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PII: S0040-4039(18)30727-5
DOI: https://doi.org/10.1016/j.tetlet.2018.05.089
Reference: TETL 50036

To appear in: *Tetrahedron Letters*

Received Date: 29 March 2018
Revised Date: 22 May 2018
Accepted Date: 30 May 2018

Please cite this article as: Lyalin, B.V., Sigacheva, V.L., Kokorekin, V.A., Petrosyan, V.A., Electrosynthesis of azopyrazoles *via* the oxidation of *N*-alkylaminopyrazoles on a NiO(OH) anode in aqueous alkali – a green method for *N-N* homocoupling, *Tetrahedron Letters* (2018), doi: https://doi.org/10.1016/j.tetlet.2018.05.089

Tetrahedron Letters
journal homepage: www.elsevier.com

Electrosynthesis of azopyrazoles *via* the oxidation of *N*-alkylaminopyrazoles on a NiO(OH) anode in aqueous alkali – a green method for *N-N* homocoupling

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
N-alkylaminopyrazoles
azopyrazoles
N-N coupling
NiO(OH) anode
electrocatalytic (mediated) oxidation

ABSTRACT

A nickel oxyhydroxide [NiO(OH)] anode was exploited to develop a new synthetic route for the electrocatalytic *N-N* homocoupling of *N*-alkylaminopyrazoles in an alkaline aqueous medium. The advantages of this green electrochemical methodology include low cost, atom economy and high yields.

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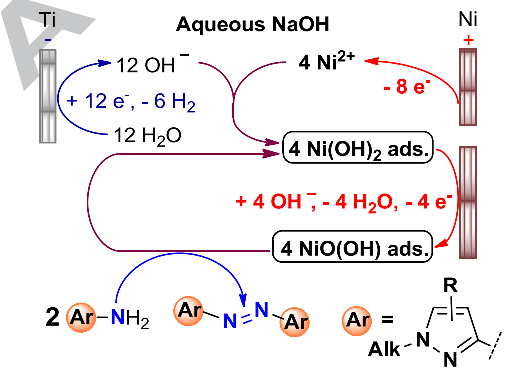
New environmentally friendly methods for synthesizing practically useful compounds based on atom economical reactions are a research area of significant interest. The development of such methods is undoubtedly important for obtaining aromatic azo compounds that have a wide spectrum of practical applications: from dyes and pharmaceuticals[1-3] to reagents in syntheses[4,5] and energetic materials.[6,7] Despite numerous efforts towards the synthesis of azo derivatives, significant challenges still remain. For example, the oxidation of aryl amines are usually carried out with excess amounts of heavy metal salts such as manganese,[8] lead,[9] mercury[10] or iron.[11] In these and a number of other studies[12-16] on the oxidative syntheses of azoarenes, ecological problems still remain.

In this regard, electrochemical methods using an anode as a green oxidizing agent are of obvious interest[17] (e.g. *N-N* homocoupling realizations[18-19]). Moreover, the mainstream methods in modern electroorganic chemistry are electrocatalytic processes involving mediators that are regenerated during electrolysis.[20] At the same time, the electrosynthesis of azoarenes based on electrocatalytic (mediated) oxidation of aminoarenes is a promising but poorly studied problem. The unique possibilities of electrogenerated NiO(OH) as a redox mediator, formed on a Ni anode during electrolysis in an aqueous alkaline medium are attractive.[21-23] Using this method enables low cost, ecological and easily scalable oxidation processes to be performed meeting the green chemistry principles.[24] A series of such syntheses of carboxylic acids from alcohols or carbonyl compounds using a NiO(OH) anode were realized by us previously.[25-29]

As the first example of azoarene synthesis on a NiO(OH) anode, we have realized the electrocatalytic conversion of aminofurazans to azofurazans.[30] Also, we recently demonstrated the possibility of azopyrazole electrosynthesis by the NiO(OH)-mediated transformation of *N*-alkylaminopyrazoles.[31] However, the latter process still required optimization because the yields did not exceed 40%. In this paper, we have identified the key factors of this process which allowed us to increase its efficiency. Therefore, the present work represents the next stage in the development of new methodology for the mediated electrosynthesis of azoheteroarenes.

