Available online at www.sciencedirect.com
ScienceDirect
*Mendeleev Commun.*, 2015, **25**, 479–481
Mendeleev Communications

# A new synthesis of azopyrazoles by oxidation of *C*-aminopyrazoles on a NiO(OH) electrode

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

*N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 499 135 5328; e-mail: petros@ioc.ac.ru*

DOI: 10.1016/j.mencom.2015.11.028

Oxidation of *C*-amino-*N*-alkylpyrazoles on a NiO(OH) electrode in an aqueous alkaline medium affords the corresponding azopyrazoles. The success in implementation of these processes is due to the structure of *C*-aminopyrazoles.

Development of new ecologically safe methods for synthesizing practically useful chemical compounds is a research area of considerable interest. Many of them are based on the use of atomically efficient chemical reactions.[1,2] In this study, we focused on the new procedure to access aromatic azo compounds. Such compounds find applications in the synthesis of pharmaceutical compounds, organic dyes,[3] polymeric zeolite-type complexes for catalysis or ion exchange,[4] as reagents in the Mitsunobu reaction,[5,6] or heterogeneous thiocyanation of arenes.[7]

One of the basic methods for the synthesis of aromatic azo compounds is chemical oxidation of arylamines. Such processes with the use of heavy metal salts (manganese,[8] lead,[9,10] mercury[11,12]) are usually ecologically not acceptable. From this point of view, electrochemical methods using the anode as a 'green' oxidizing agent are undoubtedly of interest. However, analysis of literature data shows that examples of electrosynthesis of aromatic azo compounds are scarce and have rather low efficiency. In fact, electrooxidation of anilines to azobenzenes on a Pt anode in aqueous medium provides 3–37% yields.[13,14] Of certain interest is the synthesis[15] of *N*,*N*′-bis(morpholino)-diazene (yield 80%) by oxidation of *N*-aminomorpholine on a NiO(OH) electrode, since it can be expected that the corresponding processes would be suitable for oxidation of aminoarenes. For example, it is known[15,16] that electrolysis on a NiO(OH) anode is widely employed in the oxidation of not only functionally substituted alkanes but also (het)arenes.

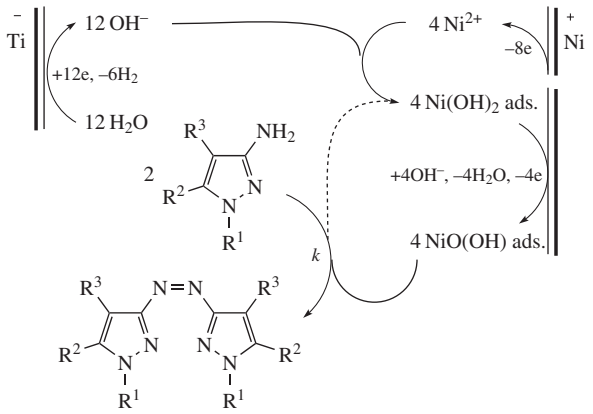
This method was classified[15,16] as heterogeneous electrocatalysis with an oxidizing catalyst, NiO(OH), that is formed on the surface of a Ni anode and is continuously regenerated in the course of the electrolysis. The procedure is ecologically safe, facile to perfom, allows an easy up-scale and occurs in aqueous alkaline media, and is therefore very attractive from the perspective of green chemistry.[17]

In the past years we gained considerable experience in using a NiO(OH) electrode for efficient synthesis (in 50–85% yields) of practically valuable compounds, for example, (tetrazol-5-yl)-acetic acid[18] [from 1-(2-hydroxyethyl)tetrazole], adipic[19] and glutaric[20] acids (from cyclohexanol and cyclopentanone, respectively), arylalkanoic acids[21] (from arylalkanols), pyrazole-4-carboxylic acids[22] (from 4-formylpyrazoles). Therefore, the prospects of using this method for oxidation of aminoarenes to the corresponding azo compounds were certainly of interest. As a first step, we successfully performed and optimized a process for synthesizing azofurazans[23,24] by electrooxidation of aminofurazans with various structures in a non-divided cell on a NiO(OH) electrode in an aqueous alkaline solution.

