Synthesis of symmetrical difurazanyl ethers

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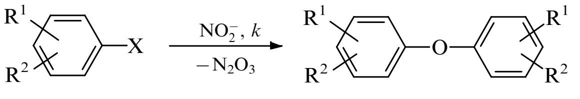
The title compounds 2 have been synthesized in a one-pot procedure through base-promoted transformation of nitrofurazans 1; the unusual reaction suggested an initial intramolecular nitro–nitrite rearrangement.

Several methods are available in the literature for the synthesis of diphenyl ethers (DPE). Special techniques are used to prepare symmetrical DPEs. Thus, research carried out by Eilingsfeld and Schaffner[1] two decades ago showed that a number of symmetrically-substituted DPEs could be efficiently synthesized by the reaction of aromatic compounds, ArX, which are suitably activated for nucleophilic aromatic displacement with nitrite ion in the presence of potassium carbonate (for absorption of nitrogen oxides) in dipolar solvents (*N*-methylpyrrolidinone, H_2O, DMF, DMSO, HMPA) at 100–220 °C.

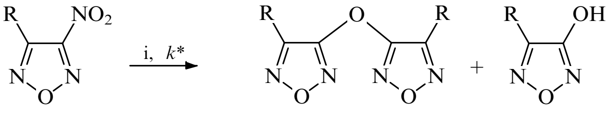


ArX DPE

Since that initial report a variety of halogeno- and nitroaromatic precursors, ArX, have been utilized, and the one-pot method has found significant use in organic synthesis. An excellent review on both the synthesis and theoretical implications of this early work has appeared.[2] It should be noted that the ability to prepare symmetrical diheteroaromatic ethers *via* this pathway has not been previously reported.

In connection with our program dealing with the chemistry of nitrofurazans **1**,[3] we have been exploring the chemical reactivity of 3,4-dinitrofurazan **1a** as a versatile building-block in organic synthesis.[4] The ability to prepare **1** on a multigram scale has prompted a new approach to their conversion into the desired derivatives.

Here we outline a preparation of symmetrical difurazanyl ethers **2**. The synthesis of **2** was first attempted by transformation of **1** using the above one-pot methodology. Dinitrofurazan **1a** failed to give any difurazanyl ether product **2** under these conditions. Nevertheless, when anhydrous acetonitrile was used as a solvent, and reaction temperature was reduced to 50–60 °C, **2a** was obtained in 54% yield. In attempting to improve this process, we found that the presence of nitrite ion in the reaction mixture proved to be unnecessary for the synthesis of **2a**. The ether **2a** can be obtained from **1a** upon treatment with any weak base (Na_2CO_3, NaOAc, KCN and others). Some by-product identified as hydroxyfurazan **3a**, was obtained. The compound **3a** was the predominant product when the reaction was run in aqueous acetonitrile.



1a–c **2a–c** **3a–c**

a R = NO_2;
b R = CN;
c R = Ac

Scheme 1 *Reagents and conditions:* i, Na_2CO_3, CH_3CN, 60 °C.

The transformation of nitrofurazans **1** involving electron-withdrawing groups, in the presence of a weak base as a promoter, resulted in the corresponding ether **2** in excellent yields (Scheme 1). The reaction occurred under heterogeneous conditions.

All attempts to effect a similar transformation of nitrofurazans with electron-donating groups (Me, NH_2, Ph, *etc.*) under the same conditions, however, proved fruitless. We observed that the formation of **2** and DPE proceeded *via* different pathways. Thus, kinetic studies by Ustinov *et al.*[2] of the reaction of ArX (X = NO_2) with nitrite ion led to the conclusion that the transformation proceeds *via* the four elementary steps depicted below (reactions 1.1–1.4).

$$\mathrm{Ar{-}NO_2 + NO_2^-} \xrightarrow{k_1} \mathrm{Ar{-}ONO + NO_2^-} \qquad (1.1)$$

