1,2,4-Thiadiazole 4-oxides

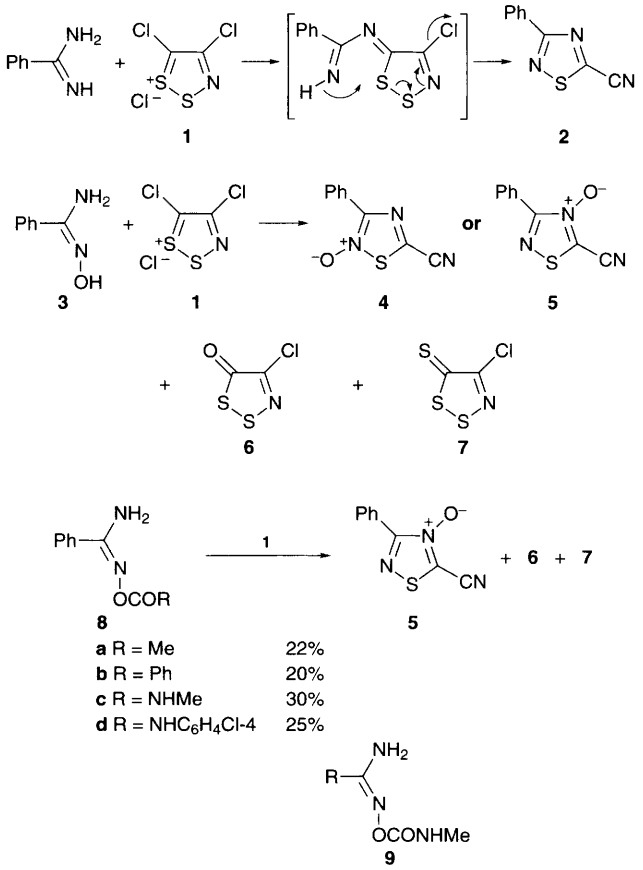
Oleg A. Rakitin,[a] Charles W. Rees[b] and Olga G. Vlasova[a]

[a] *N.D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Leninsky Prospekt 47, Moscow B-334, Russia*
[b] *Department of Chemistry, Imperial College of Science, Technology and Medicine, London, UK SW7 2AY*

The first *N*-oxides of the 1,2,4-thiadiazole ring system are prepared by condensation of benzamidoximes with 4,5-dichloro-1,2,3-dithiazolium chloride 1; they are shown by ^{15}N-labelling to be 4-oxides and a mechanism is proposed for their formation.

The ready preparation of 4,5-dichloro-1,2,3-dithiazolium chloride **1** and its reactivity towards nucleophiles[1] has resulted in the vigorous development of 1,2,3-dithiazole chemistry since 1985.[2,3] The salt **1** rapidly forms 5-imino derivatives with primary aromatic amines which yield 2-cyanobenzothiazoles on heating, and it reacts similarly with benzamidine to give 5-cyano-3-phenyl-1,2,4-thiadiazole **2** at room temperature, as shown.[2]

Whilst 1,2,4-thiadiazoles have been investigated extensively,[4] no *N*-oxides of this ring system have yet been reported. It occurred to us that *N*-oxides such as **4** or **5** might be formed in an analogous reaction of the dithiazolium salt **1** with amidoximes. Treatment of benzamidoxime **3** with salt **1** in dichloromethane at room temperature, followed by addition of pyridine, gave the 4-oxide **5** (see below) in low yield (8%) as reasonably stable, colourless crystals, mp 142–144 °C,† together with 4-chloro-1,2,3-dithiazole-5-one **6** (32%) and -5-thione **7** (15%) which are common by-products in reactions

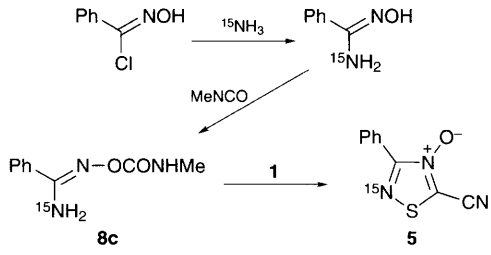


of the salt **1**. Deoxygenation of the *N*-oxide with triphenylphosphine in CH_2Cl_2 at room temperature for three days gave 5-cyano-3-phenyl-1,2,4-thiadiazole **2** (89%).

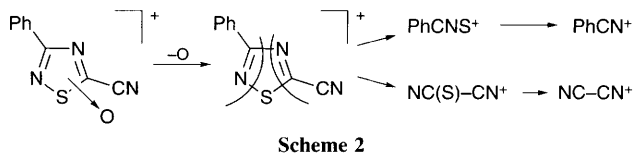
In an attempt to improve the yield of the *N*-oxide, various *O*-substituted benzamidoximes **8a–d**[5] were prepared and treated with the 1,2,3-dithiazolium salt **1** in CH_2Cl_2 at room temperature, followed by the addition of pyridine. In each case the same *N*-oxide was produced, in somewhat higher yield (20–30%), together with comparable amounts of the dithiazolone **6** and dithiazolthione **7**.