This study is the first attempt to extend this method on preparation of azopyrazoles by electrooxidation of *C*-aminopyrazoles. The analogous chemical process involves toxic (explosive) oxidants: NBS,[25] $Br_2$,[25] Bu$^t$OI,[26] or the following systems: NBS–benzoyl peroxide,[27] $I_2$–*tert*-butyl hydroperoxide[28] and CuI–1,10-phenanthroline–*tert*-butyl hydroperoxide.[28]

The main goal of this work was to show the principal possibility of electrochemical conversion of aminopyrazoles to the corresponding azopyrazoles on a NiO(OH) electrode, since the regularities of electrooxidation of aminopyrazoles were not described so far.

Based on the reported data[16] we assumed that the studied process in a undivided cell on a Ni anode in aqueous alkaline medium could be represented by Scheme 1.




**Scheme 1**

According to this scheme, anodic dissolution of $Ni^0$ in an alkaline medium gives $Ni(OH)_2$ that is readily adsorbed on the anode and then undergoes further oxidation into NiO(OH). The latter is also adsorbed on the electrode and acts as an oxidant with respect to the organic substrate. This process involving regeneration of $Ni(OH)_2$ can be considered as a variety of heterogeneous electrocatalysis.

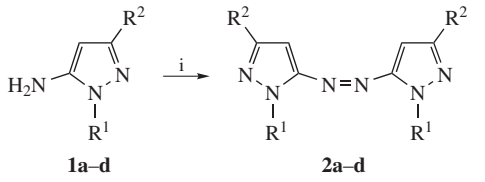
However, our first attempts to obtain azopyrazoles by electrosynthesis failed. In fact, after electrolysis of 3-amino-1*H*-pyrazole in 0.2 M aqueous NaOH with passage of 2 F per mole of the pyrazole, the corresponding azopyrazole was not found in the reaction mixture. Though the process occurred without passivation of electrodes, it gave a dark polymeric product on the anode. This material was insoluble in methanol, acetone, chloroform, DMSO, DMF and benzene. Note that data on the chemical

oxidation of N-unsubstituted aminopyrazoles to the corresponding azo derivatives are missing in literature, whereas it is known[29] that, *e.g.*, 3-amino-1*H*-pyrazole can form complexes with metal ions, $Ni^{2+}$ in particular. This fact might complicate the process in question. However, additional research is required to clarify this issue.

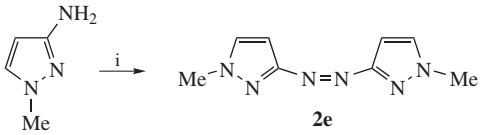
For this reason, we moved to N-alkylated aminopyrazoles bearing electron-donating or electron-withdrawing substituents at the ring. However, 5-amino-1-methyl-4-nitropyrazole on passing of 2 F per mole of the starting pyrazole gave a complex mixture of hardly identifiable products. Since electrolysis was carried out in a undivided cell, cathodic reduction of the nitro group might be a complicating factor. Nevertheless, electrolysis in the anodic compartment of a divided cell did not provide satisfactory results. Similarly, no azopyrazole was formed in a control chemical oxidation of 5-amino-1-methyl-4-nitropyrazole by a NaOCl solution. Thus, the formation of azopyrazoles upon oxidation of N-alkylated aminonitropyrazoles remains an open.

Luckily, formation of the desired azo compounds was detected upon electrooxidation of *N*-alkyl-*C*-aminopyrazoles **1a**–**e**, containing or lacking other (cyclo)alkyl in the ring (Scheme 2).† Electrolysis of these compounds turned to be highly selective. In fact, the solution after electrolysis contained the corresponding azo compounds **2a**–**e** as the only product, along with the remaining nonreacted *N*-alkylaminopyrazole.

