An unexpected transformation of 3,4-diacylfuroxans into 3-acyl-4-acylaminofurazans in the reaction with nitriles

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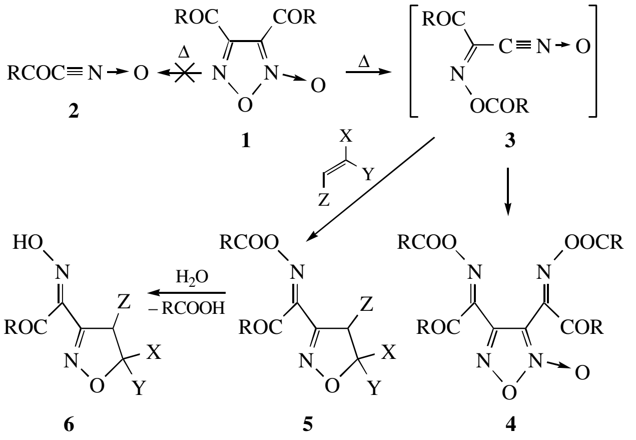
The reaction of 3,4-diacyl-1,2,5-oxadiazole 2-oxides (furoxans) with activated nitriles in ionic liquids and in ethanol unexpectedly resulted in 3-acyl-4-acylamino-1,2,5-oxadiazoles (furazans); a possible mechanism of this reaction is proposed.

We have shown previously[1] that the 1,3-dipolar cycloaddition of phenyl azide and furazanyl azides to acetylenes and enamines is accelerated considerably if organic solvents are replaced by ionic liquids, *viz*., 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4])[2] or 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF_6]),[3] which are ecologically promising reaction media.[4,5] The results obtained in these studies open prospects for the use of ionic liquids in similar reactions, particularly, in the 1,3-dipolar cycloaddition of nitrile oxides to various dipolarophiles. These reactions have been studied rather widely;[6] however, the problem of synthesising nitrile oxides in which the nitrile oxide fragment is bound to various functional groups has not yet been solved. Substituted nitrile oxides could be obtained by the thermolysis of corresponding symmetrically substituted furoxans, for example, readily available diacylfuroxans **1**. The thermolysis and subsequent reaction of furoxans type **1** with dipolarophyles under appropriate conditions can result in various acyl-substituted heterocycles.

Attempts to use diacylfuroxans as sources of acylformonitrile oxides **2** were undertaken; however, it was shown by Brittelli and Boswell[7] that, in non-polar solvents commonly used for the thermolysis of furoxans, this reaction is only possible in the case of sterically hindered substituents. Under these conditions, ordinary diacylfuroxans **1** are transformed into acyloximinoacetonitrile oxides **3**. In particular, intermediate **3b** formed in the case of dibenzoylfuroxan **1b** undergoes dimerisation to new furoxan **4b**; if alkenes are present as the dipolarophiles, isoxazolines **5b** are formed.[7] Similar cycloadducts **5a** are also formed upon refluxing diacetylfuroxan **1a** in xylene with various alkenes, whereas the reaction in a toluene–DMF mixture gives the same cycloadduct incorporating a free oxime group, *viz*., compound **6a**.[8] Obviously, the reaction occurs similarly under these conditions but is accompanied by the hydrolysis of the O-acetyl fragment (Scheme 1).



a R = Me
b R = Ph

Scheme 1

Furthermore, it has been shown[8] that diacetylfuroxan **1a** can act as a nitrone in the reaction with phenylmaleimide on refluxing in xylene. Taking earlier results[1] into account, it was of interest to find out how ionic liquids affect the direction of thermolysis of diacylfuroxans **1**.

In this work, we studied whether acylformonitrile oxides **2** could be generated by thermolysis of diacylfuroxans **1** in the above ionic liquids, followed by 1,3-dipolar cycloaddition of compound **2** to activated nitriles **7** (trichloroacetonitrile and ethyl cyanoformate), which were successfully used previously to trap nitroformonitrile oxide generated by the thermolysis of dinitrofuroxan.[9]

Heating diacetylfuroxan **1a** with trichloroacetonitrile in [bmim][BF_4] or [bmim][PF_6] at 80 °C gave a compound, the elemental analysis and mass spectrum (M^+ 271) of which did not correspond to the expected cycloadduct, *viz*., 3-acetyl-5-trichloromethyl-1,2,4-oxadiazole **8**. The ^{1}H NMR spectrum of this compound contained signals of the methyl group of the acetyl fragment (δ 2.85) and of an NH or OH proton (δ 10.42). To confirm the structure of the product, it was analysed by X-ray diffraction, which showed that the product was *N*-(4-acetyl-1,2,5-oxadiazol-3-yl)-2,2,2-trichloroacetamide **11a** (Figure 1).[†,‡] Similar compound **11b** was also obtained in the reaction of diacetylfuroxan with ethyl cyanoformate.

