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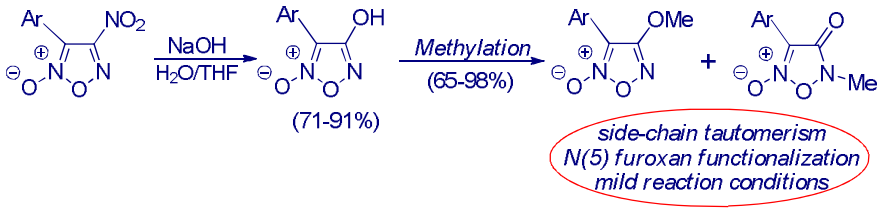

Side-chain prototropic tautomerism of 4-hydroxyfuroxans in methylation reactions

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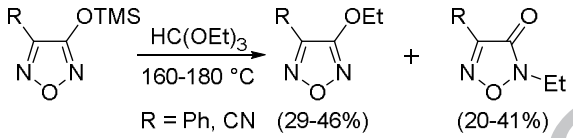
Abstract

A general and simple method for the preparation of under explored 3-aryl-4-hydroxyfuroxans by nucleophilic substitution of the nitro group in 3-aryl-4-nitrofuroxans using NaOH in H_2O-THF has been developed. The methylation of 3-aryl-4-hydroxyfuroxans was studied with various methylating reagents (CH_2N_2, MeI, $(MeO)_2SO_2$) which showed for the first time that 3-aryl-4-hydroxyfuroxans are prone to side-chain prototropic tautomerism. Furoxan derivatives of a novel type, *N*(5)-alkylation products (3-aryl-5-methyl-1,2,5-oxadiazol-4(2*H*)-one 2-oxides), were synthesized under mild conditions, along with regioselective formation of the *O*-alkylation products (3-aryl-4-methoxyfuroxans).

Keywords: 3-aryl-4-hydroxyfuroxans; nucleophilic substitution; side-chain prototropic tautomerism; *O*- and *N*-methylation; regioselectivity.

Tautomerism is a prevailing property of heterocyclic compounds and is defined as a phenomenon in which two or more molecular structures exist in dynamic equilibrium with each other. One of the most widely studied type of tautomerism is side-chain prototropic tautomerism, involving migration of a proton between a ring and a side-chain atom.[1] Our research interest is concerned with the synthesis and reactivity of different azoles, primarily, 1,2,5-oxadiazoles (furazans) and their 2-oxides (furoxans).[2] Furazans are stable systems which are not prone to tautomerism involving annular centers, and although side-chain tautomerism involving functional groups (e.g. tautomerism of OH and NH forms) can be theoretically conceived,[3] IR and NMR spectral data for hydroxyfurazans shows only the presence of the hydroxy form.[1c,4]

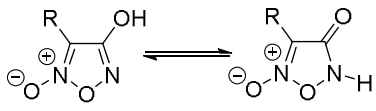
Nevertheless, the alkylation of trimethylsilyl derivatives of hydroxyfurazans with triethyl orthoformate at high temperature (160-180 °C)[5] was reported to give a mixture of *O*-alkylation products and the first representatives of *N*-alkylation products, 2-ethyl-l,2,5-oxadiazol-3(2*H*)-ones (Scheme 1). This provided evidence for possible side-chain prototropic tautomerism of hydroxyfurazans. However, the alkylation of hydroxyfurazans with diazomethane[6] and dimethyl sulfate[7] was found to yield only *O*-alkylation products.



Scheme 1. Alkylation of trimethylsiloxyfurazans with triethylorthoformate.

Only single examples of hydroxyfuroxans are described in the literature,[8-10] and their reactions with electrophilic reagents, in particular alkylation reactions, have not been studied; therefore no data about the possibility of side-chain prototropic tautomerism are currently available.

Meanwhile, furoxans represent a distinct group of heterocyclic compounds exhibiting interesting biological activities,[11] including neuroprotective and precognitive,[12] cytotoxic,[13] antihelmintic,[14] antibacterial,[15] and fungicidal[16] properties, depending on the structure of the furoxan ring substituents. Thereby we aimed to synthesize a series of under explored hydroxyfuroxans and to study their propensity for side-chain prototropic tautomerism during alkylation reactions. It could be expected that hydroxyfuroxans would be more prone to side-chain prototropic tautomerism than hydroxyfurazans, because of the lower aromaticity of the furoxan ring due to the positively charged N(2)-nitrogen atom in the *N*-oxide moiety, which interrupts conjugation[17] (Scheme 2).



