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Reaction of Nitrofurazans with Sulfur Nucleophiles

Aleksei B. Sheremetev,* Elena V. Mantseva, Natal'ya S. Aleksandrova, Vladimir S. Kuz'min and Lenor I. Khmel'nitskii

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 117913 Moscow, Russian Federation.
Fax: +7 095 135 5328; e-mail: shab@nmr1.ioc.ac.ru; L195@suearn2.bitnet

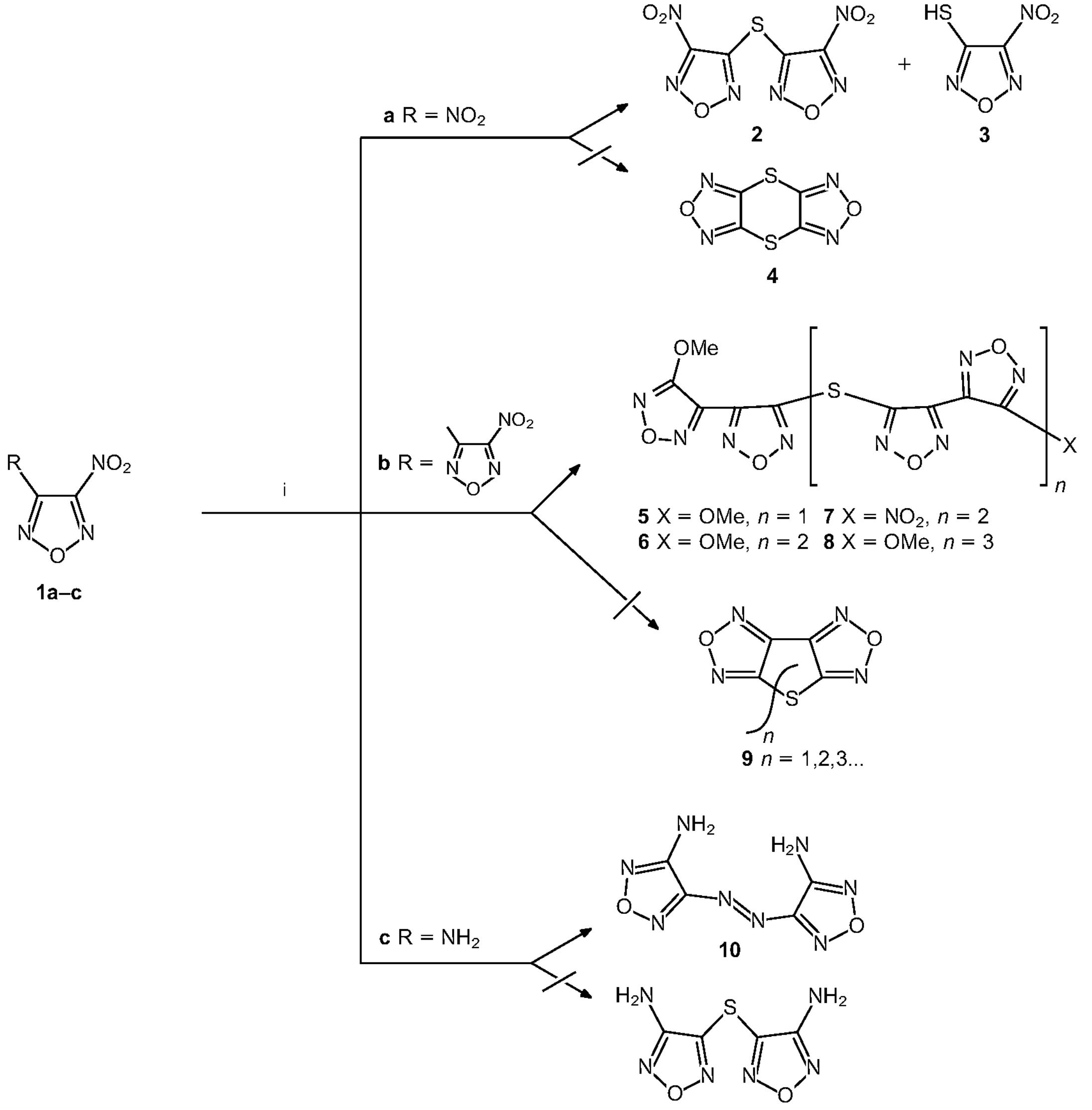
Treatment of nitrofurazans (NF) with sulfur nucleophiles affords a wide variety of product types, depending on the structure of both NF and *S*-nucleophiles.

