Electrochemical *N*-arylation of azoles in MeOH using undivided electrolysis of their mixtures with 1,4-dimethoxybenzene*

V. A. Petrosyan, A. V. Burasov, and T. S. Vakhotina*

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky prosp., 119991 Moscow, Russian Federation. Fax: +7 (095) 135 5328. E-mail: petros@ioc.ac.ru

The reactions of 1,4-dimethoxybenzene with azoles (pyrazole, triazole, and their derivatives, as well as tetrazole) were studied by undivided amperostatic electrolysis at Pt electrodes in MeOH. The process proceeds *via* the formation of a 1,1,4-trimethoxyarenonium cation as the key intermediate and affords 1,1,4,4-tetramethoxycyclohexa-2,5-diene, 1,1,4-trimethoxy-4-(azol-1-yl)cyclohexa-2,5-diene, and 1,4-dimethoxy-2-(azol-1-yl)benzene as the main products. Azole and solvent molecules compete as nucleophiles during electrolysis. A fine mechanism of the process was considered.

Key words: azoles, 1,4-dimethoxybenzene, paired electrosynthesis, *N*-dimethoxyphenylazoles.

Previous[1,2] results on undivided electrolysis of mixtures of a wide scope of azoles with 1,4-dimethoxybenzene (DMB) in MeCN showed that this process affords the *ortho*-substitution products and undescribed bisketal derivatives of *p*-quinone (Scheme 1). According to the process mechanism, the non-ionized azole species mainly acts as a nucleophile interacting with radical cation **1**.[1,2] This species exists in solution as complexes Az...H · B, where B is a base, which can be collidine or high-basicity azole molecules added to the electrolyzed solution.

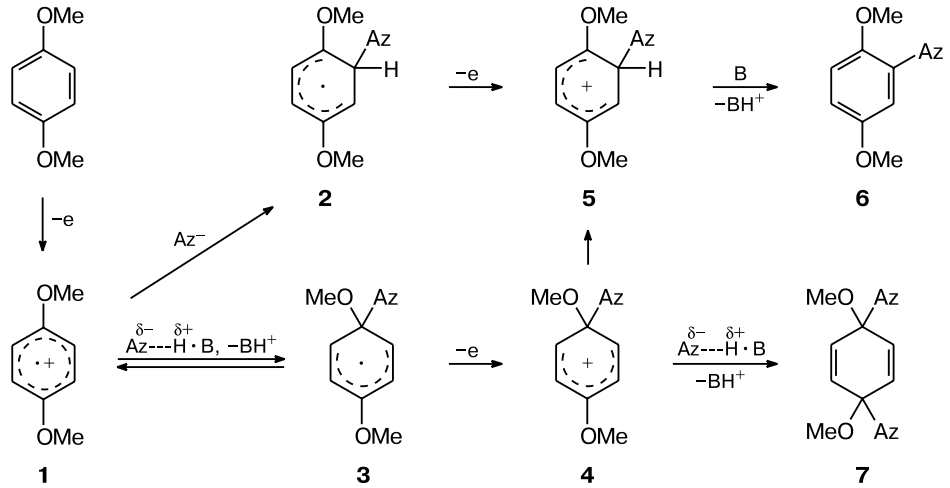
The key steps of the process[1,2] are the alternative *ipso*- or *ortho*-interaction of a nucleophile with radical cation **1** and the rearrangement of arenonium cation **4** → **5**, which indicates that the attack of the azolate anion to the *ortho*-position of radical cation **1** is not the single route providing product **6**.

In this connection, data on the electrolysis of an azole—DMB mixture in MeOH were of interest. As known, the electrolysis of DMB in a rather nucleophilic medium of MeOH proceeds according to Scheme 2 and produces[3] 1,1,4,4-tetramethoxycyclohexa-2,5-diene (**9**).

Therefore, we can expect that MeOH molecules can compete with complex Az...H · B during the electrolysis of an azole—DMB mixture in MeOH. We specially studied this problem to obtain additional information on the steps determining the mechanism of azole *N*-arylation. The objects of the study are presented in Table 1, and the

* Dedicated to Academician N. K. Kochetkov on the occasion of his 90th birthday.

