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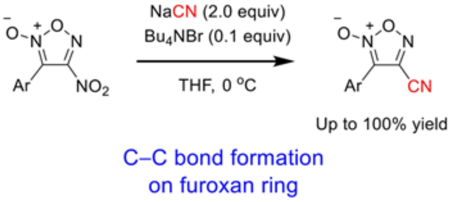

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Synthesis of cyanofuroxans from 4-nitrofuroxans via C–C bond forming reactions

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ABSTRACT

A substitution reaction of 4-nitrofuroxans to prepare 4-cyanofuroxans is described. This substitution reaction was complicated by the reverse reaction and a judicious choice of cyanide source was important to enable this direct synthesis process. The optimized reaction conditions showed an excellent applicability for the synthesis of a range of 4-cyanofuroxans. 3-Cyanofuroxans, known to be thiol-mediated nitric oxide donors, could also be obtained by the thermal or photochemical isomerization of 4-cyanofuroxans. The developed cyanation of furoxans is a rare example of C–C bond-forming reaction on a furoxan ring.

In the last two decades, 1,2,5-oxadiazole-2-oxides (furoxans) have drawn increased attention due to their unique ability to release nitric oxide (NO) under physiological conditions through the mediation of thiol.[1] Because NO has a spectrum of biological activities, including immune response, vasodilation, neurotransmission, and inhibition of platelet aggregation,[2] a series of molecules with a furoxan module have been synthesized and applied as pharmacologically active compounds. The NO-releasing ability highly depends on the substituent on the furoxan ring; specifically, the electronegative substituent on the 3-position of the furoxan ring provides the molecule with the thiol-mediated NO-releasing ability. In this context, 3-cyanofuroxans have been intensively investigated as powerful NO donors, following the pioneering work of Gasco and coworkers.[3] 3-Cyanofuroxans are also known to be therapeutic agents against parasitic diseases including trypanosomiasis[4] and schistosomiasis[5], as well as cytotoxic agents.[6] Besides, both regioisomers of cyanofuroxans can be the precursors of new energetic nitrogen-rich molecules and potential pharmacophores via azole formation from the cyano group.[7]

Despite their usefulness, only a limited number of synthesis methods for cyanofuroxans have been reported so far. Although a standard procedure for the formation of furoxans involves the treatment of the corresponding alkenes with N_2O_3,[8] the reaction of acrylonitrile with N_2O_3 fails to form the furoxan ring due to the electron-deficient nature of C−C double bond; therefore, the cyano group on the furoxan is generally formed by standard functional group manipulation after the formation of the furoxan ring. The two major pathways employed so far are dehydration reactions from the corresponding oximes and amides using dehydrating reagents such as thionyl chloride and trifluoroacetic anhydride.[3,5b,9] In both cases, the corresponding precursors need to be tediously synthesized in several steps. From the viewpoint of atom economy and step economy, direct cyanation on the furoxan ring via a C–C bond-forming reaction is preferable. However, C–C bond-forming reactions on furoxan rings have often been cumbered by their fragile nature toward nucleophilic attack, leading to ring-opening decomposition;[10] therefore, only few of these reactions are known so far.[11] Herein, the first direct cyanation of furoxans is reported.

We previously reported the synthesis of fluorofuroxans from the corresponding nitrofuroxans using Bu_4NF.[12] On the basis of this knowledge, we set out to investigate the cyanation of nitrofuroxans with Bu_4NCN.[13] Soon after the investigation was commenced, we found that the S_NAr reaction of 3-aryl-4-nitrofuroxan with Bu_4NCN proceeded at 0 °C (entry 1, Table 1); however, several byproducts were formed. The addition of MS 4Å suppressed the formation of the unidentified byproducts, but primary amide **3** was generated instead (entry 2, Table 1), probably due to the adventitious contamination by water and somewhat basic nature of the reaction conditions employed. Decreasing the reaction temperature to −78 °C was effective in suppressing the formation of any byproduct and complete conversion of **1a** to **2a** was observed by ^1H NMR analysis of the solution *before aqueous work-up* (entry 3, Table 1).[14] However, after aqueous work-up, a mixture of **1a** and **2a** (ca. 1:1) was obtained (entry 4, Table 1).[15] We surmised that the reaction of **1a** with Bu_4NCN is reversible, and that **1a** was regenerated from **2a** and Bu_4NNO_2 upon addition of water. In order to avoid detrimental aqueous work-up, concentration of the reaction mixture under reduced pressure was conducted, but then the formation of byproduct **3** was observed (entry 5, Table 1). The direct loading of the reaction mixture onto a silica-gel column led to the formation of byproducts (data not shown). For removing the coproduct Bu_4NNO_2, oxidation and silyl