To determine the scope of the reaction discovered, we also studied dibenzoyl- and di(cyclopropylcarbonyl)furoxans **1b** and **1c**. The reaction was carried out with both nitriles **7**. It was found that dibenzoylfuroxan **1b** did not react with nitriles **7** under these conditions, whereas furoxan **1c** reacted with both nitriles similarly to diacetylfuroxan to give corresponding 1,2,5-oxadiazole derivatives **11c**,**d**; more yields were reached in [bmim][BF_4] (Scheme 2). What is more, it was found that the direction of the reaction did not change if ethanol was used instead of a ionic liquid. The reaction of compound **1a**,**c** with the nitriles occurs in ethanol at the same temperature (80 °C) upon refluxing the reaction mixture for 5.5 h; the yields of the products in ionic liquids are close to those in ethanol.[†]

Obviously, the use of ionic liquids or ethanol as solvents did not change the first step of thermolysis of diacylfuroxans **1**, and it occurred in accordance with Scheme 1 with the formation of nitrile oxide **3**. Then, addition product **9** of this nitrile oxide to corresponding nitrile **7** is formed, the acyloximino group is hydrolysed, and compound **10** underwent a thermally induced heterocyclic rearrangement, which gave furazans **11** (Scheme 2). An example of the thermally induced rearrangement of 3-benzoyl-1,2,4-oxadiazole oxime into 3-formylamino-4-phenylfurazan has been reported.[10] It could be assumed with a high probability that the results differ from those expected based on published data[7] because non-polar solvents were replaced by polar solvents.

The main geometrical parameters of compound **11a** are close to values expected for substituted furazans (Figure 1).[‡] The presence of the trichloroacetylamino group leads to a significant elongation of the O(1)–N(1) bond [1.403(3) Å] in comparison with the O(1)–N(2) bond [1.375(3) Å], while the lengths of the C(1)–N(1) and C(1)–N(2) bonds are equal. In a crystal, the H(3N) atom of the trichloroacetylamino group participated in

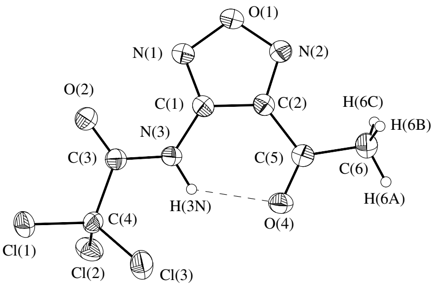
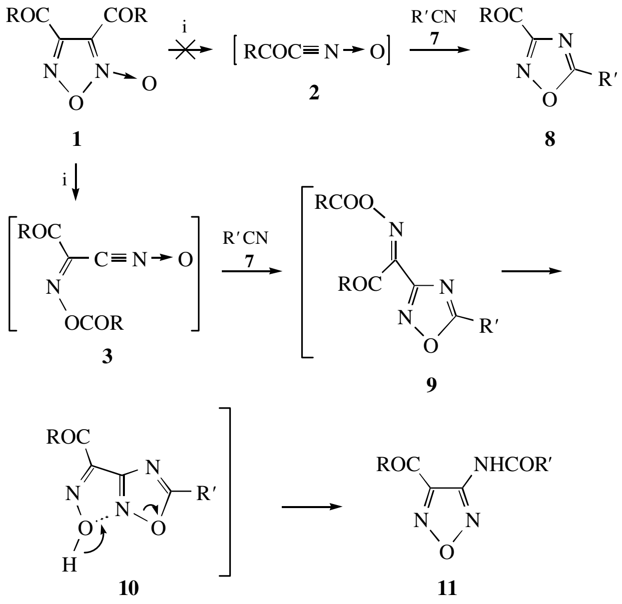


