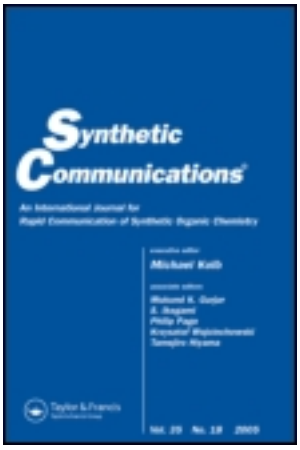

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Facile Synthesis of New Spirothiadiazolopyridazines by 1,3-Dipolar Cycloaddition

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Facile Synthesis of New Spirothiadiazolopyridazines by 1,3-Dipolar Cycloaddition

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Abstract: New derivatives of the spiro type of pyridazines have been synthesized by 1,3-dipolar cycloaddition of N-aryl-C-ethoxycarbonylnitrile imines with pyridazin-

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3(2H)-thiones. When the nitrile oxide was used, the corresponding pyridazin-3(2H)-one was obtained from the intermediate spirooxathiazole by elimination of isothiocyanate group. The peri- and regioselectivity of the reaction were ascertained by X-ray analysis and ^{13}C NMR spectroscopy of the cycloadducts **3–9**.

Keywords: Cycloadditions, pyridazin-3(2H)-thione, regioselectivity, spiro compounds, X-ray analysis

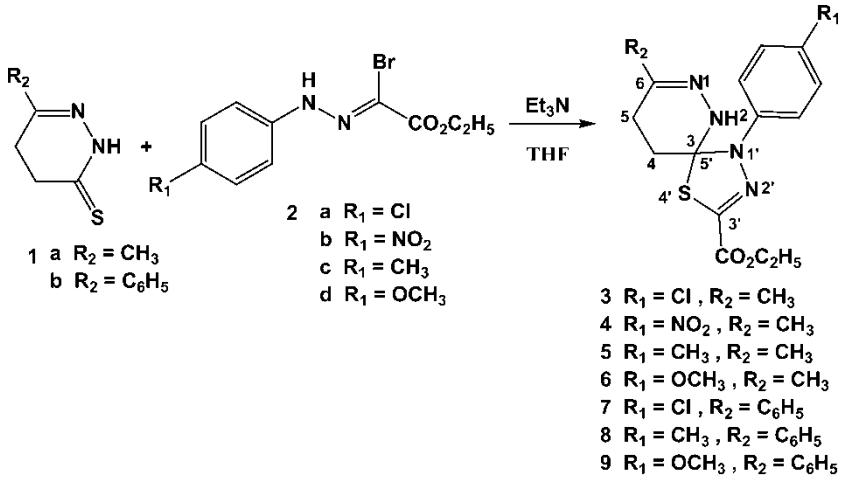
INTRODUCTION

Pyridazin-3(*2H*)-ones and their fused-ring derivatives have recently received much more attention because of their various biological activities. Several pyrrolopyridazinones are known for their antiproliferative, antiviral,[1,2] antimicrobial, and antifungal activity[3] and are inhibitors of phospholipase A2[4] or exhibit profound inhibition of lipid peroxidation in vitro.[5] Some imidazo[1,2-b]pyridazine derivatives are reported to be interesting biological substances such as cyclin-dependent kinase (CDK) inhibitors[6] and anti-histaminics.[7] Also, some thieno[3,4-d]pyridazines were used as modules of protein tyrosine phosphatases (PTPases).[8] In most cases, the pyridazino-fused-ring systems have been prepared generally by cyclization reactions of pyridazines with different intermediate reagents and by palladium-catalyzed coupling reactions of pyridazinone derivatives.[9,10] In this article we have developed a synthesis of new spirothiadiazolopyridazines by 1,3-dipolar cycloaddition. The presence of two potential dipolarophilic functionalities C═N and C═S, is making pyridazinethiones very interesting from the vantage point of dipolar cycloaddition. The reaction of pyridazin-3(2H)-thiones **1(a, b)** with N-aryl-C-ethoxycarbonylnitrile imines, generated in situ from ethylhydrazono-α-bromoglyoxylates **2(a–d)**[11] and triethylamine, was performed in tetrahydrofuran (THF) at room temperature. In all the cases, only one type of spirothiadiazolopyridazines **3–9** was obtained in good yields (Scheme 1). No adduct resulting from a condensation on the double bond C═N was detected under the identical conditions. The reaction was exclusively periselective.