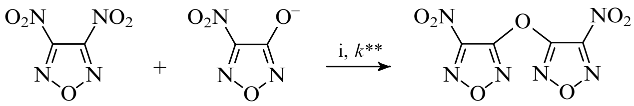
$$\mathrm{Ar{-}ONO + NO_2^-} \xrightarrow{k_2} \mathrm{Ar{-}O^- + N_2O_3} \qquad (1.2)$$

$$\mathrm{Ar{-}NO_2 + Ar{-}O^-} \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} \mathrm{Ar{-}O{-}Ar + NO_2^-} \qquad (1.3)$$

$$\mathrm{Ar{-}O{-}Ar + NO_2^-} \xrightarrow{k_4} \mathrm{Ar{-}ONO + Ar{-}O^-} \qquad (1.4)$$

Based on these steps, the reaction must start with O-attack by nitrite ion (reaction 1.1) which is specially added to the reaction mixture. We found that in the preparation of **2a** a significant role is played not so much by the nitrite ion as by the presence of any weak base in the reaction mixture. Furthermore, the reaction rate of **1a** with $NaNO_2$ was even less than with Na_2CO_3; under otherwise identical conditions **2a** was obtained in yields of 54% and 86%, respectively.

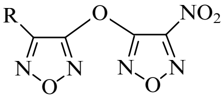
For ArX the reaction course according to reaction 1.3 was verified by special experiments.[2] Thus, when ArX reacted with the respective phenolates, symmetrical DPEs were obtained in yields >80%. The same DPEs were formed in the same or slightly reduced yields when the nitrite method was used. The rate of formation of the DPE using phenolate was higher than by using nitrite ion ($k_3 > k$). On the other hand, different results were obtained when reaction of **1a** with salts of **3a** was studied (Scheme 2).



1a **3a** **2a**

Scheme 2 *Reagents and conditions:* i, CH_3CN, 60 °C.

Studies of the reaction shown in Scheme 2 have indicated that the transformation proceeds considerably slower than formation of **2a** from **1a** and nitrite (or carbonate) of the same metals ($k^{**} \ll k^*$) in contrast to the results observed in the phenylic series where $k_3 > k$. In addition, the yield of **2a** according to Scheme 2 (12–41%) was also considerably lower than in Scheme 1. Meanwhile, if the reaction of **1a** with weak base is assumed to proceed through formation of intermediate salt **3a** the yields in both reactions (Schemes 1 and 2) must be at least equal. These results indicated that **2a** was probably not formed according to Scheme 2, similar to reaction 1.3, *i.e.* the anion of salt **3a** took no part in the reaction as a nucleophile and did not serve as a building block in the construction of **2a**. In fact, attempts to make unsymmetrical ethers **4** by the reaction of **1b** and **1c** with salt **3a** failed. In all cases the salt **3a** seems to play the role of a weak base promoting the transformation of **1** to the corresponding **2**.



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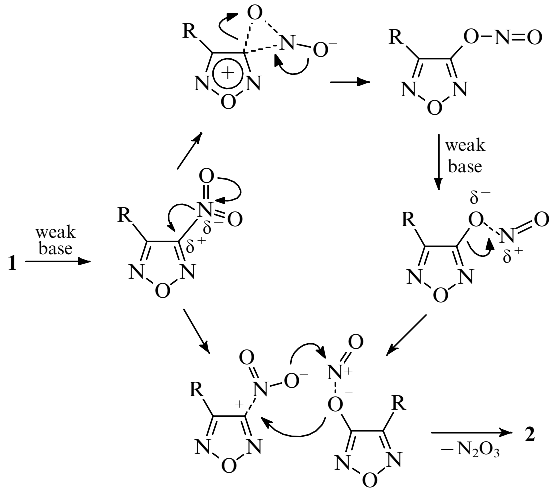
The mechanism of this transformation has not been unequivocally established, but one reasonable possibility is outlined in Scheme 3. As in the case of ArX reacting with NO_2^-, these reactions occur *via* a nitrite ester. However, it is proposed here that the intermediate nitrite ester was formed *via* base-promoted intramolecular nitro–nitrite rearrangement. The primary event in these reactions is base-excited electron transfer inside nitrofurazan with formation of a bipolar molecule. This species then undergoes an electron shift to produce oxazirine, followed by cleavage of the bond between carbon and nitrogen. It would appear that the initially-formed nitrite ester prefers to react with another molecule of base-stimulated starting material to generate the difurazanyl ether **2** and the elimination of N_2O_3.



