $(SCN)_2$: via the generation $(SCN)_2$ at the oxidation potential ($E_p{}^{ox}$) of thiocyanate ion (approach A, cf. Scheme 3, route II^b, and Scheme 13), via electrogeneration $(SCN)_2$ in the presence of $ZnCl_2$ activating additives (approach B) or via the generation of a highly reactive radical cation at $E_p{}^{ox}$ of arene (approach C, cf. Scheme 3, route I).



Scheme 14. Approaches and possible mechanisms of C–H An thiocyanation.

Approach A is used for arenes that react with $(SCN)_2$ (Scheme 13, routes B^1 and B^2), whereas approaches B and C are used for arenes that do not interact with non-activated $(SCN)_2$.

These patterns and approaches are considered below on the examples of C–H An thiocyanation of the practically useful [128–130] derivatives of 5-aminopyrazole and pyrazolo[1,5-a]pyrimidine and the original electrosynthesized 1-(hetero)arylpyrazoles [124,131].

3.2. *C–H An Thiocyanation of Pyrazole Derivatives*

The studies included a preliminary CV test in addition to electrosynthesis. The initial pyrazoles **1e–15e** and their thiocyanation products **1f–15f** are presented in Tables 4 and 5.

Table 4. C–H An thiocyanation of pyrazole derivatives (**Az-H**) via $(SCN)_2$ (approach A) [1].

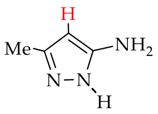
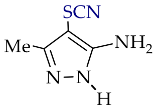
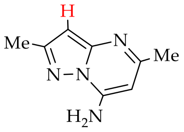
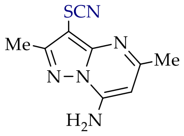
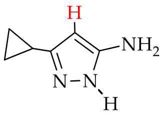
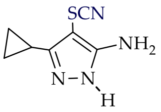
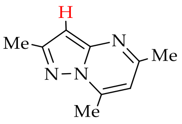
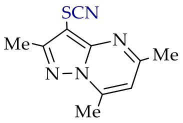
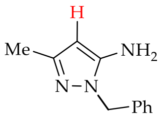
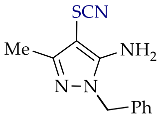
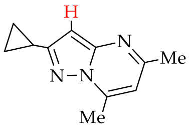
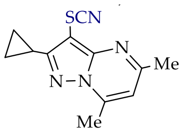
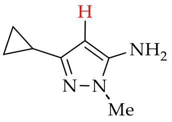
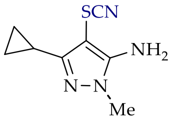
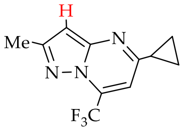
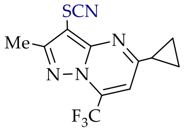
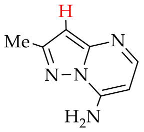
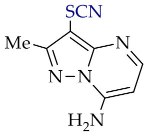
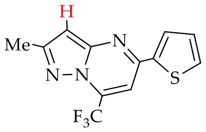
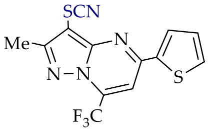
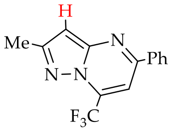
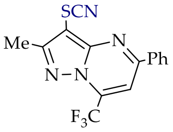
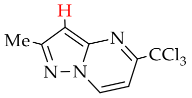
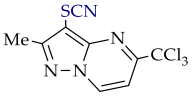
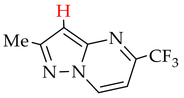
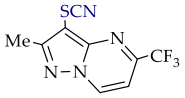
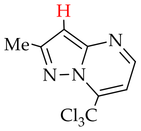
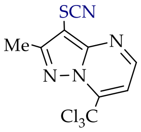
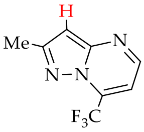
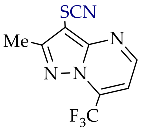
Entry	Az–H, Az–SCN (Yield, %) [22,122,123,126]		Entry	Az–H, Az–SCN (Yield, %) [22,122,123,126]	
1	 **1e**	 **1f** (83 ^{2,5,6}, 72 ^{2,4,6}, 74 ^{2,5,7}, 69 ^{3,5,7})	**6**	 **6e**	 **6f** (86 ^{2,4,6})
2	 **2e**	 **2f** (87 ^{2,5,6}, 78 ^{2,5,7}, 71 ^{3,5,7})	**7**	 **7e**	 **7f** (83 ^{2,4,6}, 80 ^{2,4,7}, 75 ^{2,5,7}, 77 ^{3,4,7}, 71 ^{3,5,7})
3	 **3e**	 **3f** (65 ^{2,4,6}, 57 ^{3,4,6})	**8**	 **8e**	 **8f** (85 ^{2,4,6}, 82 ^{2,5,6})

Table 4. *Cont.*

Entry	Az–H, Az–SCN (Yield, %) [22,122,123,126]		Entry	Az–H, Az–SCN (Yield, %) [22,122,123,126]	
4	 **4e**	 **4f** (75 [2,4,6], 68 [3,4,6])	9	 **9e**	 **9f** (75 [2,4,6], 66 [2,5,6])
5	 **5e**	 **5f** (89 [2,4,6], 64 [2,5,6])			

