David J. Anderson* and Christine R. Muchmore‡

*Medicinal Chemistry Research and ‡Physical and Analytical Chemistry,
The Upjohn Company, Kalamazoo, MI 49001

Received September 9, 1994
Revised May 3, 1995

5-Azidoisoxazoles are prepared *via* displacement of a chlorine atom in 5-chloroisoxazoles with azide ion. These 5-azidoisoxazoles contain an unsaturated group (olefin, aldehyde, oxime or hydrazone) in the 4-position which participates during thermal decomposition of the azide. Two types of products are formed which are non-interconvertible: (i) bicyclic isoxazoles which result from direct attack of the azide or nitrene on the unsaturated group; (ii) monocyclic pyrroles and pyrazoles which result from ring opening followed by bond reorganization and subsequent ring closure. Mechanisms for the two discrete processes are discussed.

J. Heterocyclic Chem., **32**, 1189 (1995).

Introduction.

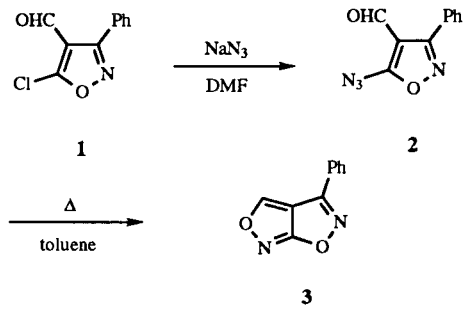
We have previously described [1] the synthesis of 5-chloro-3-phenylisoxazole-4-carboxaldehyde **1**, which was contrary to a prior literature report [2] on this molecule. This earlier data [2] has been reexamined [3] and structures now corrected. This paper describes the formation and thermolysis of 5-azidoisoxazoles derived from the displacement of the chlorine substituent of **1** with azide ion and functionalization of the carboxaldehyde substituent of **1**.

Five-membered ring heteroaromatic azides undergo a variety of rearrangements upon controlled decomposition [4]. There are two reported [5-6] examples of the decomposition of 4-azidoisoxazoles leading to ring fragmentation.

Results.

The 5-azidoisoxazole **2** was readily formed from the 5-chloro derivative **1** by displacement with azide ion (Scheme 1). The azide **2** underwent smooth thermal decomposition in refluxing toluene to afford the isoxazoloisoxazole **3**.

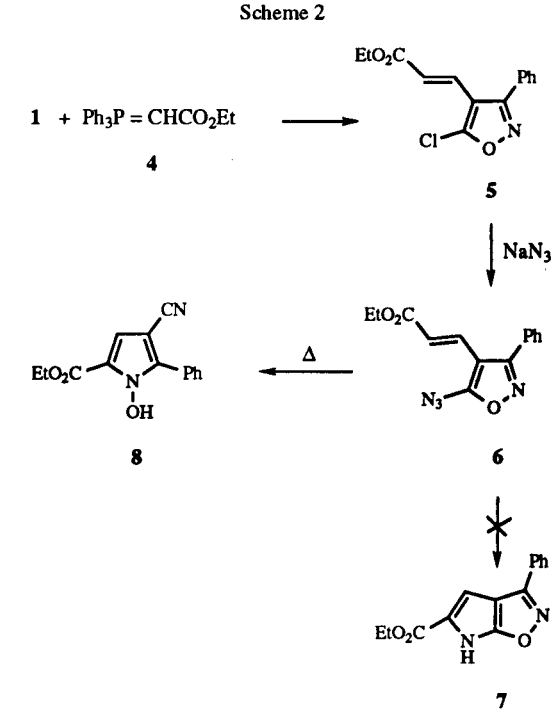
Scheme 1



The nmr spectrum of **3** showed the ring CH proton at δ 8.74 in good agreement with similar systems [7]. Furthermore, the ir spectrum of **3** showed a sharp peak at 3114 cm^{-1} assigned to the ring C-H stretching mode. This appears to be present also in similar systems [7], but not assigned.

