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Direct introduction of cyano group on furoxan ring

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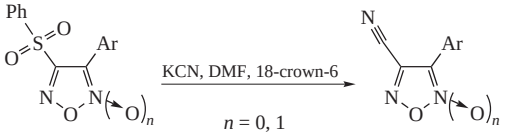
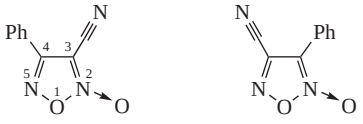
Potassium cyanide reacts with 3-aryl-4-phenylsulfonylfuroxan/furazan under mild conditions in DMF at room temperature in the presence of 18-crown-6 to afford 3-aryl-4-cyanofuroxan/furazan in 45–50% yield.

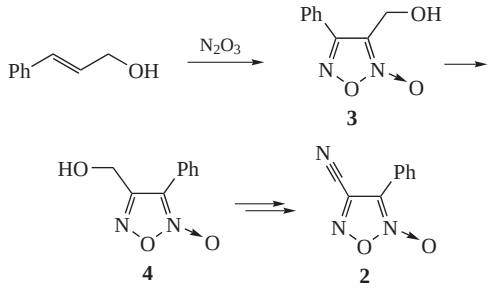


Since the discovery of the biological function of nitric oxide (NO) by Ignarro *et. al* in early 90s this small gaseous molecule was recognized as a ubiquitous regulator species involved in nearly every aspect of human biological processes. Produced from L-arginine by the NO-synthases enzyme family, NO mainly acts *via* the soluble guanylate cyclase (sGC) pathway activation.[1] Gaseous NO is poorly soluble in water and is quite difficult to handle because of its reactivity *vs*. oxygen with consequent nitrogen dioxide formation. That is why the use of molecules capable to release NO under physiological conditions (NO-donors) is required. Different classes of NO-donors were developed for biological application in the past three decades.[2–4] Among them 1,2,5-oxadiazoles (furoxans), compounds capable to release NO under biological thiols action, were extensively studied.[5–9] The ability to release NO strongly depends on the nature of substituents on carbon atoms of the furoxan ring. The presence of electron-withdrawing groups (*e.g.* cyano, nitro or sulfonyl) favours the nucleophilic attack of thiols and results in increased quantity and velocity of NO release.[9–11] In particular, the two isomers of cyanophenylfuroxan (**1** and **2**) were found to be the most effective NO donors in different biological experiments.[12,13]



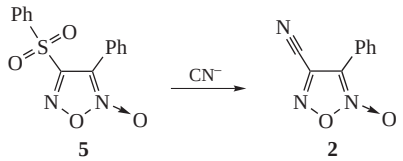
1 **2**

In our work, we have met the necessity to synthesize a significant amount of 4-cyano-3-phenyl furoxan **2**. The known procedures for the synthesis of cyano furoxans pass *via* dehydration of the corresponding amide or oxime.[14–16] The synthesis of **2** is a multistep process that requires a difficult chromatographic separation of isomeric (hydroxymethyl)phenylfuroxans **3** and **4** after thermal isomerization (Scheme 1).[17,18]



Scheme 1

Therefore, we decided to study the possibility of direct introduction of cyano group by the nucleophilic substitution of phenylsulfonyl moiety in readily available 4-phenyl-3-phenylsulfonyl furoxan **5** using cyanide anion (Scheme 2). The substitution of phenylsulfonyl group is well studied for O- and S-nucleophiles,[19] while only few papers describe the use of N- or C- nucleophiles, or halogen anions.[20–22] Herein we report the reaction between cyanide anion and phenylsulfonyl-substituted furoxans and related furazans.



Scheme 2

First, reaction of **5** with KCN was performed in acetonitrile at ~20 °C for 24 h (Table 1, entry 1), when only partial conversion of the starting compound into the target nitrile **2** was observed. All attempts to push the reaction further by increasing reaction time, temperature or KCN : **5** molar ratio were unsuccessful. Therefore, we turned to the use of phase transfer catalysis. On using 2 equiv. of KCN in CH_2Cl_2–H_2O mixture in the presence of $Bu_4N^+HSO_4^-$, the starting compound **5** was completely consumed within 72 h (entry 2), however, the yield of **2** was quite low (27%). Extensive decomposition of **5** was observed probably due to hydrolysis of KCN and the reaction of **5** with hydroxyl anion.

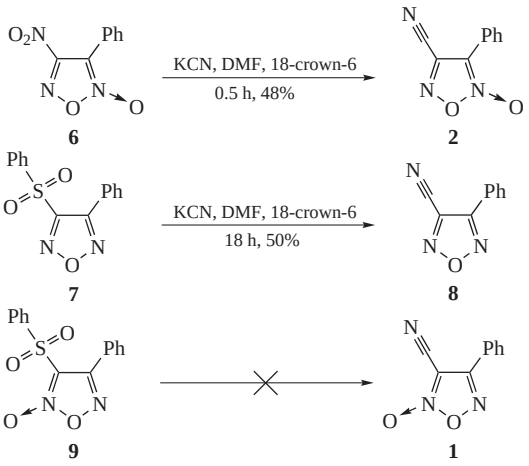
Table 1 Influence of reaction conditions on the yield of **2**.

