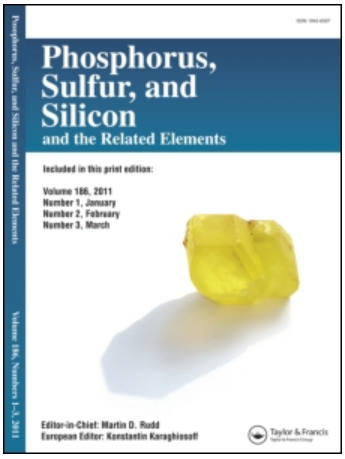

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INVESTIGATION OF THE THIAZOLE SERIES 7. SYNTHESIS, STRUCTURE AND PROPERTIES OF 2-HYDROXIMINO-1,3-THIAZOLIDINE-4-ONES

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INVESTIGATION OF THE THIAZOLE SERIES 7. SYNTHESIS, STRUCTURE AND PROPERTIES OF 2-HYDROXIMINO-1,3-THIAZOLIDINE-4-ONES

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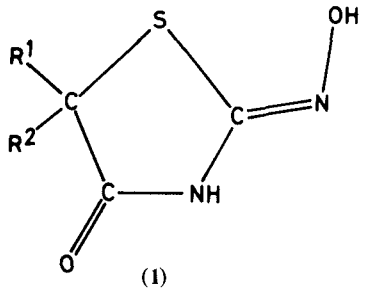
Several 2-hydroximino-1,3-thiazolidine-4-ones have been prepared by reaction of the respective α-thiocyanatocarbonic acid esters with hydroxylamine. They have been characterized by ir, uv and ^{1}H-nmr. The chemical structure was determined unequivocally by the crystal structure analysis of 5-ethyl-2-hydroximino-1,3-thiazolidine-4-one, space-group: $P2_1/c$, a = 10.0382(7), b = 5.2903(4), c = 19.305(1) Å, β = 134.233(4) at T = 24(1)°C. The structural model was refined with 3196 data to give R = 0.044. Analysis of the bonding geometry has lead to characterization of the 2-amino-1,3-thiazolidine-4-ones as cyclic *N*-thiaiminoamides.

INTRODUCTION

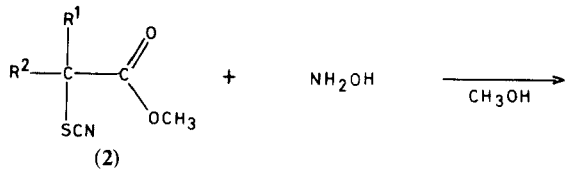
Reaction of α-thiocyanatoketones with hydroxylamine hydrochloride produces 2-amino-3-hydroxythiazolium chlorides.[2,3] Similarly, one can prepare the thermally labile α-thiocyanatoacetoneoxime by reaction of α-thiocyanatoacetone with free hydroxylamine[4] at temperatures below 0°C. We have investigated an analogous reaction, the cyclization of α-thiocyanatocarbonic acid esters with hydroxylamine and wish to report the synthesis thereby and characterization of several 2-hydroximino-1,3-thiazolidine-4-ones (**1**).



(1)

RESULTS AND DISCUSSION

Boiling hydroxylamine hydrochloride and α-thiocyanatocarbonic acid ester (**2**) solutions, for which either ethanol or acetic acid were used as solvents, displayed no evidence of reaction. In contrast, hydroxylamine free base reacted with (**2**) in methanol to give a cyclic product, the structure of which we found to be spectroscopically consistent with both (**1**) and the respective 2-imino-3-hydroxy-thiazolidine-4-ones (**3**).



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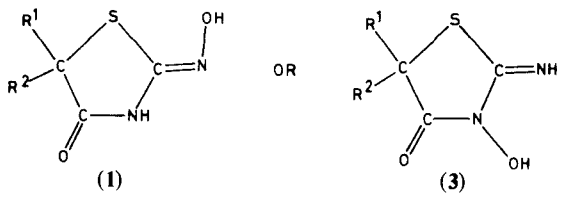

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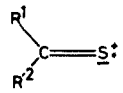
The spectroscopic characterization included ir, ^{1}H-nmr, uv and ms measurements. The carbonyl stretching frequencies of 1688–1703 cm^{-1} are in accord with literature values[5] for hydroxamic acid derivatives. In addition to signals from the R^1 and R^2 substituents, the ^{1}H-nmr spectra show broad signals for OH and NH protons at −.3 and −1.3τ, respectively. The fragmentation products in the mass spectra were mainly ions (**4**) and (**5**); neither of