Scheme 1



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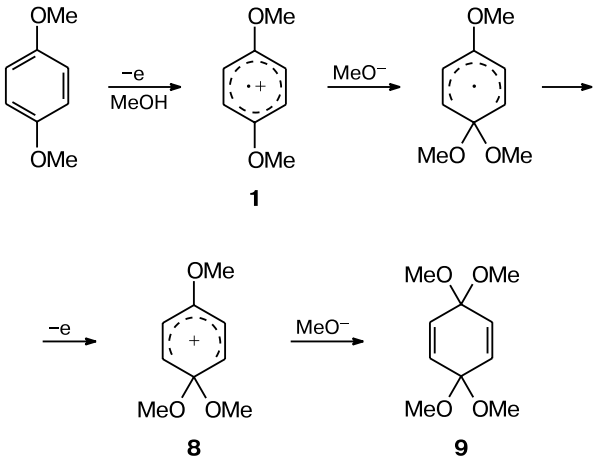
Scheme 2



azoles can conventionally be grouped as high- and low-basicity.[1,2]

Results and Discussion

The data on the electrochemical *N*-arylation of azoles in MeCN show[1,2] that the reaction between the electrophilic (radical cation DMB = E^+) and nucleophilic (azole complex) species, which proceeds according to Scheme 3, affords the primary intermediate responsible for the formation of azole arylation products during electrolysis, and the second product of this reaction is an onium compound.

The efficiency of this reaction (in which the electrophile E^+ is the same species) is determined by the difference in nucleophilic properties of possible co-reactants: azoles themselves, their complexes, and azolate anions. Low-basicity azoles (unlike high-basicity azoles) form poorly nucleophilic complexes if any. As a result, the electrolysis involving these azoles yields virtually no *N*-arylation products.[2] On the contrary, complexes of low-basicity azoles with collidine (CL) added to the reaction mixture are more nucleophilic and comparatively easily ionized[2] when approaching to E^+ (see Scheme 3). That is why only CL additives produce *N*-arylation products in the electrolysis involving low-basicity azoles, while the efficiency of these additives is less pronounced for electrolysis involving high-basicity azoles.[2]

Table 1. Azoles and their[4] pK_a*

Azole	pK_a^I	pK_a^{II}
"High-basicity" azoles		
3,5-Dimethylpyrazole (DMP)	15.0	4.1
Pyrazole (P)	14.2	2.5
1,2,4-Triazole (TA)	10.0	2.5
"Low-basicity" azoles		
3,4-Dinitro-5-methylpyrazoles (DNMP)	6.0	—
3-Nitro-1,2,4-triazole (NTA)	6.0	−3.7
Tetrazole (T)	4.9	−2.7

* The pK_a^I and pK_a^{II} values correspond to the equilibria $AzH \rightleftharpoons Az^- + H^+$ and $AzH_2^+ \rightleftharpoons AzH + H^+$, respectively.

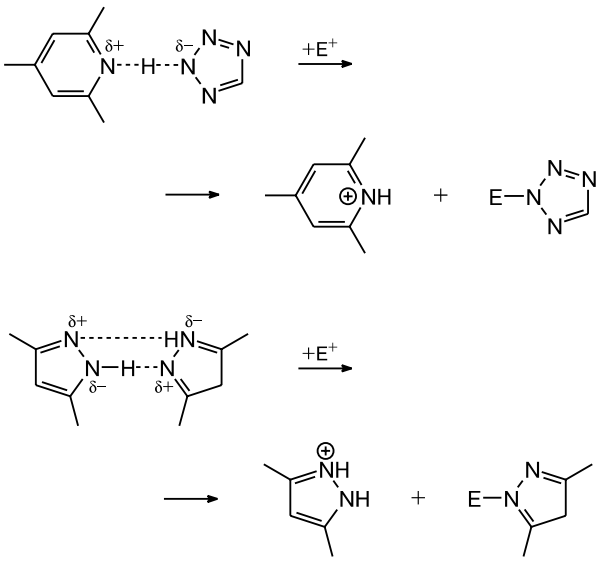
Electrophile E^+ (being radical cation **1**, see Scheme 1) predominantly undergoes the *ipso*-attack by the nucleophile[1,2] to form a radical, which is further oxidized to cation **4**. However, a solvent molecule can act as a nucleophile in the electrolysis of an azole—DMB mixture in MeOH. According to Scheme 2, the processes similar to those described above afford cation **8**. Taking into account these considerations, we proposed a series of possible reaction routes of the process (Scheme 4). Evidently, the nature of the final electrolysis products should be determined by the structure of intermediate arenonium cations **4** and **8** formed *via* alternative routes *a* and *b*.

