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Reactions of vicinal nitroamines with sulfur monochloride—a short and convenient route to fused 1,2,5-thiadiazoles and their *N*-oxides

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ABSTRACT

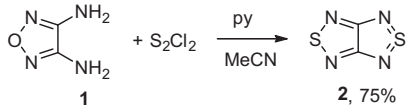
A convenient synthetic approach to fused 1,2,5-thiadiazoles and their *N*-oxides from vicinal nitroamines and sulfur monochloride has been developed.

Fused 1,2,5-thiadiazoles have attracted much attention because of their interesting chemical properties and various possibilities in use as antibacterial and antiviral agents, agrochemicals, and as π-type building blocks for organic electronics, particularly for both low- and high-molecular weight organic light-emitting diodes (OLEDs).[1] Recently 1,2,5-thiadiazole derivatives were recognized as efficient electron acceptors and were successfully used for the preparation of radical-anion salts revealing antiferromagnetic exchange interactions in their spin systems,[2] and conductive charge-transfer complexes also possessing photoconductivity.[3] Although methods for the preparation of fused 1,2,5-thiadiazoles are numerous and well elaborated,[1] there is still a lack of syntheses of derivatives containing electron-deficient heterocycles or electron-withdrawing groups.

Recently, it was found that 3,4-diamino-1,2,5-oxadiazole (**1**), on treatment with sulfur monochloride and pyridine in acetonitrile gave, unexpectedly, [1,2,5]thiadiazolo[3,4-*c*][1,2,5]thiadiazole (**2**) in high yield (Scheme 1).[3]

The main feature of this transformation is that two processes occur simultaneously: formation of a 1,2,5-thiadiazole ring via base-assisted condensation of a *vic*-diamine with sulfur monochloride, and exchange of the oxygen atom in the 1,2,5-oxadiazole ring with a sulfur atom. The first reaction can be envisaged easily because 3,4-diamino-1,2,5-thiadiazole and *o*-phenylenediamine have been cyclized previously in the presence of S_2Cl_2 to give the corresponding fused 1,2,5-thiadiazoles,[4,5] however, to the best of our knowledge, no direct exchange of oxygen with a sulfur atom in a 1,2,5-oxadiazole ring is known. Lawesson's reagent, which performs well in this exchange with various classes of compounds,[6] does not react with 2,1,3-benzoxadiazole, even on heating to 150–160 °C in 1,2-dichlorobenzene.[7] Further study of the synthesis of 1,2,5-thiadiazoles led us to a new and even more unexpected transformation of *vic*-amino-nitro derivatives into fused 1,2,5-thiadiazoles through their 1-oxides. In this Letter we report the synthesis of fused 1,2,5-thiadiazoles from *o*-nitroamines and sulfur monochloride.

We have studied the reaction between 3,4-dinitro- **3** and 4-amino-3-nitro-1,2,5-oxadiazoles **4** and sulfur monochloride. Treatment of compound **3** with S_2Cl_2 in the presence of pyridine in acetonitrile under conditions similar to those used for the synthesis of bicycle **2** from oxadiazole **1**[3] gave no reaction, and starting material **3** was recovered in almost quantitative yield. Treatment of compound **4** with the same mixture led to derivative **2** in moderate yield (Scheme 2).



1 2, 75%

Scheme 1. Synthesis of [1,2,5]thiadiazolo[3,4-*c*][1,2,5]thiadiazole (**2**) from 3,4-diamino-1,2,5-oxadiazole (**1**).

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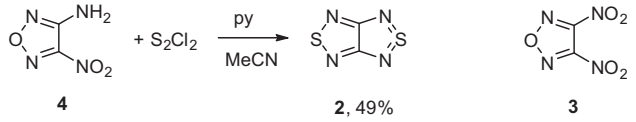


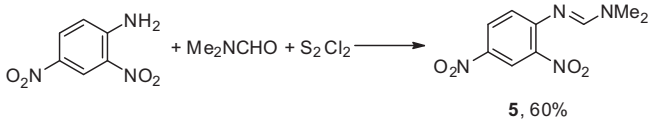
Scheme 2. Synthesis of compound **2** from oxadiazole **4**.