[1] Electrolysis in 50–85 mL of 0.1 M solution of $NaClO_4$ in MeCN-H_2O (entries 1–2), MeCN (entries 3–5, 7–9), MeCN–MeOH (entry 6), 20–25 °C, NH_4SCN (3–20 mmol), pyrazole (entries 1–5, 7–9) or its hydrochloride (entry 6) (1–6 mmol), divided cell (entries 1–2), undivided cell (entries 3–9), Q_t = 193–985 C, Q/Q_t = 1 (entries 1–6), Q/Q_t = 2 (entries 7–9). All yields were determined for the isolated and purified products; [2] CPE—controlled potential electrolysis (E_{anode} = 0.70–1.00 V); [3] GE—galvanostatic electrolysis (j_{anode} = 2.50–12.50 mA·cm^{-2}); [4] Pt electrodes; [5] GC electrodes; [6] milligram scale of electrosynthesis; [7] gram scale of electrosynthesis.

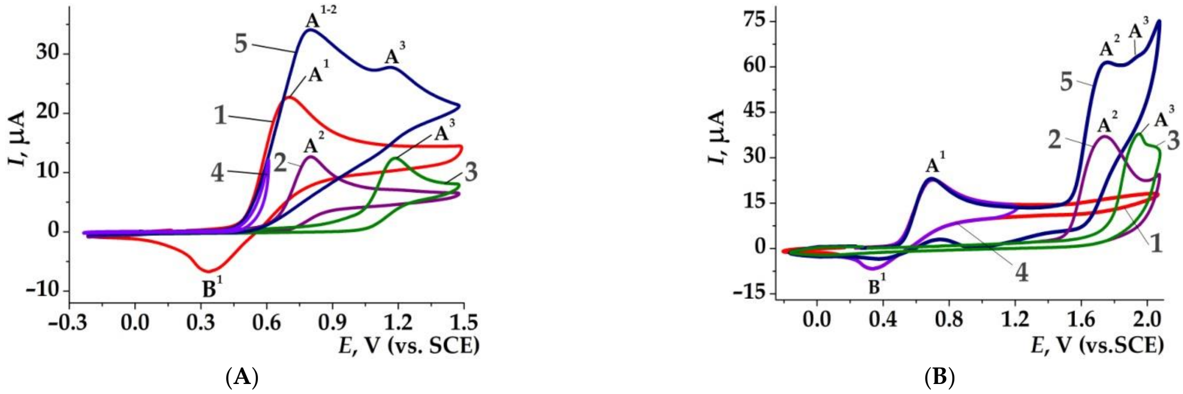
Table 5. C–H An thiocyanation of hardly oxidizable pyrazolo[1,5-a]pyrimidines (**Az-H**) (approaches B and C) [1].

Entry	Az–H (E_p^{ox}, V [2]), Az–SCN (Yield, %) [122,123]		Entry	Az–H (E_p^{ox}, V [2]), Az–SCN (Yield, %) [122,123]	
1	 **10e** (1.75)	 **10f** (81 [3,5], 65 [4,5], 60 [4,6])	4	 **13e** (1.85)	 **13f** (80 [3,5], 62 [4,5], 55 [4,6])
2	 **11e** (1.77)	 **11f** (79[3,5], 60[4,5])	5	 **14e** (1.85)	 **14f** (73 [3,5], 60 [4,5])
3	 **12e** (1.79)	 **12f** (77 [3,5], 60 [4,5], 52 [4,6])	6	 **15e** (1.88)	 **15f** (69 [3,5], 63 [4,5], 47 [4,6])

[1] Electrolysis in 60 mL 0.1 M solution of $NaClO_4$ in MeCN, 20–25 °C, undivided cell, Q_t = 193 C. All yields was determined for the isolated and purified products; [2] it was determined by CV (working electrode—Pt, reference electrode—SCE, ν = 0.10 V·s^{-1}); [3] Approach B: KSCN (4 mmol), $ZnCl_2$ (2 mmol), pyrazole (1 mmol), CPE (E_{anode} = 1.00 V), Q_t =193 C, Q/Q_t = 3; [4] Approach C: NH_4SCN (4 mmol), pyrazole (1 mmol), CPE (E_{anode} = 1.75–1.88 V), Q/Q_t = 3; [5] Pt electrodes; [6] GC electrodes.

3.2.1. CV studies and the Choice of Optimal Approach

Figure 1 shows CV curves of NH_4SCN and its mixtures with 3-methyl-1*H*-pyrazol-5-amine (**1e**), 2-methyl-5-thiophen-2-yl-7-(trifluoromethyl) pyrazolo[1,5-a]pyrimidine (**10e**), as well as curves of individual compounds and their thiocyanato products (**1e**,**10e**,**1f**,**10f**) [125,126]. The CV of NH_4SCN (curve 1, Figure 1A,B) has the anodic peak A^1 (E_p^{ox} = 0.70 V) of the thiocyanate ion and a cathodic peak B^1 (E_p^{red} = 0.34 V) of the thiocyanogen. The peak B^1 disappeared after the addition of pyrazole **1e** and did not change after the addition of pyrazole **10e** (cf. corresponding curves 1 and 4). This clearly shows that pyrazole **1e** reacts rapidly with $(SCN)_2$ (see Scheme 13, route B^1) and approach A (Scheme 14) is suitable for its thiocyanation. From the other side, the pyrazole **10e** does not react with $(SCN)_2$ and approaches B and C may be suitable for its thiocyanation. Note also that on full scans, peaks A^3 of thiocyanates **1f**,**10f** were observed, in addition to the peaks $\mathbf{A^2}$ of pyrazoles **1e**,**10e** (see curve 5, Figure 1A,B).