Analysis of the data (Scheme 2) obtained under standard (non-optimized) conditions allows us to state preliminary notes on the effect of the starting aminopyrazole on the process




**1a–d** **2a–d**




**1e** **2e**

| | $R^1$ | $R^2$ | Conversion of **1** (%) | Yield of **2** (%) on loaded (reacted) **1** |
|---|---|---|---|---|
| **a** | Me | H | 31 | 20 (67) |
| **b** | Et | H | 38 | 23 (61) |
| **c** | Me | Me | 45 | 27 (59) |
| **d** | Me | cyclopropyl | 30 | 18 (61) |
| **e** | – | – | 51 | 42 (83) |

**Scheme 2** *Conditions*: i, NiO(OH) anode, Ti cathode, undivided cell, $C$(**1**) = 0.03 M, $C$(NaOH) = 0.2 M in $H_2O$, $j$ = 6 mA $cm^{-2}$, $Q$ = 2 F $mol^{-1}$.

efficiency. First, replacement of the methyl substituent at the 1-position (compound **1a**) with ethyl (compound **1b**) has a small effect on the yield of the target azopyrazoles. On the other hand, incorporation of a methyl substituent to the 3-position (compound **1c**) increases the yield, whereas replacement of methyl with cyclopropyl (compound **1d**) at this position decreases the yield to some extent. The highest yield of the azo derivative was achieved in the case of 1-methyl-3-aminopyrazole **1e**.

Note that upon passage of the electricity amount which is theoretically required for the process (2 F per mole of the starting aminopyrazole **1**), the yield of azopyrazoles **2** and conversion of the starting aminopyrazoles **1** did not exceed 42 and 51%, respectively (see the case of **1e**). It may be assumed that this is due to comparatively slow kinetics of aminopyrazole oxidation in the presence of NiO(OH). As a result, a considerable fraction of the electricity passed is consumed for the competing water oxidation ($4\,OH^- - 4e \rightarrow 2H_2O + O_2$).

In summary, we have demonstrated the principal possibility of electrosynthesis of azopyrazoles by electrooxidation of the corresponding amino derivatives on a NiO(OH) electrode. In our subsequent studies, we plan to optimize the yields of the target azopyrazoles and find the reasons for the anomalous behaviour of N–H aminopyrazoles and N-alkylated aminopyrazoles containing an $NO_2$ group at the ring in the oxidation process.

*Online Supplementary Materials*

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2015.11.028.

† $^1$H and $^{13}$C NMR spectra of the products in $CDCl_3$ were recorded on a Bruker Avance 300 instrument (300.13 MHz for $^1$H and 75.47 MHz for $^{13}$C). IR spectra were obtained in KBr pellets using a Bruker Alpha-T instrument. HRMS spectra were measured on a Bruker micrOTOF II instrument using ESI. Merck plates were used for TLC.

Light petroleum, EtOAc, $CHCl_3$, silica gel (0.035–0.070 mm, 60 Å) for column chromatography and 3-amino-1*H*-pyrazole were commercial products from Acros Organics. The following compounds were synthesized as reported: 5-amino-1-methyl-4-nitropyrazole,[30] 5-amino-1-methyl-1*H*-pyrazole (**1a**),[31] 5-amino-1-ethyl-1*H*-pyrazole (**1b**),[32] 5-amino-1,3-dimethyl-1*H*-pyrazole (**1c**),[33] 5-amino-3-cyclopropyl-1-methyl-1*H*-pyrazole (**1d**)[34] and 3-amino-1-methyl-1*H*-pyrazole (**1e**).[35]