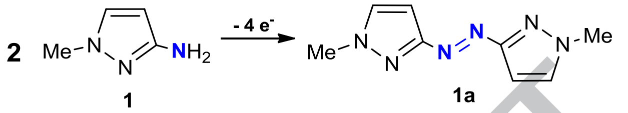
As showed earlier,[22,31] electrolysis in an undivided cell with a sacrificial Ni anode and a Ti cathode in an alkaline medium in the presence of a suitable substrate can be described by Scheme 1. During such processes, the adsorbed $Ni(OH)_2$ species formed on the anode surface are easily oxidized to adsorbed NiO(OH), which plays the role of a redox mediator.[32] The reaction of NiO(OH) with an oxidizable substrate leads to the target product and regenerates the $Ni(OH)_2$ species. This process was classified[22] as electrocatalysis with a regenerable catalyst (mediator). It was noted,[22] that the efficiency of the process depends on the interaction kinetics of NiO(OH) with the initial substrate.



Scheme 1. NiO(OH)-mediated electrosynthesis of azopyrazoles (general scheme).

Initially, we studied the behavior of *N*-alkylaminopyrazoles on a NiO(OH) anode in an aqueous alkaline medium using 1-methyl-3-amino-1*H*-pyrazole (**1**) as a model substrate. The yield of 1,2-*bis*(1-methyl-1*H*-pyrazol-3-yl)diazene (**1a**) was dependent on the concentration of aminopyrazole **1** (Entries 1–3, Table 1) and on the anodic current density (j_a, Entries 2, 4, 5). Therefore, the maximum yield (82%) was achieved using a 0.03 M concentration of aminopyrazole **1** and j_a = 6 mA·cm^{-2} (Entry 2).

Table 1. Effect of the aminopyrazole **1** electrolysis conditions on its electrocatalytic conversion to azopyrazole **1a**.[a]



Entry	Azole **1** (M)	j_a (mA·cm^{-2})	Conversion of azole **1** (%)	Yield of azopyrazole **1a** (%)
1	0.015	6	41	26
2	0.03	6	100	82
3	0.06	6	85	77
4	0.03	3	93	78
5	0.03	16	64	49

[a]Galvanostatic electrolysis, NiO(OH) coated anode, Ti cathode, C_{NaOH} = 0.5 M, Q = Q_t = 2 F per mole of aminopyrazole **1**, T = 25°C.

It can be assumed that in the case of low concentrations of aminopyrazole **1**, the rate of mediated oxidation is slow. This fact is confirmed by the moderate conversion (Entry 1, Table 1). The process rate and the yield of the target product **1a** increases with the concentration of aminopyrazole **1** (Entries 2, 3).

As with varying the aminopyrazole **1** concentration (see above), with an increase in j_a from 3 mA·cm^{-2} (Entry 4) to 6 mA·cm^{-2} (Entry 2), the yield of azopyrazole **1a** increases, and then sharply decreases (Entry 5). It can be assumed that for $j_a > 6$ mA·cm^{-2} the anode potential increases, which is accompanied by a dramatic increase in the contribution of the side process (Scheme 2).

$$4\,OH^- \xrightarrow{-\,4e} 2\,H_2O + O_2$$

Scheme 2. Anodic oxidation of the hydroxide ion (side process).

Thus, the concentration of the aminopyrazole and the current density are key factors that allowed us to optimize the electrocatalytic transformation of aminopyrazole **1** to azo product **1a** (Entry 2). These factors also include the amount of passing electricity (see below).

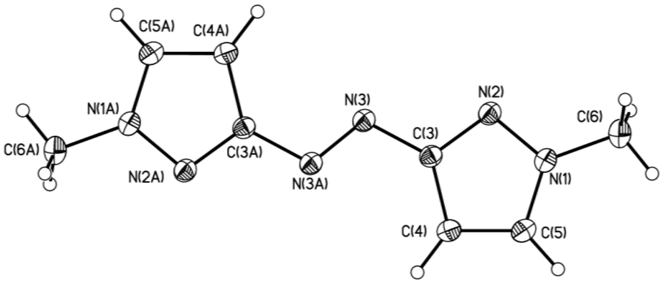


Figure 1. General view of azopyrazole **1a** with representation of atoms by thermal ellipsoids (p=50%).

According to the X-Ray diffraction data (Fig. 1), azopyrazole **1a** has *E* configuration about the N(3)=N(3A) bond as in *(E)*-1,2-*bis*(4-iodo-3-methyl-1-phenyl-1*H*-pyrazol-5-yl)diazene.[15]

Some interesting results were obtained by CV using a specially prepared NiO(OH) working electrode.[33] The CV curve **a** (Fig. 2.1) demonstrates a quasi-reversible peak (E_p^{ox} = 0.46 V) of the $Ni(OH)_2$ to NiO(OH) oxidation process. In agreement with the data,[30,34] the reverse scan of this peak leads to the appearance of a cathodic peak (E_p^{red} = 0.30 V) which corresponds to the NiO(OH) to $Ni(OH)_2$ reduction. It can be seen from curve **b** (Fig. 1.1) that the addition of aminopyrazole **1** to the background solution increases the height of the anodic peak by 44% due to the electrocatalytic oxidation (Scheme 1) of this pyrazole.