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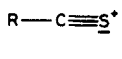
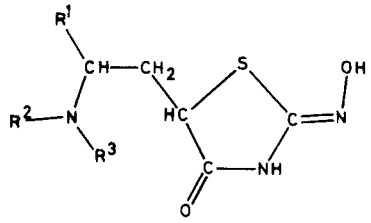


(5)

which would be expected to arise uniquely from structures (**1**) or (**3**). The products were found to form violet complexes with Fe(III) ions in a manner similar to hydroxamic acids. Attempts to prepare compounds (**3**) by reaction of α-halohydroxamic acids with potassium thiocyanate produced α-isothiocyanatohydroxamic acids which were not investigated further. A crystal structure analysis of racemic 5-ethyl-2-hydroximino-1,3-thiazolidine-4-one (**1d**) established the chemical structure (**1**) for the reaction products of hydroxylamine free base with α-thiocyanatocarbonic acid esters. Table I



(6)

presents the respective yields and physical data for the derivatives of class (**1**) prepared in this investigation.

Two derivatives with halogenated side chains, (**1k**) and (**1l**), were found to readily undergo substitution with secondary amines in the presence of potassium carbonate to give dialkylamino deriva-

TABLE I

Yield and physical data for 2-hydroximino-1,3-thiazolidine-4-ones (**1**)

	R^1	R^2	-2-hydroximino-1,3-thiazolidine-4-one	Yield[a] (%)	Melting point (°C)	Ir[c] $\nu_{C=O}/\nu_{C=NOH}$ (cm^{-1})	Uv[b] λ_{max}|mμ| (ε)	^{1}H-nmr[d] τ-values (ppm)
(**1a**)	H–	H–		53	196–7 (water)	1650 1690	210 (9000) 230 (7800)	6.23 s
(**1b**)	H–	CH_3–	5-methyl-	42	180–1 (acetonitrile)	1650 1690} 1710}	210 (8000) 230 (7250)	5.93 dd
(**1c**)	CH_3–	CH_3–	5,5-dimethyl-	39	185–6 (water)	1650 1700	210 (8700) 230 (8700)	—
(**1d**)	H–	CH_3CH_2–	5-ethyl-	52	141–2 (nitromethane)	1650 1688	210 (8700) 230 (7900)	5.93 dd
(**1e**)	H–	CH_3–$(CH_2)_4$–	5-n-butyl	21	136–7 (nitromethane)	1663 1710	211 (8500) 232 (8000)	5.84 dd
(**1f**)	H–		5-cyclohexyl-	12	214–5 (methanol)	1660 1705	213 (8450) 232 (8005)	5.50 dd
(**1g**)	H–	C_6H_5–CH_2–	5-benzyl-	41	180 (water)	1648 1685	208 (16,000) 230 sh	5.50 dd
(**1h**)	H–	C_6H_5–	5-phenyl-	71	184–5 (water)	1650 1690} 1700}	203 (19,500)	4.67 s
(**1i**)	H–	4–NO_2–C_6H_4–	5-(4-nitrophenyl)-	26	188 (nitromethane)	1660 1700	215 sh 260 (13,600)	4.39 s
(**1j**)	H–	4–Cl–C_6H_4–	5-(4-chlorphenyl)-	39	201–2 (methanol)	1650 1700	208 (14,800) 225 (18,700)	4.74 s
(**1k**)	H–	Cl–CH_2–CH_2–	5-(2-chlorethyl)-	25	160–1 (water)	1660 1710	208 (7850) 232 (7350)	5.8 dd
(**1l**)	H–	CH_3CH(Br)–CH_2–	5-(2-brom-n-propyl)-	40	180–1 (acetonitrile)	1660 1710	210 (8200) 230 (7750)	*ca.* 5.8

[a] The yields are quoted for analytically pure product relative to the initial amount of α-halocarbonic acid ester. Because of their relative instability, the α-thiocyanatocarbonic acid esters were introduced without purification.

[b] All compounds decompose upon melting. The recrystallization solvent is tabulated in parentheses under the melting point. sh = shoulder.

[c] The C=O absorption is a broad intensive bond at 1650–1660 cm^{-1} whereas the C=N bond is narrower, less intense and occurs between 1685 and 1710 cm^{-1}.