The structural assignments of the spirothiadiazolopyridazines **3–9** are based on a full characterization by 300-MHz ^1H NMR and 75-MHz ^{13}C NMR spectra. The formulae were confirmed by single crystal X-ray analysis of compound **4**.

The ^{13}C NMR spectra of cycloadducts **3–9** showed in particular a signal at 98.2–98.7 ppm because of the carbon C-3; this confirms the addition of the dipole to the double bond C═S. Furthermore, the direction of the cyclo-addition is unique (heteroatom of the dipole is linked to the carbon of the C═S dipolarophile site). The reaction is thus regioselective.

Thus, we have elucidated these peri- and regioselctivity problems using the X-ray crystallographic analysis, which reveals unambiguously that the



Scheme 1.

condensation of the dipoles happened exclusively on the C═S dipolarophile site of the pyridazin-3(2H)-thione **1(a, b)** (Fig. 1).

In contrast to N-aryl-C-ethoxycarbonylnitrile imines, the action of 2,4,6-trimethylbenzonitrile oxide **10**[12] on the pyridazin-3(2H)-thione **1a** led to a mixture of two products: pyridazin-3(2H)-one **11** and 2,4,6-trimethylphenyl-isothiocyanate **12** (Scheme 2). The monoadduct spiro type was not identified.

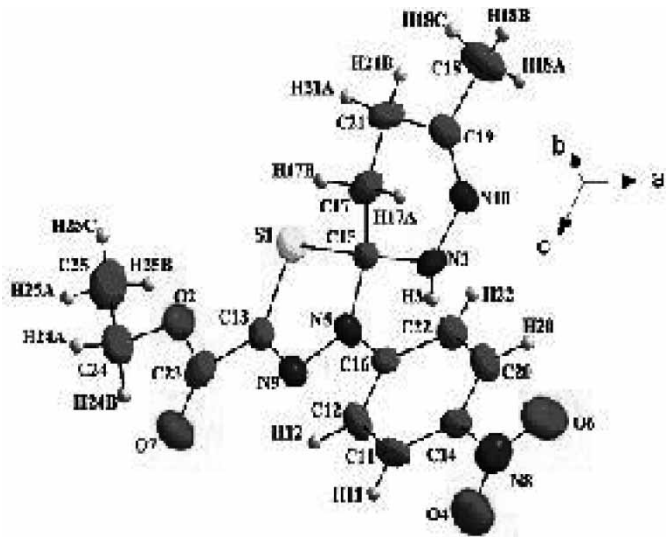
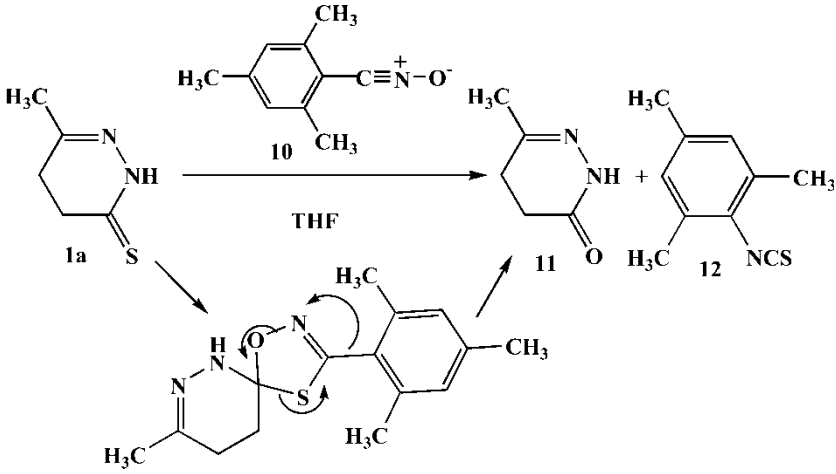


Figure 1. X-ray structure of cycloadduct 4.



Scheme 2.

The physical and spectral characteristics of compound **11** are the same as to those described in the literature.[13] The structure of **12** was checked on the basis of ^{1}H and ^{13}C NMR spectroscopies. To explain the production of compounds **11** and **12**, we propose the following mechanism: the initial phase of the reaction leads to a spiro-type cycloadduct resulting from the addition of a dipole on the double bond thioxo C═S; the spirooxathiazole thus formed is not stable. The heterocyclic ring is easily opened and the aryl group migrates toward the nitrogen (similar to Beckmann rearrangement), which finally leads to the oxo compound **11** by elimination of isothiocyanate **12**.

