Reactions of 1,2,5-Thiadiazole-3,4-dicarbonitrile

Eva H. Mørkved,*a Helge Kjøsena and Siren M. Nesesb

aThe University of Trondheim, The Norwegian Institute of Technology, Department of Organic Chemistry, Sem Sælands vei 8, N-7034 Trondheim-NTH, Norway and bThe University of Oslo, Institute of Chemistry, Section B, P.O. Box 1033 Blindern, 0315 Oslo 3, Norway


The known compound 1,2,5-thiadiazole-3,4-dicarbonitrile, 1a preferentially forms mono addition compounds 3, but also bis-addition compounds 4 with oxygen, nitrogen and sulfur nucleophiles. One preparation of 1a produced bis(4-cyano-1,2,5-thiadiazol-3-ylmethyl(imino)amine 2 as a minor product. The structure of compound 2, the facile formation of triazine 5 and the monocyclic structures of 3 and 4 indicate extensive stereoelectronic interactions between vicinal substituents of 1,2,5-thiadiazole. A bicyclic diimino imide was not formed from 1a in sulfur- or methoxide-catalysed reactions with ammonia in methanol.

The chemistry of 1,2,5-thiadiazoles was reviewed some years ago.1 In several recent studies2–5 the redox properties of their sulfur–nitrogen linkages have been reported. The interest in these heterocycles is also due to their reported biological activities, among these being antifungal, antibacterial, antiinflammatory and antidiabetic properties.1

With the objective of preparing a metal-free tetraaza-porphyrin, conversion of the known compound 1,2,5-thiadiazole-3,4-dicarbonitrile, 1a into the diimino imide 4H-pyrrolo[3,4-c][1,2,5]thiadiazole-4,6(5H)-diamine was attempted. To our consternation this compound could not be obtained under conditions where phthalonitrile6 and pyrazine-2,3-dicarbonitrile8 form such diimino imides.

To investigate why this reaction was not possible, compound 1a was reacted with a number of oxygen, nitrogen and sulfur nucleophiles in an attempt to obtain bicyclic addition compounds. To our knowledge no such investigation has been reported.

1,3-Diiminosindoline is formed from phthalonitrile by a sodium methoxide catalysed reaction with ammonia in methanol.7 Since compound 1a does not form a similar adduct, this might be due to steric strain or electronic interactions. For instance, Linstead noted9 that anhydrides from pyrrole-α-dicarboxylic acids are unstable, and that their imides are unknown. Steric strain is indicated in 1,2,5-thiadiazole-3,4-dicarboxylic acid since a dimeric anhydride is reported,10 whereas the intramolecular anhydride is apparently unknown. The monoanion of the strongly acidic 1,2,5-thiadiazole-3,4-dicarboxylic acid is stable above pH 1 and the dianion above pH 2 in accordance with the electron-withdrawing 1,2,5-thiadiazole nucleus.10 On the other hand, the high values of log \(K_f/K_s\) observed10 for the unsaturated vicinal dicarboxylic acids furan-3,4-dicarboxylic acid, cyclopentene-1,2-dicarboxylic acid and maleic acid indicate strong intramolecular hydrogen bonds in their monoanions. Thus, a coplanar \(\pi\)-electron system, favoring such hydrogen bonding is indicated. The emerging picture of the stereoelectronic effects in different vicinally disubstituted (carboxy, nitrile) aromatics is thus complex, and further experiments were required to clarify the case of compound 1a.

Results and discussion

The addition compounds obtained from 1a are shown in Scheme 1.

Oxidation of 1a with one equivalent of hydrogen peroxide in \(\text{Me}_2\text{SO}\) gave compound 1b, 4-cyano-1,2,5-thiadiazole-3-carboxamide, instead of a bicyclic imino imide. The presence of a cyano group in 1b was confirmed by an IR absorption at 2258 cm\(^{-1}\) and a \(^{13}\)C NMR signal at \(\delta\) 112. Compound 1b (16\%) was also obtained in another reaction of 1a with chlorosulfonic acid. The known10 diamide 1c was similarly obtained from 1a and two equivalents of hydrogen peroxide. The thioamide 1d was obtained somewhat unexpectedly from 1a and thioacetic acid. The expected acetyl isothioamide was perhaps hydrolysed under the reaction conditions used.

