Thermal rearrangements of 3-substituted 4-(3-ethoxycarbonylthioureido)-1,2,5-oxadiazole 2-oxides

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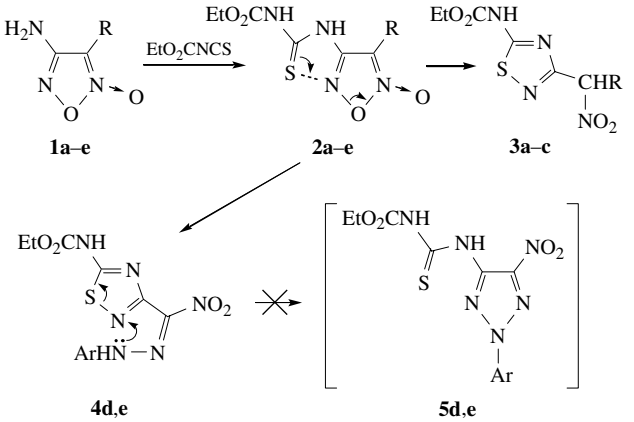
New thermally induced rearrangements in the furoxan series have been found: transformation of 3-(*R*)-substituted 4-(3-ethoxycarbonylthioureido)-1,2,5-oxadiazole 2-oxides (furoxans) into derivatives of 5-amino-3-(α-nitroalkyl)-1,2,4-thiadiazole for R = Me, Ph, MeCO and into (5-amino-1,2,4-thiadiazol-3-yl)nitroformaldehyde arylhydrazones for R = N=N–Ar.

Recently, we found a number of new heterocyclic rearrangements in the series of uncondensed furoxan derivatives,[1–4] which were almost not studied previously.[5] In particular, three new cascade rearrangements of azofuroxan derivatives [3,3′-azo-4,4′-bis(acetylamino)furoxans,[1] 3-arylazo-4-acetylaminofuroxans[2] and 3-arylazo-4-(3-ethoxycarbonylureido)furoxans[3]] into 4-amino-5-nitro-2*H*-1,2,3-triazole derivatives, as well as a rearrangement of furoxanyl ketone phenylhydrazones into 5-(α-nitroalkyl)-2*H*-1,2,3-triazole derivatives,[4] were discovered. Thus, with the use of the heterocyclic rearrangements of furoxans, the nitro group can be introduced in one preparative step either into the α-position with respect to the carbon atom of a new azole or (in the case of cascade rearrangements) directly at the carbon atom of a newly formed heterocyclic ring.

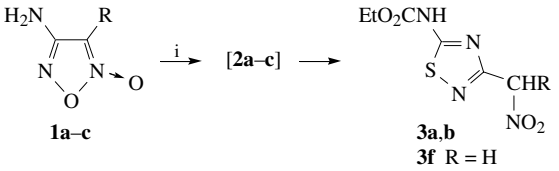
In this work, we studied the heterocyclic rearrangements of furoxans using 4-thioureido derivatives as an example. We intended to synthesise 4-(3-ethoxycarbonylthioureido)-3-R-furoxans **2a–e** by the interaction of ethoxycarbonyl isothiocyanate with corresponding 4-amino-3-R-furoxans **1a–e**. For R = Me, Ph and Ac, we expected to obtain corresponding 3-(α-nitroalkyl)-5-ethoxycarbamoyl-1,2,4-thiadiazoles **3a–c**, whereas two consecutive (cascade) rearrangements with the formation of 2-aryl-substituted 4-amino-5-nitro-2*H*-1,2,3-triazole derivatives **5d**,**e** would be expected for R = Ar (C_6H_4OMe or $C_6H_2Me_3$) (Scheme 1) by analogy with a similar rearrangement of 3-arylazo-4-(3-ethoxycarbonylureido)furoxans[3]. We intended to initiate the rearrangements either thermally or in the presence of bases.



a R = Me **d** R = N=NC$_6$H$_2$Me$_3$
b R = Ph **e** R = N=NC$_6$H$_4$OMe
c R = COMe