The results obtained suggested an important role of the amino group in the transformation of the oxadiazole ring into a thiadiazole. Although it is the second example where an oxygen atom in a 1,2,5-oxadiazole ring is exchanged by a sulfur atom, the formation of the second 1,2,5-thiadiazole ring from the *vic*-amino-nitro moiety was even more surprising because no similar reaction was described previously in the literature. Since the basicity of compound **4** ($pK_{aBH+} = -4.46$)[8] is near to that of *o*-nitroanilines (pK_{aBH+} of 2,4-dinitroaniline is -4.52),[9] we tried to extend these S_2Cl_2 reactions to readily available or commercial 2,4,6-trinitroaniline, 2,4-dinitroaniline, and *o*-nitroaniline.

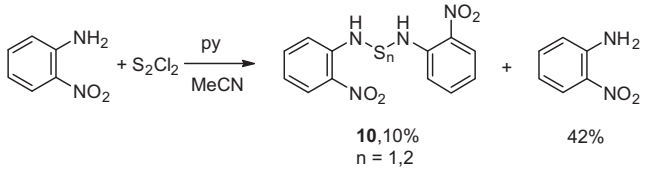
In an attempt to find the best conditions for the synthesis of benzothiadiazoles, we investigated the reaction of 2,4-dinitroaniline with sulfur monochloride in detail. Treatment of S_2Cl_2 in DMF—a solvent, which is frequently used in S_2Cl_2 reactions[10]—gave amidine **5** in 60% yield (Scheme 3). Thus, DMF was not a suitable solvent for the reactions of anilines with S_2Cl_2.

The type of a base used was important for the success of reactions with S_2Cl_2 in other solvents (acetonitrile or chloroform). Triethylamine and *N*-ethyldiisopropylamine did not catalyze these reactions at room temperature or at reflux. Treatment of 2,4-dinitroaniline with S_2Cl_2 and 1,4-diazabicyclooctane (DABCO) in MeCN led to a mixture of the target thiadiazole together with unconsumed starting material, even in the presence of a large excess of reagents. Reaction of 2,4-dinitroaniline with a fivefold excess of S_2Cl_2 and pyridine led, selectively, after prolonged refluxing, to 5-nitro-2,1,3-benzothiadiazole (**6**) in a moderate yield (Scheme 4).[11]

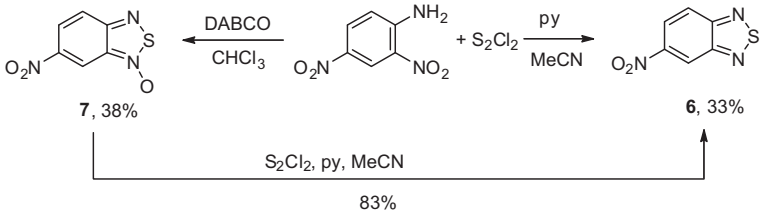
On further investigation of the reaction between 2,4-dinitroaniline and S_2Cl_2 it was found that the transformation could be stopped at the formation of 6-nitro-2,1,3-benzothiadiazole 1-oxide (**7**) using DABCO as the base and chloroform as the solvent. Derivative **7** can be converted into compound **6** in high yield with S_2Cl_2 and pyridine in acetonitrile using the same protocol as for 2,4-dinitroaniline (Scheme 4). The structures of compounds **6** and **7** were



Scheme 3. Reaction of 2,4-dinitroaniline with S_2Cl_2 in DMF.



Scheme 6. Reaction of *o*-nitroaniline with S_2Cl_2.



Scheme 4. Synthesis of fused 1,2,5-thiadiazoles **6** and **7**.