Scheme 2. Possible tautomeric forms of hydroxyfuroxans.

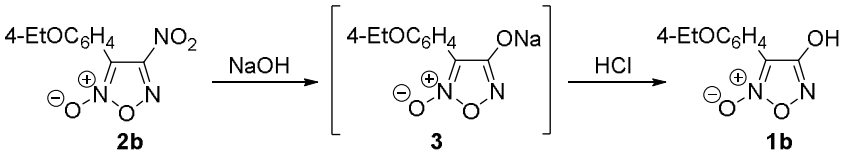
Several hydroxyfuroxan derivatives are described in the literature.[8-10] However, to the best of our knowledge, there is no general method for their synthesis.

Herein, we present the development of a general method for the preparation of 3-aryl-4-hydroxyfuroxans **1** by nucleophilic substitution of the nitro group in 3-aryl-4-nitrofuroxans **2** under the action of NaOH in H_2O-THF and their methylation by different methylating reagents

(CH_2N_2, MeI, $(MeO)_2SO_2$). For the first time hydroxyfuroxans **1** were shown to be prone to side-chain prototropic tautomerism and novel furoxan derivatives, *N*(5)-alkylation products (3-aryl-5-methyl-1,2,5-oxadiazol-4(2*H*)-one 2-oxides) along with *O*-alkylation products (3-aryl-4-methoxyfuroxans), were formed in different molar ratios, depending on the methylating reagent used and the aromatic ring substituents of the starting 3-aryl-4-nitrofuroxans **2**, with regioselective formation of *O*-alkyl derivatives achieved under very mild conditions.

3-Aryl-4-hydroxyfuroxans **1** were selected as suitable substrates for this research and were prepared using a modification of Wieland's approach[8] based on nucleophilic displacement of the nitro groups in readily accessible 3-aryl-4-nitrofuroxans[18] **2** under the action of NaOH in water-Et_2O. Investigations began with screening the optimal conditions for the reaction of model substrate 3-(4-ethoxyphenyl)-4-nitrofuroxan **2b** with NaOH. The **2b**:NaOH molar ratio and the reaction medium were varied (Table 1). The conditions of Wieland's method proved to be unsuitable for the synthesis of hydroxyfuroxan **1b** (Table 1, entry 1). Evidently, according to literature data,[19] the furoxan ring was substantially opened in the presence of a large excess of NaOH. Decreasing the amount of NaOH (2 equiv.) and homogenization of the reaction medium by replacing Et_2O with dioxane resulted in an increased yield (50%, entry 2). Replacement of dioxane by THF resulted in a further minor increase in yield (56%, entry 3). The optimal conditions for the synthesis of 3-(4-ethoxyphenyl)-4-hydroxyfuroxan **1b** proved to be: **2b**:NaOH (molar ratio 1:3) in H_2O-THF (1:1 v/v) for 5 h at 20 °C (Entry 5). Use of a decreased **2b**:NaOH molar ratio (1:2.5) was less successful in terms of yield (Entry 4). The use of an increased **2b**:NaOH molar ratio (1:4) resulted in a small decrease in yield (Entry 6), while further increasing the **2b**:NaOH molar ratio (1:5) significantly decreased the yield of **1b** (Entry 7). Hydroxyfuroxan **1b** was isolated in all cases from the intermediate sodium salt **3** by acidification of the reaction mixture to pH 1.

Table 1. Screening of reaction conditions for the preparation of 3-(4-ethoxyphenyl)-4-hydroxyfuroxan **1b**[a]



2b **3** **1b**

Entry	NaOH (equiv.)	Reaction medium	Yield **1b**[b] (%)
1	8	H_2O/ether (1:1 v/v)	10
2	2	H_2O/dioxane (1:1 v/v)	50
3	2	H_2O/THF (1:1 v/v)	56