In fact, if the electrolysis of an azole—DMB mixture in MeOH proceeds *via* route *a*, then the *ipso*-interaction of cation **8** with the nucleophiles, which are present in the reaction mixture (MeOH molecules and complex Az...H · B), would give the corresponding *ipso*-bisaddition products **9** and **10**. If the process proceeds *via* route *b*, then in both MeOH and MeCN media[2] the *ipso*-interaction of the primarily formed arenonium cation **4** with the same nucleophiles should result in both product **10** and *ipso*-bisaddition product **7**, whose structure differs substantially from the structure of product **9**.

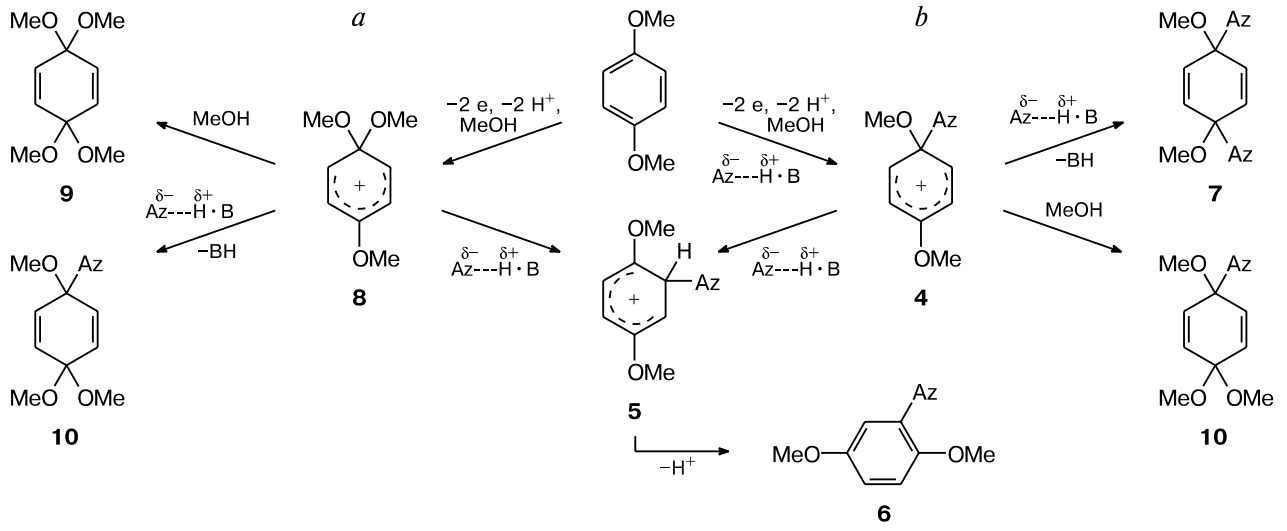
In addition, for both routes *a* and *b*, the final reaction mixture can contain *ortho*-substitution product **6**, whose formation routes will be discussed below.

Let us consider the results of electrolysis of an azole—DMB mixture in MeOH and the influence of various factors on this process from the above-discussed point

Scheme 3



Scheme 4



of view. We have previously[1,2] found that the electrolysis of an azole—DMB mixture with CL additives in MeCN produces *ipso*-bisaddition product **7**. However, its formation was detected in none of experiments on the electrolysis under the same conditions but in MeOH instead of MeCN (Table 2). Moreover, the tabulated data show that the electrolysis in MeOH gives *ipso*-bisaddition products **9** and **10** and not an alternative (see Scheme 4) pair of products **7** and **10**. These results almost unambiguously indicate that the electrolysis in MeOH proceeds through the formation of arenonium cation **8** as the key intermediate, *i.e.*, route *a* occurs.