[d] The signals are those for the proton at C(5) of the thiazolidine ring (s = singlet, dd = doublet of doublets).

TABLE II

Yield and physical data for products (**6**) of the reaction of 5-(2-halogenalkyl)-2-hydroximino-1,3-thiazolidine-4-ones with secondary amines

	2-(5-[2-hydroximino-1,3-thiazolidine-4-onyl])ethyl (HTOE)	Yield[a] (%)	mp[b] (°C)	Ir[c] $\nu_{C=O}/\nu_{C=N}$ (cm^{-1})	^{1}H-nmr[d] τ-value (ppm)	Uv $\lambda_{max}[\mu m]$ (ε)
(**6a**)	*N*-HTOE-pyrrolidine	61	205–6	1565 1640	5.46 dd	263 (16,900)
(**6b**)	*N*-HTOE-morpholine	72	193	1560 1640	5.34 dd	263 (16,600)
(**6c**)	*N,N'*-bis-HTOE-*N,N'*-dimethyl-ethylendiamine	69	208–10	1570 1625	5.47 dd	268 (27,600)
(**6d**)	*N,N*-bis-HTOE-piperazine	47	230	1560 1630	5.25 dd	

[a] Analytically pure product.
[b] Compounds decompose on melting.
[c] Broad, intensive bond at *ca.* 1565 cm^{-1}, narrow bond of less intensity at *ca.* 1630 cm^{-1}.
[d] Signal for the proton at C(5) of the thiazolidine ring.

tives (**6**). Spectroscopic data indicate that derivatives of type (**6**) are present as zwitterions. The carbonyl stretching frequencies are strongly depressed in comparison with those for the starting materials (**1**) and uv spectra show a bathochromic shift of *ca.* 30 μm, Table II.

The halogen free 2-hydroximino-1,3-thiazolidine-4-ones, as represented experimentally by (**1d**), form salt-like adducts with amines such as morpholine. They display the same spectroscopic properties as (**6**), but rapidly dissociate in water to give the starting reagents.

Representative 2-hydroximino-1,3-thiazolidine-4-one derivatives [(**1a**), (**1c**), (**1g**), (**6b**) and (**6c**)] were tested for microbiological and vasodilatory activity and were found to be inactive.

The crystals of (**1d**) displayed space-group symmetry $P2_1/c$ with $Z = 4$, $a = 10.0382(7)$, $b = 5.2903(4)$, $c = 19.305(1)$ Å and $\beta = 134.233(4)°$C at 24(1)°C. The refined fractional atomic coordinates and temperature factors are presented in Table III. A stereoscopic projection[6] of a molecule of 5-ethyl-2-hydroximino-1,3-thiazolidine-4-one is presented with the applicable atom labeling scheme in Figure 1. The atoms of the heterocyclic ring and the carbonyl oxygen atom are coplanar within 0.019 Å; the 2-hydroximino substituent is displaced slightly to one side of the mean plane of the ring,

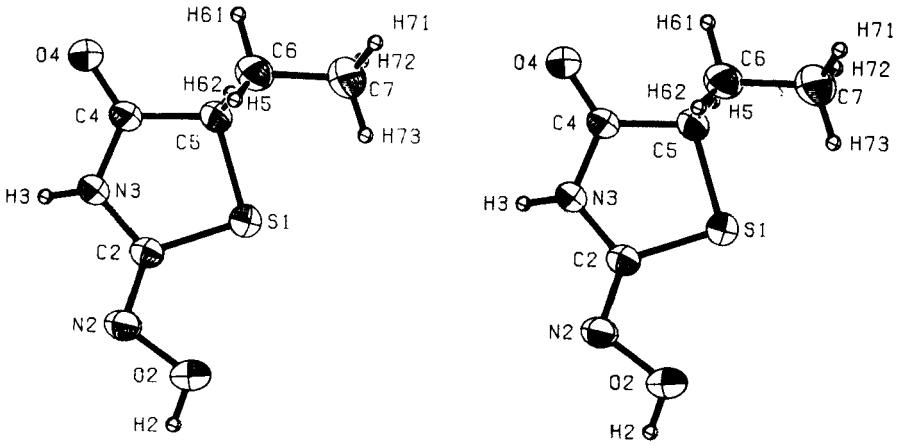


FIGURE 1 Stereoscopic projection[6] of 5-ethyl-2-hydroximino-1,3-thiazolidine-4-one (**1d**). Anisotropic atoms are depicted with thermal ellipsoids consistent with the 50% probability level for their refined temperature factors. Hydrogen atoms are depicted with arbitrary isotropic temperature factors. The applicable atom labeling scheme is depicted for all atoms.