(**A**) (**B**)

Figure 1. CV curves on Pt working electrode in 0.1M $NaClO_4$ in MeCN, $\nu = 0.10\ V{\cdot}s^{-1}$. (**A**) NH_4SCN (0.002M)—1; 3-methyl-1*H*-pyrazol-5-amine **1e** (0.002M)—2; 3-methyl-4-thiocyanato-1*H*-pyrazol-5-amine **1f** (0.002M)—3; mixture NH_4SCN/azole **1e** (1:1) with the reverse scan from 0.60 V—4; the same on the reverse scan from 1.45V—5; (**B**) NH_4SCN (0.002M)—1; 2-methyl-5-thiophen-2-yl-7-(trifluoromethyl)pyrazolo[1,5-a]pyrimidine **10e**—2; 2-methyl-3-thiocyanato-5-thiophen-2-yl-7-(trifluoromethyl)pyrazolo[1,5-a]pyrimidine **10f**—3; mixture NH_4SCN/ azole **10e** (1:1) on the reverse scan from 1.20 V—4; the same on the reverse scan from 2.10 V—5.

3.2.2. Electrosynthesis

Electrolyses were carried out in 0.1M solution of $NaClO_4$ in MeCN (MeCN–H_2O) in undivided or divided cells (UC or DC) in controlled-potential or galvanostatic mode (CPE or GE), passing a theoretical or excess amounts of electricity (Q/Q_t = 1–3). Pt or glassy carbon (GC) electrodes were used.

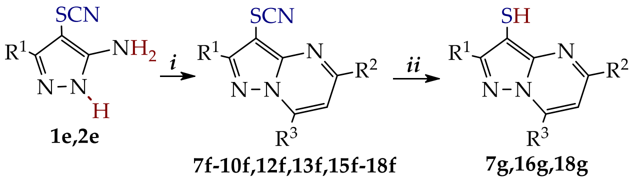
The amino compounds **1e–6e** gave thiocyanates **1f–6f** with yields 64–89% (under CPE at $E_p{}^{ox}{}_{SCN^-}$) and 57–71% (under GE) at Q/Q_t = 1 (Table 4, entries 1–6) when implementing approach A (see Scheme 14).

From the less reactive pyrazolo[1,5-a]pyrimidines **7e–9e**, products **7f–9f** were obtained with yields 66–85% at Q/Q_t = 2 (entries 7–9). The electrode material affected things differently: the yield of thiocyanate **2a** (entry 1) was 83% (GC) and 72% (Pt), while the yield of thiocyanate **2g** (entry 7) was 64% (GC) and 89% (Pt). Most of the processes (entries 3–9) were successfully carried out in an undivided cell. The possibility of scaling the process was also shown (entries 1, 2 and 7).

It was noted [121–123,125] that approach A is not suitable for the thiocyanation of hardly oxidizable ($E_p{}^{ox}$ > 1.70 V) pyrazoles **10e–15e** with acceptor substituents (Table 5) and leads to trace amounts of target thiocyanates **10f–15f** and polythiocyanogen (see Scheme 13, route B^3). In this case, the process proceeds quite efficiently with an increase in the reactivity of the thiocyanogen (Scheme 14, approach B) or the initial pyrazole (approach C). As a result, CPE in the presence of $ZnCl_2$ activating additives (approach B) allowed us to obtain products **10f–15f** with yields 69–81% [121,123], while metal-free CPE at $E_p{}^{ox}{}_{AzH}$ with Q/Q_t = 3 (approach C) also led to the products **10f–15f** with smaller yields of 47–65% [122,123].

Note that the possibility of approach C realization can also be tested by CV: a decrease in the peak B^1 is observed on the full scan (cf. curves 5 and 1, Figure 1B), which corresponds to the interaction of the thiocyanate ion and the pyrazole cation radical via the ECE mechanism [122,123,132] (see Scheme 14, approach C, and Scheme 3, route I).

In addition to approaches A–C, an equally effective approach was developed [41] based on the HCl-catalyzed condensation of previously obtained 4-thiocyanatopyrazoles **1e**, **2e** (see entries 1 and 2, Table 4) with 1,3-dicarbonyl compounds or their derivatives (Scheme 15). As a result, 3-thiocyanatopyrazolo[1,5-a]pyrimidines both without substituents and with donor (acceptor) substituents in the pyrimidine ring were obtained with yields of 77–96% [126].