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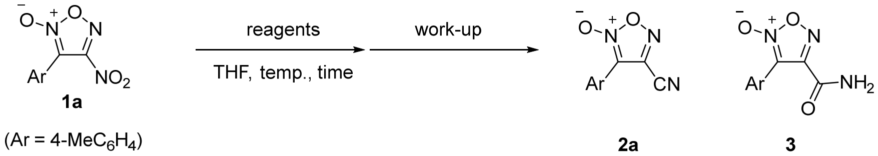
∗ Corresponding author. Tel.: +0-000-000-0000; fax: +0-000-000-0000; e-mail: author@university.edu trapping of the nitrite anion were tried (entries 6–8, Table 1). However, no beneficial effects were observed. The use of polymer-supported ammonium cyanide (PSA CN), with the expectation that the coproduct ammonium nitrite would be removed by filtration instead of aqueous work-up, resulted in the successful isolation of pure product **2a** (entry 9, Table 1). However, the reaction time was sacrificed. Eventually a combination of NaCN and a catalytic amount of Bu_4NBr proved to be suitable (entry 10, Table 1). The reaction was completed in 3 h at room temperature, and product **2a** remained untouched after aqueous work-up. The use of KCN in lieu of NaCN or the exclusion of Bu_4NBr caused a decrease on the reaction rate (entries 11–13, Table 1).

Table 1
Optimization of the reaction conditions for the cyanation of 4-nitrofuroxan **1a**



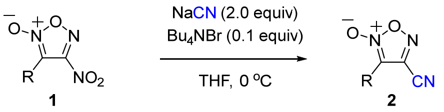
entry	reagents	temp. (°C)	time (h)	work-up procedure	Product Ratio (%)[a]		
					2a	**3**	**1a**
1	Bu_4NCN (1.3 equiv)	0	1	–	(74)[b]	(9)	(0)
2	Bu_4NCN (1.3 equiv) MS 4Å[c]	0	1	–	(79)	(21)	(0)
3	Bu_4NCN (1.3 equiv) MS 4Å[c]	−78	1	–	(100)	(0)	(0)
4	Bu_4NCN (1.3 equiv) MS 4Å[c]	−78	1	aqueous work-up	45–51	0	49–55
5	Bu_4NCN (1.3 equiv) MS 4Å[c]	−78	1	solvent evaporation	65	35	0
6	Bu_4NCN (1.3 equiv) MS 4Å[c]	−78	1	DDQ (1 equiv), 2 h then aqueous work-up	56	0	44
7	Bu_4NCN (1.3 equiv) MS 4Å[c]	−78	1	Oxone® (1.5 equiv), 4 h then aqueous work-up	42–96[d]	0	4–58[d]
8	Bu_4NCN (1.3 equiv) MS 4Å[c]	−78	1	Me_3SiCl (1.5 equiv), 30 min then aqueous work-up	43–88[d]	0	12–57[d]
9	PSA CN (2 equiv)[e] MS 4Å[c]	26	118	filtration	100	0	0
10	NaCN (2 equiv) Bu_4NBr (0.1 equiv)	26	3	aqueous work-up	100	0	0
11	KCN (2 equiv) Bu_4NBr (0.1 equiv)	26	24	aqueous work-up	82	0	18
12	KCN (2 equiv)	26	24	aqueous work-up	11	0	89
13	NaCN (2 equiv)	26	24	aqueous work-up	84	0	16

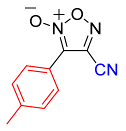
[a] Yields before work-up are shown in parentheses.
[b] Unidentified furoxan-derived byproducts were formed in 17% yield.
[c] Powder MS 4Å (220 mg/mmol **1a**).
[d] The results were not reproducible.
[e] Polymer-supported ammonium cyanide (PSA CN) prepared from Dowex^{TR}. The loading was 2.34 mmol/g.

The substrate scope was next evaluated using 4-nitrofuroxans with different types of aryl and alkyl groups at the 3-position. The results are summarized in Table 2. A range of different electron-withdrawing and electron-donating substituents on the aryl group were tolerated (products **2a**–**h**). Sterical hindrance caused by bis-substitution at the ortho positions did not affect the reactions (products **2i** and **2j**). Some heteroaryl variants were also obtained in good yields (products **2m** and **2n**). The cyanation reaction of 3-

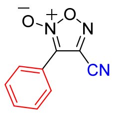
alkyl 4-nitrofuroxan was low yielding due to the formation of byproducts (product **2o**).