Compound 2 (1\%), was isolated from one preparation of 1a where the removal of thionyl chloride was incomplete before extraction with sodium hydrogen carbonate and chloroform. Compounds 3a (58\%) and 4a (25\%) were formed from 1a and ammonia in methanol with
sodium methoxide as the catalyst. When sulfur was used as the catalyst,\textsuperscript{12} only compound 4a (42\%) was isolated. Sulfur also was an efficient catalyst for the reaction of 1a with 4-methylaniline; thus the yield of 3b increased from 7\% without sulfur, to 58\% with sulfur added.

Compound 4c (35\%) was obtained from 1a and butylamine in the presence of sulfur. However, the secondary amine bis(2-pyridyl)amine, 1a and sulfur gave a solid which showed a depressed melting point with either reactant. This product had a strong IR absorption at 3337 cm\(^{-1}\) but dissociated to 1a and the amine in chloroform solution. Consequently, neither NMR nor mass spectra could be obtained.

A reaction of 1a with an excess of hydroxylamine gave 4b. The reaction conditions were the same as those used by Linstead\textsuperscript{13} to prepare the cyclic compound 2,5-dihydroxyimino-3,4-dimethylpyrrolidine from the acyclic DL-\(\alpha,\alpha\)’-dimethylsuccinimide.

The three thiols thiophenol, \(\alpha\)-toluenethiol and ethanethiol add to only one cyano group when reacted with 1a. The addition compound 3e decomposed to some extent to the reactants when stored at ambient temperature. Chromatography on silica of crude 3e separated a small amount (ca. 5\%) of a compound which was considerably more polar. No molecular ion was obtained for this compound in the mass spectrum, but a MS fragment \(C_6H_7N_2S_2\) and IR and NMR spectra indicated that water had been added.

The triazine 5 (83\%) was formed when 1a was heated in ethyleneglycol or with hydroquinone. These reaction conditions were used\textsuperscript{14,15} to prepare phthalocyanines from diiminoisoindolines or phthalonitriles. It should be noted that the formation of triazines from other aromatic dinitriles requires far more drastic conditions than those used in this investigation. Phthalonitrile, for instance, trimerises in chlorosulfonic acid\textsuperscript{16} or in the presence of other strong acids.\textsuperscript{17}

Conclusions

The five-membered heterocyclic compound 1a does not form a bicyclic dinitro imide under reaction conditions previously used to prepare 1,3-diiminoisoindoline\textsuperscript{7} from phthalonitrile and the bicyclic dinitro imide\textsuperscript{8} from the six-membered pyrazine-2,3-dicarbonitrile. The structures of compounds 3 and 4, obtained from 1a and oxygen, nitrogen and sulfur nucleophiles, show that no new cycle is formed. The preferred formation of monosubstituted compounds 3 instead of compounds 4 also indicates extensive stereoelectronic interactions between vicinal substituents of 1,2,5-thiadiazole. The formation of compound 2 and the ease with which compound 5 is formed, also support this conclusion.

The formation of compounds 2–5 indicated that a metal-ion template is probably required for the cycloketramerisation of 1a. This has subsequently been proved correct.\textsuperscript{18}

Experimental

General. Mass spectra were obtained on an AEI MS-902 spectrometer at 70 eV (IP). IR spectra were obtained on a Nicolet 20-SXC FT-IR spectrometer. \(^1\)H and \(^{13}\)C NMR spectra were recorded on a Jeol EX400 NMR spectrometer, \(^{13}\)C spectra were obtained at 100.40 MHz, \(^1\)H spectra at 399.65 MHz. Tetramethylsilane (TMS) was used as the internal standard. Melting points were obtained on a Buchi 530 melting-point apparatus and are uncorrected. Merck Kieselgel 60F 254 was used for TLC.
and Merck silica 63–200 μm was used for column chromatography.