TABLE III

a) Fractional atomic coordinates for C, N, O and S atoms

Atom	10^4x	10^4y	10^4z
S(1)	772(0)[a]	−154(1)	6675(0)
C(2)	296(2)	2139(2)	5877(1)
N(2)	−1192(1)	2296(2)	4974(1)
O(2)	−2393(1)	287(3)	4728(1)
N(3)	1732(1)	3874(2)	6334(1)
C(4)	3197(1)	3598(2)	7299(1)
O(4)	4536(1)	5035(2)	7797(1)
C(5)	2979(2)	1353(3)	7704(1)
C(6)	3035(2)	2171(4)	8486(1)
C(7)	2690(3)	7(6)	8863(1)

b) Anisotropic temperature factors[b]

Atom	10^2U_{11}	10^2U_{22}	10^2U_{33}	10^2U_{12}	10^2U_{13}	10^2U_{23}
S(1)	3.8	3.5	3.2	−.5	2.0	.2
C(2)	2.9	3.1	2.7	.3	1.8	.0
N(2)	3.0	4.0	2.8	.1	1.6	.0
O(2)	3.4	5.7	3.2	−1.0	1.6	−.3
N(3)	3.2	3.3	2.5	.0	1.6	.4
C(4)	2.7	3.3	2.6	.3	1.7	.3
O(4)	3.1	4.2	3.2	−.5	1.7	.2
C(5)	2.8	3.5	2.9	.3	1.8	.6
C(6)	4.1	6.1	3.2	−.7	2.5	−.1
C(7)	6.2	10.3	4.1	−2.6	3.3	.6

c) Fractional coordinates of isotropically refined atoms and their temperature factors.

Atom	10^4x	10^4y	10^4z	10^2U
H(2)	−3338(28)[a]	290(37)	4093(15)	5.0
H(3)	1735(29)	4953(40)	6026(15)	5.6
H(5)	3981(27)	147(35)	7951(14)	4.7
H(61)	4292(30)	2901(43)	9040(16)	6.1
H(62)	2015(28)	3448(39)	8189(14)	5.3
H(71)	2885(36)	442(54)	9432(19)	8.7
H(72)	3537(32)	−1248(42)	9043(15)	5.8
H(73)	1413(39)	−712(53)	8329(19)	8.4

[a] The values in parentheses are the estimated standard deviations in the last significant digit(s).

[b] The estimated standard deviation is one unit in the last significant digit.

Table IV. The 5-ethyl substituent displays a nearly ideal staggered conformation, both with respect to the ring and, internally, with respect to its hydrogen atoms.

The observed bond distances and bond angles, with their estimated standard deviations, are presented in Figure 2; average values from the symmetry independent molecules of 2-phenylimino-3-methyl-5-phenylthiazolidine-4-one,[7] PMPT, are also presented therein for comparison. The similarities are obvious; also, the distribution of the substituents in both compounds clearly favors a thiazolidine (**1**) structure rather than a thiazoline

TABLE IV

Least squares plane fit to the ring atoms of (**1d**). Equation of the plane, x, y, z are in fractional coordinates: $-8.0361x + 3.0440y + 13.0974z - 8.0927 = 0$

Atom	Distance from the plane (Å)
S(1)[a]	−0.017
C(2)[a]	0.019
N(3)[a]	−0.010
C(4)[a]	−0.006
C(5)[a]	0.015
O(4)	0.006
N(2)	0.078
O(2)	0.110
H(3)	−0.088

[a] Atoms determining the plane.

structure. Adman, Jensen and Warrener[8] have pointed out the difficulty in deciding between the aforementioned tautomers in the case of thiazoli(di)ne-4-one derivatives on the basis of bond

