# Anodic azolation of 1,2- and 1,3-dimethoxybenzenes

*V. A. Petrosyan* and A. V. Burasov*

*N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences,*
*47 Leninsky prosp., 119991 Moscow, Russian Federation.*
*Fax: +7 (499) 135 5328. E-mail: petros@ioc.ac.ru*

Electrochemical azolation of 1,2- and 1,3-dimethoxybenzenes with tetrazole, pyrazole and triazole derivatives in MeCN in an undivided cell with Pt electrodes proceeds through the formation of intermediate arenonium cations of the *ipso*-structure. Nature of the starting arenes and the corresponding intermediate arenonium cations determine composition and yields of the target products.

**Key words:** 1,2- and 1,3-dimethoxybenzenes, azoles, anodic functionalization, *N*-(dimethoxyphenyl)azoles, arenonium cations.

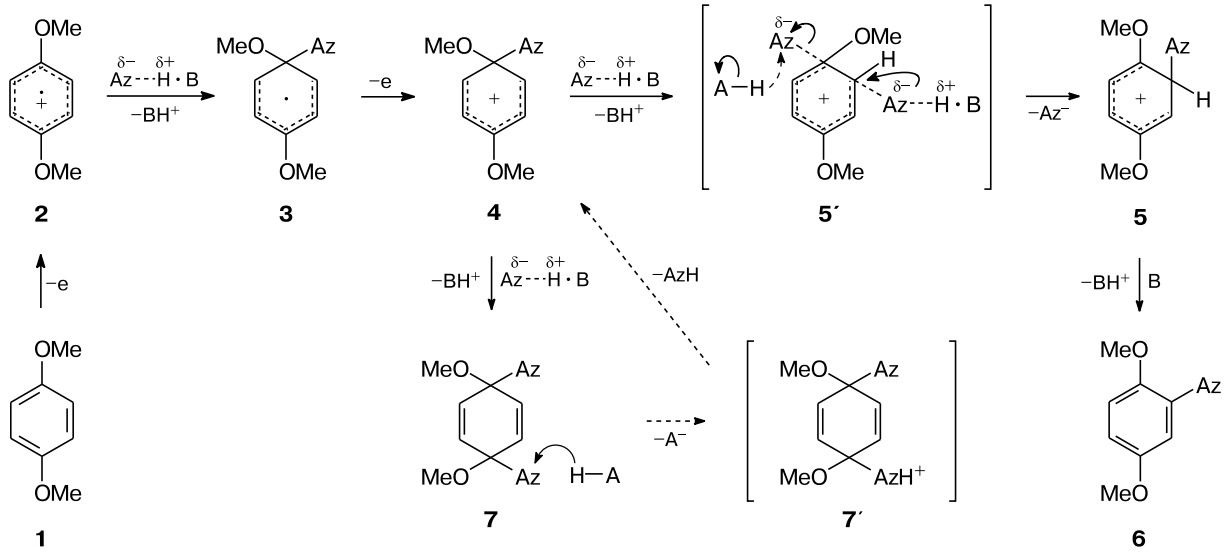
In the preceding publications,[1—3] we have revealed the regularities of electrosynthesis of *N*-arylazoles using galvanostatic electrolysis of an azole (AzH) (pyrazole, triazole, their substituted derivatives, tetrazole) and 1,4-dimethoxybenzene (1,4-DMB) in an undivided cell.

According to the concept proposed (Scheme 1), radical cation **2** emerged in the first step undergoes the *ipso*-attack by the azole nucleophile to form radical **3**, oxidizing further to arenonium cation **4**. The *ipso*-reaction of cation **4** with a nucleophile leads to hydrolytically labile product of the *ipso*-bisaddition **7**, whereas the rearrangement of this cation to cation **5** with subsequent deprotonation, to the product of *ortho*-substitution **6**.