1,2,5-Thiadiazole-3,4-dicarbonitrile (1a). The following procedure is an adaptation of previously reported methods. A mixture of (Z)-2,3-diamino-2-butenedinitrile (5 g, 46 mmol) and thionyl chloride (70 ml) was heated under reflux for 2.5 h. Excess thionyl chloride was removed under reduced pressure, the residue was dissolved in chloroform, and the organic phase was washed with 5% aqueous sodium hydrogen carbonate (4 × 20 ml). Drying over magnesium sulfate and removal of the solvent gave 6.2 g (98%) crude product which was chromatographed on silica (63 g). Chloroform eluted 5.1 g (80%), R_{CHCl_3} = 0.53 of m.p. 47–50°C, lit. 48–49°C. IR (KBr): 2246, 1442, 1398, 1290, 1138, 847, 770 cm\(^{-1}\). \(^{13}\)C NMR (CDCl_3): δ 136.8, 108.9.

4-Cyano-1,2,5-thiadiazole-3-carboxamide, 1b and 1,2,5-thiadiazole-3,4-dicarboxamide, 1c. General procedure. Potassium carbonate (0.2 g for 1b, 0.4 g for 1c) was added to an ice-cold solution of 1a (1.35 g, 10 mmol) in dimethyl sulfoxide (6 ml). 30 min. Aqueous hydrogen peroxide (1.1 ml, 10 mmol for 1b, 2.2 ml for 1c) was added dropwise over 10–20 min. The cold reaction mixture was stirred for 25 min and then poured onto ice (30 g), after which the precipitate was filtered off, washed with water and air-dried. 1b: yield 0.88 g (57%), m.p. 148–150°C. MS [m/z (% rel. int.):] 156 (12.7, M + 2), 155 (15.1, M + 1), 154 (72.8, M). Found 153,9948, calc. for C_5H_5N_2O_S 153,9949. IR (KBr): 3370, 3306, 3170, 2727, 2711, 2258, 1699 (s), 1620, 1460, 1341, 1117, 850, 778, 684 cm\(^{-1}\). \(^{1}H\) NMR [(CD_3)_2CO]: δ 7.45 (1 H), 7.90 (1 H). \(^{13}\)C NMR [(CD_3)_2CO]: δ 159.69, 159.12, 149.65, 112.56. 1c: yield after recrystallisation from H_2O 1.23 g (71%), m.p. 238–240°C. MS [m/z (% rel. int.):] 174 (2.1, M + 2), 173 (2.8, M + 1), 172 (41.3, M), 129 (100, M – CONH). IR (KBr): 3479, 3200, 3031, 1700 (s), 1670 (s), 1590, 1544, 1433, 1382, 1289, 1115, 1071, 876, 818, 794, 771, 672 cm\(^{-1}\). \(^{1}H\) NMR [(CD_3)_2SO]: δ 7.88 (2 H), 8.27 (2 H). \(^{13}\)C NMR [(CD_3)_2SO]: δ 161.9, 156.5.

Compound 1b from 1a in chlorosulfonic acid. Compound 1a (0.9 g, 7 mmol) was added in one portion to ice-cold chlorosulfonic acid (3 ml). The ice-cold solution was stirred for 2 h after which it was left at ambient temperature for 48 h then poured onto ice (50 g). The aqueous solution was extracted with dichloromethane (2 × 30 ml), the combined organic extracts were washed with water (20 ml) and dried and the solvent was evaporated off. Crystallisation of the residue from acetone–diethyl ether gave 270 mg (16%) 1b of m.p. 147–151°C. MS and IR spectra of the product were identical with those obtained of 1b as described above.

4-Cyano-1,2,5-thiadiazole-3-carboxthioamide, 1d. Method (i). Thioacetic acid (0.53 g, 7 mmol) was added to a solution of 1a (0.4 g, 3 mmol) in benzene (10 ml). The reaction mixture was stirred at ambient temperature for 2 h. The yellow precipitate was filtered off and washed with benzene. Yield 0.23 g (45%) of m.p. 140–141°C (decomp.). The filtrate was stirred for another 28 h, and a second crop [0.13 g, (25%), m.p. 140–141°C (decomp.)] was obtained. MS [m/z (% rel. int.):] 172 (9.6, M + 2), 171 (7.2, M + 1), 170 (100, M). Found 169,9722, calc. for C_7H_5N_2S_2 169,9721. IR (KBr): 3358, 3280, 3190, 2243 (w), 1624 (s), 1436, 1368, 1300, 1242, 1121, 930, 864, 842, 664, 601 cm\(^{-1}\). \(^{1}H\) NMR [(CD_3)_2SO]: δ 10.9 (1 H), 10.53 (1 H). \(^{13}\)C NMR [(CD_3)_2SO]: δ 112.23 (CN), 134.01 (C-4), 160.3 (C-3), 185.50 (C = S).