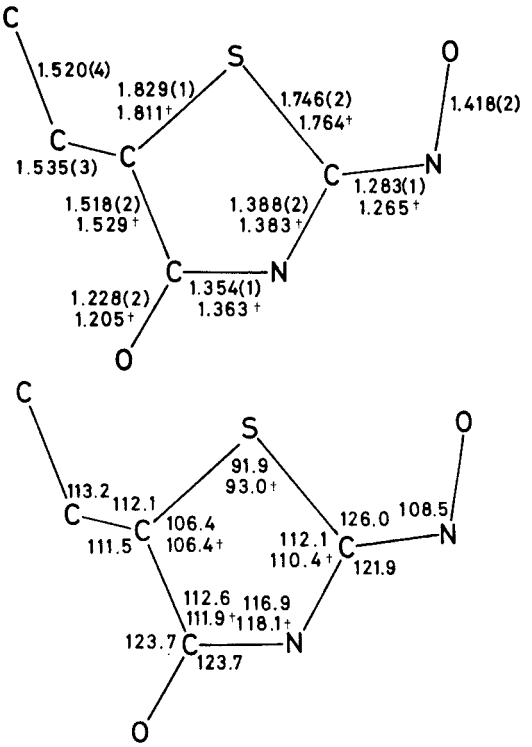


FIGURE 2. Bond distances (with estimated standard deviations) and bond angles (maximum estimated standard deviation 0.2 deg.) for 5-ethyl-2-hydroximino-1,3-thiazolidine-4-one (**1d**). Averaged bond distances and endocyclic bond angles for 2-phenylimino-3-methyl-5-phenylthiazolidine-4-one,[7] PMPT, are also presented for comparison (designated with symbol: †).

distances because there is extensive delocalization in endo- and exocyclic bonds. In the case of (**1d**), the delocalization can be examined in terms of demonstrated structural properties of functional groups not unique to the thiazolidine-thiazoline system.

The N(3)—C(4), C(4)—O(4) and C(4)—C(5) bond distances are very similar to those observed in high precision secondary amide crystal structures as exemplified by that for alanylalanine[9] (N—C = 1.344(4), C=O = 1.226(4) and C—C = 1.530(4) Å) and for *N*-acetylactinoblin[10] ($\langle$N—C$\rangle$ = 1.342, $\langle$C=O$\rangle$ = 1.226 and $\langle$C—C$\rangle$ = 1.521 Å, values are averages of 2 examples each with individual esds of 0.004 Å). Similarly, the exocyclic bond distances in the hydroximino moiety (an oxime) are, within experimental error, identical to those in formamidoxime,[11] FO, (N—O = 1.415 and C=N = 1.288 Å, esds not reported). We therefore conclude that the C(2)—N(2) bond in (**1d**) and its analog in FO are of very similar bond order. In contrast, the C(2)—N(3) bond distance in (**1d**) is considerably longer than the analog in FO for which the C—NH_2 bond distance is 1.334 Å. Clearly the latter C—N bond contains considerably more double bond character than its analog in (**1d**). These observations provide the basis for assignment of significant double bond character to the C(2)—S(1) bond; the rather short bond distance therein is consistent[12] with such an assignment.

With the foregoing discussion in mind, we would like to suggest that thiazolidine-4-one derivatives, as exemplified by (**1d**), can be appropriately characterized as cyclic *N*-thiaiminoamides in which the delocalization between the amide and thiaimino moieties appears to be more modest than that within each moiety.

Further substantiation that (**1d**) displays amide-like properties is presented by the differences in the C(4)—O(4) and C(4)—N(3) bond distances observed for (**1d**) and PMPT, Figure 2. Dunitz and Winkler[13] have observed that partial protonation lengthens amide C=O bonds and shortens the associated C—N bonds. As pointed out by the authors, hydrogen bonding to an amide oxygen atom is one source of such partial protonation. Atom O(4), the carbonyl oxygen atom of (**1d**), is intermolecularly hydrogen bonded to the hydrogen atom of the hydroximino group of a symmetry related molecule (O(4) $\cdots$ O(2) = 2.720(1), O(4) $\cdots$ H(2) = 1.84(2), H(2)—O(2) = 0.88(2) Å and O(4)H(2)O(2) = 171(3)°). There are no appropriate donor groups for hydrogen bonding in PMPT. The relevant bonds in (**1d**) and PMPT display the expected trends for amides. Additional intermolecular hydrogen bonding in (**1d**) occurs in a reciprocating manner, via a crystallographic inversion center, between the hydrogen atom of the amide nitrogen and the imino nitrogen atoms (N(2) $\cdots$ N(3) = 2.976(2), N(2) $\cdots$ H(3) = 2.16(3), H(3)—N(3) = 0.83(3) Å and N(2)H(3)N(3) = 169(2)°).