Scheme 1

Ethoxycarbonyl isothiocyanate was chosen as the most reactive of isothiocyanates commonly used in analogous reactions;[6] this is associated with the very low basicity of the amino group in furoxans.[7] The reaction was performed by refluxing a mixture of aminofuroxans **1a–e** with ethoxycarbonyl isothiocyanate in various aprotic solvents (chloroform, diethyl ether, acetone, benzene, and ethyl acetate) and monitored by TLC. Among the tested solvents, ethyl acetate was the best, in which the reaction was complete in 2 h. However, rearrangement products were obtained at once in place of expected 4-(3-ethoxycarbonylthioureido)-3-R-furoxans **2a–e**. In particular, for R = Me and Ph, corresponding 5-amino-3-(α-nitroalkyl)-1,2,4-thiadiazole derivatives **3a**,**b**† were obtained. In the case of **2c** (R = Ac), the reaction occurred analogously with the formation of **3c**;† however, under conditions of isolation, the hydrolysis of the acetyl group occurred, and 3-nitromethyl-5-ethoxycarbamoyl-1,2,4-thiadiazole **3f** was isolated as the product (Scheme 2). The structure of compound **3f** was supported by X-ray diffraction analysis.



Scheme 2 *Reagents and conditions*: i, EtO$_2$CNCS (2 mol), EtOAc, reflux, 2 h.

An unexpected result was also obtained in the case of 4-amino-3-arylazofuroxans **1d**,**e**. On refluxing with ethoxycarbonyl isothiocyanate in ethyl acetate, these compounds also entered a rearrangement without the release of intermediates **2d**,**e**; however, in place of the expected cascade rearrangement to form 1,2,3-triazole derivatives **5d**,**e**, the reaction was stopped at the step of formation of 1,2,4-thiadiazole derivatives, which did not enter a subsequent rearrangement, and the molecules were stabilised as nitrohydrazones **4d**,**e**‡ (Scheme 3). The

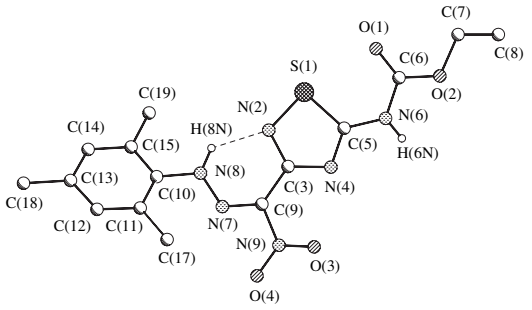
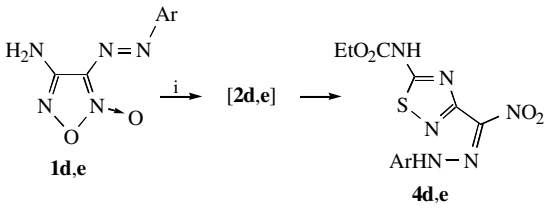


Figure 1 The general view of one of the independent molecules of **4d**. Selected bond lengths (Å): S(1)–N(2) 1.655(2), S(1)–C(5) 1.710(2), N(2)–C(3) 1.312(3), C(3)–N(4) 1.361(3), N(4)–C(5) 1.309(3), C(3)–C(9) 1.460(3), C(5)–N(6) 1.357(3), O(1)–C(6) 1.200(3), N(6)–C(6) 1.365(3), N(7)–C(9) 1.294(3), N(7)–N(8) 1.304(3), N(8)–C(10) 1.414(3), S(1)···O(1) 2.678(2); bond angles (°): N(2)–S(1)–C(5) 91.1(1), C(3)–N(2)–S(1) 108.9(1), N(2)–C(3)–N(4) 118.8(2), C(5)–N(4)–C(3) 108.1(2), N(4)–C(5)–S(1) 113.2(1), N(6)–C(5)–S(1) 124.6(2), C(5)–N(6)–C(6) 121.7(2), C(9)–N(7)–N(8) 121.1(2), N(7)–N(8)–C(10) 119.6(2), N(7)–C(9)–C(3) 128.0(2); H-bond: H(8N)···N(2) 2.15Å, N(8)···N(2) 2.938(3)Å, N(8)H(8N)N(2) 159°.

structure of compound **4d** was confirmed by both physicochemical and X-ray diffraction analysis. The isolation of compounds **4d**,**e** indirectly supports the previously proposed mechanism of the cascade rearrangements of various 4-amino-3-aryl(heteroaryl)azofuroxan derivatives.[1–3]