Figure 1 General view of the molecule of **11a**. Selected bond lengths (Å): Cl(1)–C(4) 1.755(3), Cl(2)–C(4) 1.773(3), Cl(3)–C(4) 1.767(3), O(1)–N(1) 1.403(3), O(1)–N(2) 1.375(3), N(3)–C(1) 1.378(4), N(3)–C(3) 1.362(4), O(2)–C(3) 1.206(4), O(4)–C(5) 1.216(4), N(1)–C(1) 1.307(4), N(2)–C(2) 1.301(4), C(1)–C(2) 1.427(4); bond angles (°): N(2)–O(1)–N(1) 111.5(2), C(1)–N(1)–O(1) 103.9(2), C(2)–N(2)–O(1) 105.8(2), C(3)–N(3)–C(1) 125.3(2), N(1)–C(1)–N(3) 125.9(3), N(1)–C(1)–C(2) 110.1(3), N(3)–C(1)–C(2) 124.0(3), N(2)–C(2)–C(1) 108.8(3), N(2)–C(2)–C(5) 124.5(3), C(1)–C(2)–C(5) 126.7(3), Cl(1)–C(4)–Cl(3) 110.2(2), Cl(1)–C(4)–Cl(2) 109.7(2), Cl(3)–C(4)–Cl(2) 109.5(2).



1 **a** R = Me
b R = COPh
c R = cyclopropyl
7 R′ = CCl_3, EtOCO

11 **a** R = Me, R′ = CCl_3
b R = Me, R′ = EtOCO
c R = cyclopropyl, R′ = CCl_3
d R = cyclopropyl, R′ = EtOCO

Scheme 2 *Reagents and conditions:* i, [bmim][BF_4] or EtOH, 80 °C, 5.5 h.

an intramolecular N–H···O hydrogen bond [N(3)···O(4) 2.084(2) Å] with the formation of a six-membered H-cycle. In spite of this fact, the dihedral angle between the plane of the furazan ring and the trichloroacetylamino group is 14.4° (for comparison, it is only 5.5° in the acetyl group).

Analysis of crystal packing revealed that the observed deviation from planarity, as well as the variation of the C–Cl bond length in compound **11a**, is the result of the shortened Cl···Cl and Cl···O contacts (Figure 2). Taking into account the directionality of these contacts (the corresponding C–Cl···O and C–Cl···Cl angles are close to 180°), we can conclude that the elongation of the C(4)–Cl(3) and C(4)–Cl(2) bonds is caused by charge transfer from the lone electron pairs of chlorine and oxygen to the antibonding orbitals of the C(4)–Cl(2) and C(4)–Cl(3) bonds, respectively.

Due to the above contacts, molecules in a crystal are assembled into tubes directed along the crystallographic axis *c*. Within the tubes 'layer', parallel to the crystallographic plane *ab*, is the trimer in which molecules are connected by the shortened Cl···Cl contacts, while Cl···O contacts between 'layers' assemble molecules into an infinite tube-like structure.

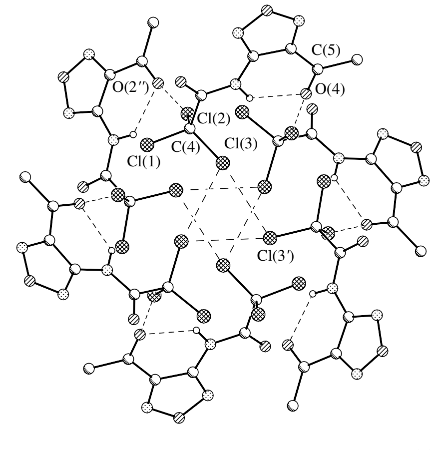


Figure 2 A fragment of the crystal structure of compound **11a** (projection to the plane *ab*) illustrating the formation of shortened Cl···Cl and Cl···O contacts. Parameters of the C(4)–Cl(3)···Cl(3″) contact: Cl(3)···Cl(3′) 3.275(1) Å, C(4)–Cl(3)···Cl(3′) 166.9(1)°. Parameters of the C(4)–Cl(2)···O(2″) contact: Cl(2)···O(2″) 2.983(2) Å, C(4)–Cl(2)···O(2″) 159.9(1)°.

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† *Characteristic and spectroscopic data.* Structures of all new compounds were confirmed by NMR spectroscopy and mass spectrometry. ^{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). Mass spectra were recorded on a Finnigan MAT INCOS-50 spectrometer. TLC monitoring was performed on Silufol UV 254 silica gel plates using chloroform or a chloroform–petroleum ether mixture (10:1) as an eluent. Melting points were determined on a Boetius PHMK 05 instrument. All compounds were isolated by column liquid chromatography (Silica gel Merck 60 F_{254} with $CHCl_3$ as an eluent).