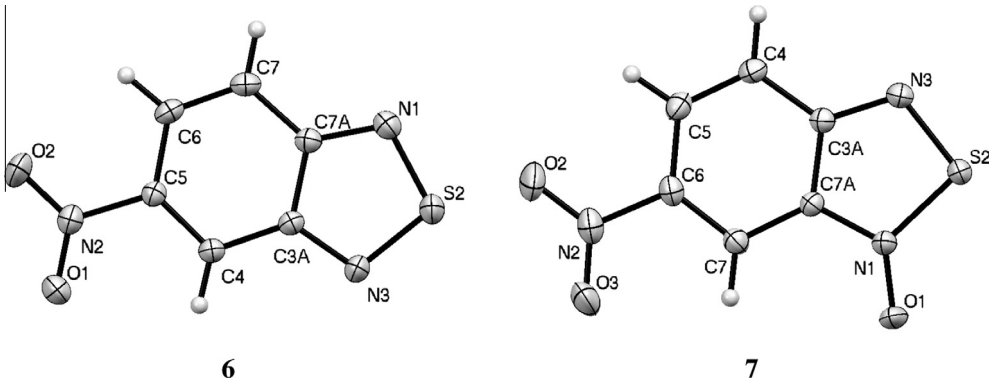
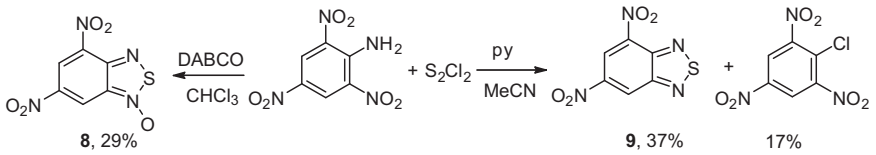
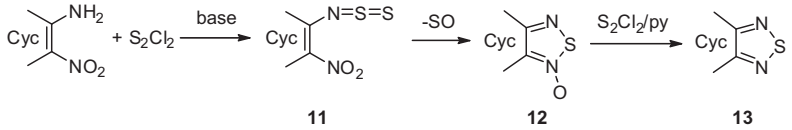


Figure 1. XRD structures of compounds **6** and **7** (displacement ellipsoids at 30%).



Scheme 5. Synthesis of thiadiazole **9** and its 1-oxide **8**.



Scheme 7. A suggested mechanism for the synthesis of fused 1,2,5-thiadiazoles and their 1-oxides.

confirmed by X-ray diffraction (XRD, Fig. 1).[12] The compounds were also characterized by elemental analyses and spectral data (NMR, MS, and IR).[11]

Treatment of 2,4,6-trinitroaniline (picramide) with a mixture of S_2Cl_2 and DABCO in chloroform gave 4,6-dinitro-2,1,3-benzothiadiazole 1-oxide (**8**) in moderate yield (Scheme 5). Although a solution of compound **8** was unstable on storage at room temperature in organic solvents (e.g., chloroform or acetonitrile), its structure was confirmed by the aforementioned methods. Reaction of picramide with a mixture of S_2Cl_2 and pyridine in acetonitrile led to the formation of 4,6-dinitro-2,1,3-benzothiadiazole (**9**) (37%) together with picryl chloride (17%) (Scheme 5).

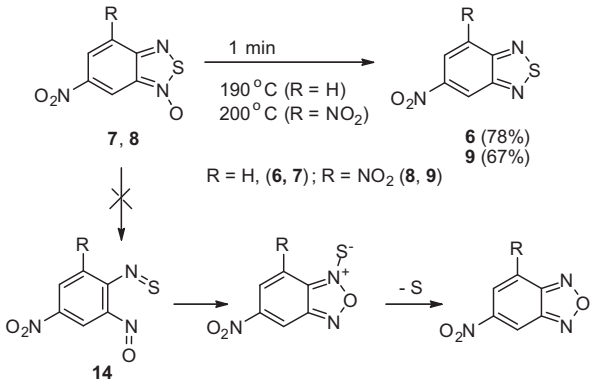
The more basic compound *o*-nitroaniline reacted differently in the presence of S_2Cl_2 and pyridine in chloroform, and gave a mixture of bis-anilines **10** in low yields connected by one or two sulfur atoms (NMR, MS, and IR), the 2-nitro group on the benzene ring remained intact (Scheme 6).