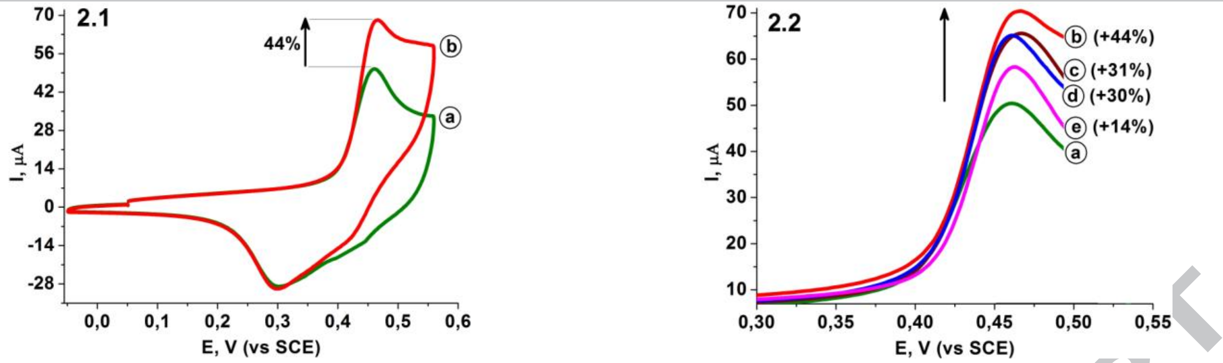


Figure 2. Cyclic voltammograms of $Ni(OH)_2$ electrogenerated on a Ni electrode in 0.2 M aqueous NaOH. **2.1** **a** – CV curve of $Ni(OH)_2$; **b** – CV curve of $Ni(OH)_2$ with the addition of aminopyrazole **1**. **2.2** **a** – an enlarged fragment of the $Ni(OH)_2$ oxidation peak; **b**, **c**, **d**, **e** – an enlarged fragment of the $Ni(OH)_2$ oxidation peak with the addition of aminopyrazoles **1**, **4**, **5**, **7** (see Table 2), respectively. $C_{1,4,5,7}$ = 0.002 M, ν = 0.1 $V \cdot s^{-1}$, 25 °C.

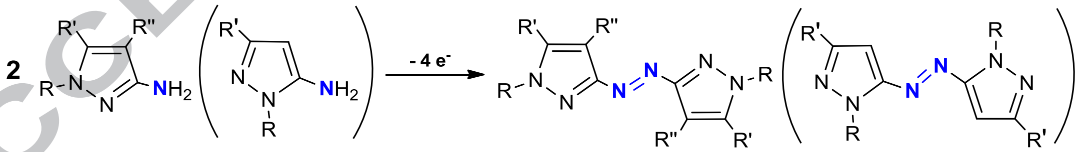
The effect of the aminopyrazole structure (the nature of substituents and position of the amino group on the pyrazole ring) on the efficiency of their electrocatalytic *N-N* homocoupling on a NiO(OH) anode[35] is shown in Table 2. The highest yield of the azo product **1a** (82%) was obtained in the electrolysis of aminopyrazole **1** with a conversion of 100% after passing the theoretical amount of electricity (Q_t = 2F/mol, or Q/Q_t = 1). However, the homocoupling of other 3-aminopyrazoles with Et or *i*-Pr groups at position 1 or a Me group at positions 4 or 5 was less efficient. Thus, the conversions of azoles **2**–**5** and the yields of the corresponding azo compounds **2a**–**5a** decreased to 45–50% (Table 2).

These results were in agreement with the CV data. The height of the $Ni(OH)_2$ anodic peak in the presence of aminopyrazole **1** increases by 44% (Fig. 2.2, curves **a** and **b**), whereas addition of aminopyrazoles **4** and **5** decreased the growth of the corresponding anodic peaks to 30–31% (Fig. 2.2, curves **c** and **d**). This indicates that the oxidation rate of aminopyrazoles **4**, **5** decreases which correlates with the lower yields of the corresponding products (Table 2). The reason for the observed effect was somewhat unexpected. It was found that the solubility of azopyrazoles **2a**–**5a** in water is ~2.5 times lower than that of azopyrazole **1a**.[36] Owing to this, removal of products **2a**–**5a** from the anode surface after their generation may be hindered. Such shielding of the anode surface is likely to decrease the rate of the target process. We succeeded in solving this problem by increasing the electrolysis duration and amount of electricity passed (Q/Q_t = 2). As a result, azopyrazoles **2a**–**5a** were obtained in high yields 71–88% (Table 2).