7f (7g): R^1=R^2=R^3=Me; 96% (69%)
8f: R^1=*cyclo*-Pr, R^2=R^3=Me; 92%
9f: R^1=Me, R^2=*cyclo*-Pr, R^3=CF_3; 87%
10f: R^1=Me, R^2=thienyl, R^3=CF_3; 91%
12f: R^1=Me, R^2=H, R^3=CCl_3; 89%
13f: R^1=Me, R^2=Ph, R^3=CF_3; 84%
15f: R^1=Me, R^2=H, R^3=CF_3; 78%
16f (16g): R^1=Me, R^2=R^3=H; 77% (77%)
17f: R^1=*cyclo*-Pr, R^2=R^3=H; 84%
18f (18g): R^1=R^2=Me, R^3=CF_3; 71% (61%)

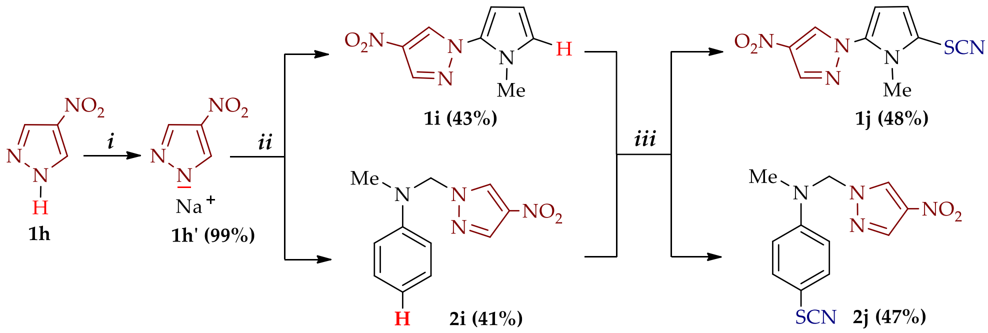
i. Azole **1e**,**2e** (5 mmol), $R_2C(O)CHC(O)R_3$ or its derivative (6 mmol), H_2O (**7f**,**8f**,**16f**,**17f**), H_2O-EtOH (1:4) (**9f**,**12f**,**15f**,**18f**) or EtOH (**10f**,**13f**), HCl, 20-25 °C, 24 h. ***ii.*** H_2O, HCl, argon or nitrogen barbotation, 20-25 °C, 72 h.

Scheme 15. Synthesis of 3-thiocyanatopyrazolo[1,5-a]pyrimidines and pyrazolo[1,5-a]pyrimidine-3-thiols.

Developing this direction, the opportunity of transformation of the SCN group into the SH group [94,123] was shown, which opens the way to thiols as promising nucleophiles for C–H functionalization (e.g., see [133–135]). Hydrolysis with HCl was the most effective (yields of thiols **7g**, **16g**, **18g** were 61–77%), while the use of chemical reductants or strong acids ($LiAlH_4$, $NaBH_4$, Zn in AcOH, $HClO_4$, H_2SO_4) was ineffective.

Thus, a series of thiocyanates of substituted pyrazoles and pyrazolo[1,5-a]pyrimidines were obtained on the basis of electrolysis of the "thiocyanate ion/pyrazole" mixture.

In addition, during the development of research on the electrosynthesis of aryl thiocyanates [22] and N-arylpyrazoles [131,136–138] we showed [124] the possibility of synthesizing new molecules with pyrazole and thiocyanate fragments (Scheme 16) as promising hybrid polyfunctional [139] structures.



i. Na, dry MeOH, argone, 8h; ***ii***. Electrolysis in 60 mL 0.1 M $NaClO_4$ in MeCN-MeOH, 30 °C, Pt electrodes, divided cell, Q_t=386 C, 4-nitropyrazolate **1h'** (4 mmol), *N*-methylpyrrole or *N*,*N*-dimethylaniline (2 mmol), E_{anode}=1.28 V or 0.75 V, Q/Q_t=1 or 1.5; ***iii***. Electrolysis in 60 mL 0.1 M $NaClO_4$ in MeCN, 25 °C, Pt electrodes, divided cell, Q_t=386 C, E_{anode}=0.70 V, NH_4SCN (8 mmol), N-arylazole **1i** or **2i** (2 mmol), Q/Q_t=2 or 1.5

Scheme 16. N–H An arylation of 4-nitropyrazole followed by C–H An thiocyanation of resulting N-arylazoles.

The N–H arylation of pyrazole **1h** was carried out by activating its N–H bond (i) followed by the introduction of electrolysis with N-methylpyrrole or N,N-dimethylaniline (ii). In the latter case, the reaction proceeded selectively at the Me group without affecting the aromatic ring. Subsequent C–H An thiocyanation (iii) of the isolated N-arylazoles **1i**, **2i** led to the target products **1j**, **2j**.

3.3. *Antifungal and Antibacterial Activity of Thiocyanated Pyrazole Derivatives*

Tests for antifungal (*C. albicans*, *A. niger*) and antibacterial (*S. aureus*, *E. coli*) activity [91,94,123,124] showed that thiocyanate-pyrazoles are more active against fungi than bacteria. The greatest activity is observed against *A. niger* at thiocyanate **7f** [94] and thiocyanatoazolylaniline **2j** [124], whose minimum inhibitory concentration (MIC) is

0.24–0.48 μg/mL (it is superior to the antifungal drugs amphotericin B and fluconazole and is comparable to itraconazole).

The contribution of thiocyanate and pyrazole fragments to antifungal and antibacterial activity was clearly shown in the individual examples (Figure 2). Thus, the activity of compound **1j** increased more than 2000-fold for *A. niger* and more than 16-fold for *C. albicans* after the introduction of the SCN group. The presence of 4-nitropyrazole in 4-thiocyanatoaniline **2j′** provided a selective increase in antifungal activity by a factor of 16–64, while *N*-arylazole **2i** was inactive in all cases.