The described reaction provides a new synthetic pathway to fused 1,2,5-thiadiazoles and their 1-oxides from *vic*-nitroamines. To the best of our knowledge, this reaction was previously unknown. The closest formal analogy is the reaction of nitroanilines with $(NSCl)_3$ affording 2,1,3-benzothiadiazoles.[13] However, the reaction pathways seem to be very different since the latter reaction is thought to proceed via vicarious nucleophilic substitution of hydrogen.[14] Furthermore, persistent sulfur-nitrogen radicals were detected in anilines/$(NSCl)_3$ reaction mixtures by EPR.[14]

The key steps of the reactions described in this work may be explained by the sulfurization of the amine with sulfur monochloride in the presence of the base to give *N*-thiosulfinylamines **11**, as has been described for other anilines,[15] followed by cyclization into 1,2,5-thiadiazole 1-oxide **12** via a cycloaddition/retrocycloaddition with extrusion of sulfur monooxide (SO) (the latter is thermodynamically unstable and decomposes very rapidly).[16] Final formation of 1,2,5-thiadiazole **13** from its 1-oxide **12** was confirmed by separately converting the *N*-oxide **12** into **13** using the conditions of the cyclization reaction (see Scheme 7). The obtained results showed that *vic*-nitro-amines containing strong electron-withdrawing substituents (nitro groups) on the benzene ring or attached to an electron-deficient heterocycle (1,2,5-oxadiazole) can take part in this reaction, since the *ortho*-nitro group should be activated toward nucleophilic attack of an *N*-thiosulfinyl moiety.

It should be emphasized that 1,2,5-thiadiazole 1-oxides are rare compounds. They have been obtained by the reaction of sulfur monochloride with *o*-aminonitroso derivatives[17–19] and α-dioximes.[20] The thermal behavior of these compounds was not investigated previously. We attempted to open the 1,2,5-thiadiazole ring to give *o*-nitrosothionitroso compounds **14** (similar to the ring-opening transformation of 1,2,5-oxadiazole 1-oxides into *o*-dinitroso derivatives).[21] Earlier, reversible transformation of 2,1,3-benzothiadiazole 1-oxide into the corresponding *o*-nitrosothionitroso derivative was observed in an argon matrix under low-temperature photochemical conditions.[22] In the thermal experiments, however, oxides **7** and **8**, upon heating at 190–200 °C, lose an oxygen atom to produce thiadiazoles **6** and **9** in high yields (Scheme 8). The thermal extrusion of an oxygen atom from 1,2,5-oxadiazole 1-oxides is rare.[23]

In conclusion, a new reaction, namely that of vicinal nitroamines with sulfur monochloride, has been described as a one-pot synthetic route to fused 1,2,5-thiadiazoles and their 1-oxides.



Scheme 8. Thermolysis of 1-oxides **7** and **8**.

The reaction contributes to synthetic approaches to sulfur-nitrogen heterocycles via sulfur chlorides and nitrogen reagents.[24] The nitrated 2,1,3-benzothiadiazoles synthesized are of interest as precursors of persistent radical anions.[2,25] The described experimental procedures may serve as an efficient basis for a new synthesis of 1,2,5-thiadiazoles fused with both carbo- and heterocycles.

Acknowledgments

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11. *General procedure for the reaction of vic-amino-nitro derivatives with S_2Cl_2 and pyridine in acetonitrile.* S_2Cl_2 (0.72 mL, 9.00 mmol) was added dropwise to a stirred solution of the *vic*-amino-nitro derivative (2.0 mmol) and pyridine

(0.96 mL, 12.0 mmol) in dry MeCN (20 mL) under argon at −25 °C. The mixture was stirred for 20 h at room temperature and then refluxed for 15 h. The mixture was cooled to 20 °C, filtered and the solvent evaporated under reduced pressure. The residue was separated by column chromatography (silica gel Merck 60, hexane/CH_2Cl_2 mixtures).

1,2,5Thiadiazolo[3,4-c][1,2,5]thiadiazole (**2b**). Yield 49%. Colorless needles, mp 116–118 °C (Lit.[3] mp 117–118 °C).

5-Nitro-2,1,3-benzothiadiazole (**6**). Yield 33%. Colorless needles, mp 126–127 °C (Lit.[26] mp 128 °C).

4,6-Dinitro-2,1,3-benzothiadiazole (**9**). Yield 37%. Light yellow solid, mp 127–128 °C (Lit.[27] mp 136–138 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.33 (1H, d, CH, *J* 3.0), 9.37 (1H, d, CH, *J* 3.0). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 121.1, 125.4, 139.7, 147.1, 148.4, 155.2. MS (EI, 70 eV), *m*/*z* (%): 226 (M^+, 65), 92 (25), 83 (30), 64 (15), 46 (15), 30 (100). IR (KBr), ν_{max}, cm^{-1}: 3111, 3078 (C–H), 1619 (C=N), 1570, 1537, 1342 (NO_2).