As shown further, the composition, nature, and current efficiency of the final electrolysis products depend substantially on the conditions and even treatment procedure of the final reaction mixture. Analyzing these results, we revealed several regularities, which are important for the understanding of the electrochemical *N*-arylation of azoles, and refined substantially the process mechanism (Scheme 5).

According to this scheme, arenonium cation **8**, which is the key intermediate of the process that occurs during the electrolysis of an azole—DMB mixture in MeOH, interacts with nucleophiles in solution to form *ortho*-substitution products **6** and *ipso*-bisaddition products **9** and **10**. Note that the factors determining the relative content of these products are worth of careful analysis. On the one hand, the **9** : **10** ratio depends on the nucleophilicity of azole and changes during the electrolysis of an azole—DMB—CL mixture, for example, from 13 : 43 (for DMB) to 13 : 2 (NTA) or 38 : 2 (T) (see Table 2, entries *1*, *10*, and *14*, respectively). This result is not surprising, because, unlike complex DMP·CL, the complexes of less basic NTA or T with CL are more nucleophilic (see discussion of Scheme 3).

Table 2. Dependences of the composition and current efficiency of the electrolysis products of an azole—DMB mixture in MeOH on the nature of the additive used and treatment procedure of the reaction mixture[a]

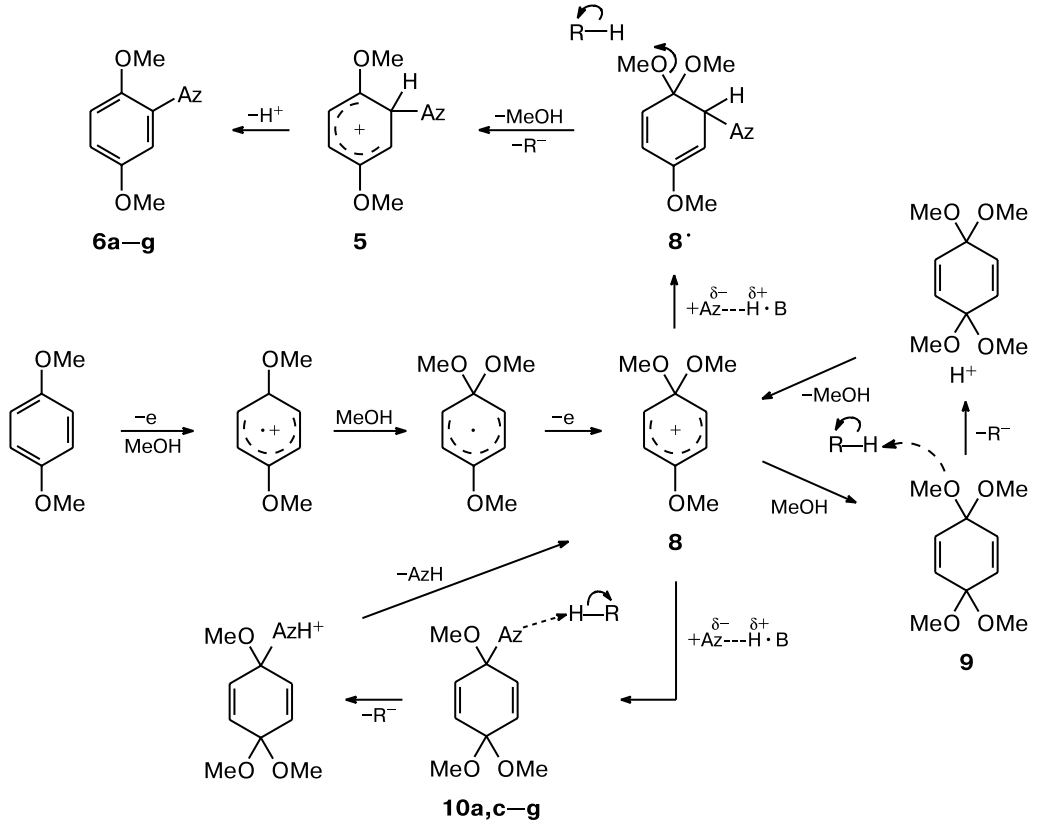
Entry	Azole	Additive	Treatment procedure	Product (current efficiency (%))		
				6	**9**	**10**
1	DMP	CL	*A*	**6a** (5)	43	**10a** (13)
2	DMP	CL	*B*	**6a** (57)	—	—
3	P	CL	*A*	—	54	—
4	P	CL	*B*	**6b** (17.5)	—	—
5	TA	CL	*A*	**6c** (5)	21	**10c** (38)
6	TA	CL	*B*	**6c** (10)[b]		—
7	DMP	AcOH	*A*	**6a** (11.5)	—	**10a** (13)
8	P	AcOH	*A*	**6b** (11.5)	—	—
9	TA	AcOH	*A*	**6c** (3)	—	—
10	NTA	CL	*A*	**6d** (5)	<2	**10d** (13)
11	NTA	CL	*B*	**6d** (18)		—
12	DNMP	CL	*A*	**6e** (4)	<2	**10e** (13)
13	DNMP	CL	*B*	**6e** (16)	—	—
14	T	CL	*A*	**6f** + **6g** (20)	<2	**10f** + **10g** (38)
15	T	CL	*B*	**6f** + **6g** (52)	—	—

