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Mendeleev Commun., 2018, **28**, 518–520

Mendeleev Communications

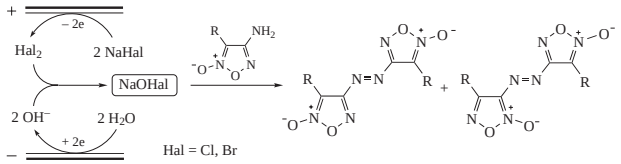
Eco-friendly N–N coupling of aminofuroxans into azofuroxans under the action of electrogenerated hypohalites

Boris V. Lyalin, Vera L. Sigacheva, Leonid L. Fershtat, Nina N. Makhova 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.2018.09.023

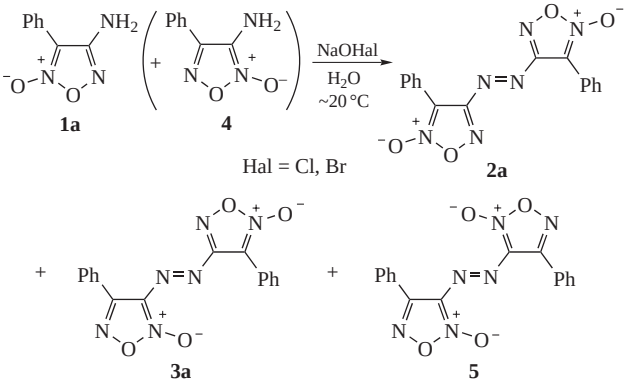
A new eco-friendly synthesis of azofuroxans comprises the oxidative N–N coupling of aminofuroxans under the action of electrogenerated NaOCl and NaOBr. In addition, an oxidative isomerization of the aminofuroxan motif was found for the first time, which resulted in a formation of unsymmetrical azofuroxans.



In recent decades, 1,2,5-oxadiazole 2-oxides (furoxans) have attracted considerable attention due to their ability to release nitric oxide (NO) under physiological conditions.[1] On the other hand, furoxan derivatives are of interest as potential components of high-energy formulations due to a positive enthalpy of formation and the presence of two active oxygen atoms.[2] Energy-rich furoxans have been comprehensively studied by researchers of the N. D. Zelinsky Institute of Organic Chemistry.[3] Among the structures of this type, azofuroxans are promising high energy compounds, for example, 4,4′-dinitro-3,3′-azofuroxan possesses a density of 2.002 g cm^{-3} and enthalpy of formation of 1114 kcal kg^{-1}.[4] However, synthesis of azofuroxans requires oxidative condensation of aminofuroxans under the action of toxic transition metal-based reagents (*e.g.*, $KMnO_4$) in an organic solvent–HCl mixture. Therefore, a search for novel eco-safe procedures for the conversion of aminofuroxans into azofuroxans remains relevant.

Electrochemical methods which employ anode as a 'green oxidizing agent' look promising since the electrooxidation can be carried out under environmentally benign conditions in water in the absence of transition metals. Recently, we created a novel method for the N–N coupling of aminofurazans[5] and N-alkylated aminopyrazoles[6,7] using electrogenerated NiO(OH), NaOCl and NaOBr as redox mediators. Herein, we describe a new, efficient, regioselective and environmentally friendly method for the synthesis of isomeric azofuroxans by the N–N coupling of aminofuroxans under the action of electrogenerated NiO(OH), NaOCl and NaOBr in aqueous media.

To find the optimum reaction conditions, 4-amino-3-phenylfuroxan **1a** was tested as a model compound. Its electrolysis in the presence of 0.2 M NaOH in an undivided cell equipped with Ni anode and Ti cathode at 25 °C resulted in a low substrate **1a** conversion as well as in a low azofuroxan **2a** yield (Scheme 1, Table 1, entry 1).† Raising the reaction temperature to 70 °C increased the amine conversion up to 50%, however, azofuroxan **2a** yield was only 5% (entry 2), which was probably caused by decomposition of amine **1a** in basic medium.[8] Therefore, the electrogeneration of NiO(OH) as redox-mediator in a one-pot process was found to be unsuccessful.



Scheme 1

Table 1 Optimization of the N–N coupling of 4-amino-3-phenylfuroxan **1a** at ~20 °C.