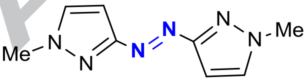
Unlike 3-aminopyrazoles, the electrooxidation of 5-aminopyrazoles **6** and **7** was accompanied by the formation of noticeable amounts of resinous products. As a consequence, azopyrazoles **6a** and **7a** were obtained in moderate yields (46–55%) even with a large excess of electricity passed (Q/Q_t = 3 or 4, Table 2). These results agree with the CV data which indicate a low rate of the reaction of aminopyrazole **7** with NiO(OH). In fact, upon addition of aminopyrazole **7**, the growth of the $Ni(OH)_2$ anodic peak was only 14% (Fig. 2.2 , see curves **a** and **e**).

As expected, the presence of an electron-withdrawing substituent on the pyrazole ring decreases the rate of the reaction of an aminopyrazole with NiO(OH). Indeed, electrolysis of 4-halosubstituted aminopyrazoles **8** and **9** under the standard conditions (Q/Q_t = 1) gave azo products **8a** and **9a** in only 25–26% yield (Table 2). However, upon passing a larger amount of electricity (Q/Q_t = 4), azopyrazoles **8a** and **9a** were obtained in high yields (77–87%).

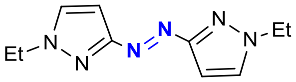
Table 2. Electrocatalytic *N-N* homocoupling of aminopyrazoles **1**–**9** on a NiO(OH) electrode: effect of its structure and the amount of electricity passed (Q/Q_t) on the yield of azopyrazoles **1a**–**9a**.[a]



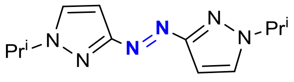
1 - 5, **8 - 9** **6**, **7** **1a - 5a**, **8a - 9a** **6a**, **7a**



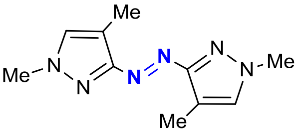
1a (82%[b])



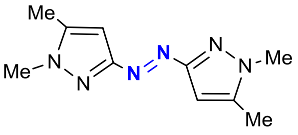
2a (50%[b], 71%[c])



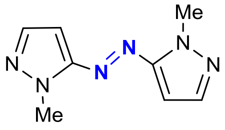
3a (48%[b], 86%[c])



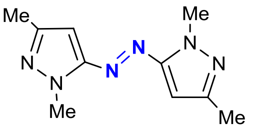
4a (49%[b], 88%[c])



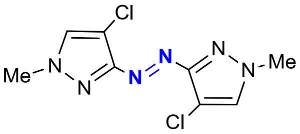
5a (45%[b], 79%[c])



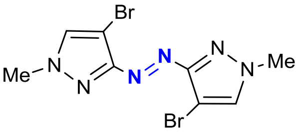
6a (23%[b], 55%[d], 50%[e])



7a (28%[b], 52%[d], 46[e])



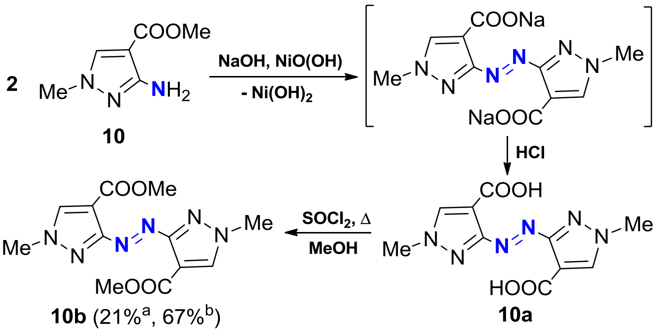
8a (26%[b], 87%[e])



9a (25%[b], 77%[e])

[a] Reaction conditions: undivided cell, NiO(OH) coated anode, Ti cathode, 0.5M NaOH in H_2O (100 mL), substrate **1**–**9** (0.003 mol), current density j_a = 6 $mA \cdot cm^{-2}$, Q_t= 2F per a mole of aminopyrazole **1**–**9**, 25 °C. In all cases where the yield of isolated azo product was moderate or low, 45–70% of the starting aminopyrazole were recovered. Electricity passed: [b] Q/Q_t = 1; [c] Q/Q_t = 2; [d] Q/Q_t = 3; [e] Q/Q_t = 4.