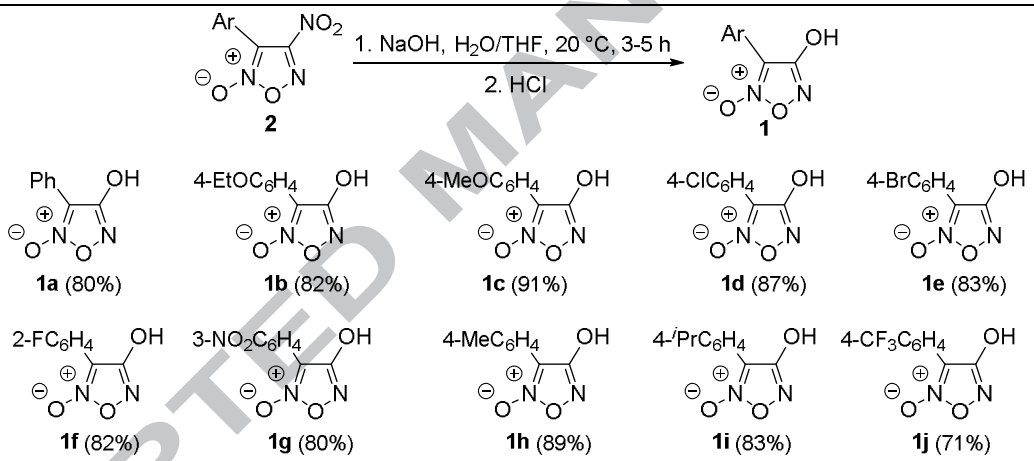
4	2.5	H_2O/THF (1:1 v/v)	70
5	3.0	H_2O/THF (1:1 v/v)	82
6	4.0	H_2O/THF (1:1 v/v)	76
7	5.0	H_2O/THF (1:1 v/v)	67

[a] Reaction conditions: 1M NaOH, **2b** (1 mmol), solvent (5 mL), 5-10 °C, then r.t.

[b] Isolated yield.

With the optimized conditions in hand, we investigated the substrate scope for the synthesis of 3-aryl-4-hydroxyfuroxans **1**. It was found that target 4-hydroxyfuroxans **1a-j** were formed in high yields under very mild conditions, regardless of the presence of electron-donating (AlkO, Alk) or electron-withdrawing (Hal, NO_2, CF_3) groups and their position on the aromatic ring (Table 2).

Table 2. Substrate scope for the synthesis of 3-aryl-4-hydroxyfuroxans **1a-j**[a,b]



[a] Reaction conditions: NaOH (0.96 g, 24 mmol), 4-nitrofuroxan **2** (8 mmol), H_2O (24 mL), THF (24 mL), 5-10 °C, then r.t., 3-5 h.

[b] Isolated yield.

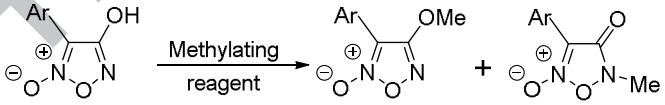
The structures of the synthesized 3-aryl-4-hydroxyfuroxans **1a-j** were determined by IR, ^1H, ^{13}C, and ^{19}F NMR spectroscopy as well as high-resolution mass spectrometry. The ^1H NMR and IR spectra of synthesized hydroxyfuroxans only showed the presence of the OH forms.

The methylation reaction of hydroxyfuroxans **1a-j** was studied using three different methylating reagents: CH_2N_2, MeI, and $(MeO)_2SO_2$. The investigations began using CH_2N_2 and were carried out in Et_2O at room temperature with an excess of CH_2N_2 (molar ratio **1**:CH_2N_2 = 1:3). In all cases, with the exception of hydroxyfuroxan **1j** containing the 4-$CF_3C_6H_4$ substituent, alkylation occurred with moderate regioselectivity to give two regioisomers, namely, *O*-methylation products, 3-aryl-4-methoxyfuroxans **4a-j**, and previously unknown *N*-methylation

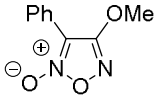
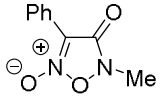
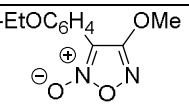
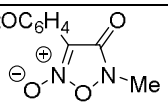
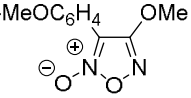
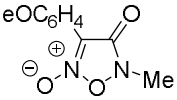
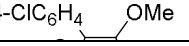
products, 3-aryl-5-methyl-1,2,5-oxadiazol-4(2*H*)-one 2-oxides **5a-i**, in ratios of 1.4:1 to 3:1 and good total yields. The alkylation of hydroxyfuroxan **1j** resulted in only *O*-methylation product **4j**. The molar ratio of the regioisomers **4**:**5** was determined on the basis of ^{1}H NMR data by comparison of the integral intensity of the methyl group proton signals, because the proton chemical shifts of the OMe (4.3-4.5 ppm) and NMe (3.3-3.5 ppm) groups were significantly different.