Entry	Substrate	Reagent (equiv.)	Conversion (%)	Products	Isolated yield (%)
1	**1a**	NiO(OH)[a] (1)	3	**2a**	3
2	**1a**	NiO(OH)[a,b] (1)	50	**2a**	5
3	**1a**	NaOCl[a] (1)	50	mixture	~20[d]
4	**1a**	NaOCl[c] (1)	95	**2a**	40
				3a	20
5	**1a**	NaOCl[c] (3)	95	**2a**	69[e]
				3a	23[e]
6	**1a** + **4** (1 : 1)	NaOCl[c] (1)	97	**2a**	20[e]
				3a	10[e]
				5	50[e]
7	**4**	NaOCl[c] (1)	85	**5**	80
8	**1a**	NaOBr[c] (1)	80	**2a**	48[e]
				3a	24[e]
9	**1a**	NaOBr[c] (1)	80	**2a**	60[e]
				3a	20[e]
10	**1a**	NaOBr[c] (2)	95	**2a**	80

[a] One-pot reaction. [b] At 70 °C. [c] Two step-procedure. [d] Of product mixture. [e] Isomer ratio from ^{1}H NMR data.

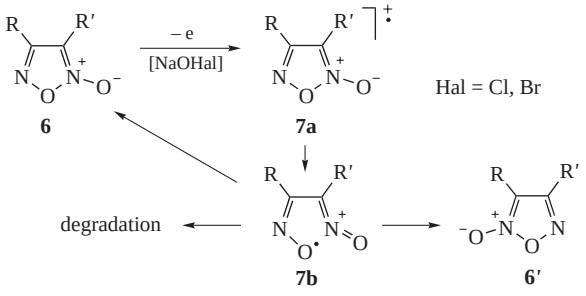
† *Oxidation of 4-amino-3-phenylfuroxan* **1a** *with redox mediator NiO(OH).* Sodium hydroxide (0.2 M solution, 100 ml) and 4-aminofuroxan **1a** (0.354 g, 2 mmol) were placed in an undivided cell equipped with a NiO(OH) anode[13] (S = 48 cm^2) and Ti cathode (S = 20 cm^2). Electrolysis was carried out at 290 mA current and room temperature (or 70 °C) by passing 2 F of electricity per mole of the starting aminofuroxan **1a** (Q = 386 C). After the electrolysis was stopped, the reaction mixture was stirred for 30 min, extracted with CH_2Cl_2 (3 × 50 ml), the combined organic layers were washed with water and dried over $MgSO_4$.

The N–N coupling using NaOCl in a one-pot electrolysis of a mixture of aminofuroxan **1a** and saturated NaCl aqueous solution proved to be more effective.‡ On using equimolar reagent ratio, 50% amine conversion was achieved and a complex mixture of products including target azofuroxan **2a** (TLC monitoring) was obtained (see Table 1, entry 3). It can be proposed that under one-pot conditions the rate of amine **1a** decomposition was higher than the rate of its oxidative coupling.

The more effective two-step protocol included: 1) electrolysis of saturated aqueous NaCl for the preparation of electrogenerated NaOCl, 2) addition of aminofuroxan, and further stirring the reaction mixture at room temperature in the absence of electric current until the full consumption of the starting amine **1a**.§ When equimolar amounts of reagents were used, 95% conversion of amine **1a** was achieved. However, along with required azofuroxan **2a** (40% yield), unexpected regioisomer **3a** was also isolated in a 20% yield (see Scheme 1 and Table 1, entry 4). Compound **3a** may be regarded as a product of N–N coupling of amine **1a** and isomeric 3-amino-4-phenylfuroxan **4**. Azofuroxans **2a** and **3a** were separated by column chromatography and completely characterized. An increase in NaOCl amount up to 3 equiv. afforded the same products but in higher overall yield and with better regioselectivity (entry 5). When a mixture of isomeric aminofuroxans **1a** and **4** (1 : 1) was taken, symmetrical azofuroxans **2a** and **5** (see Scheme 1) were mostly formed with predominance of the latter, however, small amounts of unsymmetrical isomer **3a** were also detected (see Table 1, entry 6). A higher yield of 4,4′-diphenyl-3,3′-azofuroxan **5** is possibly due to the higher rate of the oxidative N–N coupling because of the higher nucleophilicity of 3-amino derivative **4** in comparison with that of 4-amino one **1a**.[9] A possibility of formation of azofuroxan **5** in the course of oxidation of 3-aminofuroxan **4** was confirmed independently by a treatment of the latter with NaOCl under the same conditions (entry 7). Nevertheless, the most effective oxidant for the N–N coupling of aminofuroxan **1a** into azo derivative **2a** proved to be electrogenerated NaOBr. In a one-pot process, NaOBr provided 80% conversion of amine **1a** and 72% overall yield of azo compounds **2a** and **3a** (**2a** : **3a** = = 2 : 1, entry 8). Moving to a two-step protocol for the equimolar amounts of reagents resulted in an increase of the overall yield (80%) and regioselectivity (**2a** : **3a** = 3 : 1, entry 9). Raising NaOBr amount up to 2 equiv. afforded only symmetrical azofuroxan **2a** in a 80% yield (entry 10).