[a] Reactant ratios: 1.5 moles of azole, 1 mole of DMB, 0.5 mole of CL, and 1.5 moles of AcOH; treatment procedure: *A*: after electrolysis, MeOH was distilled *in vacuo* at 20—25 °C; *B*: after MeOH was distilled off, the reaction mixture was stored for 5 h at 110 °C. Electrolysis conditions: Pt electrodes, 0.022 *M* Bu_4NClO_4, I = 50 mA, Q = 2 F per mole of DMB.

[b] 1,4-Dimethoxy-1,4-di(1,2,4-triazol-1-yl)cyclohexa-2,5-diene (**7c**) is also formed (11% current efficiency).

On the other hand, the electrolysis of azole—DMB—CL systems involving the most acidic azoles NTA, DNMP, and T produces only trace quanti-

Scheme 5



6, 10: Az is 3,5-dimethylpyrazol-1-yl (**a**), pyrazol-1-yl (**b**), 1,2,4-triazol-1-yl (**c**), 3-nitro-1,2,4-triazol-1-yl (**d**), 3,5-dinitro-5-methylpyrazol-1-yl (**e**), tetrazol-1-yl (**f**), tetrazol-2-yl (**g**)

RH = AzH, AzH_2^+, AcOH

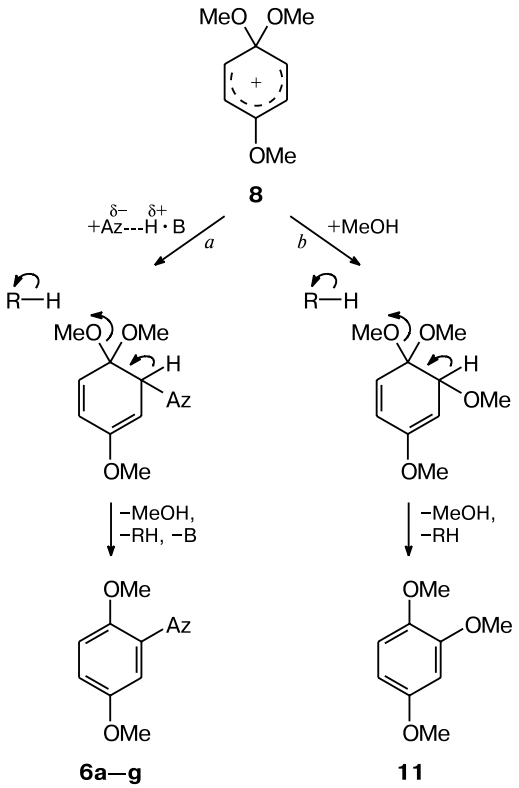
ties of **9** (see Table 2, entries *10*, *12*, and *14*). Moreover, for the electrolysis of high-basicity azoles, the replacement of CL additives in the initial reaction mixture by AcOH additives results in the complete disappearance of compound **9** from the electrolysis products (*cf.* entries *1—3* and *7—9*). As a whole, it follows from the data in Table 2 that the higher the acidity of the reaction mixture, the higher the content of products of *ipso*-bisaddition **10** and *ortho*-substitution **6** and the lower the content of *ipso*-bisaddition product **9** in the final reaction mixture. This acidity can be created by either rather acidic azoles ($pK \leq 6$), or special AcOH additives for electrolysis of low-acidity azoles.