Based on the $pK_a^{II}$ values (see Ref. 4), the azoles studied were conventionally divided[1,3] to the highly basic (3,5-dimethylpyrazole (DMP), 1,2,4-triazole (TA)) and poorly basic (4-nitropyrazole (NP), 3-nitro-1,2,4-triazole (NTA), tetrazole (T)). This allowed us to relate the yields and ratios of products **6** and **7** with acidity and basicity of azoles and medium, as well as with effects of different additives (for example, collidine (CL)).

As it has been found earlier,[1,2] the key steps in the electrochemical N-dimethoxyphenylation of azoles are the competing irreversible *ortho*-interaction of arenonium cation **4** with the azole and reversible *ipso*-interaction of the same species (see Scheme 1).

**Scheme 1**




AH = AzH, $AzH_2^+$, AcOH; B = AzH, collidine (CL)

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 3, pp. 512—516, March, 2010.

The combination of the data given[1–3] allows one to consider arenonium cation **4** as the key intermediate in the process studied. This conclusion is of principal importance, since cation **4** in its structure is identical to the Wheland σ-complex being the key intermediate in electrophilic aromatic substitution.[5] This indicates that electrochemical azolation of 1,4-DMB[1–3] takes places as electroinduced nucleophilic aromatic substitution, proceeding through the formation of the Wheland complex. In the present work, this mechanistic concept was extended to the 1,4-DMB isomers, *viz.*, 1,2- and 1,3-dimethoxybenzenes (1,2- and 1,3-DMB, respectively). Electrosynthesis of *N*-(dimethoxyphenyl)azoles was performed in MeCN under conditions similar to those described earlier.[1–3]

## Results and Discussion

It is reasonable to compare results on the azolation of 1,2- and 1,3-DMB with the data obtained earlier on the azolation of 1,4-DMB. The electrochemical azolation of 1,3-DMB differs from the analogous reaction involving 1,4-DMB by high selectivity of the process, products of the *ortho*-substitution **8** are exclusively formed independent on the azole structure (Table 1).

The methoxy groups in the aromatic ring of 1,3-DMB are arranged so that formation of the *ipso*-bisaddition product is energetically unfavorable. According to the calculated data,[6] in radical cations of phenol ethers a positive charge at *ipso*-position to the methoxy group is noticeably higher than at other positions. This is the reason that an azole nucleophile reacts at *ipso*-position of the radical cation formed in the first step of the 1,3-DMB oxidation, whereas anodic oxidation of a free radical emerging in this case leads to arenonium cation of the *ipso*-structure (Scheme 2).

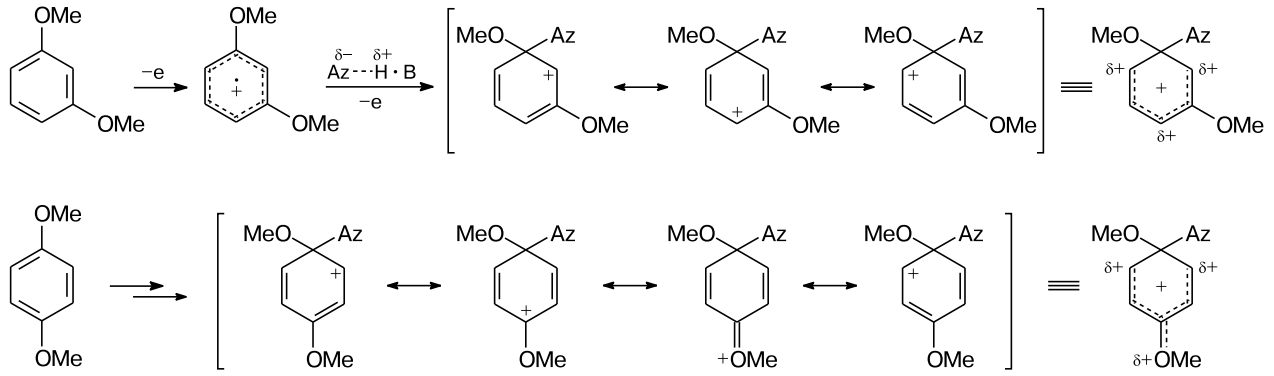
The structure of such a cation is represented by three resonance forms (see Scheme 2). The second methoxy group in this cation is not able to stabilize the cation through delocalization of the positive charge by its electron pair as it happens, for example, in anodic azolation of 1,4-DMB. Thus, the 1,3-DMB radical cation is closer to the anisole, rather than 1,4-DMB, radical cation in its reactivity in the functionalization process. Arenonium cation **9** of the *ipso*-structure emerged from 1,3-DMB is transformed to the corresponding cation **10** of the *ortho*-structure (Scheme 3) by the mechanism of *cine*-substitution (described earlier[1,2] in anodic azolation of 1,4-DMB) faster than adds the second molecule of nucleophile to form the diazolation product, which in fact is absent in the electrolyte.