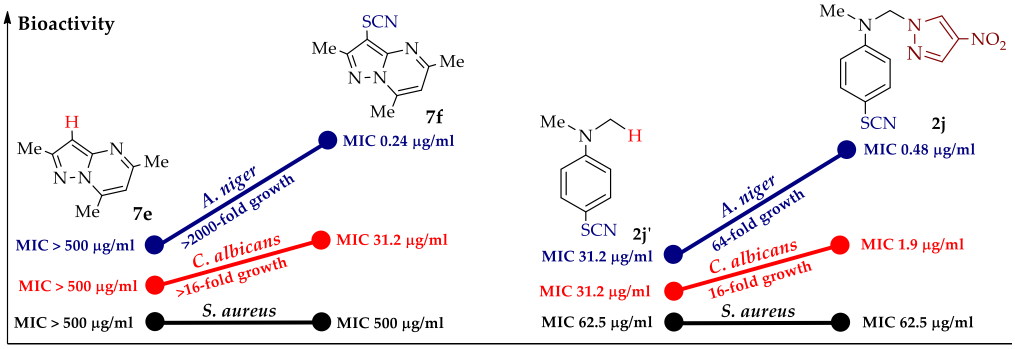
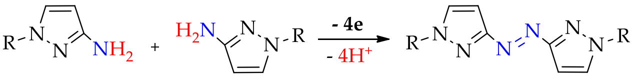


Figure 2. Effect of thiocyanate and pyrazole fragments on antifungal and antibacterial activity.

Therefore, this Section is devoted to the efficient C–H An thiocyanation of various pyrazole derivatives (in some cases, their N–H An arylation), leading to pharmacologically active target mono- and polyfunctional products. The next Section is devoted to the N–H functionalization of amino pyrazoles followed by their N–N coupling and obtaining azopyrazoles.

4. (Electro)oxidative N–N Coupling of Aminopyrazoles

Azoarenes are widely used in practice: from dyes and pharmaceuticals [140–142] to reagents in syntheses [143,144] and energy-rich materials [145,146]. One of the most popular methods for the synthesis of azoarenes is the oxidation of corresponding amines (Scheme 17), predominantly by chemical oxidants ($BaMnO_4$ [147], $Pb(OAc)_4$ [148], HgO [149], K_2FeO_4 [150], TCICA [151], t-BuOI [152]) or oxidation systems (CuBr-pyridine-O_2 [153], I_2-t-BuOOH [154], t-BuOCl-NaI [155]). The synthesis of polyfunctional azopyrazoles by silver catalyzed cascade conversion of diazo compounds [156] is also of interest.

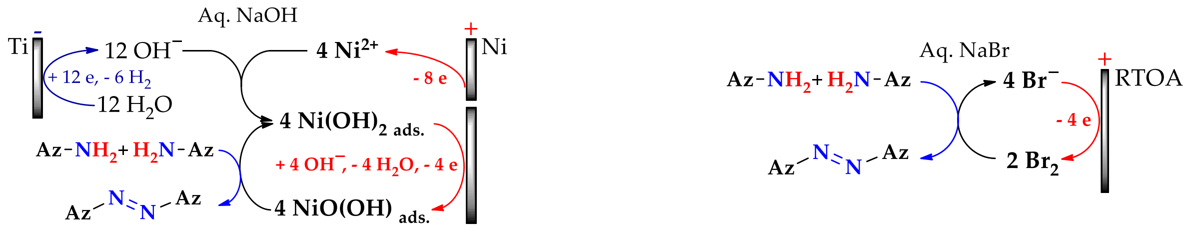


Scheme 17. Synthesis of azopyrazoles by (electro)oxidative N–N coupling of aminopyrazoles.

At the same time, a more promising electrochemical approach is poorly studied. In particular, electrosyntheses of azobenzene on the Pt anode [157,158] or N,N′-bis(morpholino)diazene on the NiO(OH) anode [159] are described. Note that NiO(OH) is one of the popular electrogenerated redox mediators [80,159]. The use of such redox-mediators is a trend in modern electroorganic chemistry [18], since it allows the processes to be carried out under milder conditions, increasing their efficiency and selectivity. This Section describes the original approaches to the synthesis of azopyrazoles using electrogenerated redox mediators NiO(OH) [160–162] and Br_2 [163], or electrogenerated hypohalites as oxidants [164,165].

4.1. *(Electro)oxidative N-N Coupling of Aminopyrazoles: Approaches and General Patterns*

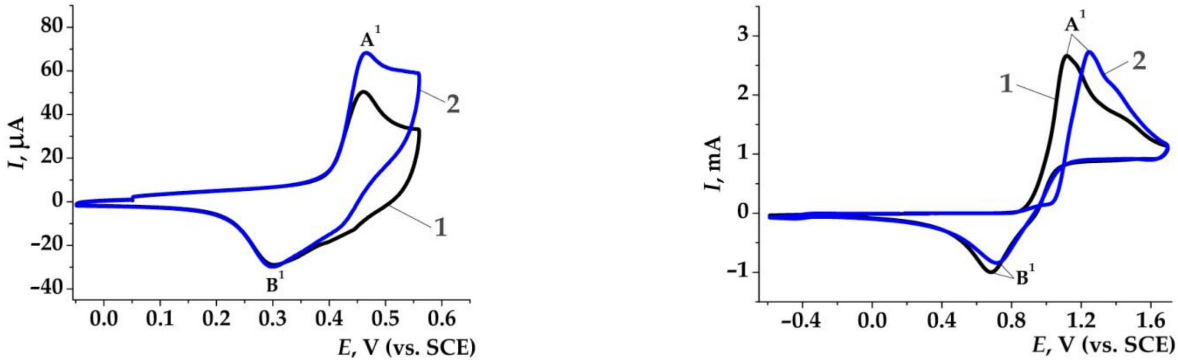
One-stage Approach A (Scheme 18) is carried out in alkaline medium via the anodic dissolution of the Ni and the formation of adsorbed $Ni(OH)_2$, followed by its anodic oxidation to adsorbed NiO(OH). It oxidizes aminopyrazoles (**Az–NH$_2$**) to azopyrazoles (**Az–N = N–Az**) and forms $Ni(OH)_2$, after which the cycle repeats [80,161]. In Approach B, the metal-free oxidant is Br_2 [164], which is effectively electro(re)generated on the ruthenium–titanium oxide anode (RTOA).