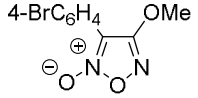
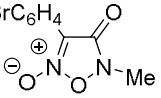
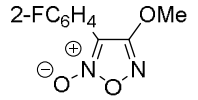
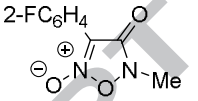
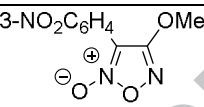
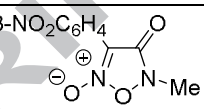
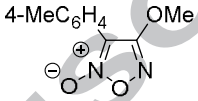
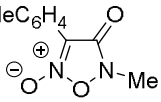
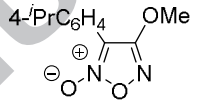
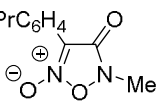
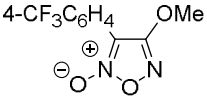
The methylation of hydroxyfuroxans **1** using MeI and $(MeO)_2SO_2$ were carried out under conditions commonly used for similar reactions (aprotic solvent in the presence of base).[20] The reactions were performed in different solvents (Et_2O, THF, MeCN, DMF) in the presence of organic and inorganic bases (TEA, DBU, K_2CO_3, Cs_2CO_3). Utilization of THF as the solvent and Cs_2CO_3 as the base proved to be most appropriate for the reaction with MeI, whereas the reaction with $(MeO)_2SO_2$ proceeded more successfully in DMF in the presence of K_2CO_3. Using organic bases in these reactions resulted in decomposition of the initial hydroxyfuroxans. The methylation of hydroxyfuroxans by MeI and $(MeO)_2SO_2$ proceeded with higher regioselectivities. The molar ratios of regioisomers **4**:**5** was ~3:1 to 5:1 in the reactions with MeI and 10:1 to 19:1 in the reactions with $(MeO)_2SO_2$. Only the *O*-methylation product was isolated upon the methylation of hydroxyfuroxan **1j**. After the reaction with diazomethane, compounds **4** and **5** were separated by column chromatography on SiO_2 and all yields are summarized in Table 3.

Table 3. Hydroxyfuroxans **1a-j** methylation with various methylating reagents



1a-j **4a-j** **5a-i**

Entry	Ar	Methylating reagent	Molar ratio **4**:**5**[c]	Total yield (%)[d]	Compound **4**[e]	Compound **5**[e]
1	Ph (**a**)	CH_2N_2	2:1	98		
		MeI[a]	2:1	74		
		$(MeO)_2SO_2$[b]	11:1	80	**4a** (57%)	**5a** (31%)
2	4-$EtOC_6H_4$ (**b**)	CH_2N_2	1.4:1	90		
		MeI[a]	4:1	81		
		$(MeO)_2SO_2$[b]	19:1	97	**4b** (49%)	**5b** (40%)
3	4-$MeOC_6H_4$ (**c**)	CH_2N_2	1.5:1	94		
		MeI[a]	3.5:1	69		
		$(MeO)_2SO_2$[b]	18:1	84	**4c** (51%)	**5c** (39%)
4	4-ClC_6H_4 (**d**)	CH_2N_2	2:1	82		

		MeI[a]	5:1	73		
		$(MeO)_2SO_2$[b]	11:1	91		
5	4-BrC_6H_4 (**e**)	CH_2N_2	2.5:1	90		
		MeI[a]	3.3:1	76		
		$(MeO)_2SO_2$[b]	12:1	90	**4e** (59%)	**5e** (25%)
6	2-FC_6H_4 (**f**)	CH_2N_2	2.5:1	91		
		MeI[a]	4:1	71		
		$(MeO)_2SO_2$[b]	12:1	81	**4f** (49%)	**5f** (23%)
7	3-$NO_2C_6H_4$ (**g**)	CH_2N_2	3:1	94		
		MeI[a]	3:1	77		
		$(MeO)_2SO_2$[b]	10:1	92	**4g** (64%)	**5g** (22%)
8	4-MeC_6H_4 (**h**)	CH_2N_2	1.5:1	87		
		MeI[a]	5:1	65		
		$(MeO)_2SO_2$[b]	20:1	79	**4h** (53%)	**5h** (36%)
9	4-$^{i}PrC_6H_4$ (**i**)	CH_2N_2	1.5:1	86		
		MeI[a]	4:1	77		
		$(MeO)_2SO_2$[b]	12:1	90	**4i** (48%)	**5i** (35%)
10	4-$CF_3C_6H_4$ (**j**)	CH_2N_2	-[f]	85		-[f]
		MeI[a]	-[f]	69		
		$(MeO)_2SO_2$[b]	-[f]	78	**4j** (85%)	