Reaction of the azidoaldehyde **2** with a stabilized yield such as **4** was exceedingly complex and was accompanied by azide decomposition. However, the chloroaldehyde **1** reacted readily with the yield **4** to give the olefin **5**.

Scheme 2



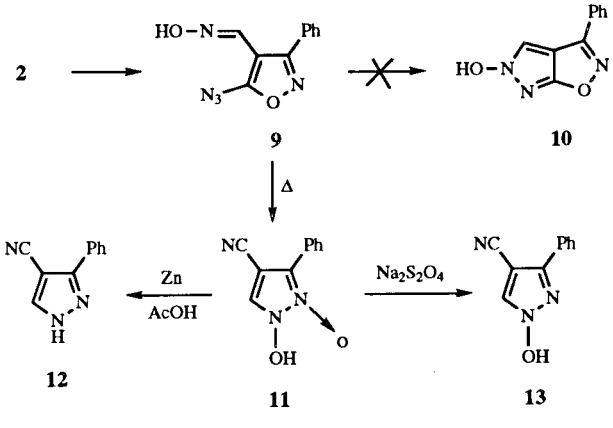
Displacement of the chloro substituent of **5** with sodium azide gave **6**. Thermolysis of **6** was expected to give the pyrroloisoxazole **7** by analogy with literature examples [8-9]. However, the product isolated from **6** showed a cyanide peak in the ir spectrum at 2222 cm^{-1} plus an OH at 3297 cm^{-1} and a very sharp peak at 3143

cm^{-1}. Mechanistic considerations (discussed later) suggested that this material was the *N*-hydroxypyrrole **8**. The 3143 cm^{-1} peak is attributable to the pyrrole ring C-H stretching mode. The structure of **8** was confirmed [10] by X-ray.

The azidoaldehyde **2** formed an oxime **9** (Scheme 3) which was expected to rearrange with loss of nitrogen, to the pyrazoloisoxazole **10**.

However when **9** was refluxed in toluene, a material was obtained which possessed a cyanide peak in the ir spectrum in addition to a sharp peak at 3152 cm^{-1}. By analogy to Scheme 2, this compound was identified as the *N*-hydroxypyrazole *N'*-oxide **11**. This ring system has previously been prepared from the nitrosation of α,β-unsaturated oximes [11]. Reduction of **11** with zinc-acetic acid gave the known [12] pyrazole **12**. Reduction of **11** with sodium dithionite removed only the *N*-oxide to give the *N*-hydroxypyrazole **13**.

Scheme 3



The azidoaldehyde **2** reacted with *O*-substituted hydroxylamines **14a,b** to give the oximes **15** (Scheme 4).

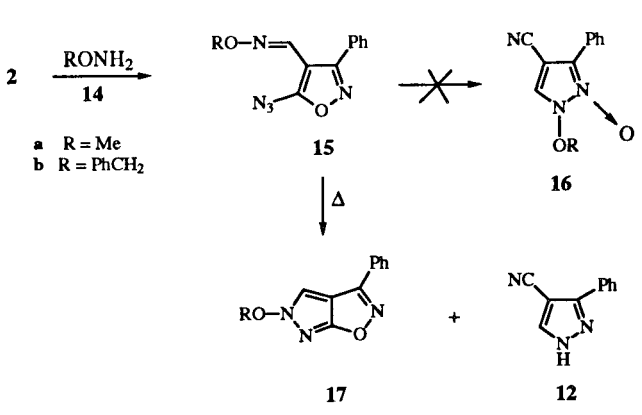
Thermolysis of the azido methyloxime **15a** did not give the cyanopyrazole **16a**, instead the pyrazoloisoxazole **17a** was formed as evidenced from spectral data. However, thermolysis of the azido benzyloxime **15b** gave not only the bicyclic **17b** but also the deoxygenated cyanopyrazole **12**.