**Table 1.** The influence of electrolysis conditions on the yields of *ortho*-substitution **6** (**8**) and *ipso*-bisaddition **7** products in electrochemical azolation of 1,3- and 1,4-DMB (3 mmol of azole per 2 mmol of arene, Pt electrodes, 0.022 *M* $Et_4NClO_4$, *I* = 50 mA)

| Entry | Azole | $pK_a^{I}$ [a] | $pK_a^{II}$ [a] | Azole/DMB[b] | Additive[c] | Product yields (%) in electrolysis of the mixture | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | AzH—1,4-DMB[1,3] | | AzH—1,3-DMB |
| | | | | | | **6** | **7** | **8** |
| | | | | | Highly basic azoles | | | |
| *1* | DMP | 15.0 | 4.1 | 1.5 | AcOH (3) | 38 | 14 | 15 |
| *2* | DMP | | | 1.5 | — | 28 | 30 | ~0 |
| *3* | DMP | | | 1.5 | CL (0.5) | 15 | 42 | 15 |
| *4* | TA | 10.0 | 2.5 | 1.5 | AcOH (3) | 8 | 33 | 12 |
| *5* | TA | | | 1.5 | — | 7 | 40 | 8.5 |
| *6* | TA | | | 1.5 | CL (0.5) | 2 | 56 | 25 |
| | | | | | Poorly basic azoles | | | |
| *7* | NP | 9.7 | −2.0 | 1.5 | — | 1.5 | 0 | 0 |
| *8* | NP | | | 1.5 | CL (0.5) | 4 | 52 | 1.5 |
| *9* | NP | | | 1 | $Bu_4N^+$-salt of NP (0.5) | — | — | 50 |
| *10* | NP | | | 1 | $Me_4N^+$-salt of NP (0.5) | 8 | 43 | — |
| *11* | NTA | 6.0 | −3.7 | 1.5 | CL (0.5) | 3 | 10 | 25 |
| *12* | NTA | | | 1 | $Me_4N^+$-salt of NTA (0.5) | 28 | 18 | 54 |
| *13* | T | 4.9 | −2.7 | 1.5 | — | 4 | 0 | 0 |
| *14* | T | | | 1.5 | CL (0.5) | 50 | 29 | 80[d] |
| *15* | T | | | 1 | $Bu_4N^+$-salt of T (0.5) | 88 | 0 | 86[d] |

[a] The $pK_a^{I}$ and $pK_a^{II}$ values are for the equilibria $Az^- + H^+ \leftrightarrows AzH$ and $AzH + H^+ \leftrightarrows AzH_2^+$, respectively.
[b] The molar ratio.
[c] In parentheses are given the amount of moles per 1 mol of DMB.
[d] A mixture of N-isomers (1 : 1).