[a] Cs_2CO_3 used as base.
[b] K_2CO_3 used as base.
[c] Determined by ^1H NMR spectroscopy.
[d] Isolated yield of a mixture of regioisomers.
[e] Isolated yield after methylation with CH_2N_2 and subsequent column chromatography.
[f] Only isomer **4j** was isolated.

4-Methoxy-3-phenylfuroxan **4a** is a known compound.[21] The structures of compounds **4b-j** and **5a-i** were determined by spectral (IR, ^1H, ^{13}C, and ^{19}F NMR spectroscopy and mass spectrometry) and analytical methods. An important difference between the structures of the *O*- and *N*-methylation products, apart from the ^1H NMR chemical shifts of the Me groups, was the appearance of a C=O absorption band (~ 1700 cm^{-1}) in the IR spectra of *N*-methylation products **5a-i**. Also, the fragmentation patterns of the molecular ions in the EI mass spectra of compounds **4** and **5** were substantially different. The major fragment ion in compounds **4** was (M^+ – 2NO), while for compounds **5**, this was (M^+ – ONMe – CO). Finally, the structure of 3-aryl-5-methyl-1,2,5-oxadiazol-4(2*H*)-one 2-oxides **5** was unambiguously confirmed by the single-crystal X-ray diffraction of compound **5a** (Fig. 1). Notably, lengths of the N(2)-O(2), N(1)-O(1), N(2)-C(2) and N(1)-C(1) bonds in the furoxan ring of **5a** fall within the expected range according to CSD,[22] with the only exception being the C(1)-C(2) bond, which was markedly elongated in comparison

with previously reported phenylfuroxans (1.467(5) Å vs 1.404 – 1.444 Å according to CSD), probably due to disruption of π-conjugation in the 1,2,5-oxadiazolone ring (see the ESI for a detailed discussion of **5a**).

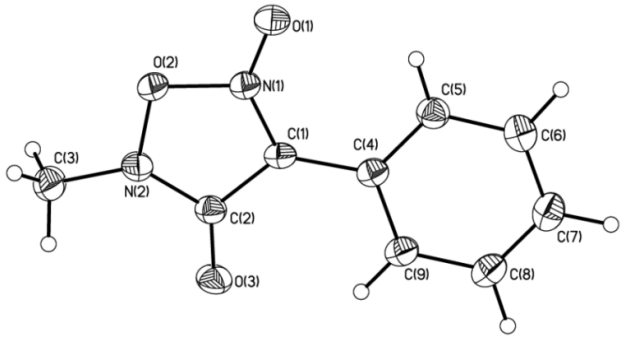
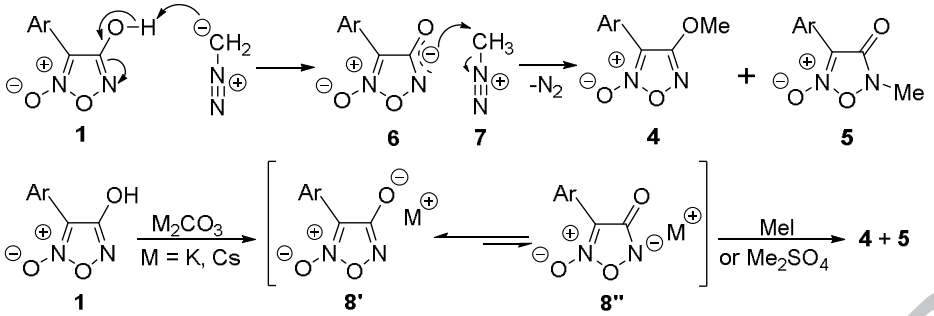


Figure 1. General view of **5a**. Non-hydrogen atoms are represented by probability ellipsoids of atomic vibrations (p = 50%).