Scheme 3

The structure of these compounds has been confirmed by elemental analysis, NMR, IR and mass spectroscopy.[†] The structure of **2a** has also been established by an X-ray monocrystal investigation (Figure 1).[‡] Each of the two independent molecules of **2a** consists of two approximately planar nitrofurazan moieties. The torsion angles N–C–O–C′ (τ) are equal to 15.2, 16.6° in one molecule and 12.0, 44.6° in the other. The intramolecular non-bonded contacts N(5)...N(5′) and N(51)...N(51′) are equal to 2.74 and 2.94 A and are shorter than the two-fold van der Waals radius (3.0 A). The bond lengths and bond angles in the independent molecules are close to the standard values. The packing coefficient in the crystal is 0.653.

The variations of τ (12.0–44.6°) found in the crystal show good agreement with the results of optimization by molecular mechanics methods (PCMODEL 3.2): the energy barrier to rotation about the C–O bond does not exceed 1.7 kcal mol^{-1} on varying τ from 10 to 100°. The data provide an explanation for more than one polymorphic modification of **2a**.

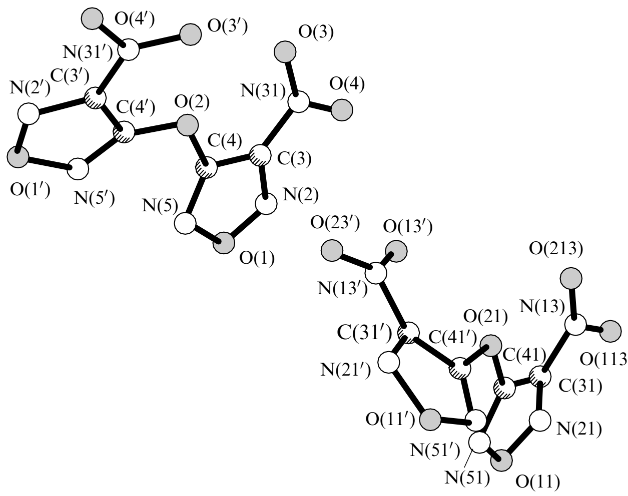


Figure 1 Independent molecules of **2a** in the crystal. The main bond lengths/A: O–C 1.36, C–C 1.42, C–N_{ring} 1.26, N–O_{ring} 1.38, C–N 1.47, N–O 1.20.

In conclusion, we have developed the first synthesis of **2a** which is amenable to scaling up and adaptable for the synthesis of other members of the symmetrical difurazanyl ether series. The ready availability of starting nitrofurazans, combined with the high yields of this reaction, make this straightforward approach highly appealing and very practical. We are currently investigating the generality of this process for the construction of other compounds and its application in target-oriented synthesis.

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[†] All new compounds gave satisfactory combustion analyses and accurate mass measurements. Some selected data, for **2a**: mp 63–64 °C , MS, *m*/*z*: 244(M^+), ^{13}C NMR ([$^2H_6$]acetone) 153.9 ($C–NO_2$), 156.3 (C–O); ^{14}N NMR ([$^2H_6$]acetone) −38.7 (NO_2). For **2b**, mp 68–69 °C; MS, *m*/*z*: 204(M^+). For **3b**, mp 37–39 °C; **2c**, mp 21–22 °C; **3c**, mp 25–26 °C.

[‡] *Crystal data for* **2a**: $C_4N_6O_7$, *M* = 244.08, monoclinic, space group $P2_1/c$, a = 12.796(7), b = 10.602(5), c = 12.944(6) A, β = 103.18(4)°, V = 1710(1) A^3, D_x = 1.898 g cm^{-3}, Z = 8, λ(Mo-Kα) = 0.7107 A. The intensities of 1172 reflections (1208 observed) were measured on a Syntex $P2_1$ diffractometer, using the $\theta-2\theta$ scan technique ($2\theta < 47°$). The structure solution, correcting of the positional and anisotropic thermal parameters and geometric calculations were performed on an IBM PC using SHELX software. The final R_F was 0.055 for 1172 $F_{hkl} > 4\sigma$. Atomic coordinates, bond lengths and angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, *Mendeleev Commun.*, 1996, issue 1. Any request to the CCDC for data should include the full literature citation and the reference number 1135/6.

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