(**A**) (**B**)

Scheme 18. One-stage redox-mediated N–N coupling of aminopyrazoles using electrogenerated NiO(OH) (**Approach A**) and Br_2 (**Approach B**).

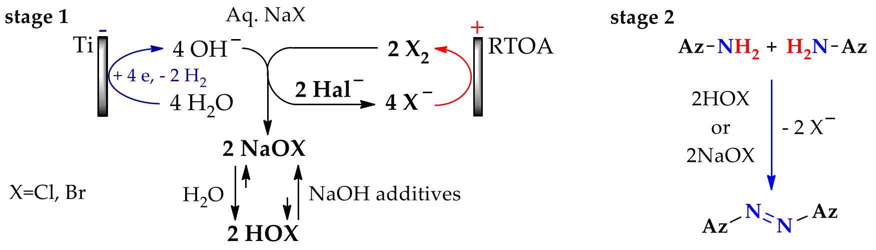
In addition, special voltammetric tests showed that an increase in the $Ni(OH)_2$ peak (Figure 3, A, peak A^1, E_p^{ox} = 0.46 V) or a decrease in the Br_2 peak (Figure 3B, peak B^2, E_p^{red} = 0.69 V) after the adding of aminopyrazole is proportional to the process efficiency [162,164].



(**A**) (**B**)

Figure 3. CV curves, ν = 0.10 $V \cdot s^{-1}$. (**A**) On Ni working electrode in 0.2M aq. NaOH: electrogenerated $Ni(OH)_2$—1; after addition of 1-methyl-1*H*-pyrazol-3-amine **1k** (0.002M)—2; (**B**) on Pt working electrode in 1M aq. $NaNO_3$: NaBr (0.3M)—1; after addition of 1-methyl-1*H*-pyrazol-3-amine **1k** (0.002M)—2.

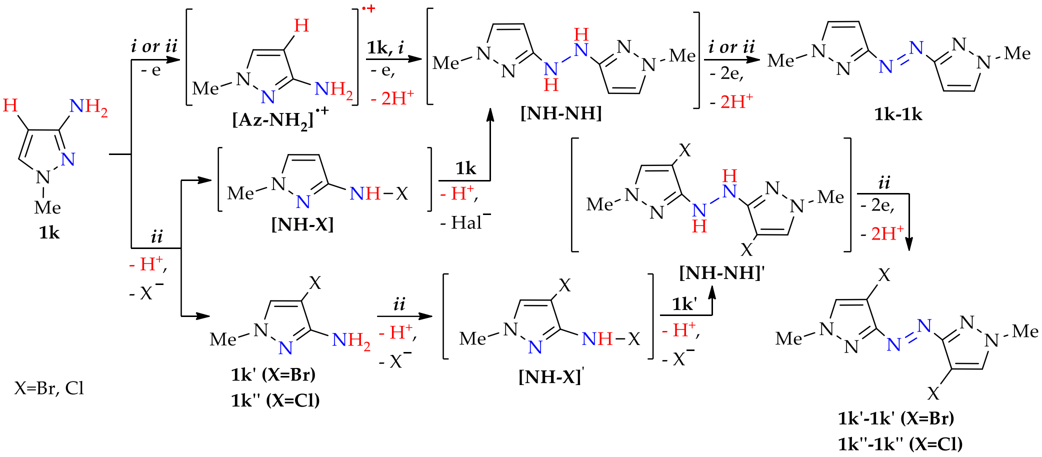
Two-stage approaches (Scheme 19) include preliminary electrogeneration of hypogalites followed by addition of aminopyrazoles [164,165]. Note, that hypohalites exist in equilibrium forms: predominantly HOCl (HOBr) in a neutral medium, and predominantly NaOCl (NaOBr) after adding NaOH (approaches C, D, C′, D′, respectively).



Scheme 19. Two-stage N–N coupling of aminopyrazoles using electrogenerated HOCl (HOBr) or NaOCl (NaOBr) (Approaches C, D, C′, D′, respectively).

According to the data [80,152,154,155,159,163–165], the possible mechanisms (Scheme 20) involve the oxidation of 1-methyl-1*H*-pyrazol-3-amine **1k** (step **1k**→$\mathbf{[Az–NH_2]^{\cdot +}}$) or its

N–H halogenation (step **1k**→**[NH–X]**) followed by N–H amination to hydrazopyrazole **[NH–NH]** and its oxidation to the target azopyrazole **1k–1k** (see also Schemes 3 and 9).



i: NiO(OH) in aq. NaOH (Approach A); or NaOCl (Approach C′); or NaOBr (Approach D′)
ii: Br_2 in H_2O (Approach B); or HOCl (Approach C); or HOBr (Approach D)

Scheme 20. N–N coupling of aminopyrazoles (possible mechanisms).