*Electrolysis* (*general procedure*). Electrolysis was carried out using a B5-49 direct current source, 0.2 M aqueous NaOH as the supporting electrolyte, in a glass temperature-controlled (25 °C) cell ($V$ = 150 ml) with a NiO(OH) anode ($S$ = 48 $cm^2$) prepared by a reported procedure[36] and a Ti cathode ($S$ = 20 $cm^2$). The supporting electrolyte (100 ml) and amine **1a**–**e** (0.003 mol) were placed into the cell and electrolysis was carried out at a current of 290 mA. Once a 2 F per mole of the starting amine was passed ($Q$ = 579 C), electrolysis was stopped. The reaction mixture was stirred for more 0.5 h in the absence of current and analyzed by TLC with light petroleum–ethyl acetate (1:1) as the eluent. Concentrated HCl was then added to the reaction mixture to pH ~ 3 and the mixture was extracted with $CHCl_3$ (3×50 ml). The extracts were combined, dried with anhydrous $MgSO_4$ and concentrated *in vacuo*. Column chromatography on $SiO_2$ with light petroleum–ethyl acetate (10:1) as the eluent gave azopyrazoles **2a**–**e** which were identified using the reported characteristics.[26,28] The aqueous solution that remained after extraction (see above) was concentrated *in vacuo* and NaOH was added with stirring (to pH ~ 10). The nonreacted starting amines **1a**–**e** were extracted with $CHCl_3$ (3×30 ml) and identified by TLC and $^1$H NMR.

*(*E*)-1,2-Bis(1-methyl-1*H*-pyrazol-5-yl)diazene* **2a**: yellow solid, mp 140 °C. $^1$H NMR, $\delta$: 4.20 (s, 6H, Me), 6.56 (d, 2H, CH, $J$ 2.1 Hz), 7.57 (d, 2H, CH, $J$ 2.1 Hz). $^{13}$C NMR, $\delta$: 36.20 (2NMe), 94.05 (2CH), 139.38 (2CH), 153.62 (2C). IR (KBr, $\nu$/$cm^{-1}$): 3101, 2955, 2492, 2362, 1782, 1735, 1569, 1504, 1474, 1403, 1316, 1290, 1202, 1046, 925, 896, 786, 755. HRMS (ESI), *m/z*: 191.1042 (calc. for $C_8H_{11}N_6$, *m/z*: 191.1040 $[M+H]^+$). The mp and $^1$H NMR spectra of compound **2a** disagree with the data reported[28] (where compound **2a** was obtained for the first time). A special study (see Online Supplementary Materials) confirmed that our results were correct.

*(*E*)-1,2-Bis(1-ethyl-1*H*-pyrazol-5-yl)diazene* **2b**: yellow solid, mp 94 °C. $^1$H NMR, $\delta$: 1.53 (t, 6H, Me, $J$ 7.2 Hz), 4.59 (q, 4H, $CH_2$, $J$ 7.2 Hz), 6.54 (s, 2H, CH), 7.67 (s, 2H, CH). HRMS (ESI), *m/z*: 219.1386 (calc. for $C_{10}H_{15}N_6$, *m/z*: 219.1358 $[M+H]^+$).

*(*E*)-1,2-Bis(1,3-dimethyl-1*H*-pyrazol-5-yl)diazene* **2c**: yellow solid, mp 140–143 °C. $^1$H NMR, $\delta$: 2.31 (s, 6H, Me), 4.10 (s, 6H, Me), 6.31 (s, 2H, CH). HRMS (ESI), *m/z*: 219.1357 (calc. for $C_{10}H_{15}N_6$, *m/z*: 219.1358 $[M+H]^+$).

*(*E*)-1,2-Bis(3-cyclopropyl-1-methyl-1*H*-pyrazol-5-yl)diazene* **2d**: red oil. $^1$H NMR, $\delta$: 0.70–0.80 (m, 4H, $CH_2$), 0.93–1.01 (m, 4H, $CH_2$), 1.83–1.98 (2H, CH), 4.15 (s, 6H, Me), 6.74 (s, 2H, CH). HRMS (ESI), *m/z*: 271.1674 (calc. for $C_{14}H_{19}N_6$, *m/z*: 271.1671 $[M+H]^+$).