**Scheme 2**



In the *cine*-substitution, attack of the azole nucleophile is possible at positions 2, 4, and 6 of the arenonium cation ring, *i.e.*, at the atoms with the highest positive charge. In fact, the formation of addition products at positions 4 and 6 of the aromatic ring of 1,3-DMB (*ortho*-position to the methoxy groups) has been determined experimentally (see Table 1). As to position 2, it is apparently the less favorable site for the attack by azole nucleophile due to steric hindrance.

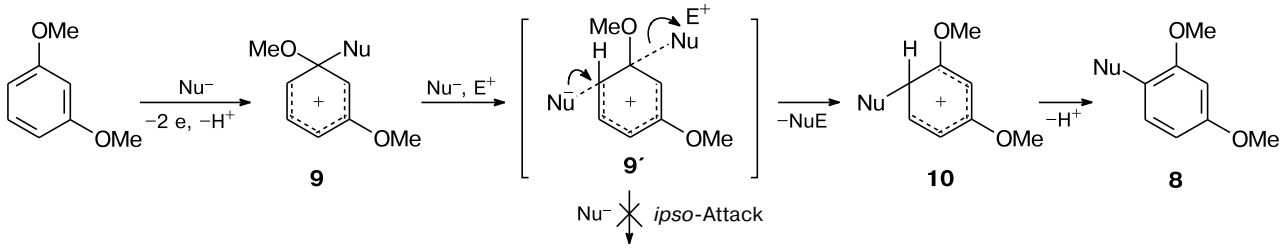
Efficiency of the formation of the *ortho*-substitution products **8** is noticeably affected by the nature of azole (see Table 1). The best result was achieved for the mixtures of acidic azoles with CL (see Table 1, entries *8*, *11*, and *14*) or $Alk_4N^+$ salts of these azoles (see Table 1, entries *9*, *10*, *12*, and *15*). Therefore, azolation with acidic azoles is more effective in such a case, when an azole or azole anion act as nucleophiles, whose N—H bond is noticeably polarized upon the action of CL ($Az^{\delta-}$—$H^{\delta+}$ · CL). The general mechanism of the process is represented in Scheme 3, with the additives of acids or molecules of acidic enough azoles[1,2] playing the part of electrophile $E^+$ catalyzing elimination of azole in the transition state **9′**. Note that the 1,3-DMB radical cation is less electrophilic than that of 1,4-DMB, since, contrary to electrolysis involving the latter, electrolysis of a mixture of acidic (low basic) azoles with 1,3-DMB does not lead even to traces of the target products (see Table 1, entries *7* and *13*).

An interesting effect is observed in the azolation of 1,3-DMB with highly basic azoles: the yields of products **8** increase when additives of both CL (see Table 1, entries *3* and *6*) and AcOH (see Table 1, entries *1* and *4*) are used (contrary to the corresponding data involving 1,4-DMB, where addition of AcOH or CL to the electrolyte changes the ratio of products **6** and **7** in the final solution (see Table 1, entries *1*—*6*)).

Effect of the CL additives indicates that the azole molecule, noticeably polarized by the additives ($Az^{\delta-}$—$H^{\delta+}$ · · CL), rather than its anion serves as the nucleophile in the electrolysis involving difficult-to-reduced highly basic azoles. The nucleophilicity of such a molecule is increased, which leads to more effective formation of product **8**.

The increase in the yields of products **8** when additives of AcOH were used was rather unexpected fact, since, in principle, they should suppress the nucleophilicity of azoles, thus decreasing the yield of compounds **8**. We explain this fact from the same viewpoint as in the case of the increase in the yield of the *ortho*-substitution product **6** in azolation of 1,4-DMB in the presence of AcOH additives (see Scheme 1). Such additives catalyze[1,2] the rearrangement of arenonium cation **4** to cation **5** of the *ortho*-structure, which leads to the decrease in the yield of the *ipso*-bisaddition product **7** and increase in the yield of the *ortho*-product **6**. In the case of 1,3-DMB, reluctant to the formation of the type **7** product on electrolysis (see above),