Entry	Cyanide source	Solvent	5 : CN^- molar ratio	*t*/h	Catalyst	Yield (%)
1	KCN	MeCN	up to 1 : 10	72	–	25
2	KCN	CH_2Cl_2–H_2O	1 : 2	72	$Bu_4N^+HSO_4^-$	27[a]
3	$Bu_4N^+CN^-$	CH_2Cl_2	1 : 1	24	–	42
4	$Bu_4N^+CN^-$	CH_2Cl_2	1 : 2	1.5	–	32
5	KCN	DMF	1 : 1	1	–	45
6	KCN	DMF	1 : 1	1	18-crown-6	58

[a] Much decomposition took place.

The use of $Bu_4N^+CN^-$ in dry CH_2Cl_2 helped to overcome this problem, and product **2** was obtained in 42% yield in 24 h (entry 3). When the excess (2 equiv.) of tetrabutylammonium cyanide was employed, the reaction time reduced to 90 min (entry 4), however, the decomposition rate also grew. Finally, the use of dry DMF as a solvent and 1 equiv. of KCN gave **2** in 45% yield after 1 h (entry 5). The yield was further improved by the use of 18-crown-6 as a catalyst (entry 6).†

Once the optimal reaction conditions were found, we tested the scope of this reaction for other furoxans and furazans bearing good leaving groups. Starting from 3-phenyl-4-nitrofuroxan **6** under the analogous conditions, we obtained product **2** in nearly the same yield, but in a shorter time (Scheme 3). The corresponding 3-phenyl-4-phenylsulfonylfurazan **7** was transformed into 3-cyano-4-phenylfurazan **8** in a good yield within 18 h.‡ Meanwhile, we were unable to isolate any product from the reaction of isomeric 4-phenyl-3-phenylsulfonylfuroxan **9** with KCN (see Scheme 3). It seems likely that nucleophilic attack of CN^- on 3-positioned carbon atom of **9** results in furoxan ring opening with consequent formation of highly hydrophilic compounds.



Scheme 3

Finally, the possibility to extend this reaction for 3-R-substituted 4-phenylsulfonyl furoxans and furazans (R = SO_2Ph, OEt, Me) as well as 3-methyl-4-nitrofuroxan was studied (for details, see Online Supplementary Materials). Unfortunately, in all these cases either full decomposition took place or no reaction occurred. Most probably, this reaction is restricted to substrates bearing 3-positioned aryl group.

In summary, the results obtained allow one to synthesize 3-aryl-4-cyano furoxans and furazans *via* direct nucleophilic substitution of phenylsulfonyl or nitro leaving group under the action of cyanide anion.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2017.11.008.

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† *4-Cyano-3-phenylfuroxan* **2**. Potassium cyanide (65 mg, 1.00 mmol) was added in one portion to a solution of 3-phenyl-4-phenylsulfonylfuroxan (300 mg, 1.00 mmol) in dry DMF (10 ml). After that, 18-crown-6 (260 mg, 1.00 mmol) was added and the mixture was stirred at room temperature for 1 h, then poured into cold water (30 ml) and extracted with CH_2Cl_2 (2×25 ml). The organic phase was washed with water (20 ml), brine (20 ml), dried (Na_2SO_4) and evaporated. The obtained yellow oil was purified by flash chromatography (eluent light petroleum–CH_2Cl_2, 8:2) to give the target cyano derivative as a white solid. Yield 98 mg (58%). Analytically pure sample was obtained by crystallization from hexane, mp 84–85 °C (lit.,[15] mp 81 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.99–8.02 (m, 2H), 7.60–7.62 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 133.0 (C^4, furoxan), 132.1 (CH, Ph), 129.7 (2CH, Ph), 126.4 (2CH, Ph), 119.6 (C, Ph), 112.6 (C^3, furoxan), 108.4 (CN).

‡ *3-Cyano-4-phenylfurazan* **8**. Potassium cyanide (65 mg, 1.00 mmol) was added in one portion to a solution of 3-phenyl-4-phenylsulfonylfurazan (290 mg, 1.00 mmol) in dry DMF (10 ml). After that, 18-crown-6 (260 mg, 1.00 mmol) was added and the mixture was stirred at room temperature for 18 h, then poured into cold water (30 ml) and extracted with CH_2Cl_2 (2×25 ml). The organic phase was washed with water (20 ml), brine (20 ml), dried (Na_2SO_4) and evaporated. The obtained yellow oil was purified by flash chromatography (eluent light petroleum–CH_2Cl_2, 9:1) to give the target cyano derivative as a white solid. Yield 86 mg (50%). Analytically pure sample was obtained by crystallization from hexane, mp 45–46 °C, (lit.,[23] mp 40–41 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.00–8.04 (m, 2H), 7.57–7.68 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 154.4 (C^3, furazan), 132.4 (CH, Ph), 130.6 (C^4, furazan), 129.7 (2CH, Ph), 127.7 (2CH, Ph), 122.5 (C, Ph), 108.3 (CN).