Method (ii). A solution of 1a (0.41 g, 3 mmol) and sodium sulfide nonahydrate (1.44 g, 6 mmol) in methanol (15 ml) was stirred at ambient temperature for 26 h. The solvent was removed under reduced pressure, the red liquid residue was dissolved in water (10 ml) and the solution was made acidic with 2 M hydrochloric acid and extracted with diethyl ether (3 × 20 ml). The combined organic phases were dried and concentrated to about 1 ml, whereupon a crystalline material separated. Yield: 0.17 g (33%) of m.p. 135–140°C (decomp.). This compound gave the same IR and \(^{1}H\) NMR spectra as obtained for compound 1d from method (i).

Bis[4-cyano-1,2,5-thiadiazol-3-yl(mino)methyl]amine, 2, was prepared as described for the dinitrile 1a, above, but on a fourfold scale. After removal of most of the thionyl chloride, the reaction mixture reacted exothermically with sodium hydrogen carbonate (5%, 100 ml). The crude product (10.9 g) obtained from the dried chloroform extract, was chromatographed on silica gel (110 g) with chloroform. The combined fractions of R_{CHCl_3} = 0.7 yielded 1a (9 g, 36%), while one fraction of R_{CHCl_3} = 0.09 yielded 2 (390 mg, 1%), m.p. 151–259°C (slow decom). MS [m/z (% rel. int.):] 291 (10, M + 2), 290 (14.5, M + 1), 289 (100, M). Found 288.955, calc. for C_7H_5N_2S_2 288.9593. IR (KBr): 3235, 3283 (s), 2260, 2247 (w), 1620 (s), 1525, 1465, 1353, 1167, 1008, 848 cm\(^{-1}\). \(^{1}H\) NMR [(CD_3)_2SO]: δ 10.7 (1 H, amine), 10.1 (2 H, imines). \(^{13}\)C NMR [(CD_3)_2SO]: δ 112.49 (CN), 133.05 (C-4), 158.14 (C-3), 159.03 (imines).