The above-presented results enabled us to conclude that the role of the acidic component in the reaction mixture is the acid catalysis due to the electrophilic assistance for the elimination of the azole functional group from product **10** just as the elimination of the methoxy group from product **9** (see Scheme 5). Therefore, it is not accidental that the electrolysis involving azoles with the lowest acidity, which are incapable of efficient acid catalysis, produces noticeable amounts of product **9** in the reaction mixture (see Table 2, entries *1—3*). The validity of these conclusions are confirmed by an experiment on the replacement of CL additives by AcOH additive during the electrolysis involving low-acidity azoles. As a consequence, the results of these electrolyses become similar to the results of electrolyses involving the most acidic azoles (*cf.* entries *1—3* and *10*, *12* and *14*). Note that the transformations of compound **9** by nucleophilic agents (alcohols, thiols, and others) into the *ortho*-substituted DMB derivatives under the catalytic conditions by H-acids or Lewis acids have been described earlier.[5] We believe that the role of the catalyst in the electrolysis of an azole—DMB mixture can belong to the most acidic azoles or special AcOH additives and also onium species formed according to Scheme 3. This explains, for instance, the appearance of compounds **6** in the electrolysis products of a DMP—DMB mixture containing no special additives.[2]

The above-presented results indicate an important role of the acid catalysis, due to which (see Scheme 5) transformations **8** → **9** and **8** → **10** become reversible, to a

noticeable extent, for all azoles under study. These factors enhance the role of the third reaction route involving arenonium cation **8** and producing *ortho*-substitution product **6**. According to the earlier developed concepts, transformation **8** → **6** in MeCN for low-basicity azoles proceeds *via* the *cine*-substitution mechanism.[2] However, the above-mentioned reversibility of transformations **8** → **9** and **8** → **10** suggests that the steps describing the *cine*-substitution mechanism (Scheme 6, route *a*) can also occur in the electrolysis involving high-basicity azoles. Moreover, it follows from this scheme that the presence of R—H acids in the electrolyzed mixture can exert an electrophilic assistance for methoxy group elimination in this case as well.

Scheme 6



It cannot be ruled out that arenonium cation **8** can undergo an alternative nucleophilic attack to form 1,2,4-trimethoxybenzene (**11**) in such a nucleophilic medium as MeOH (see Scheme 6, route *b*). The fact that compound **11** was not observed among the electrolysis products in MeOH is explained by its substantially lower oxidation potential compared to that of DMB and, as a consequence, the complete "burning out" of **11** during electrolysis. Considerable electricity expenses to the formation of **11** and its subsequent oxidation explain, for instance, the low current efficiency of the arylation products when complex NTA · CL is used. For the more nucleophilic complex T · CL (see Table 2, entry *9*), the influence of this side process is less pronounced.

The mechanism proposed for azole *N*-arylation in MeOH is additionally confirmed by the data on the dependence of the nature, composition, and yield of the target products on the temperature of reaction mixture treatment after electrolysis. For this purpose, we carried out a special series of experiments in which methanol was removed from the reaction mixture after electrolysis at temperatures not higher than room temperature. A half of the obtained residue was analyzed immediately, and the remaining portion was analyzed only after its 5-h storage at 110 °C (see Table 2).

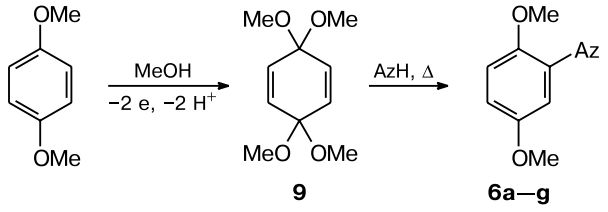
As can be seen from the data in Table 2, the heating of the reaction mixture after electrolysis always decreases the content (down to the complete disappearance) of *ipso*-bisaddition products **9** and **10** and simultaneously increases the content of *ortho*-substitution product **6**. A quite obvious reason for this effect is the facilitation of the acid-catalyzed steps of elimination of the methoxyl and azole functional groups from structures **8**$^{\bullet}$, **9**, and **10** (see Scheme 5) with the temperature increase.