**Scheme 3**



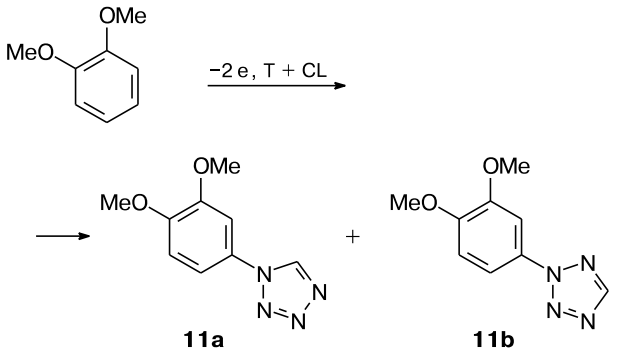
$Nu^-$ = $Az^{\delta-}$—$H^{\delta+}$ · B, $Az^-$; $E^+$ = AzH, $AzH_2^+$, AcOH

the AcOH additives assist in the transformation of arenonium cation of the *ipso*-structure **9** to cation of the *ortho*-structure **10** (see Scheme 3), which results in the increase in the yield of *ortho*-products **8**.

To sum up, an effective azolation of 1,3-DMB can be performed only with participation of nucleophiles with the pronounced enough anionic character. In this case, the intermediate cation **9**, which is not stabilized by electrons of the second methoxy group, is transformed to *ortho*-cation **10** significantly easier than undergoes the *ipso*-addition of the second azole.

Electrochemical azolation of 1,2-DMB differs from the analogous processes involving 1,4- and 1,3-DMB by intensive resinification of the reaction mixture. The very azolation occurs only in the case of tetrazole, the most acidic azole capable of forming anionic nucleophile in the mixture with CL[1,3] (Scheme 4, Table 2).

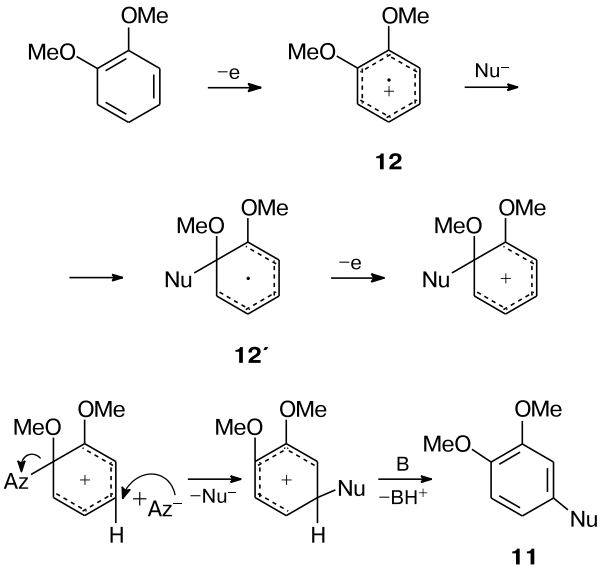
**Scheme 4**




The process proceeds with the selective formation of a mixture of N-isomeric *para*-substitution products **11a** and **11b** with relatively low (as compared to the azolation of 1,4- and 1,3-DMB) overall yield (*cf.* Table 2, entry *1* and Table 1, entry *14*). Note that the methoxylation of 1,2-DMB gives *o*-quinone derivatives,[7] whereas its cyanation gives the *ipso*-substitution products of the methoxy group.[8] However, the azolation of 1,2-DMB gives no products of such a structure (see Table 2, entries *2* and *3*). This fact, as well as intensive resinification in the course of electrolysis are, most likely, due to the high nucleophilicity of position 4 in 1,2-DMB, which successfully competes with the azole nucleophile in the reaction with the 1,2-DMB radical cation.

It should be noted that the exclusive formation of *para*-substitution products **11** in the tetrazolation of 1,2-DMB in the presence of CL (Scheme 5) is not the evidence of the nucleophilic attack at only *para*-position of radical cation **12**.