Methyl 4-cyano-1,2,5-thiadiazole-3-carboximidate, 3a, and dimethyl 1,2,5-thiadiazole-3,4-dicarboximidate, 4a. Method (i). Sodium methyolate (0.6 mmol) in methanol (20 ml) was added to a solution of 1a (1.36 g, 10 mmol) in methanol (50 ml). Gaseous ammonia was passed through the stirred solution for 20 min, stirring was continued at ambient temperature for 1 h, and the solvent was removed under reduced pressure at 50°C. Dichloromethane (40 ml) was added and some solid material (0.15 g) removed by filtration. The residue from the filtrate was dissolved in acetone (5 ml) and chromatographed on silica gel with acetone. The fractions with R_{acetone} = 0.89 were combined and yielded 3a 0.97 g (58%), m.p. 77–78°C. MS [m/z (% rel. int.):] 169 (1.3, M + 1), 168 (11.4, M), 111 (100). Found 168.0108, calc. for C_9H_9N_2OS.
Compound 3e was chromatographed on silica gel with chloroform. 3f. Yield 0.55 g (75.4%), m.p. 102–103°C (dec.) (demp.). MS [m/z (% rel. int.):] 247 (0.6, M + 1), 246 (1.2, M), 245 (5.6, M – 1). Found 244.9588, calc. for C_{10}H_{11}N_{2}S_{2} (M – 1) 244.9586. IR (KBr): 3274, 3058, 2246, 1598, 1477, 1452, 1440, 1294, 1246, 1139, 875, 827, 753 cm⁻¹. 1H NMR [(CD₃)₂SO]: δ 7.63 (5 H, m), 10.31 (1 H, s). 13C NMR [(CD₃)₂SO]: δ 112.87 (CN), 126.33 (Ph), 131.71 (Ph), 131.13 (Ph), 133.36 (C-4), 137.34 (Ph), 160.37 (imine). 162.14 (C-3). 3d. Yield 0.64 g (82%), m.p. 92–93°C (demp.). MS [m/z (% rel. int.):] 262 (4.1, M + 2), 261 (6.7, M + 1), 260 (39.7, M). Found 260.0195, calc. for C_{10}H_{11}N_{2}S (M + 1) 260.0190. IR (KBr): 3288, 3062, 3026, 2928, 2245, 1575, 1494, 1454, 1307, 1297, 1219, 897, 870, 834, 753, 707, 692, 515 cm⁻¹. 1H NMR [(CD₃)₂SO]: δ 4.40 (2 H, s), 7.43 (4 H, m), 11.34 (1 H, s). 13C NMR [(CD₃)₂SO]: δ 33.94 (CH₃), 113.04 (CN), 128.57 (Ph), 129.37 (Ph), 129.68 (Ph), 129.79 (Ph), 136.24 (C-4), 161.20 (imine). 161.56 (C-3). 3e. Yield 0.53 g (89%), m.p. 88–90°C (demp.) Rf (CHCl₃) = 0.3. MS [m/z (% rel. int.):] 200 (2.7, M + 2), 199 (3.0, M + 1), 198 (30.0, M). Found 198.0036, calc. for C_{10}H_{11}N_{2}S_{2}, 198.0034. IR (KBr): 3268, 2978, 2964, 2929, 2245, 1654, 1582, 1454, 1398, 1226, 1138, 1119, 889, 850, 835, 566 cm⁻¹. 1H NMR (CDCl₃): δ 1.44 (t, 3 H, J = 7.8 Hz), 2.95 (br, 2 H), 10.47 (br, 1 H). 13C NMR [(CD₃)₂SO]: δ -10.91 (CN), 13.32 (CH₂), 119.43 (CN), 132.40 (C-4), 164.42 (imine), 162.45 (C-3). A second compound was eluted from compound 3e. Yield 0.02 g, m.p. 181–184°C (demp.) Rf (CHCl₃) = 0.0. MS [m/z (% rel. int.):] 201 (8.0), 200 (10.6), 199 (81.3), 198 (15.6). Found 199.0114, calc. for C_{10}H_{11}N_{2}S_{2}, 199.0112. IR (KBr): 3350, 3316, 2970, 2925, 2781, 1679 (s), 1587 (s), 1452, 1375, 1322, 1269, 1126, 984, 906, 847, 754, 668, 578 cm⁻¹. 1H NMR [(CD₃)₂SO]: δ 1.13 (3 H, t, J = 7.3 Hz), 2.70 (2 H, q, J = 7.3 Hz), 7.52 (1 H, s). 13C NMR [(CD₃)₂SO]: δ 76.04, 153.95, 160.93, 177.50.

1.2.5-Thiadiazole-3,4-bis[N'-hydroxy carbamoylamine], 4b. A mixture of 1a (0.4 g, 3 mmol), hydroxylamine hydrochloride (0.46 g, 6.6 mmol) and sodium carbonate (0.23 g, 2.2 mmol) in ethanol (8 ml) and water (6 ml) was heated with stirring at 90°C for 22 h. The solvents were removed under reduced pressure and the solid residue was stirred with pyridine (15 ml) and filtered. The pyridine was removed from the filtrate, and 0.25 g (41%) of 4b m.p. 210–215°C (demp.) was obtained. MS [m/z (% rel. int.):] 204 (4.1, M + 2), 203 (6.6, M + 1), 202 (81.6, M), 155 (100). Found 202.0271, calc. for C_{10}H_{11}N_{2}O_{2}S 202.0273. IR (KBr): 3417, 3292–3136 (s, br), 2833, 1679 (s), 1578, 1412, 1262, 1088, 1052, 877, 822 cm⁻¹. 1H NMR [(CD₃)₂SO]: δ 3.5–4.2 (br), 7.27–8.54 (m, br), 9.68–9.90 (m), 11.05 (s). 13C NMR [(CD₃)₂SO]: δ 149.07 (C-3, C-4), 149.85 (amines).