*(*E*)-1,2-Bis(1-methyl-1*H*-pyrazol-3-yl)diazene* **2e**: yellow solid, mp 201 °C. $^1$H NMR, $\delta$: 4.01 (s, 6H, Me), 6.69 (d, 2H, CH, $J$ 2.4 Hz), 7.38 (d, 2H, CH, $J$ 2.4 Hz). HRMS (ESI), *m/z*: 190.0965 (calc. for $C_8H_{10}N_6$, *m/z*: 190.0967 $[M]^+$).

## References


1 V. P. Ananikov, L. L. Khemchyan, Yu. V. Ivanova, V. I. Bukhtiyarov, A. M. Sorokin, I. P. Prosvirin, S. Z. Vatsadze, A. V. Medved'ko, V. N. Nuriev, A. D. Dilman, V. V. Levin, I. V. Koptyug, K. V. Kovtunov, V. V. Zhivonitko, V. A. Likholobov, A. V. Romanenko, P. A. Simonov, V. G. Nenajdenko, O. I. Shmatova, V. M. Muzalevskiy, M. S. Nechaev, A. F. Asachenko, O. S. Morozov, P. B. Dzhevakov, S. N. Osipov, D. V. Vorobyeva, M. A. Topchiy, M. A. Zotova, S. A. Ponomarenko, O. V. Borshchev, Yu. N. Luponosov, A. A. Rempel, A. A. Valeeva, A. Yu. Stakheev, O. V. Turova, I. S. Mashkovsky, S. V. Susolyatin, V. V. Malykhin, G. A. Bukhtiyarova, O. A. Terent'ev and I. B. Krylov, *Russ. Chem. Rev.*, 2014, **83**, 885.

2 V. P. Ananikov, E. K. Khokhlova, M. P. Egorov, A. M. Sakharov, S. G. Zlotin, A. V. Kucherov, L. M. Kustov, M. L. Gening and N. E. Nifantiev, *Mendeleev Commun.*, 2015, **25**, 75.

3 K. Hunger, *Industrial Dyes: Chemistry, Properties, Applications*, Wiley-VCH, Weinheim, 2003.

4 L. Carlucci, G. Giani, D. M. Proserpio and S. Rizzato, *New J. Chem.*, 2003, **27**, 483.

5 N. Iranpoor, H. Firozabadi, D. Khaliili and S. Molevalli, *J. Org. Chem.*, 2008, **73**, 4882.

6 N. Iranpoor, H. Firozabadi and D. Khaliili, *Org. Biomol. Chem.*, 2010, **8**, 4436.

7 N. Iranpoor, H. Firozabadi, R. Shahin and D. Khaliili, *Synth. Commun.*, 2012, **42**, 2040.

8 H. E. Baumgarten, A. Stakis and E. M. Miller, *J. Org. Chem.*, 1965, **30**, 1203.

9 H. Firouzabadi and Z. Mostafavippor, *Bull. Chem. Soc. Jpn*., 1983, **56**, 914.

10 J. M. Birchall, R. N. Haszeldine and J. E. G. Kemp, *J. Chem. Soc., Chem. Commun.*, 1970, 449.

11 K. Wenkert and B. Wickberg, *J. Am. Chem. Soc*., 1962, **84**, 4914.

12 S. Farbagi, P. Zaringhadam and R. Z. Sahamieh, *Acta Chim. Slov*., 2007, **54**, 647.

13 S. Wawzonek and T. W. McInture, *J. Electrochem. Soc*., 1967, **114**, 1025.

14 S. Wawzonek and T. W. McInture, *J. Electrochem. Soc.*, 1972, **119**, 1350.

15 H. J. Schäfer, *Top. Curr. Chem.*, 1987, **142**, 101.

16 B. V. Lyalin and V. A. Petrosyan, *Russ. J. Electrochem.*, 2010, **46**, 1199 (*Elektrokhimiya*, 2010, **46**, 1283).

17 R. A. Sheldon, I. Arends and U. Hanefeld, *Green Chemistry and Catalysis*, Wiley-VCH, Weinheim, 2007.

18 B. V. Lyalin and V. A. Petrosyan, *Russ. J. Electrochem.*, 1996, **32**, 88 (*Elektrokhimiya*, 1996, **32**, 96).

19 B. V. Lyalin and V. A. Petrosyan, *Russ. Chem. Bull., Int. Ed.*, 2004, **53**, 688 (*Izv. Akad. Nauk, Ser. Khim.*, 2004, 657).