**Scheme 5**




$Nu^- = T + CL$

As in the case of analogous reaction with 1,4-DMB, we suggest that the process starts from the attack of the azole nucleophile at the *ipso*-position of the radical cation **12**; substitution in the ring takes place only in the final step (see Scheme 5).

A probability of *ipso*-interaction of the azole nucleophile with the 1,2-DMB radical cation in the first step (see Scheme 5) is confirmed by the data of electrochemical azolation of 1,2-DMB upon the action of NP, which leads to a 1,2-DMB dimer, *viz.*, 3,3′,4,4′-tetramethoxybiphenyl (**13**) as the only product (see Table 2, entry *2*).

In principle, biphenyl derivative **13** could have been the product of electrooxidation of 1,2-DMB itself. However, product **13** is formed only in such a case, when a salt (anion) of NP is present in the reaction mixture, which, in our view, indicates an intermediate generation of radical **12**′, the coupling of which and subsequent aromatization

**Table 2.** The influence of electrolysis conditions on the yields of the 1,2-DMB anodic azolation products (3 mmol of azole per 2 mmol of arene, Pt electrodes, 0.022 *M* $Et_4NClO_4$, $I = 50$ mA)

| Entry | Azole | Azole/DMB[a] | Additive[b] | Product (current efficiency (%)) |
|---|---|---|---|---|
| *1* | T | 1.5 | CL (0.5) | **11a** + **11b** (35) |
| *2* | NP | 1.5 | $Bu_4N^+$-salt of NP (0.5) | **13**[c] (25) |
| *3* | DMP | 1.5 | — | — |

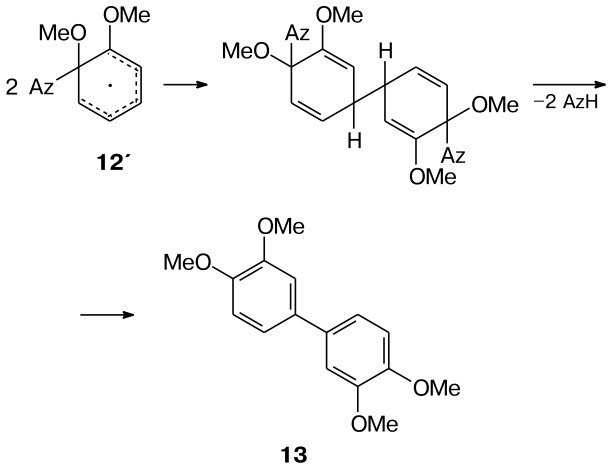
[a] The molar ratio.

[b] In parentheses are given the amount of additive in moles per 1 mol of DMB.

[c] 3,3′,4,4′-Tetramethoxybiphenyl (**13**).

(due to elimination of two molecules of NP) lead to biphenyl **13** (Scheme 6).

**Scheme 6**




AzH = NP

In conclusion, anodic azolation of isomeric 1,2- and 1,3-DMB can be described in the framework of the same mechanism as for azolation of 1,4-DMB (see Scheme 1). The structure of starting azoles, arenes, and the intermediately formed arenonium cations determine efficiency of either step of the process. This is indicated by the absence of the *ipso*-bisaddition product of the type **7** in the azolation of 1,3-DMB or formation of products **11** only in the azolation of 1,2-DMB with the mixture of T and CL.

On the whole, the studied anodic azolation of 1,2-, 1,3-, and 1,4-DMB proceeding through the formation of arenonium cation of the *ipso*-structure as a key intermediate is very unusual electrochemical process, which should be considered as electroinduced nucleophilic aromatic substitution proceeding through the formation of the Wheland complex.