The use of nucleophilic displacement in heterocyclic chemistry is well known. This reaction has been used in the furoxan series, *e.g.* in ref. 1, but has, however, hardly been utilized to date for furazan derivatives. The reason may lie in the inaccessibility of the objects to be investigated in reactions of this type; the halogen derivatives usually emloyed for these purposes in the furazan series are not readily accessible.[2] At the same time, 3-nitro-4-R-furazans (NF), for which synthetic methods have been actively developed in recent years,[3] may be used as active substrates in nucleophilic reactions.[4] So far only the preparation of alkoxyfurazans by treatment of NF with alcoholates has been known.[5]

Here we present evidence on reactions of NF with sulfur nucleophiles. The sulfur derivatives of furazan synthesized earlier by reduction of the corresponding furoxans are known to show antimicrobial activity.[6]

We have found that the result of the reaction depends strongly on the structure of both NF (Scheme 1) and the sulfur nucleophile (Scheme 2). Thus, treatment of **1a** with sodium sulfide gives the thioether **2** (78%) and mercaptan **3** (5–10%). No products with two sulfur groups substituted for both nitro groups, *e.g.* **4**, were observed. In contrast, under similar conditions **1b** reacts *via* displacement of both nitro groups to produce a number of thioethers which differ both in the number of repeating subunits and in the terminal groups, **5** (5.5%), **6** (16.8%), **7** (35%) and **8** (14.3%); methanol as the reaction medium is also a reagent. However, no cyclic products of type **9** were found. The same reagent gives no thioether when treated with **1c**; only reduction product **10**[7] is observed.

Reaction of **1a** with thiophenol gives compound **11** in 92% yield, whereas reaction with 2-mercaptobenzimidazole affords



Scheme 1 *Reagents and conditions:* i, $Na_2S{\cdot}9H_2O$, MeOH.

thioether **2** (34%) along with a product of usual nucleophilic substitution, **12** (47%). Treatment of **1a** with potassium thiocyanate leads to thiocyanate **13** (83.5%), or to a mixture of the disulfide **14** (38.5%) and tricycle **4**[†] (27%) depending on the temperature. Compound **3** is formed as a by-product in both cases. Formation of the cyclic product **4** is likely due to a radical reaction mechanism,[8] whereas usual nucleophilic displacement occuring on reaction of **1a** with Na_2S stops at the thioether **2** formation stage.

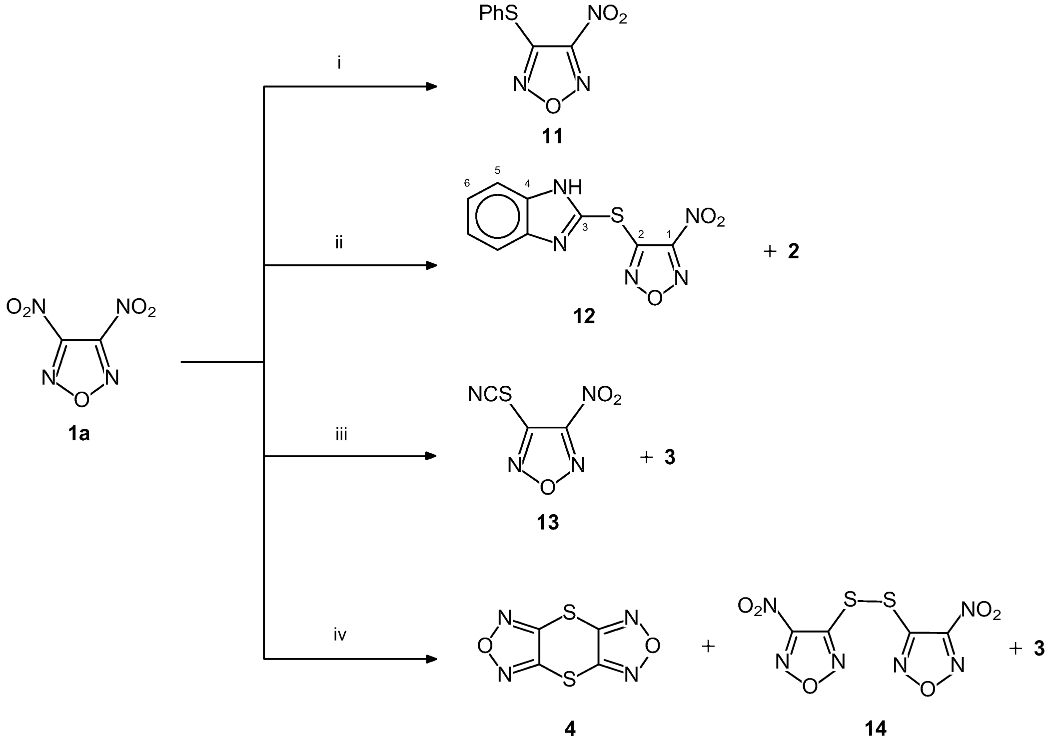
The structure of these compounds has been confirmed by elemental analysis, NMR, IR and mass spectroscopy.[‡] The structure of **2** has also been established by an X-ray monocrystal investigation (Fig. 1).[§] The furazan rings are planar and the nitro groups are almost coplanar with their heterocycles (the dihedral angles cycle/nitro group are 2.6 and 12.3°). The dihedral angle between the nitrofurazan moieties is 107.8°. The S(1)...O(2) intramolecular distance is shorter than the sum of the van der Waals radii (2.922 Å *vs.* 3.2 Å). This distance corresponds to a S...O secondary bond which supplements the coordination of the S atom to a T-shape. All of the bond lengths and angles are close to standard values. Intermolecular contacts are van der Waals'.