In summary, we have prepared new spirothiadiazolopyridazines by 1,3-dipolar cycloaddition of N-aryl-C-ethoxycarbonylnitrile imines to the corresponding pyridazin-3(2H)-thiones. These cycloadditions were found to be highly peri- and regioselective, giving the cycloadducts in good yields.

EXPERIMENTAL

General Instrumentation

Melting points were determined using a Büchi-Tottoli apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 577 spectrometer using KBr disks; only noteworthy IR absorptions are listed (cm^{-1}). ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ and solution (unless otherwise specified) with TMS as an internal reference using a Bruker AC 300-MHz (^{1}H) or 75-MHz (^{13}C) instruments; chemical shifts are given in δ ppm downfield from TMS. Multiplicities of ^{13}C NMR resources were assigned by distortionless enhancement by polarization transfer (DEPT) experiments.

Elemental-analysis data were taken on a Perkin-Elmer 240C elemental-analytical instrument. Column chromatography was carried out on SiO_2 (silica gel 60, Merck, 0.063–0.200 mm). TLC was carried out on SiO_2 (silica gel 60, F 254 Merck, 0.063–0.200 mm) and the spots located with UV light. All solvents were dried or purified by standard methods.[14] Commercial reagents were used without further purification unless stated.

Compounds **1(a, b)** were prepared by reaction of pyridazin-3(2H)-ones[13] with P_2S_5 in refluxing pyridine.

6-Methyl-4,5-dihydropyridazine-3(2H)-thione 1a: Yield 80%, yellow solid; mp 127–129°C; ^{1}H NMR ($CDCl_3$) δ 2.10 (s, 3H, CH_3), 2.36 (m, 2H, CH_2), 2.90 (m, 2H, CH_2), 10.75 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 23.8 (CH_3), 24.3 (CH_2), 33.5 (CH_2), 158.7 (C-6), 193.4 (C═S). Anal. calcd. for $C_5H_8N_2S$: C, 46.85; H, 6.29; N, 21.85. Found: C, 46.90; H, 6.25; N, 21.89.

6-Phenyl-4,5-dihydropyridazine-3(2H)-thione 1b: Yield 60%, yellow solid; mp 156–158°C; ^{1}H NMR ($CDCl_3$) δ 2.85 (m, 2H, CH_2), 3.06 (m, 2H, CH_2), 7.51 (m, 3H), 7.78 (m, 2H), 10.72 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 20.9 (CH_2), 33.8 (CH_2), 126.1 (2CH), 128.8 (2CH), 130.7 (CH), 142.0 (C), 155.5 (C-6), 194.0 (C═S). Anal. calcd. for $C_{10}H_{10}N_2S$: C, 63.13; H, 5.30; N, 14.72. Found: C, 63.19; H, 5.26; N, 14.68.

Preparation of Spiro[1′-H-4,2,1-Thiadiazolo-(3,5′)-4,5-dihydro-2H-pyridazine] 3–9, General Procedure

Triethylamine (2 mL, 9 mmol) dissolved in THF (5 mL) was added dropwise to a solution of pyridazin-3(2H)-thione **1(a, b)** (5 mmol) and ethylhydrazono-α-bromoglyoxylate **2(a–d)** (5 mmol) in THF (50 mL). The mixture was stirred 18 h at room temperature. After evaporation of the solvent, the residue was purified by column chromatography on silica gel using hexane and ethyl acetate as eluents.

3′-Ethoxycarbonyl-6-methyl-1′-(p-chlorophenyl)spiro[1′H-4,2,1-thiadiazolo-(3,5′)-4,5-dihydro-2H-pyridazine] 3: Yield 65%, orange solid; mp 84–86°C. IR: 1720 (CO), 3020 (NH); ^{1}H NMR ($CDCl_3$): δ 1.36 (t, $J = 7.2$ Hz, 3H, CH_3), 1.94 (s, 3H, CH_3), 2.24 (m, 2H, CH_2), 2.47 (m, 2H, CH_2), 4.36 (t, $J = 7.2$ Hz, 2H, CH_2O), 6.15 (s, 1H, NH), 7.25 (d, $J = 7.8$ Hz, 2H), 7.48 (d, $J = 7.8$ Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 14.5 (CH_3), 23.2 (CH_3), 27.6 (CH_2), 30.7 (CH_2), 62.7 (CH_2O), 98.6 (C-3), 122.9 (2CH), 129.2 (2CH), 130.7 (C), 134.4 (C), 139.8 (C-3′), 148.5 (C-6), 160.5 (CO). Anal. calcd. for $C_{15}H_{17}ClN_4O_2S$: C, 51.06; H, 4.86; N, 15.88. Found: C, 51.12; H, 4.82; N, 15.92.