Since the best yield of *N*-oxide **5** was obtained from the *N*-methylcarbamoyl derivative **8c**, we used this derivative to explore the scope of the reaction with other amidoximes, and to determine the reaction pathway by ^{15}N-labelling. The former was disappointing. Alkyl amidoximes **9** (R = Me, Bu^t, $PhCH_2$) and arylamidoximes with electron-withdrawing substituents **9**, (R = 4-ClC_6H_4, 4-BrC_6H_4, 4-$O_2NC_6H_4$, 3-$O_2NC_6H_4$ and 2,4-$Cl_2C_6H_3$) did not give *N*-oxides, but only the dithiazolone **6** (up to 38%) and the dithiazolthione **7** (up to 60%), often in high combined yield. However, with **9** (R = 4-MeC_6H_4 and 4-$Me_2NC_6H_4$), the analogous *N*-oxides were isolated (16 and 11%), together with the dithiazolone **6** (15 and 20%) and the dithiazolthione **7** (25 and 28%), respectively.

The site of *N*-oxidation was determined as follows. The carbamoyl derivative **8c** was specifically labelled with ^{15}N (94% ^{15}N) as shown in Scheme 1, and treated with dithiazolium salt **1** exactly as before to give an *N*-oxide (30%, 91% ^{15}N) which was shown to be isomer **5** by analysis of the NMR and mass spectra of labelled and unlabelled products. In the ^{15}N NMR spectrum of the *N*-oxide there is only one signal, corresponding to the unoxidised nitrogen atom of the thiadiazole ring, at δ −110.86. In the ^{14}N NMR spectrum the *N*-oxide nitrogen signal is δ −70.69 (half height width $\Delta\nu_{1/2}$ = 76.5 Hz), characteristic of heterocyclic *N*-oxides. This shows that all the ^{15}N label is on the unoxidised ring nitrogen atom. In the mass spectrum of unlabelled *N*-oxide the first fragmentation was loss of the oxygen atom, followed by the usual fragmentation of the 1,2,4-thiadiazole ring (Scheme 2).[6] The mass spectrum of the labelled compound showed that all the label



Scheme 1

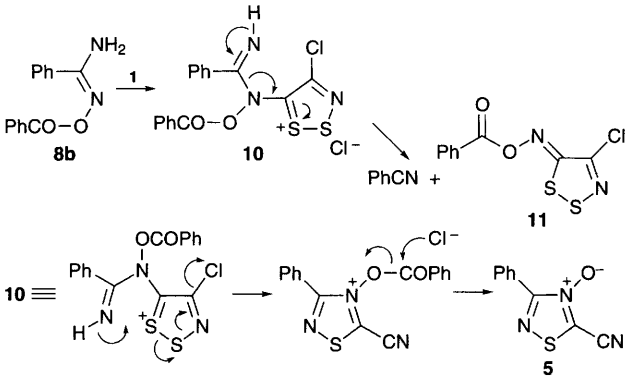


Scheme 2

resides on the 2-nitrogen atom linked to sulfur [peaks PhC^{15}NS (*m/z* 136) and PhC^{15}N (*m/z* 104)], and the 4-nitrogen is completely unlabelled [peaks NC(S)CN (*m/z* 84) and NCCN (*m/z* 52)]. This proves that the *N*-oxide isolated is the 4-oxide **5**.

Additional support for isomer **5** was given by the ^{13}C NMR spectrum of the labelled compound. It is known that for geminal ^{13}C–C–^{15}N interactions the proximity of the nitrogen lone pair to the β-carbon atom greatly enhances the coupling constant (^2J = 9–10 Hz).[7] In our case the ^{15}N does indeed couple strongly to the *ipso*-carbon of the phenyl ring (^2J = 5.2 Hz), but does not couple to the cyanide carbon as would be expected for the 2-oxide **4**.

Formation of the 4-oxide **5** requires that initial attack by the amidoxime upon the salt **1** occurs through the oxime nitrogen atom. This pathway is in agreement with the isolation of two other products from the reaction of *O*-benzoyl benzamidoxime **8b**: benzonitrile (23%) and the stable benzoyloxyimine **11** (15%). All three products are derivable from the initial intermediate **10** in Scheme 3, which shows how the *N*-oxide **5** is probably formed. The novel benzoyloxyimine **11** was prepared independently (34%) from *O*-benzoylhydroxylamine and dithiazolium salt **1** in CH_2Cl_2 followed by the addition of pyridine.



Scheme 3

The 1,2,4-thiadiazole 4-oxides reported here formed colourless to pale yellow crystals, although not of X-ray diffraction quality, of only modest stability. They decompose slowly on standing in solution or as solids at room temperature, and rapidly in boiling toluene, to give the deoxygenated 1,2,4-thiadiazole.

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Footnote

† All new compounds were fully characterized by spectroscopy and elemental analysis

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