## Experimental

$^1$H NMR spectra were recorded in the mixture DMSO-$d_6$—$CCl_4$ (1 : 1 v/v) on a Bruker AC-300 spectrometer. Commercial DMP, T, TA, P, CL (Lancaster, purity 98—99%), 1,3-DMB, 1,2-DMB (Aldrich, purity 99%), and glacial acetic acid (pure for analysis grade) were used in this work; NTA and NP were synthesized according to the described procedures.[9] Tetramethyl- and tetrabutylammonium salts of NP, NTA, and T were obtained according to the known procedure.[10]

**Electrochemical experiments** were performed using a source of the direct current B5-50 according to the following procedure: a mixture of DMB (2 mmol), azole (3 mmol) with the additive (if necessary) of AcOH (3 mmol) or CL (1 mmol) (see Table 1 and 2) was dissolved in MeCN (45 mL) and subjected to galvanostatic electrolysis ($I$ = 50 mA) in an undivided cell with Pt electrodes (the anode and cathode were of 37.2 and 12.3 cm$^2$, respectively). In some cases, a mixture of azole (2 mmol) and its salts (1 mmol) was used instead of azole itself (see Table 1 and 2). Solution of $Bu_4NClO_4$ (0.022 *M*) served as a supporting electrolyte. After passing of 2 *F* of electricity per 1 mol of arene, the electrolysis was stopped, the solvent was evaporated on a rotary evaporator at room temperature (25—30 Torr), and the residue was analyzed by $^1$H NMR. The current yields were determined by calculation on the two-electron transformation of the starting arene by comparison of the integral intensities of characteristic singlets of the products (the protons of the OMe and Me groups) and signals of tetrabutylammonium cation of the electrolyte salts of known concentration (the protons of the $CH_2$ and Me groups).

Examples of isolation of the target products, their spectral characteristics, and elemental analysis data are given below.

**1,3-Dimethoxy-4-(tetrazol-1(2)-yl)benzenes** (see Table 1, entry *14*). The residue after evaporation of the solvent (20—35 °C, 25 Torr) was treated with diethyl ether, the ethereal extract was concentrated *in vacuo*, after chromatographic purification of the residue on silica gel (benzene), a mixture of indicated isomers was obtained (330 mg, 80%). Found (%): C, 62.15; H, 5.88; N, 32.07. $C_9H_{10}N_4$. Calculated (%): C, 62.05; H, 5.79; N, 32.16. $^1$H NMR, δ: 3.81—3.92 (m, 6 H, 2 MeO); 6.60—6.78 (m), 7.38 (d), 7.56 (d) (3 H, $C_6H_3$); 8.76, 9.34 (both s, 1 H each, H tetrazole). The product isolated in entry *15* had the same spectrum.

**1,3-Dimethoxy-4-(3-nitro-1,2,4-triazol-1-yl)benzene.** Similar treatment of the dry residue (see Table 1, entry *12*) led to the target product (220 mg, 44%). Found (%): C, 54.98; H, 4.70; N, 25.63. $C_{10}H_{10}N_4O_2$. Calculated (%): C, 55.04; H, 4.62; N, 25.68. $^1$H NMR, δ: 3.85, 3.92 (both s, 3 H each, 2 MeO); 6.66 (d), 6.78 (s), 7.60 (d) (3 H, $C_6H_3$); 8.96 (s, 1 H, H triazole). The reaction mixture obtained in entry *11* contained product with the same spectrum.

**1,3-Dimethoxy-4-(4-nitropyrazol-1-yl)benzene.** Similar treatment of the dry residue (see Table 1, entry *9*) led to the target product (240 mg, 48%). Found (%): C, 60.63; H, 5.61; N, 19.12. $C_{11}H_{12}N_3O_2$. Calculated (%): C, 60.54; H, 5.54; N, 19.25. $^1$H NMR, δ: 3.85, 3.94 (both s, 3 H each, 2 MeO); 6.52 (d), 6.72 (s), 7.57 (d) (3 H, $C_6H_3$); 8.21, 8.81 (both s, 2 H, H pyrazole). The reaction mixture obtained in entry *8* contained product with the same spectrum.