The geometry parameters of compound **3f** are close to the corresponding values in **4d** (Figures 1 and 2).§ Note that in compound **3f** the S(1)–N(2) bond is longer than that in **4d**, and the S(1)···O(1) intramolecular contact is shortened. Previously,[3] we found that the corresponding N···O contact is responsible for the n(O)–σ*(N–O) interaction in ethoxycarbonyl ureidofuroxans; on this basis, we can assume that the S···O contact in 1,2,4-thiadiazoles is of a similar nature. The supramolecular organization of molecules in dimers in the crystal of compound **3f** also results from intermolecular N(6)–H(6N)···N(4) bonds [N···N is 2.891(3) Å].



Scheme 3 *Reagents and conditions*: i, EtO_2CNCS (2 mol), EtOAc, reflux, 2 h.

Thus, we studied the interaction of 4-amino-3-R-furoxans **1a**–**e** with ethoxycarbonyl isothiocyanate in aprotic organic solvents and found new thermally induced rearrangements in the furoxan series: the transformation of 4-(3-ethoxycarbonylthioureido)-3-R-furoxans **2a**–**e** into 5-amino-3-(α-nitroalkyl)-

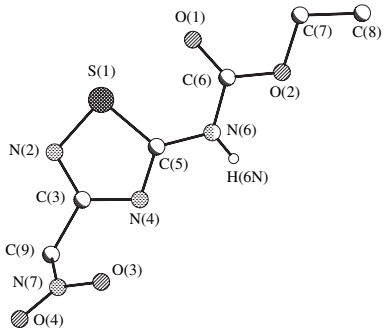


Figure 2 The general view of **3f**. Selected bond lengths (Å): S(1)–N(2) 1.675(2), S(1)–C(5) 1.734(2), N(2)–C(3) 1.315(3), C(3)–N(4) 1.375(3), N(4)–C(5) 1.322(3), C(5)–N(6) 1.372(3), N(6)–C(6) 1.379(3), O(1)–C(6) 1.220(3), C(3)–C(9) 1.505(3), S(1)···O(1) 2.638(2); bond angles (°): N(2)–S(1)–C(5) 91.4(1), C(3)–N(2)–S(1) 108.0(2), N(2)–C(3)–N(4) 120.0(2), C(5)–N(4)–C(3) 107.9(2), N(4)–C(5)–N(6) 122.0(2), N(4)–C(5)–S(1) 112.6(2), N(6)–C(5)–S(1) 125.3(2), C(5)–N(6)–C(6) 119.7(2).

† All new compounds exhibited satisfactory elemental analyses, and their structures were confirmed by IR, ^{1}H and ^{13}C NMR spectroscopy. The IR spectra were measured on an UR-20 spectrometer in KBr; the ^{1}H and ^{13}C NMR spectra were recorded on Bruker WM-250 (250 MHz) and Bruker AM-300 (75.5 MHz) spectrometers, respectively (TMS was used as an internal standard). The mass spectra were measured on a Finnigan MAT INCOS-50 instrument. TLC was carried out on Silufol UV-254 plates, eluent: CCl_4–acetone, 7:1.

The initial aminofuroxans were synthesised according to known methods: 4-amino-3-methylfuroxan **1a**,[8] 4-amino-3-phenylfuroxan **1b**,[9] 4-amino-3-acethylfuroxan **1c**,[10] 4-amino-3-(4-methoxyphenylazo)furoxan **1d**,[3] 4-amino-3-(2,4,6-trimethylphenylazo)furoxan **1e**.[2]

5-Ethoxycarbamoyl-3-(α-nitroethyl)-1,2,4-thiadiazole **3a**: 47% yield, mp 83–85 °C, R_f 0.46. ^{1}H NMR ([^{2}H$_6$]DMSO) δ: 1.28 (t, 3H, *Me*CH$_2$), 1.85 (d, 3H, MeCH, ^3J 9.8 Hz), 4.30 (q, 2H, MeCH$_2$), 6.11 (q, 1H, MeCH, ^3J 9.8 Hz), 12.77 (s, 1H, NH). ^{13}C NMR ([^{2}H$_6$]acetone) δ: 14.62 (*Me*CH$_2$), 17.88 (*Me*CH), 64.26 (MeCH$_2$), 83.24 (MeCH), 155.25 (CO), 165.75 (C-3 of thiadiazole ring), 179.53 (C-5 of thiadiazole ring). ^{14}N NMR ([^{2}H$_6$]acetone) δ: 6.05 (NO_2). MS, *m*/*z* (%): 200 ($M^+ - NO_2$, 100), 128 (95), 86 (68).