As a whole, our studies showed that compounds **9** and **10** are formed along with *ortho*-substitution product **6** as real primary products of the electrochemical *N*-dimethoxyphenylation of azoles in MeOH (see Scheme 5). An experimentally found possibility of the reversible transformation of arenonium cation **8** into compounds **9** and **10** during electrolysis is principally important. This suggests, in turn, that the *ortho*-attack of cation **8** by the azolic nucleophile with the simultaneous removal of the methoxy group *via* the *cine*-substitution mechanism makes a determining contribution to the formation of *ortho*-substitution product **6**.

A possibility to obtain *ortho*-substitution products **6** by the alternative method is also significant. The matter is that the *N*-arylation of azoles occurred in the present and previous[1,2] works directly during electrolysis, *i.e.*, the direct electrochemical synthesis of the target products was carried out. However, the data in Table 2 indicate a probable transformation of *ipso*-bisaddition products **9** and **10** into *ortho*-substitution product **6** by the simple heating of the reaction mixture, which is a prerequisite for the preparation of the target products by indirect electrochemical synthesis. This approach consists of the preparation of bisketal **9** in the first step by electrochemical DMB oxidation in MeOH and the reaction of **9** with azoles on heating to form product **6** in the second step (Scheme 7).

A principal possibility to carry out the indirect electrosynthesis of arylazoles is confirmed by the fact (in addition to the already mentioned data in Table 2) that bisketal **9** formed by DMB electrolysis in MeOH is capable of irreversible exchange interacting with T under mild conditions (70 °C, 30 min), when T is added to the

Scheme 7



reaction mixture after electrolysis. As a result, product **6** was obtained in high yield.[2] In future, we are intending to develop this approach to the synthesis of *N*-arylazoles.

Experimental

^{1}H NMR spectra of sample solutions in a DMSO-d_6—CCl_4 (1 : 1, vol/vol) mixture were recorded on a Bruker AC-300 instrument.

Azole salts Alk_4N^+ were synthesized according to a general procedure,[6] and Bu_4NClO_4 was synthesized by the exchange reaction of the corresponding bromide and $NaClO_4$ followed by recrystallization from ethanol. Commercial (Lancaster) DMB, TA, NTA, T, and CL (purity 98—99%) were used. 4-Nitropyrazole and 3,4-dinitro-5-methylpyrazole were synthesized according to a previously described procedure.[7] Commercial MeOH was used without preliminarily dehydration.

Electrosynthesis of *N*-arylazoles (general procedure). A mixture of DMB (2 mmol) and azole (3 mmol) was dissolved in methanol (45 mL) containing AcOH or CL additives (see Table 2). The resulting solution was subjected to amperostatic electrolysis (I = 50 mA) under argon, passing 2 F electricity per 1 mole of DMB (see Table 2). After the end of electrolysis, the solvent was distilled off on a rotary evaporator at 20—25 °C (25—30 Torr), and the residue was analyzed by ^{1}H NMR. In some cases, the residue after solvent evaporation was additionally heated for 5 h at 110 °C. The apparatus and typical procedure of experiments are similar to those described in Refs 1 and 2 along with the procedure of determination of the current efficiencies of compounds **6** and **9** (calculated for the two-electron transformation of DMB) without their isolation from the mixture, which is based on the spectral data and was used for the identification of compounds of **6**, **9** series.

The spectral (^{1}H NMR) characteristics of the compounds[2] were used to identify and determine the content of synthesized *N*-arylazoles **6**, **7**, and **10** in reaction mixtures.

1,4-Dimethoxy-2-(3,5-dimethylpyrazol-1-yl)benzene (6a). ^{1}H NMR, δ: 2.14, 2.20 (both s, 6 H, Me); 3.70, 3.78 (both s, 6 H, MeO); 5.90 (s, 1 H, CH azole); 6.80—7.07 (m, 3 H, CH arom.).