General procedure for the reaction of vic-amino-nitro derivatives with S_2Cl_2 and DABCO in chloroform. S_2Cl_2 (0.80 mL, 5.0 mmol) was added dropwise to a stirred solution of the *vic*-amino-nitro derivative (1.0 mmol) and DABCO (1.12 g, 10.00 mmol) in $CHCl_3$ (15 mL) under argon at −30 °C. The mixture was stirred for 48 h at ambient temperature, refluxed for 5 h, cooled to 20 °C, and worked-up as described above (silica gel Merck 60 was pretreated with triethylamine prior to chromatography).

6-Nitro-2,1,3-benzothiadiazole 1-oxide (**7**). Yield 38%. Yellow solid, mp 149–150 °C.

Anal. Calcd for $C_6H_3N_3O_3S$ (197.17) C, 36.55; H, 1.53; N, 21.31. Found C, 36.37; H, 1.46; N, 21.23. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.03 (1H, d, CH *J* 9.0), 8.27 (1H, dd, CH, *J* 3.0 and 9.0), 8.46 (1H, d, CH, *J* 3.0). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 111.9, 124.6, 125.0, 138.1, 145.7, 151.2. MS (EI, 70 eV), *m*/*z* (%): 197 (M^+, 65), 181 (90), 167 (40), 151 (15), 135 (80), 89 (35), 46 (100). IR (KBr), ν_{max}, cm^{-1}: 3091, 2926 (C–H), 1596 (C=N), 1564, 1504, 1335 (NO_2).

4,6-Dinitro-2,1,3-benzothiadiazole 1-oxide (**8**). Yield 29%. Dark yellow solid, mp 186–187 °C. Anal. calcd for $C_6H_2N_4O_5S$ (242.17) C, 29.76; H, 0.83; N, 23.14. Found C, 29.83; H, 0.75; N, 23.02. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.94 (1H, d, CH, *J* 3.0), 9.19 (1H, d, CH, *J* 3.0). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 118.1, 121.3, 124.2, 124.3, 129.3, 141.6. MS (EI, 70 eV), *m*/*z* (%): 242 (M^+, 20), 226 (10), 196 (5), 64 (25), 46 (15), 30 (100). IR (KBr): ν_{max} = 3071, 2923 (C–H), 1608 (C=N), 1539, 1515, 1332 (NO_2).

Thermolysis of 1,2,5-thiadiazole 1-oxides **7** *and* **8**. Compound **7** or **8** (20 mg) was heated for 1 min under argon at 190 °C (**7**) or at 200 °C (**8**). The residue was separated by column chromatography (silica gel Merck 60, gradual elution with light petroleum or mixtures with CH_2Cl_2). Yields: **6** (78%), **9** (67%).

12. XRD structures of compounds **6** (CCDC 929367) and **7** (CCDC 929368) will be discussed elsewhere, crystallographic data can be obtained free of charge via www.ccdc.cam.uk/conts/retrieving.html.

    Compound **6**: triclinic, space group $P\bar{1}$, a = 5.7385(4), b = 7.8571(5), c = 8.3539(5) Å, α = 112.262(2), β = 93.986(2), γ = 91.902(2)°, V = 347.02(4) Å^3, Z = 2, D_c = 1.734 g cm^{-3}, μ(Mo Kα) = 0.419 cm^{-1}, 2016 unique reflections, R_1 = 0.0309 (1779 $I > 2\sigma(I)$).

    Compound **7**: triclinic, space group $P\bar{1}$, a = 4.1585(2), b = 9.5722(5), c = 9.7750(6) Å, α = 106.169(2), β = 101.536(2), γ = 98.104(2)°, V = 358.08(3) Å^3, Z = 2, D_c = 1.829 g cm^{-3}, μ(Mo Kα) = 0.424 cm^{-1}, 2102 unique reflections, R_1 = 0.0295 (1885 $I > 2\sigma(I)$).

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