Table 2
Substrate scope[a]

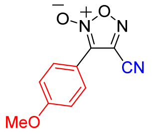




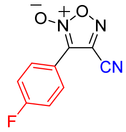
2a
95%



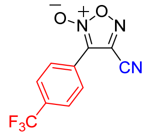
2b
100%



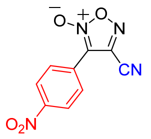
2c
100%



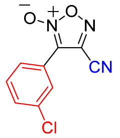
2d
100%



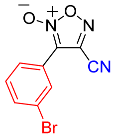
2e
62%



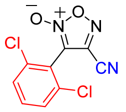
2f
71%



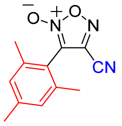
2g
90%



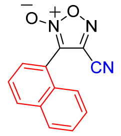
2h
87%



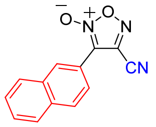
2i
52%



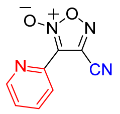
2j
86%



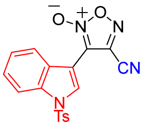
2k
87%



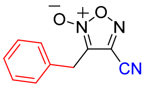
2l
100%



2m
94%



2n
72%



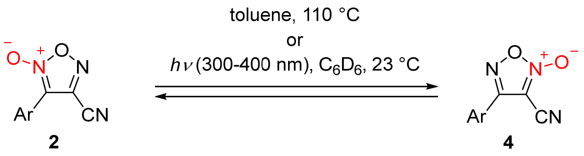
2o[b]
10%

[a] To a mixture of NaCN (2.0 equiv) and Bu_4NBr (10 mol%) in THF was added a THF solution of 4-nitrofuroxan **1** (0.3 mmol) at 0 °C. The reaction was stirred at 0 °C for 3–48 h (see the Supplementary data for details).

[b] 1.5 mmol scale.

It is known that regioisomers of furoxans isomerize into each other under thermal and photochemical conditions.[16] With a widely applicable method to prepare 4-cyanofuroxans in hand, we examined the isomerization of 4-cyanofuroxans to 3-cyanofuroxans, which are known to be biologically active compounds. The isomeric ratios at the thermal and photochemical equilibrium states in an aromatic hydrocarbon solvent are listed in Table 3. Under both isomerization conditions, 3-cyanofuroxans **4** were obtained as the major products. Thus, a straightforward synthesis method for both regioisomers of cyanofuroxans has been established.

Table 3
Thermal and photochemical isomerization of 4-cyanofuroxans **2**[a]



	Substrate		Ratio (2:4)[b]	
entry	2	Ar	*thermal*	*photo*
1	**2a**	*p*-tolyl	35:65	3:97
2	**2l**	naphthalene-2-yl	38:62	11:89
3	**2m**	pyridin-2-yl	55:45	7:93

[a] Thermal conditions: at 110 °C in toluene. Photochemical conditions: irradiated with light (λ = 300–400 nm) at 23 °C in C_6D_6.

[b] Product ratio in equilibrium (thermal condition) or at photostationary state (photochemical condition). Determined by ^1H NMR analysis.

As mentioned in Table 1, the anomalous reverse reaction was observed in the cyanation of 4-nitrofuroxan using Bu_4NCN as cyanide source. Starting material 4-nitrofuroxan **1a** was not observed in the ^1H NMR analysis of the reaction mixture *before aqueous work-up*; however, a significant amount of **1a** was obtained *after aqueous work-up*. To clarify the reaction mechanism, several probe reactions were conducted. At first, cyanated product **2a** was treated with an equimolar amount of Bu_4NNO_2 (Figure 1a). ^1H NMR analysis of the reaction mixture before and after aqueous work-up confirmed that no formation of **1a** occurred. Next, crossover experiments were carried out. 4-Nitrofuroxan **1a** was treated with Bu_4NCN to form **2a**, then 4-cyanofuroxan **2m** was added (Figure 1b). While **1a** was not observed before work-up, **1a** was regenerated after aqueous work-up, however, **1m** was not obtained. A similar experiment was conducted using **1m** and **2a** instead of **1a** and **2m** (Figure 1c). As a result, **1m** was regenerated after aqueous work-up while **1a** was not observed. The lack of formation of crossover products suggests that the regeneration of the starting 4-nitrofuroxans in the cyanation reaction using Bu_4NCN after aqueous work-up is not ascribed to the simple reverse reaction of the 4-cyanofuroxans with Bu_4NNO_2 coproduct. The use of less than 1 equiv of Bu_4NCN resulted in two sets of independent signals ascribed to **1a** and **2a** (Figure 1d). This result clearly denies the rapid equilibrium between **1a** and **2a** in the NMR sample before work-up, which would result in the observation of averaged single species. Although the rationalization for this anomalous reverse reaction is proposed based on the above results (see Supplementary Material), further investigation needs to be conducted to fully unravel the mechanism.