5-Ethoxycarbamoyl-3-(α-nitrobenzyl)-1,2,4-thiadiazole **3b**: 40% yield, mp 145–146 °C, R_f 0.32. ^{1}H NMR ([^{2}H$_6$]DMSO) δ: 1.35 (t, 3H, *Me*CH$_2$), 4.39 (q, 2H, MeCH$_2$), 7.09 (s, 1H, PhCH), 7.50–7.71 (m, 5H, Ph), 12.57 (s, 1H, NH). ^{13}C NMR ([^{2}H$_6$]acetone) δ: 14.64 (*Me*CH$_2$), 64.27 (MeCH$_2$), 90.68 (O_2NCH), 129.53, 130.87, 130.91, 133.09 (Ph), 155.30 (CO), 164.84 (C-3 of thiadiazole ring), 179.57 (C-5 of thiadiazole ring). ^{14}N NMR ([^{2}H$_6$]acetone) δ: 3.16 (NO_2). MS, *m*/*z* (%): 262 ($M^+ - NO_2$, 90), 216 (21), 190 (100), 116 (37).

5-Ethoxycarbamoyl-3-(nitromethyl)-1,2,4-thiadiazole **3f**: 59% yield, mp 121–122 °C, R_f 0.36. ^{1}H NMR ([^{2}H$_6$]DMSO) δ: 1.30 (t, 3H, *Me*CH$_2$), 4.28 (q, 2H, MeCH$_2$), 6.19 (s, 2H, O_2NCH$_2$), 12.81 (s, 1H, NH). ^{13}C NMR ([^{2}H$_6$]acetone) δ: 14.87 (*Me*CH$_2$), 63.87 (MeCH$_2$), 78.45 (O_2NCH$_2$), 156.47 (CO), 166.02 (C-3 of thiadiazole ring), 176.12 (C-5 of thiadiazole ring). ^{14}N NMR ([^{2}H$_6$]acetone) δ: 6.32 (NO_2). MS, *m*/*z* (%): 186 ($M^+ - NO_2$, 100), 114 (82), 72 (35).

(5-Ethoxycarbamoyl-1,2,4-thiadiazol-3-yl)nitroformaldehyde 4-methoxyphenylhydrazone **4d**: 60% yield, mp 190–191 °C, R_f 0.51. ^{1}H NMR ([^{2}H$_6$]DMSO) δ: 1.32 (t, 3H, *Me*CH$_2$), 3.88 (s, 3H, MeO), 4.35 (q, 2H, MeCH$_2$), 7.02, 7.36 (4H, AA′BB′, ^3J 7.3 Hz), 11.72 (s, 1H, ArNH), 12.93 (s, 1H, EtO_2CNH). ^{13}C NMR ([^{2}H$_6$]DMSO) δ: 14.17 (*Me*CH$_2$), 55.38 (MeO), 63.20 (MeCH$_2$), 114.85, 116.90, 119.88, 125.88 (Ar), 135.33 (O_2NC), 154.62 (C-3 of thiadiazole ring), 156.40 (CO), 177.81 (C-5 of thiadiazole ring). ^{14}N NMR ([^{2}H$_6$]acetone) δ: –13.96 (NO_2). MS, *m*/*z* (%): 366 (M^+, 5), 319 (10), 135 (20), 121 (100).