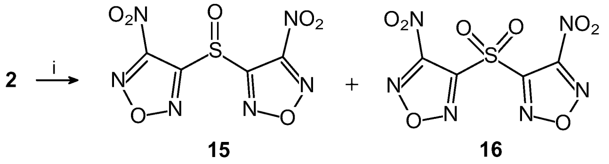
Some chemical transformations of the compounds have been studied. Thus, oxidation of the thioethers by Caro's acid gives the respective sulfoxides and sulfones, *e.g.* **15** (52%) and **16** (23%) have been obtained from **2** (Scheme 3).

[†] Previously the compound was prepared by a ring closure reaction of 2,3,5,6-tetrahydroxyimino-1,4-dithiane with $SOCl_2$ in boiling MeCN, see: A. B. Sheremetev, G. A. Karozo, A. O. Rakitin, T. S. Novikova, T. I. Godovikova and L. I. Khmel'nitskii, *Pat. USSR* 1643546, 1991.

[‡] All new compounds gave satisfactory combustion analyses and accurate mass measurements. Some selected data: for **12**, m.p. 136 °C, MS, *m/z*: 263 (M^+); ^{13}C NMR ([$^2H_6$]acetone) 116.5 (C5), 124.5 (C6), 139.3 (C3), 140.7 (C4), 149.6 (C2), 160.3 (C1); ^{14}N NMR ([$^2H_6$]acetone) –35.1 (NO_2). For **13**, m.p. 41 °C; MS, *m/z*: 172 (M^+); ^{13}C NMR ([$^2H_6$]acetone) 104.9 (CN), 145.9 (C–S), 160.8 (C–NO_2); ^{14}N NMR ([$^2H_6$]acetone) –35.6 (NO_2). For **2**, m.p. 72–73 °C; **4**, m.p. 151–152 °C; **5**, m.p. 105–106 °C; **6**, m.p. 135–138 °C; **7**, m.p. 110–112 °C; **8**, m.p. 179–180 °C; **14**, m.p. 86–87 °C.

[§] *Crystal data for* **2**: $C_4N_6O_6S$, $M = 260.14$, monoclinic, space group $P2_1/n$, $a = 8.831(2)$, $b = 10.343(2)$, $c = 10.247(2)$ Å, $\beta = 98.45(1)°$, $V = 925.8(2)$ Å^3, $D_x = 1.867$ g cm^{-3}, $Z = 4$, λ(Mo-$K\alpha$) = 0.7107 Å. The intensities of 1264 reflections (1188 observed) were measured on a Syntex $P2_1$ diffractometer using the θ-2θ scan technique ($2\theta < 50°$). The structure was solved by direct methods and refined by a full-matrix least-squares method in an anisotropic approximation for all atoms. The final R_F was 0.032 for 1188 $F_{hkl} > 4\sigma$. All calculations were performed on an IBM PC using SHELX software. Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre, see Notice to Authors, *Mendeleev Commun.*, 1995, this issue.


Scheme 2 *Reagents and conditions:* i, PhSH, NaOH, H_2O/acetone, room temperature; ii, 2-mercaptobenzimidazole, NaOH, H_2O/acetone, room temperature; iii, KSCN, AcOH, 10–20 °C; iv, KSCN, AcOH, 70–75 °C.


Scheme 3 *Reagents and conditions*: i, H_2SO_5, 20→55 °C.

In conclusion, the great variety of NF transformations combined with the high yields and diversity of the sulfur-containing furazan derivatives formed give us good reason to believe that this research may be fruitful not only from a theoretical but also from a practical point of view.

A detailed study of the chemical and pharmacological properties of the compounds is in progress.

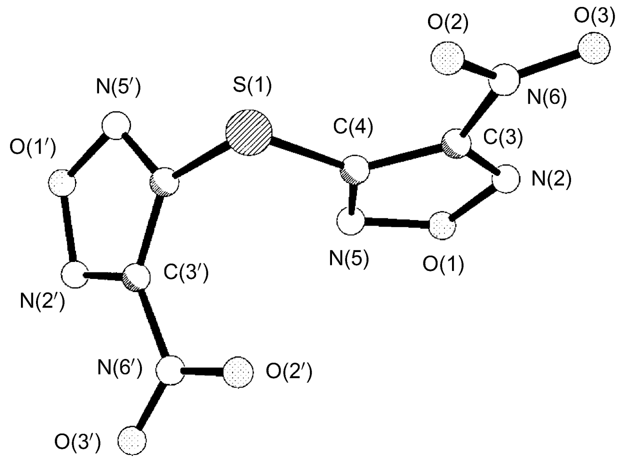


Fig. 1 Molecular structure of **2**. Intramolecular nonvalence distances (Å): O(2′)...S(1) 3.161; O(2′)...N(5) 3.097. Bond distances (av.) are: S–C 1.744, C–C 1.415, C–NO_2 1.446, C=N 1.291, N–O(cycle) 1.377, N–O(nitro) 1.212.

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