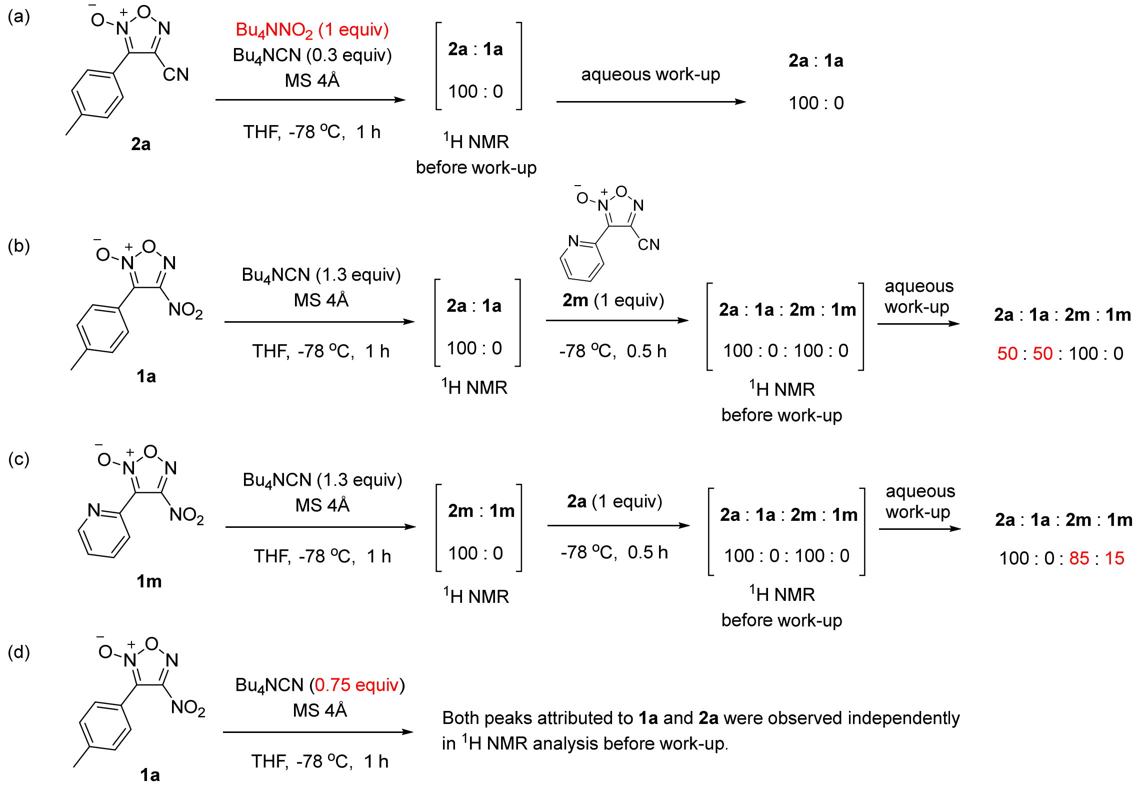


Figure 1. Probe reactions to get an insight into the reverse reaction mechanism.

In conclusion, this paper demonstrates a direct cyanation reaction of furoxans, one of the rare examples of a C–C bond forming reaction on a furoxan ring. Due to the reverse reaction, a choice of cyanating reagent was important to obtain the 4-cyanofuroxans in high yield. The regioisomeric 3-cyanofuroxans, known to have several biological activities, could be readily generated from 4-cyanofuroxans via thermal or photochemical isomerization, making the developed method a straightforward approach for the construction of a library of biologically applicable candidates based on a furoxan architecture.

Acknowledgments

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13. Bu_4NCN purchased from Sigma-Aldrich contained Bu_4NO^iPr (<5%), which resulted in the formation of 4-isopropoxyfuroxan. Pure Bu_4NCN was synthesized from commercially available $Bu_4NOH{\bullet}30H_2O$ and KCN according to the literature; Dobbs, K. D.; Marshall, W. J.; Grushin, V. V. *J. Am. Chem. Soc.* **2007**, *129*, 30–31.
14. The sample for NMR analysis was prepared by taking an aliquot out of the reaction followed by direct dilution by $CDCl_3$ (without evaporation).
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Supplementary Material

Supplementary Material (experimental procedures and spectral data) associated to this article can be found in the online version, at http://dx.doi.org/xxxxxx.

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