Products from entries *1*, *3—6* (see Table 1), and entry *1* (see Table 2) were not isolate.

$^1$H NMR spectra of reaction mixtures obtained in entries *1* and *3* exhibited the following signals, δ: 2.01, 2.11 (both s, 3 H each, 2 Me); 3.84 (br.s, 6 H, 2 MeO); 5.81 (s, 1 H, H pyrazole); 6.51—6.61 (m, 3 H, $C_6H_3$), which were assigned to **1,3-dimethoxy-4-(3,5-dimethylpyrazol-1-yl)benzene** based on analysis of the simulated $^1$H NMR spectra of compounds using the ACDlabs program. Such an approach has been used by us earlier.[11]

$^1$H NMR spectra of reaction mixtures obtained in entries *4—6* (see Table 1) exhibited the following signals, δ: 3.84, 3.90 (both s, 3 H each, 2 MeO); 6.59 (d), 6.60 (s), 7.54 (d) (3 H, $C_6H_3$); 7.90, 8.60 (both s, 2 H, H triazole), which were assigned to **1,3-dimethoxy-4-(1,2,4-triazol-1-yl)benzene**. $^1$H NMR spectra of reaction mixtures obtained in entry *1* (see Table 2) exhibited the following signals, δ: 3.89, 3.91 (both s, 6 H, 2 MeO); 7.02 (m, 1 H, H arom.); 7.35—7.50 (m, 1 H, H arom.); 7.62 (m, 1 H, H arom.); 8.81, 9.82 (both s, 1 H each, H tetrazole), which were assigned to isomers **1,2-dimethoxy-4-(tetrazol-1-yl)benzene** and **1,2-dimethoxy-4-(tetrazol-2-yl)benzene**.

This work was financially supported by the Council on Grants at the President of the Russian Federation (Program for the State Support for Leading Scientific Schools of the Russian Federation, Grant NSh-2942.2008.3).

## References

1. V. A. Petrosyan, A. V. Burasov, *Izv. Akad. Nauk, Ser. Khim.*, 2007, 2101 [*Russ. Chem. Bull., Int. Ed.*, 2007, **56**, 2175].
2. V. A. Petrosyan, A. V. Burasov, *Izv. Akad. Nauk, Ser. Khim.*, 2008, 285 [*Russ. Chem. Bull., Int. Ed.*, 2008, **57**, 292].
3. V. A. Petrosyan, *Elektrokhimiya*, 2003, 1353 [*Russ. J. Electrochem. (Engl. Transl.)*, 2003, 1211].
4. J. Catalan, J. L. M. Abbaud, J. Elguero, *Adv. Heterocycl. Chem.*, 1987, 250.
5. J. March, *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, McGraw-Hill, New York, 1968.
6. K. Yoshida, *Electrooxidation in Organic Chemistry*, J. Wiley and Sons, New York, 1984.
7. N. L. Weinberg, B. Belleau, *Tetrahedron*, 1973, **29**, 279.
8. S. Andreades, E. W. Zahnow, *J. Am. Chem. Soc.*, 1969, **91**, 4181.
9. L. I. Bagal", M. S. Pevzner, A. N. Frolova, N. I. Sheludyakova, *Khim. Geterotsikl. Soedin.*, 1970, 259 [*Chem. Heterocycl. Compd. (Engl. Transl.)*, 1970, **6**].
10. H. Kai, M. E. Niyazymbetov, D. H. Evans, *Tetrahedron Lett.*, 1995, **36**, 7027.
11. V. A. Chauzov, V. Z. Parchinskii, E. V. Sinel´shchikova, V. A. Petrosyan, *Izv. Akad. Nauk, Ser. Khim.*, 2001, 1215 [*Russ. Chem. Bull., Int. Ed.*, 2001, **50**, 1274].

*Received May 18, 2009;*
*in revised form September 21, 2009*