Condensation of the azidoaldehyde **2** with the hydrazides **18a,b** gave the hydrazones **19** (Scheme 5). Thermolysis of **19** produced both the pyrazoles **20** and pyrazoloisoxazoles **21**, which were not thermally interconvertible. The hydrazone **19b** derived from *t*-butyl carbazate was particularly unstable and could not be isolated in a pure state. It was always contaminated with the pyrazoloisoxazole **21b**.

The structure of the acetyl compound **20a** was confirmed by X-ray. The *N*-oxide functionality of **20a** was removed *via* zinc-acetic acid reduction to produce **22**.

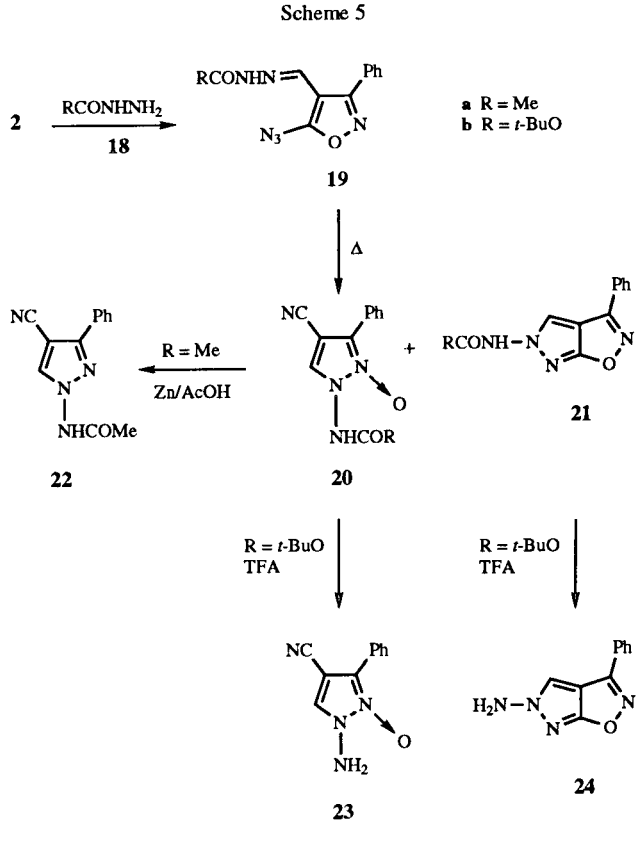
The *t*-BOC groups of **20b** and **21b** were removed with

Scheme 4



trifluoroacetic acid to give the *N*-amino compounds **23** and **24**. These latter two compounds were thermally stable in refluxing xylene and showed no tendency to interconvert.

Scheme 5



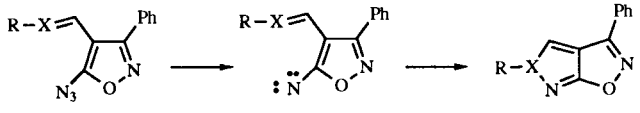
Mechanisms.

Two types of product have been identified from the thermal decomposition of 5-azidoisoxazoles, substituted in the 4-position with an unsaturated group. The two products have been assigned to the monocyclic cyanopyrazole (or pyrrole) and the bicyclic fused isoxazole struc-

tures. Since these basic structures appear to be thermally stable and non-interconvertible, it seems logical that decomposition of the initial azide can occur *via* two discrete mechanisms.

It is speculated that the formation of the bicyclic structures involves a nitrene **25** as shown in Scheme 6. The nitrene reacts with the double bond in the 4-position to eventually afford the bicyclic structure, after bond reorganization.