3′-Ethoxycarbonyl-6-methyl-1′-(p-nitrophenyl)spiro[1′H-4,2,1-thiadiazolo-(3,5′)-4,5-dihydro-2H-pyridazine] 4: Yield 60%, orange solid; mp

143–145°C. IR: 1730 (CO), 3080 (NH); ^{1}H NMR ($CDCl_3$): δ 1.36 (t, $J = 7.2$ Hz, 3H, CH_3), 1.95 (s, 3H, CH_3), 2.28 (m, 2H, CH_2), 2.52 (m, 2H, CH_2), 4.36 (t, $J = 7.2$ Hz, 2H, CH_2O), 6.32 (s, 1H, NH), 7.67 (d, $J = 9.3$ Hz, 2H), 8.06 (d, $J = 9.3$ Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 14.3 (CH_3), 23.0 (CH_3), 27.1 (CH_2), 30.1 (CH_2), 62.8 (CH_2O), 98.4 (C-3), 118.7 (2CH), 124.9 (2CH), 137.1 (C), 143.2 (C-3′), 146.8 (C), 148.7 (C-6), 159.8 (CO). Anal. calcd. for $C_{15}H_{17}N_5O_4S$: C, 49.58; H, 4.72; N, 19.27. Found: C, 49.54; H, 4.70; N, 19.24.

3′-Ethoxycarbonyl-6-methyl-1′-(p-methylphenyl)spiro[1′H-4,2,1-thiadiazolo-(3,5′)-4,5-dihydro-2H-pyridazine] 5: Yield 75%, white solid; mp 101–103°C. IR: 1720 (CO), 3040 (NH); ^{1}H NMR ($CDCl_3$): δ 1.37 (t, $J = 7.2$ Hz, 3H, CH_3), 1.92 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.35 (m, 2H, CH_2), 2.43 (m, 2H, CH_2), 4.36 (t, $J = 7.2$ Hz, 2H, CH_2O), 6.09 (s, 1H, NH), 7.10 (d, $J = 8.1$ Hz, 2H), 7.41 (d, $J = 8.1$ Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 14.5 (CH_3), 21.1 (CH_3), 23.2 (CH_3), 27.8 (CH_2), 31.0 (CH_2), 62.4 (CH_2O), 98.7 (C-3), 122.7 (2CH), 129.6 (2CH), 133.2 (C), 135.6 (C), 138.6 (C-3′), 148.2 (C-6), 160.7 (CO). Anal. calcd. for $C_{16}H_{20}N_4O_2S$: C, 57.81; H, 6.06; N, 16.85. Found: C, 57.78; H, 6.05; N, 16.82.

3′-Ethoxycarbonyl-6-methyl-1′-(p-methoxyphenyl)spiro[1′H-4,2,1-thiadiazolo-(3,5′)-4,5-dihydro-2H-pyridazine] 6: Yield 70%, yellow solid; mp 79–81°C. IR: 1710 (CO), 3000 (NH); ^{1}H NMR ($CDCl_3$): δ 1.36 (t, $J = 7.2$ Hz, 3H, CH_3), 1.91 (s, 3H, CH_3), 2.41 (m, 2H, CH_2), 2.43 (m, 2H, CH_2), 3.79 (s, 3H, OCH_3), 4.36 (t, $J = 7.2$ Hz, 2H, CH_2O), 6.07 (s, 1H, NH), 6.83 (d, $J = 9.0$ Hz, 2H), 7.41 (d, $J = 9.0$ Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 14.6 (CH_3), 23.2 (CH_3), 27.8 (CH_2), 31.2 (CH_2), 55.8 (OCH_3), 62.4 (CH_2O), 98.7 (C-3), 114.3 (2CH), 125.3 (2CH), 132.9 (C), 134.0 (C-3′), 148.2 (C-6), 158.2 (C), 160.8 (CO). Anal. calcd. for $C_{16}H_{20}N_4O_3S$: C, 55.16; H, 5.79; N, 16.08. Found: C, 55.14; H, 5.81; N, 16.11.