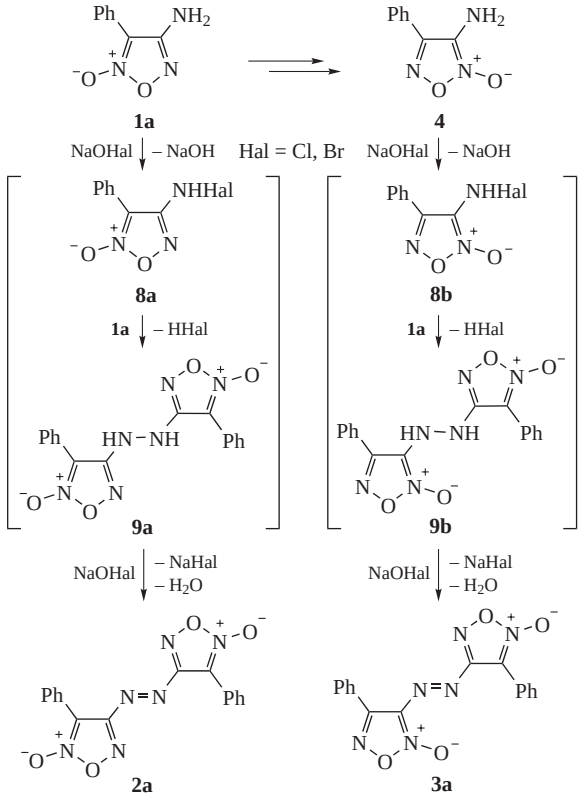
In ^{1}H NMR spectra of isomeric azofuroxans **2a**, **3a** and **5**, the differences in chemical shifts of *ortho*-protons in phenyl substituents are distinctive. For isomer **2a**, these protons resonate as a doublet at 7.60 ppm, and for isomer **5** their signals appear at 8.05 ppm. For unsymmetrical azofuroxan **3a**, the chemical shifts for *ortho*-protons in nonequivalent aromatic rings are observed at 7.70 and 7.76 ppm. ^{13}C NMR spectrum of furoxan **3a** contains a signal at 124.1 ppm corresponding to the C(3) carbon atom of the furoxan ring connected to the azo group.[4(*b*)]

The formation of unsymmetrical azofuroxan **3a** is rather unexpected, since this compound was never formed during oxidation of aminofuroxans with $KMnO_4$.[4(*b*),10] Previously,[11] the study of electrooxidation of furoxans **6** on Pt anode showed that this process involved the generation of unstable radical cation intermediate **7a** followed by ring cleavage to another unstable radical cation **7b** which either underwent degradation or recyclization with the formation of initial furoxan **6** or isomeric furoxan **6′** (Scheme 2). It may be assumed, that a similar process is responsible for the isomerization of 4-amino-3-phenylfuroxan **1a** into 3-amino-4-phenylfuroxan **4** under the action of hypohalites.



Scheme 2

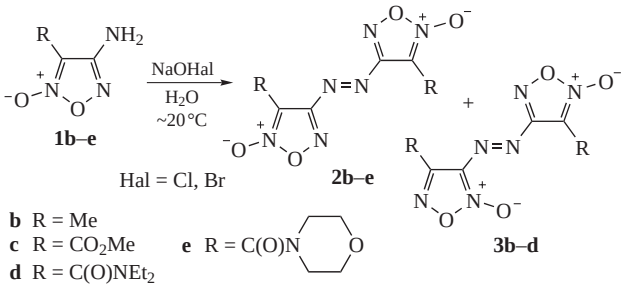
Based on this assumption, some literature precedents[12] and our recent results on the synthesis of azopyrazoles,[7] we proposed the plausible mechanism for the oxidative N–N coupling of aminofuroxans. Since hypohalites can serve simultaneously as halogenating reagents and oxidants, the transformation of isomeric furoxans **1a** and **4** into azofuroxans **2a** and **3a** should occur in several steps (Scheme 3). At first, initial amines transform into



Scheme 3

‡ *One-pot oxidation of aminofuroxans with electrogenerated NaOCl and NaOBr*. Saturated NaCl solution (100 ml) or 2 M NaBr solution (100 ml) and aminofuroxan **1a**,**b** were placed in an undivided cell and electrolysis was carried out as described above with passing 2 F of electricity per mole of the starting aminofuroxan **1a**,**b** (Q = 386 C). After the electrolysis was stopped, the reaction mixture was stirred at 25 °C for 5 h, extracted with CH_2Cl_2 (3 × 50 ml), the combined organic layers were washed with water and dried over $MgSO_4$. After evaporation of the solvent the corresponding azofuroxans were isolated by column chromatography on SiO_2 (eluent $CHCl_3$).