20 B. V. Lyalin and V. A. Petrosyan, *Russ. Chem. Bull., Int. Ed*., 2009, **58**, 2426 (*Izv. Akad. Nauk, Ser. Khim*., 2009, 2348).

21 B. V. Lyalin and V. A. Petrosyan, *Russ. Chem. Bull., Int. Ed*., 2007, **56**, 499 (*Izv. Akad. Nauk, Ser. Khim*., 2007, 481).

22 B. V. Lyalin and V. A. Petrosyan, *Russ. Chem. Bull., Int. Ed.*, 2012, **61**, 1148 (*Izv. Akad. Nauk, Ser. Khim*., 2012, 1139).

23 B. V. Lyalin and V. A. Petrosyan, in *Proceedings of III All-Russian Scientific Conference 'Advances in Synthesis and Complexing'*, Moscow, 2014, vol. 1, p. 28 (in Russian).

24 A. B. Sheremetev, B. V. Lyalin, A. M. Kozeev, N. V. Palysaeva, M. A. Syroeshkin, M. I. Struchkova and K. Yu. Suponitsky, *RCS Adv.*, 2015, **5**, 37617.

25 A. M. Salaheldin, A. M. F. Oliveira-Campos and L. M. Rodriges, *Tetrahedron Lett*., 2007, **48**, 8819.

26 S. Okimura, C. H. Lin, Y. Takeda and S. Minakava, *J. Org. Chem.*, 2013, **78**, 12090.

27 D. B. Silva, A. Samadi, L. Infantes, M. C. Carreiras and J. Marco-Contelles, *Tetrahedron Lett*., 2010, **51**, 6278.

28 B. Jiang, Y. Ning, W. Fan, S. J. Tu and J. Li, *J. Org. Chem*., 2014, **79**, 4018.

29 B. Banerjee, S. K. Nandi, S. R. Chaudhuri and B. Sur, *Indian J. Chem., Sect. A*, 1983, **22**, 675.

30 V. P. Perevalov, L. I. Baryshnenkova, M. A. Andreeva, Yu. A. Manaev and I. A. Denisova, *Chem. Heterocycl. Compd*., 1983, **19**, 1322 (*Khim. Geterotsikl. Soedin*., 1983, 1672).

31 E. V. Tret'yakov and S. F. Vasilevsky, *Russ. Chem. Bull., Int. Ed.*, 1996, **45**, 2585 (*Izv. Akad. Nauk, Ser. Khim*., 1996, 2725).

32 J. Craig, Mc. K. Darren and P. K. Gordon, *Patent WO 2005/80359 A1*, 2005.

33 X. Dengming, C. Liang, L. Xijie, H. Yuandong, H. Xinhe, L. Zhihua, Z. Lipeng, W. Wei, W. Shylong, S. Yu, L. Gen, W. Yin, Z. Sheng, L. Chonglong, T. Jia and Y. Honghao, *Patent WO 2012/92880 A1*, 2012.

34 A. Yamamori, H. Sakai, S. Kawakami and U. Ueda, *Chem. Pharm. Bull*., 1987, **35**, 3235.

35 K. Zheng, S. Idbal, P. Hernandes and H. Park, *J. Med. Chem*., 2014, **57**, 10013.

36 J. Kaulen and H. Schaefer, *Tetrahedron*, 1982, **38**, 3299.


*Received: 20th April 2015; Com. 15/4606*