3′-Ethoxycarbonyl-6-phenyl-1′-(p-chlorophenyl)spiro[1′H-4,2,1-thiadiazolo-(3,5′)-4,5-dihydro-2H-pyridazine] 7: Yield 80%, yellow solid; mp 167–169°C. IR: 1715 (CO), 3120 (NH); ^{1}H NMR ($CDCl_3$): δ 1.37 (t, $J = 7.2$ Hz, 3H, CH_3), 2.58 (m, 2H, CH_2), 2.94 (m, 2H, CH_2), 4.36 (t, $J = 7.2$ Hz, 2H, CH_2O), 6.83 (s, 1H, NH), 7.24 (d, $J = 8.1$ Hz, 2H), 7.37 (m, 3H), 7.51 (d, $J = 8.1$ Hz, 2H), 7.71 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 14.5 (CH_3), 23.9 (CH_2), 30.5 (CH_2), 62.6 (CH_2O), 98.2 (C-3), 122.8 (2CH), 125.1 (2CH), 128.6 (2CH), 129.2 (2CH), 129.4 (CH), 130.6 (C), 134.3 (C), 136.8 (C), 139.6 (C-3′), 145.2 (C-6), 160.3 (CO). Anal. calcd. for $C_{20}H_{19}ClN_4O_2S$: C, 57.90; H, 4.62; N, 13.50. Found: C, 57.88; H, 4.62; N, 13.51.

3′-Ethoxycarbonyl-6-phenyl-1′-(p-methylphenyl)spiro[1′H-4,2,1-thiadiazolo-(3,5′)-4,5-dihydro-2H-pyridazine] 8: Yield 76%, yellow solid; mp 141–143°C. IR: 1710 (CO), 3110 (NH); ^{1}H NMR ($CDCl_3$): δ 1.38 (t, $J = 7.2$ Hz, 3H, CH_3),

2.35 (s, 3H, CH_3), 2.52 (m, 2H, CH_2), 2.92 (m, 2H, CH_2), 4.37 (t, $J = 7.2$ Hz, 2H, CH_2O), 6.67 (s, 1H, NH), 7.13 (d, $J = 8.4$ Hz, 2H), 7.38 (m, 3H), 7.45 (d, $J = 8.4$ Hz, 2H), 7.70 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 14.5 (CH_3), 21.1 (CH_3), 24.1 (CH_2), 30.9 (CH_2), 62.4 (CH_2O), 98.4 (C-3), 122.7 (2CH), 125.1 (2CH), 128.6 (2CH), 129.1 (CH), 129.7 (2CH), 133.1 (C), 135.7 (C), 137.1 (C), 138.5 (C-3′), 145.0 (C-6), 160.6 (CO). Anal. calcd. for $C_{21}H_{22}N_4O_2S$: C, 63.94; H, 5.62; N, 14.20. Found: C, 63.90; H, 5.64; N, 14.17.

3′-Ethoxycarbonyl-6-phenyl-1′-(p-methoxyphenyl)spiro[1′H-4,2,1-thiadiazolo-(3,5′)-4,5-dihydro-2H-pyridazine] 9: Yield 75%, red solid; mp 105–107°C. IR: 1725 (CO), 3100 (NH); ^{1}H NMR ($CDCl_3$): δ 1.37 (t, $J = 7.2$ Hz, 3H, CH_3), 2.47 (m, 2H, CH_2), 2.90 (m, 2H, CH_2), 3.80 (s, 3H, OCH_3), 4.36 (t, $J = 7.2$ Hz, 2H, CH_2O), 6.62 (s, 1H, NH), 6.86 (d, $J = 8.4$ Hz, 2H), 7.36 (m, 3H), 7.46 (d, $J = 8.4$ Hz, 2H), 7.68 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 14.5 (CH_3), 24.2 (CH_2), 31.2 (CH_2), 55.8 (OCH_3), 62.4 (CH_2O), 98.3 (C-3), 114.4 (2CH), 125.1 (2CH), 125.3 (2CH), 128.6 (2CH), 129.1 (CH), 132.8 (C), 133.9 (C), 137.1 (C-3′), 145.1 (C-6), 158.3 (C), 160.7 (CO). Anal. calcd. for $C_{21}H_{22}N_4O_3S$: C, 61.45; H, 5.40; N, 13.65. Found: C, 61.40; H, 5.41; N, 13.64.