It should be noted that the mediated conversion of methyl ester **10** (Scheme 3) gave azopyrazole-5-carboxylic acid **10a** (HRMS data). Presumably, electrolysis in an alkaline medium was accompanied by the hydrolysis of ester **10**. Since product **10a** is poorly soluble in water and in organic solvents, it was identified as the corresponding methyl ester **10b**. The isolated yield of ester **10b** was 21% at $Q/Q_t = 1$, but it increased to 67% at $Q/Q_t = 4$.



Electricity passed: [a] $Q/Q_t = 1$; [b] $Q/Q_t = 4$.

Scheme 3. Synthesis of azopyrazole **10b**.

In summary, we have developed an original green methodology for the electrosynthesis of azopyrazoles based on the unique capabilities of the electrocatalytic oxidation of aminopyrazoles under the action of NiO(OH) as a redox mediator. The developed method for direct *N-N* homocoupling of *N*-alkylaminopyrazoles is atom economical, low cost and environmentally friendly. The process is efficiently performed in an aqueous medium and the use of NiO(OH) as a mediator allows chemists to abandon unrecyclable chemical oxidants which are often toxic. As a result, this method opens the possibility to obtain the target azopyrazoles both with donor and acceptor substituents under mild conditions and in high yields.

Electrolysis and CV methods have shown that the aminoheteroarene concentration, current density and amount of passed electricity are key factors in the investigated process. The mild reaction conditions and high bond-forming efficiency make this electrooxidative coupling strategy highly viable for future applications.

Acknowledgments

The authors are grateful to Dr. Yu. A. Strelenko (Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences) for measurement of NMR spectra as well as Prof. K.A. Lyssenko (Center for Molecules Composition of the Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences) for obtaining X-ray diffraction data. This study was supported by the Russian Foundation for Basic Research (Grant No. 16-03-00173 a).

Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.... Crystallographic data for structure **1a** have been deposited to the Cambridge Crystallographic Data Centre as supplementary no.: CCDC – 1844509. These data can be obtained free of charge from The Cambridge Crystallographic Data *via* http://www.ccdc.cam.ac.uk/data_request/cif

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33. CV studies were carried out under a nitrogen atmosphere. $Ni(OH)_2$ on the Ni surface was generated by successive 100-fold pulses at +0.7 and -1.3 V (pulse duration 3 s). A saturated calomel electrode (SCE) was used as the reference electrode.
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35. Typical procedure for the electrosynthesis of azopyrazole **1a**: A 0.5 M solution of NaOH in water (100 mL) containing aminopyrazole **1** (3 mmol, 0.29 g) was placed into a glass cell with a cylindrical Ni anode ($S = 48$ cm^2, activated before the synthesis according to the literature procedure[23]) and a Ti cathode (20 cm^2). Electrolysis was carried out at a current of 290 mA. After passing 2 F of electricity per mol of the substrate ($Q = 579$ C), the electrolysis was stopped. The reaction mixture was stirred for 0.5 h and concentrated HCl was added until the solution was pH ~ 3. The mixture was then extracted with $CHCl_3$ (3×40 mL). The extracts were combined, dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography on silica with light petroleum ether : ethyl acetate (10 : 1) gave the pure azopyrazole **1a** (82%, 0.47 g).
36. Solubility of azopyrazole **1a** is ~110 mg in 100 mL of water, while that of azopyrazoles **2a–5a** is ~45 mg.

Graphical Abstract

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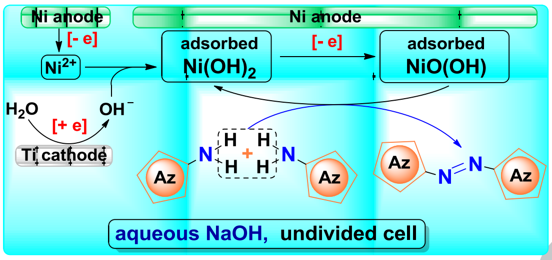
Electrosynthesis of azopyrazoles *via* the oxidation of *N*-alkylaminopyrazoles on a NiO(OH) anode in aqueous alkali – a green method for *N-N* homocoupling

Boris V. Lyalin, Vera L. Sigacheva, Vladimir A. Kokorekin, Vladimir A. Petrosyan



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- Green electrocatalytic method for N-N coupling of N-alkylaminopyrazoles leading to azopyrazoles
- Electrogenerated NiO(OH) as effective and easily accessible redox-mediator
- Galvanostatic electrolysis, undivided cell, aqueous medium, mild conditions
- Yield of azopyrazoles up to 88%