EXPERIMENTAL

Ir spectra were recorded for KBr disks with a Perkin Elmer 457 spectrometer and uv spectra, for 10^{-4} M methanol solutions, were determined with a Beckman Acta VI spectrometer. Proton nmr spectra were measured with either a Varian A60 or T60 spectrometer for deuteromethylsulfoxide solutions with tms as an internal standard. Tabulated melting points are uncorrected.

2-Hydroximino-1,3-thiazolidine-4-ones (**1**), general preparative procedure. Sodium methoxide (0.02 moles) in 20 ml of Methanol, was added to a solution of 1.38 g (0.02 moles) of hydroxylamine hydrochloride in 40 ml of methanol. After filtration, 0.02 moles of the respective α-thiocyanatocarbonic acid ester (prepared in the usual manner[14] from α-halocarbonic acid esters and used without further purification) were added with stirring to the filtrate at temperatures between 0 and 10°C. The reaction mixture was allowed to stand for 12 hr at room temperature, after which the solvent was removed by vacuum distillation. A crystalline product was obtained from the residue, generally an oil, by introduction of a small amount of acetonitrile. The crude crystalline material was recrystallized from an appropriate solvent, Table I.

2-(5-[2-hydroximino-1,3-thiazolidine-4-onyl]-ethylamines (**6**), general preparative procedure. A 50 ml ethanolic solution of 0.02 moles of (**3k**) or (**3l**) with an appropriate quantity of amine (0.02 moles of morpholine or pyrrolidine, 0.01 moles of piperazine or *N,N'*-dimethylethylenediamine) and 0.01 moles of potassium carbonate were refluxed for 12 hr. Solvent was subsequently removed by vacuum distillation until a precipitate formed. The precipitate was washed with water, then dissolved in a minimum volume of 1 N NaOH solution and filtered. The product was reprecipitated by addition of 2 N H_2SO_4. After one or two such purification steps, the product was analytically pure.

Crystallographic data and structure analysis. Crystals of (**1d**) were obtained as long colorless needles by slow evaporation of a room temperature *n*-propanol solution. Buerger Precession photographs revealed 2/*m* Laue symmetry; the diffraction patterns were found to display systematic extinctions uniquely assignable to space group $P2_1/c$. A crystal, displaying the morphology of an irregular hexagonal prism (0.75 mm long with adjoining sides of length 0.13, 0.23, 0.23, 0.13, 0.18 and 0.25 mm), enclosed in thin-walled glass capillary, was used for all quantitative crystallographic measurements. Lattice parameters were obtained by least-squares refinement[15] with 2θ values for 58 reflections in the angular range $33.07 \leqslant 2\theta \leqslant 48.85°$, Mo K_α radiation (λ = 0.71069 Å).

Diffraction intensities were measured at room temperature, 24(1)°C, with a Syntex *P*1 autodiffractometer (mono-

chromatized Mo radiation) operating in an ω-scan mode. The scan range was 0.75° and the scan rate varied, as a function of maximum peak intensity, from 2.0 to 24.0° min^{-1}; background radiation was measured on each side of the reflection, $\Delta\omega = 1.0°$, for one half the scan time. Three reference reflections, monitored after each 200 data were measured, remained constant to within 1.7% of their respective average intensities. Of a total of 4186 independent reflections, $2\theta \leqslant 75.0°$, 2458 had $I \geqslant 3.0\sigma(I)$ and were classified as observed. All reflections were corrected for Lorentz and polarization effects; absorption corrections, $\mu = 3.7$ cm^{-1} were not deemed necessary.

The crystal structure was determined by direct methods in combination with difference Fourier techniques. Initial atomic coordinates for all atoms were obtained either from E-maps or difference Fourier maps. A total of 3196 data (all observed reflections and those unobserved for which the calculated intensity was greater than the cut off value) contributed to the full matrix least-squares refinement of 123 variables (all fractional atomic coordinates, anisotropic temperature factors for C, N, O, and S atoms, isotropic temperature factors for H atoms, and a single scale factor) to give conventional residuals $R = 0.044$ and $R_w = 0.061$;[16] empirical weights were calculated with the formula:

$$w = 1/\sigma^2 = (\sigma^2(F_o) + 0.0125|F_o| + 0.001|F_o|^2)^{-1}$$

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