N-*(4-Acetyl-1,2,5-oxadiazol-3-yl)-2,2,2-trichloroacetamide* **11a**: yield 40%, mp 120–122 °C (octanol). R_f 0.65 (chloroform–light petroleum, 10:1). ^{1}H NMR ($CDCl_3$) δ: 2.85 (s, 3H, Me), 10.42 (s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 28.20 (Me), 90.76 (CCl_3), 143.21 (CO), 148.47 (C-4), 158.10 (C-3), 193.33 (CO at C-3). MS, *m/z*: 271 (M^+) 271 (Cl 79).

N-*(4-acetyl-1,2,5-oxadiazol-3-yl)oxamic acid, ethyl ester* **11b**: yield 32%, mp 88–91 °C (hexane). R_f 0.25 (chloroform–light petroleum, 10:1). ^{1}H NMR ($CDCl_3$) δ: 1.30 (t, 3H, Me), 2.81 (s, 3H, Me), 4.46 (m, 2H, CH_2), 10.61 (s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 14.91 (Me), 28.61 (Me), 63.97 (CH_2), 144.01 (CO), 148.57 (C-4), 153.40 (CO), 159.12 (C-3), 192.05 (CO at C-3). MS, *m/z*: 226 ($M^+ - 1$).

N-*(4-Cyclopropylcarbonyl-1,2,5-oxadiazol-3-yl)-2,2,2-trichloroacetamide* **11c**: yield 35%, mp 87–89 °C (hexane). R_f 0.80 (chloroform–light petroleum, 10:1). ^{1}H NMR ($CDCl_3$) δ: 1.35 (m, 2H, CH_2), 1.44 (m, 2H, CH_2), 3.03 (m, 1H, CH), 10.61 (s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 15.01 (2CH_2), 22.13 (CH), 88.95 (CCl_3), 143.37 (CO), 149.02 (C-4), 157.71 (C-3), 194.8 (CO). MS, *m/z*: 297 (M^+) (Cl 79).

N-*(4-Cyclopropylcarbonyl-1,2,5-oxadiazol-3-yl)oxamic acid, ethyl ester* **11d**: yield 34%, mp 64–66 °C (hexane). R_f 0.30 (chloroform–light petroleum, 10:1). ^{1}H NMR ($CDCl_3$) δ: 1.32 (m, 4H, 2CH_2), 1.43 (t, 3H, Me), 2.98 (m, 1H, CH), 4.47 (m, 2H, CH_2), 10.66 (s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 13.88 (Me), 14.39 (2CH_2), 20.19 (CH), 64.28 (CH_2), 143.37 (CO), 148.19 (C-4), 153.24 (CO at NH), 158.52 (C-3), 195.08 (CO at C-3). MS, *m/z*: 252 ($M^+ - 1$).

‡ *Crystallographic data*: crystals of **11a** ($C_6H_4Cl_3N_3O_3$, $M = 272.47$) are rhombohedral, space group $R\bar{3}$, at 110 K: $a = 24.227(4)$, $c = 9.145(2)$ Å, $V = 4648.3(15)$ Å^3, $Z = 18$ ($Z' = 1$), $d_{calc} = 1.752$ g cm^{-3}, μ(MoKα) = = 8.76 cm^{-1}, $F(000) = 2448$. Intensities of 6481 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, $2\theta < 54°$] and 2211 independent reflections ($R_{int} = 0.0255$) were used in the further refinement. The structure was solved by a 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 refinement converged to $wR_2 = 0.1296$ and GOF = 1.048 for all independent reflections [R_1 = = 0.0525 was calculated against F for 1750 observed reflections with $I > 2\sigma(I)$]. All calculations were performed using 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 number 223126. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2003.

Thus, a study of the effects of ionic liquids on the direction of the thermolysis of 3,4-diacylfuroxans unexpectedly gave 3-acyl-4-acylaminofurazans. It was found that the reaction occurred both in ionic liquids and in ethanol as a multistep one-pot process; this makes it possible to synthesise polyfunctional furazan derivatives in two preparative stages: synthesis of the starting diacylfuroxans and their transformation in the presence of activated nitriles.

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