When Br_2 and HOX are used, C–H halogenation of aminopyrazole **1k** also occurs (step **1k**→**1k′**(**1k″**), see Scheme 9), followed by the formation of halogenated azopyrazole (steps **1k′**→**[NH–X]′**→**[NH–NH]′**→**1k′–1k′**(**1k″–1k″**)). These patterns are consistent with the experimental results below.

4.2. Synthesis of Azopyrazoles

Approach A is most versatile and allows us to obtain target azopyrazoles with yields of 52–88% (Table 6, entries 1–6, 8–11). On the contrary, approaches B, C and D are more suitable for 4-substituted pyrazoles (entries 2, 6 and 7) or pyrazole with acceptor (CF_3) group (entry 12), where the yields of the corresponding azo products were 62–93%.

Table 6. N–N homo-coupling of aminopyrazoles (Az–NH_2) using approaches A, B, C (C′), D (D′) [1].

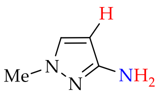
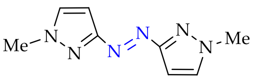
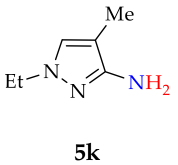
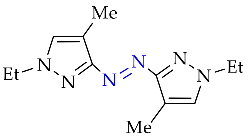
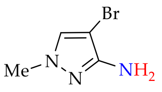
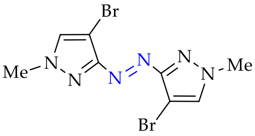
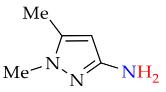
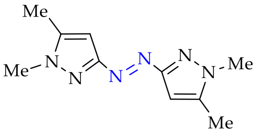
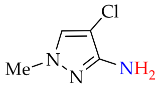
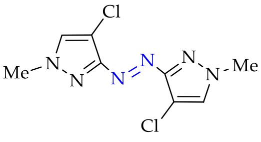
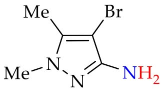
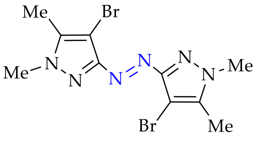
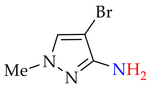
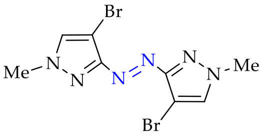
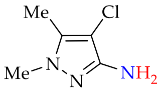
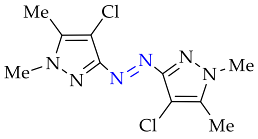
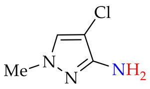
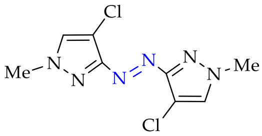
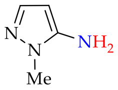
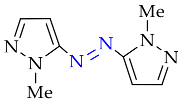
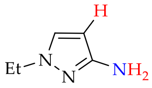
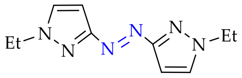
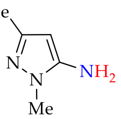
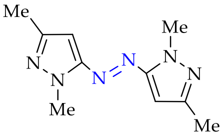
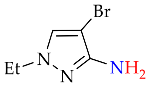
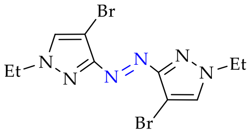
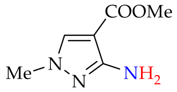
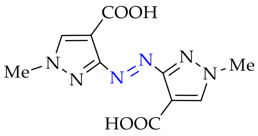
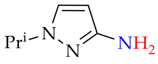
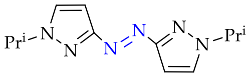
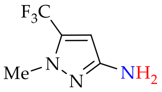
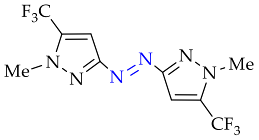
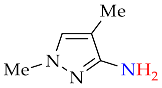
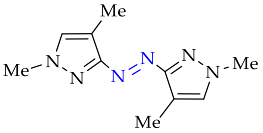
Entry	Az–NH_2, Az–N=N–Az and Other Products (Yield, %) [161,163,165]		Entry	Az–NH_2, Az–N=N–Az and Other Products (Yield, %) [161,163,165]	
1	 **1k**	 **1k-1k** (82 [2], 34 [4], 72 [5], 40 [6], 75 [7])	7	 **5k**	 **5k-5k** (86 [3])
	 **1k′** (59[3], 22[4], 1[5])	 **1k′-1k′** (28[3], 48 [4])	8	 **6k**	 **6k-6k** (79[2], 2 [6])
	 **1k″** (7[6], 5[7])	 **1k″-1k″** (40 [6], 14 [7])		 **6k′** (3 [3])	 **6k′-6k′** (80 [3])