Reaction of 2,4,6-Trimethylbenzonitrile Oxide 10 with Pyridazin-3(2H)-Thione 1a

A solution of pyridazin-3(2H)-thione **1a** (0.5 g, 4 mmol) and 2,4,6-trimethylbenzonitrile oxide **10** (0.65 g, 4 mmol) in THF was stirred at room temperature for 20 h. The reaction mixture was concentrated in vacuo and the residue was purified by column chromatography on silica gel using hexane and ethyl acetate as eluents.

6-Methyl-4,5-dihydropyridazin-3(2H)-one 11: Yield 65%, white solid, mp 75–77°C; ^{1}H NMR ($CDCl_3$) δ 2.05 (m, 2H, CH_2), 2.12 (s, 3H, CH_3), 2.48 (m, 2H, CH_2), 8.71 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 22.9 (CH_3), 25.9 (CH_2), 26.1 (CH_2), 152.9 (C-6), 167.2 (CO). Anal. calcd. for $C_5H_8N_2O$: C, 53.56; H, 7.19; N, 24.98. Found: C, 53.48; H, 7.22; N, 24.94.

2,4,6-Trimethylphenyl isothiocyanate 12: Yield 54%, yellow solid; mp 62–63°C; ^{1}H NMR ($CDCl_3$) δ 2.25 (s, 6H, CH_3), 2.36 (s, 3H, CH_3), 7.20 (s, 2H, H-Ph); ^{13}C NMR ($CDCl_3$) δ 18.8 ($2CH_3$), 21.3 (CH_3), 129.0 (2CH), 135.1 (2C), 137.3 (C). Anal. calcd. for $C_{10}H_{11}NS$: C, 67.77; H, 6.21; N, 7.91. Found: C, 67.78; H, 6.19; N, 7.89.

Crystal Structure Determination

Crystal data for **4**: $C_{15}H_{17}N_5O_4S$; monoclinic; space group $C2/c$; a = 21.053(4), $\alpha = 90.00$; b = 7.891(2), $\beta = 113.16(3)$; c = 21.788(4) Å,

Table 1. Selected geometrical parameters (Å, °) of the cycloadduct **4**

Bond lengths		Angles	
S1 C13	1.736(4)	C13 S1 C15	89.9(2)
S1 C15	1.873(4)	N9 N5 C16	117.5(4)
N3 N10	1.402(5)	C16 N5 C15	123.5(4)
N5 N9	1.369(4)	O6 N8 O4	123.4(4)
N5 C16	1.406(5)	O6 N8 C14	118.3(4)
O7 C23	1.193(5)	N9 C13 C23	120.0(4)
N8 C14	1.467(5)	N3 C15 N5	109.0(4)
N9 C13	1.291(5)	C17 C15 S1	108.6(3)

$\gamma = 90.00°$, $V = 3327.9(12)\,Å^3$, $Z = 8$; $D_c = 1.451\,g\,cm^{-3}$, $T = 293\,K$, $\lambda(MoK\alpha) = 0.71073\,Å$, $\mu = 0.227\,mm^{-1}$, $F(000) = 1520$; 4835 reflections measured; 1046 reflections observed [$I \geq 2\sigma(I)$]; final $R = 0.3847$ for 1046 reflections observed [$I \geq 2\sigma(I)$]. All measurements of the crystals with dimensions of $0.075 \times 0.125 \times 0.225\,mm$ were performed on a CAD-4 Enraf-Nonius diffractometer equipped with a graphite monochromator for $\theta_{max} = 30°$ [h: $-29:29$, k: $0:11$, l: $-30:30$]. The structure was refined using the SHELXL program.[15] The refinement was based on F^2. All the non-hydrogen atoms were anisotropically refined. Hydrogen atoms were located in an electron-difference map and refined using a riding model. Refinement was finished at $R_1 = 03847$, $wR_2 = 0.0582$.

Supplementary data on this structure have been deposited [CCDC 255529], which can be obtained free of charge using the link www.ccdc.cam.ac.uk or from the CCDC, 12 Union Road Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk]. Selected geometrical parameters, bond lengths and angles are listed in Table 1 according to the numbering scheme adopted in Figure 1.

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