A plausible mechanism for the methylation of 3-aryl-4-hydroxyfuroxans **1** is outlined in Scheme 3. Firstly, diazomethane acts as a base, deprotonating hydroxyfuroxan to give anionic intermediate **6** and MeN_2 cation **7**. The negative charge in intermediate **6** is delocalized between the O and N atoms and subsequent nucleophilic substitution in MeN_2 results in a mixture of *O*-Me and *N*-Me regioisomers **4** and **5** with predominance for compounds **4** in a 1.4:1 to 3:1 molar ratio. The amount of regioisomer **4** grows with an increase in the electron-withdrawing character of the aromatic ring substituent.

The two other alkylation reagents can only be used in the presence of inorganic bases. In these cases, the reaction begins with the formation of contact ion pair **8′**, and hence, delocalization of the negative charge between the O and N atoms and ion pair **8′′** is rather complicated (Scheme 3). As expected, in these cases *O*-alkylation predominates over *N*-alkylation and **4**:**5** molar ratio increases to 10:1-19:1 for $(MeO)_2SO_2$ (hard alkylating reagent), while for MeI (a softer alkylating reagent) the **4**:**5** molar ratio was 4:1-5:1. An alternative mechanism for formation of *N*-Me products **5** could be *O*- to *N*-methyl migration, which is known to occur at high temperature in the presence of catalysts (e.g. NaI or LiI).[23,24] However, attempts to perform this process by prolonged heating of compound **4a** in different solvents or under solvent-free conditions at 100 °C in the presence of NaI or LiI were not successful.



Scheme 3. Plausible mechanism for the formation of *O*-Me and *N*-Me regioisomers **4** and **5**.

Conclusion

In summary, a facile and highly efficient method for the synthesis of practically unknown 3-aryl-4-hydroxyfuroxans by nucleophilic substitution of the nitro group in readily available 3-aryl-4-nitrofuroxans under the action of NaOH in H_2O-THF has been developed. The methylation of these products using different methylating reagents (CH_2N_2,[25] MeI, $(MeO)_2SO_2$) under very mild conditions, demonstrated for the first time that hydroxyfuroxans are prone to side-chain prototropic tautomerism, resulting in the formation of the first representatives of a new type of furoxan derivatives containing substituents on the N(5) nitrogen atom, *N*(5)-alkylfuroxan-4-ones, as well as *O*-alkylation products. In all cases, the latter were formed regioselectively and the molar ratio of *O*-Me and *N*-Me regioisomers were dependent on the aromatic ring substituents and the nature of the methylating reagents. To the best of our knowledge, this study represents the first experimental evidence for side-chain prototropic tautomerism in the furoxan ring.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at

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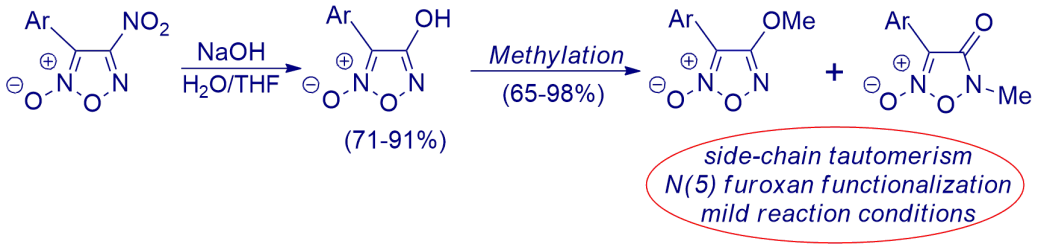
25. A solution of CH_2N_2 (1.67M in Et_2O, 2.6 mL) was added dropwise to a stirred mixture of the corresponding hydroxyfuroxan **1** (1.4 mmol) in Et_2O (7 mL). The resulting solution was stirred for 24 h at room temperature, then the solvent evaporated and the residue purified by column chromatography on SiO_2 (eluent – $CHCl_3$:CCl_4, 1:1). The OMe derivative **4** eluted first, and the NMe derivative **5** eluted second.



26.

Highlights

- A method for the synthesis of hardly accessible hydroxyfuroxans has been developed.
- Ring-chain prototropic tautomerism for the furoxan ring was found for the first time.
- Furoxan derivatives of the novel type — *N*(5)-alkylation products were synthesized.

27.