1.2.5-Thiadiazole-3,4-bis[N'-butyl carbamoylamine], 4c. Compound 4c was prepared from 1a, butylamine and sulfur as described for compound 3b. Yield 0.30 g (35%)
after recrystallisation from acetone–diethyl ether, m.p. 76–78°C. MS [m/z (% rel. int.)]: 284 (1.6, M + 2), 283 (3.2, M + 1), 282 (17.4, M), 210 (100, M – C₆H₄N). Found 282.1628, calc. for C₁₃H₁₂N₅S 282.1628. M – C₆H₄N found 210.0814, calc. for C₁₃H₁₂N₅S 210.0813. IR (KBr): 3463, 3437, 3313, 3263, 3111, 2955, 2930, 2868, 2863, 1655 (s), 1607 (s), 1430, 1377, 1194, 1094, 885, 817, 530 cm⁻¹. ¹H NMR (CDCl₃): δ 0.97 (6 H, t, J 7.3 Hz), 1.46 (4 H, q, J 7.3 Hz), 1.70 (4 H, q, J 7.3 Hz), 3.33 (4 H, t, J 7.3 Hz). ¹³C NMR (CDCl₃): δ 0.91 (6 H, t, J 7.3), 1.37 (4 H, q, J 7.3), 1.57 (4 H, q, J 7.3), 2.09 (2 H, s), 3.24 (H₂O + 2 H, m), 7.88 (2 H, s). ¹⁵N NMR (CDCl₃): δ 13.30, 20.65, 31.44, 43.16, 153.29, 155.06.

**Reaction of 1a with bis(2-pyridyl)amine.** A mixture of 1a (0.41 g, 3 mmol) and sulfur (0.1 g, 3 mmol) in ethanol (10 ml) was stirred at ambient temperature for 26 h. TLC of the reaction mixture showed Rᵣ(CHCl₃) = 0.93 (sulfur). 0.6 (1a). Bis(2-pyridyl)amine (0.5 g, 3 mmol) was added and stirring was continued for 19 h. The solid material (0.09 g) was removed by filtration. Evaporation of the filtrate gave a solid which was triturated with hexane (15 ml) and filtered to give 0.74 g. m.p. 81–83°C. Rᵣ(CHCl₃) = 0.0. The solid compound was heated with hexane (15 ml) and filtered to give undissolved material: 0.56 g. m.p. 83–84°C. The filtrate was concentrated to give a further 0.15 g. m.p. 83–84°C. Bis(2-pyridyl)amine: m.p. 95°C, mixed m.p. 70–75°C. MS [m/z (% rel. int.)]: 172 (7.7), 171 (64.7), 170 (100), 136 (18). IR (KBr): 3337 (s), 3020, 1605, 1590, 1529, 1440, 1346, 773 cm⁻¹.

**2,4,6-Tris(4-cyano-1,2,5-thiadiazol-3-yl)-1,3,5-triazine, S.**

**Method (i).** A solution of 1a (0.4 g, 3 mmol) in 1.2-ethanediol (10 ml) was heated with stirring at 100°C for 15 h. The reaction mixture, with some white precipitate, was poured onto ice (50 g), and filtered and the filter was washed with acetone. Yield 0.34 g (83%), m.p. > 290°C. MS [m/z (% rel. int.)]: 410 (12.5, M + 2), 409 (17.0, M + 1), 408 (86.3, M), 382 (38.6, M – CN), 136 (100, 1a). Found 407.9526, calc. for C₁₃N₁₂S₈ 407.9531. M – CN, found 381.9498, calc. for C₁₀N₁₂S₈ 381.9500. IR (KBr): 2248 (w), 1532 (vs), 1472 (s), 1318, 1281, 1126, 835, 811, 712, 560 cm⁻¹. ¹³C NMR [(CD₃)₂SO]: δ 112.05 (CN), 134.71, 157.68, 165.53.

**Method (ii).** 1,4-Hydroquinone (0.22 g, 2 mmol) and 1a (0.27 g, 2 mmol) were mixed together in a mortar, trans-fused to a small flask and heated with stirring at 165–170°C for 15 h. The dark, glassy product was ground in a mortar, heated under reflux with ethanol (20 ml) and filtered. The dark solid was triturated with acetone (10 ml) and diethyl ether (10 ml) to yield 0.23 g (85%) of S, m.p. > 280°C. The IR spectrum was the same as for compound S obtained by method (i).

**Acknowledgements.** Support from Nansenfondet og de dermed forbundne Fond is gratefully acknowledged.

**References**


Received November 8, 1993.