Table 6. *Cont.*

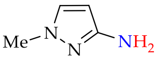
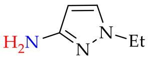
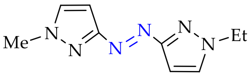
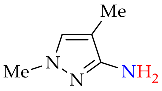
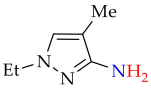
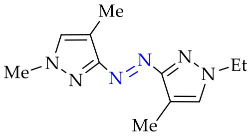
Entry	Az–NH$_2$, Az–N=N–Az and Other Products (Yield, %) [161,163,165]		Entry	Az–NH$_2$, Az–N=N–Az and Other Products (Yield, %) [161,163,165]	
2	 **1k′**	 **1k′-1k′** (77 [2], 62 [4])		 **6k″** (6)	 **6k″-6k″** (79 [6])
3	 **1k″**	 **1k″-1k″** (87 [2])	9	 **7k**	 **7k-7k** (55 [2])
4	 **2k**	 **2k-2k** (71[2], 73[5])	10	 **8k**	 **8k-8k** (52 [2])
	 **2k′** (2[5])	 **2k′-2k′** (6 [5])	11	 **9k**	 **9k-9k**[8] (67 [2])
5	 **3k**	 **3k-3k** (86 [2])	12	 **10k**	 **10k-10k** (93 [4], 86 [6])
6	 **4k**	 **4k-4k** (88 [2], 62 [3], 70 [4])			

[1] Electrolysis in 100 mL of supporting electrolyte, 20–25 °C, undivided cell galvanostatic electrolysis; [2] Approach A: 0.5M aq. NaOH, NiO(OH) anode, pyrazole (3 mmol), j_{anode} = 6 mA·cm^{-2}, Q_t = 579 C, Q/Q_t = 1–4; [3] Approach B: 2M aq. NaBr, RTOA, pyrazole (3 mmol), j_{anode} = 100 mA·cm^{-2}, 48% HBr additives during electrolysis until reaching pH~7 (entries 1, 8), Q_t = 579 C, Q/Q_t = 1–4; [4] Approach C: 1. electrogeneration of NaOBr (HOBr) in 2M aq. NaBr, RTOA, j_{anode} = 100 mA·cm^{-2}, Q = 661–1983 C; 2. pyrazole (2 mmol), NaOBr (HOBr) (2–4 mmol), 5 h; [5] Approach C′: see Approach C, but with NaOH (6 mmol) additives; [6] Approach D: 1. electrogeneration of HOCl (NaOCl) in 4M aq. NaCl, RTOA, j_{anode} = 161.5 mA·cm^{-2}, Q= 588–1764 C; 2. Pyrazole (2 mmol), HOBr (NaOBr) (2–4 mmol), 5 h; [7] Approach D′: see Approach D, but with NaOH (6 mmol) additives; [8] it was identified after preparation and isolation of the corresponding methyl ester.

Nevertheless, approaches C′ and D′ (entries 1 and 4) allow to obtain rather selectively azopyrazoles **1k–1k** and **2k–2k** (yields 72–75%), and approaches C and D (entry 8) open the way to azohalogenopyrazoles **6k″–6k″** and **6k″–6k″** (yields 79–80%).

Moreover, the approach A is useful for previously unexplored chemical and electrochemical N–N cross-coupling of aminopyrazoles [162] (Table 7), and yields of the target azo compounds **1k–2k** and **4k–5k** were 48–50%. Such results create prospects for obtaining useful multifunctional azo compounds [152,156].

Table 7. N–N cross-coupling of aminopyrazoles (Az–NH_2) using approach A [1].

Entry	Az^1–NH_2	H_2N–Az^2	Az^1–N=N–Az^2	Yield, %
1	 **1k**	 **2k**	 **1k-2k**	50 (**1k-2k**) 36 (**1k-1k**) 37(**2k-2k**)
2	 **4k**	 **5k**	 **4k-5k**	48 (**4k-5k**) 29 (**1k-1k**) 23 (**2k-2k**)

[1] Electrolysis in 100 mL of 0.5 M aq. NaOH, 20–25 °C, undivided cell,; [2] Approach A: NiO(OH) anode, Ti cathode, pyrazole (1.5 mmol), galvanostatic electrolysis (j_{anode} = 6 mA·cm^{-2}), Q = $2Q_t$ = 579 C.

5. Conclusions

This review is the first step in summarizing the data on promising, but poorly studied electrooxidative functionalization of C-H and N-H bonds in pyrazole derivatives. It paves the way for the efficient synthesis of C-Cl, C-Br, C-I, C-S and N-N coupling products using cheap, affordable and environmentally promising electric currents.

Additional advantages are the predominantly galvanostatic electrolysis mode and the reusability of commercially available electrodes, salts and solvents, as well as the gram-scalability of the processes. In half of the cases, a simple isolation of pure target products without chromatography is also possible. Moreover, the key regularities of the corresponding processes are considered, including the dependence of the efficiency of functionalization of pyrazoles on their structure and oxidation potential. An increasingly important role is played by cyclic voltammetry, which makes it possible both to study mechanisms and to predict the efficiency of synthesis.

All this makes the electrooxidative functionalization of pyrazole-type compounds very viable for further application and development.

Author Contributions: Conceptualization, V.A.P.; writing—original draft preparation, V.A.K. and V.A.P.; writing—review and editing, B.V.L., V.L.S., A.S.K. and S.V.N. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by the Russian Science Foundation. Grant 19-73-20259.

Conflicts of Interest: The authors declare no conflict of interest.

Sample Availability: Samples of the compounds **2b**, **4b**, **9b–13b**, **1c–4c**, **6c**, **8c**, **10c–13c**, **1d–4d**, **8d**, **10d–14d**, **1f–15f**, **1j**, **2j**, **1k-1k–8k-8k** are available from the authors.

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