1,4-Dimethoxy-2-(pyrazol-1-yl)benzene (6b). ^{1}H NMR, δ: 3.79, 3.84 (both s, 3 H, MeO); 6.40 (t, 1 H, CH azole, J = 9.1 Hz); 6.84 (dd, 1 H, CH arom., J_1 = 3.1 Hz, J_2 = 10.0 Hz); 7.10, 7.30 (both d, 1 H each, CH arom., J = 3.1 Hz); 7.60, 8.15 (both d, 1 H each, CH azole, J = 9.1 Hz).

1,4-Dimethoxy-2-(1,2,4-triazol-1-yl)benzene (6c). ^{1}H NMR, δ: 3.80, 3.90 (both s, 6 H, MeO); 6.94—7.35 (m, 3 H, C_6H_3); 8.04, 8.85 (both s, 2 H each, $C_2H_2N_3$).

1,4-Dimethoxy-2-(3,4-dinitro-5-methylpyrazol-1-yl)benzene (6d). ^{1}H NMR, δ: 2.60 (s, 3 H, Me); 3.80, 3.83 (both s, 6 H, MeO); 7.04—7.17 (m, 3 H, CH arom.).

1,4-Dimethoxy-2-(3-nitro-1,3,4-triazol-1-yl)benzene (6e). ^{1}H NMR, δ: 3.82, 3.92 (both s, 6 H, MeO); 7.05—7.30 (m, 3 H, CH arom.); 9.13 (s, 1 H, CH azole).

1,4-Dimethoxy-2-(tetrazol-1-yl)benzene (6f) and 1,4-dimethoxy-2-(tetrazol-2-yl)benzene (6g) (mixture of *N*-isomers, 3 : 2). ^{1}H NMR, δ: 3.76—3.89 (four s, 6 H, MeO); 7.05—7.32 (m, 3 H, C_6H_3); 8.96, 9.59 (both s, 1 H, CHN_4).

1,4-Dimethoxy-1,4-di-(1,2,4-triazol-1-yl)cyclohexa-2,5-diene (7c) (mixture). ^{1}H NMR, δ: 3.20, 3.30 (both s, 6 H, Me); 6.59, 6.70 (both s, 4 H, CH arom.); 7.88, 7.92, 8.61, 8.72 (all s, 4 H, CH azole).

1,1,4,4-Tetramethoxycyclohexa-2,5-diene (9). ^{1}H NMR, δ: 3.20 (s, 12 H, MeO); 6.00 (s, 4 H, *p*-C_6H_4).

1,1,4-Trimethoxy-4-(1,2,4-triazol-1-yl)cyclohexa-2,5-diene (10c). ^{1}H NMR, δ: 3.20, 3.25, 3.30 (all s, 9 H, MeO); 6.25, 6.35 (both d, 4 H, *p*-C_6H_4, J_1 = J_2 = 12 Hz); 7.80, 8.52 (both s, 2 H, $C_2H_2N_3$).

1,1,4-Trimethoxy-4-(3,4-dinitro-5-methylpyrazol-1-yl)cyclohexa-2,5-diene (10d). ^{1}H NMR, δ: 2.70 (s, 3 H, Me); 3.30, 3.32, 3.62 (all s, 9 H, MeO); 4.93—6.20 (m, 4 H, *p*-C_6H_4).

1,1,4-Trimethoxy-4-(3-nitro-1,2,4-triazol-1-yl)cyclohexa-2,5-diene (10e). ^{1}H NMR, δ: 3.20, 3.25, 3.60 (all s, 9 H, MeO); 5.07—6.16 (m, 4 H, *p*-C_6H_4); 8.60 (s, 1 H, $C_2HN_4O_2$).

1,1,4-Trimethoxy-4-(tetrazol-1-yl)cyclohexa-2,5-diene (10f) and 1,1,4-trimethoxy-4-(tetrazol-2-yl)cyclohexa-2,5-diene (10g) (mixture of *N*-isomers in a ratio of 2 : 1). ^{1}H NMR, δ: 3.20—3.30, 3.60 (all br.s, 9 H, MeO); 4.97—6.15 (m, 4 H, *p*-C_6H_4); 8.50, 8.84 (both s, 1 H, CHN_4).

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