§ *Two-step oxidation of aminofuroxans with electrogenerated NaOCl (NaOBr)*. Saturated NaCl solution (100 ml) was placed in an undivided cell equipped with a ruthenium–titanium oxide anode (S = 7.85 cm^2) and Ti cathode (S = 10 cm^2). Electrolysis was carried out at 1260 mA current and 25 °C. Electrosynthesis of NaOBr was performed analogously using 2 M NaBr solution and 785 mA current. Then appropriate aminofuroxan **1a**–**e** (2 mmol) was added. The reaction mixture was stirred at 25 °C for 5 h, extracted with CH_2Cl_2 (3 × 50 ml), the combined organic layers were washed with water and dried over $MgSO_4$. After evaporation of the solvent, the corresponding azofuroxans **2** and **3** were isolated by column chromatography on SiO_2 (eluent $CHCl_3$). Full characterization of the products is given in Online Supplementary Materials.



Scheme 4

Table 2 Substrate scope and conditions for the preparation of azofuroxans **2b–e** and **3b–d** (see Scheme 4).

Entry	Amine **1**	Reagent (equiv.)	Products	Isolated yield (%)
1	**1b**	NaOBr (1)	**2b**	57
			3b	9
2	**1b**	NaOBr (2)	**2b**	83
3	**1b**	NaOCl (1)	**2b**	34[a]
			3b	4[a]
4	**1b**	NaOCl (3)	**2b**	66
5	**1c**	NaOCl (3)	**2c**	38
			3c	26
6	**1d**	NaOCl (3)	**2d**	42
			3d	28
7	**1e**	NaOCl (3)	**2e**	69

[a] Isomer ratio from ^{1}H NMR data.

N-haloamines **8a**,**b** which upon condensation with amines form hydrazo compounds **9a**,**b**. The oxidation of the latter with hypohalites brings about the target azo derivatives.

Using the found optimal conditions, we investigated the substrate scope for the synthesis of azofuroxans **2b**–**e** and **3b**–**e** (Scheme 4, Table 2). In all cases the conversion of initial aminofuroxans **1** was not less than 95–99%. The reaction of 4-amino-3-methylfuroxan **1b** with NaOBr (1 equiv.) was quite similar to that of aminofuroxan **1a** and gave a mixture of isomeric azofuroxans **2b** and **3b** with predominance of symmetrical one **2b** (see Table 2, entry 1). Increase in NaOBr amount to 2 equiv. provided a single isomer **2b** in high yield (entry 2). In the presence of equimolar amount of NaOCl, a mixture of isomers **2b** and **3b** with predominance of isomer **2b** was obtained (entry 3), while increase in NaOCl amount to 2 equiv. afforded only azofuroxan **2b** (entry 4), the total yields of the products being somewhat lower than with the use of NaOBr. Aminofuroxans **1c**–**e** bearing electron-withdrawing substituents decomposed on contact with NaOBr, therefore, their coupling was performed with NaOCl. Aiming to obtain only symmetrical azofuroxans **2c**–**e**, we carried out these oxidations with excess of NaOCl (entries 5–7). However, a single isomer (**2e**) was formed only from aminofuroxan **1e** bearing a bulky morpholinocarbonyl substituent at C(3) carbon of the furoxan ring (entry 7). In two other cases, even with excess of NaOCl the corresponding mixtures of isomers **2c**,**d** and **3c**,**d** (luckily, separable) were obtained in moderate yields (entries 5, 6). Insufficiently high yields of these azo compounds along with high conversion of aminofuroxans **1b**–**e** can be explained by a strong decomposition of initial amines under reaction conditions. This side process prevailed for aminofuroxans bearing electron-withdrawing groups that reduced nucleophilicity of their amino groups, which, in turn, decelerated the N–N coupling step.

In conclusion, the oxidative N–N coupling of aminofuroxans into azofuroxans using electrogenerated sodium hypohalites has been elaborated for the first time. A two-step oxidation comprising electrogeneration of hypohalite followed by its reaction with aminofuroxan proceeds more efficiently than one-pot electrolysis. A capability of 4-aminofuroxans to undergo oxidative isomerization into 3-aminofuroxans on contact with hypohalites has been discovered. The oxidation of aminofuroxans bearing aliphatic and aromatic substituents with NaOBr is more effective than that with NaOCl. However, for aminofuroxans with electron-withdrawing substituents only NaOCl is suitable. As a result, a simple, efficient, eco-friendly, regioselective method for the synthesis of isomeric azofuroxans by oxidation of 3- and 4-aminofuroxans excluding the utilization of toxic oxidants has been developed. All these advantages make the electrooxidative N–N coupling methodology quite promising for the subsequent applications. The synthesized compounds are of interest as potential substrates for the synthesis of new energetic furoxan derivatives.

This work was supported by the Russian Foundation for Basic Research (grant no. 16-03-00173a).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2018.09.023.

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Received: 5th April 2018; Com. 18/5529