(5-Ethoxycarbamoyl-1,2,4-thiadiazol-3-yl)nitroformaldehyde (2,4,6-trimethylphenyl)hydrazone **4e**: 52% yield, mp 184–185 °C, R_f 0.54. ^{1}H NMR ([^{2}H$_6$]DMSO) δ: 1.25 (t, 3H, *Me*CH$_2$), 2.29 (s, 3H, *p*-Me), 2.35 (s, 6H, *o*-Me), 4.18 (q, 2H, MeCH$_2$), 7.09 (s, 2H, Ar), 11.01 (s, 2H, NH). ^{13}C NMR ([^{2}H$_6$]DMSO) δ: 14.17 (*Me*CH$_2$), 18.30 (*p*-Me), 20.41 (*o*-Me), 63.23 (MeCH$_2$), 129.41, 129.65, 130.49, 135.70 (Ar), 135.3 (O_2NC), 154.69 (C-3 of thiadiazole ring), 156.55 (CO), 177.81 (C-5 of thiadiazole ring). ^{14}N NMR ([^{2}H$_6$]acetone) δ: –14.00 (NO_2). MS, *m*/*z* (%): 380 (M^+, 3), 334 (12), 135 (100).

‡ According to X-ray diffraction data, compound **4d** crystallises with two independent molecules in a unit cell. The main geometry parameters of independent molecules, including the intramolecular N–H···N bond, are similar (Figure 1). The main difference consists in mutual dispositions of the mesitylene substituent with respect to the six-membered H-bonded ring [the C(15)C(10)N(8)N(7) torsion angles are 135.1 and 179.8°]. An analysis of the crystal packing revealed that the variation of conformation of the mesitylene ring around the C(10)–N(8) bond in one of the independent molecules is, probably, because the aryl group participates in the stacking interaction, whereas this type of intermolecular contact does not occur in the other one. In addition to the stacking interaction, intermoecular N(6)–H(6N)···N(4) hydrogen bonds [N···N is 2.643(2) Å], which assemble the independent molecules into dimers, were also observed in the crystal of compound **4d**.

§ *Crystallographic data for* **3f**: $C_6H_8N_4O_4S$, M = 232.22, triclinic, space group $P\bar{1}$, at 120 K a = 5.456(1), b = 7.216(2), c = 12.527(3) Å, α = = 86.767(5), β = 86.435(4), γ = 71.863(5)°, V = 467.4(2) Å^3, Z = 2 (Z' = 1), d_{calc} = 1.650 g cm^{-3}, μ(MoKα) = 3.48 cm^{-1}, F(000) = 240.

For **4d**: $C_{15}H_{18}N_6O_4S$, M = 378.41, triclinic, space group $P\bar{1}$, at 120 K a = 12.021(3), b = 12.187(3), c = 13.768(4) Å, α = 97.998(6), β = 98.229(6), γ = 114.561(5)°, V = 1770.9(8) Å^3, Z = 4 (Z' = 2), d_{calc} = 1.419 g cm^{-3}, μ(MoKα) = 2.18 cm^{-1}, F(000) = 792.

Intensities of 2933 (**3f**) and 37142 (**4d**) reflections were measured with a Smart 1000 CCD diffractometer [λ(MoKα) = 0.71072 Å, ω-scans with a 0.3° step in ω and 10 s per frame exposure, $2\theta < 54°$ (**3f**) and 56° (**4d**)]; 1940 (**3f**) and 8542 (**4d**) independent reflections [R_{int} = 0.02753 (**3f**) and 0.0505 (**4d**)] were used in further refinement. The structures were solved by direct method and refined by the full-matrix least-squares technique against F^2 in the anisotropic-isotropic approximation. Hydrogen atoms were located from the Fourier synthesis and refined in the isotropic approximation. The positions of the disordered NO_2 group in one of the independent molecules in **4d** were refined with equal occupancies. The refinement converged to wR_2 = 0.1204 and GOF = 1.053 for all independent reflections [R_1 = 0.0515 was calculated against F for 1736 observed reflections with $I > 2\sigma(I)$] for **3f** and to wR_2 = 0.1284 and GOF = 1.042 for all independent reflections [R_1 = 0.0544 was calculated against F for 5414 observed reflections with $I > 2\sigma(I)$] for **4d**. All calculations were performed using the SHELXTL PLUS 5.0.

Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). These data can be obtained free of charge *via* www.ccdc.cam.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk). Any request to the CCDC for data should quote the full literature citation and CCDC reference numbers 217806 and 217807. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2003.

1,2,4-thiadiazole derivatives **3a**,**b**,**f** for R = Me, Ph and COMe or into (5-amino-1,2,4-thiadiazol-3-yl)nitroformaldehyde arylhydrazones **4d**,**e** for R = N=N–Ar.

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