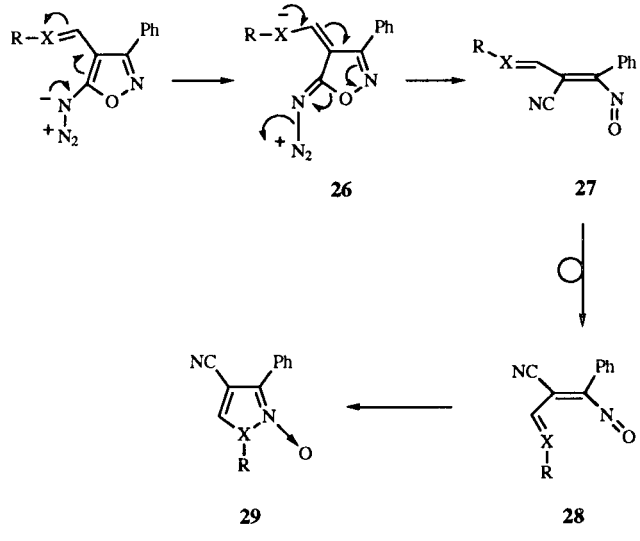
Scheme 6



25

A second alternative mechanism [13] involves an independent decomposition of the azide with assistance from the double bond in the 4-position (Scheme 7) leading to resonance structure **26**.

Scheme 7



26 **27** **28** **29**

This species may then lose nitrogen with concomitant ring opening to afford the cyano vinyl nitroso intermediate **27**. This intermediate in turn may undergo bond rotation to give the conformationally more attractive **28**, which simply undergoes an intramolecular cyclization to give the final product **29**. Vinyl nitroso compounds are now well documented [14] and Abramovitch has proposed [15] unsaturated nitroso intermediates to explain the ring contraction of 2-azidopyridine *N*-oxides to 2-cyano-*N*-hydroxypyrroles.

X-ray of *N*-(4-Cyano-3-phenyl-1*H*-pyrazol-1-yl)acetamide *N*-Oxide **20a**.

Fractional coordinates, bond lengths, torsion angles and other parameters are listed in Tables 1-6.

Table 1

Fractional Coordinates (x10^4) and Beq for *N*-(4-Cyano 3-phenyl-1*H*-pyrazol-1-yl)acetamide *N*-oxide **20a**

$Beq = 4/3\ (a^2B_{11}+b^2B_{22}+c^2B_{33}+abcos\gamma B_{12}+accos\beta B_{13}+bccos\alpha B_{23})$

	x	y	z	B_{eq} (Å^2)
N (1)	5078 (2)	-844 (1)	3206 (1)	1.86 (5)
N (2)	4151 (2)	105 (1)	2632 (1)	1.69 (5)
O (2)	4105 (1)	1004 (1)	3289 (1)	1.98 (4)
C (3)	3453 (2)	-118 (2)	1399 (1)	1.77 (6)
C (4)	4004 (2)	-1221 (2)	1200 (2)	1.95 (6)
N (4)	3242 (2)	-2313 (1)	-898 (2)	3.39 (7)
C (N4)	3573 (2)	-1825 (2)	34 (2)	2.43 (7)
C (5)	5017 (2)	-1629 (2)	2331 (2)	2.06 (6)
N (6)	6174 (2)	-736 (1)	4395 (1)	1.89 (5)
C (7)	7476 (2)	-117 (2)	4519 (2)	2.16 (7)
O (7)	7695 (1)	199 (1)	3606 (1)	3.07 (6)
C (8)	8537 (2)	81 (2)	5856 (2)	2.50 (7)
C (9)	2352 (2)	681 (2)	507 (2)	1.80 (6)
C (10)	1318 (2)	1322 (2)	826 (2)	2.42 (7)
C (11)	255 (2)	2037 (2)	-56 (2)	2.95 (8)
C (12)	229 (2)	2120 (2)	- 1262 (2)	3.01 (7)
C (13)	1260 (2)	1493 (2)	-1577 (2)	2.88 (8)
C (14)	2318 (2)	769 (2)	-709 (2)	2.31 (7)

Table 2

Fractional Coordinates (x10^3) and Isotropic Temperature Factors for Hydrogen Atoms for *N*-(4-Cyano-3-phenyl-1*H*-pyrazol-1-yl)acetamide *N*-Oxide **20a**

	x	y	z	B (Å^2)
H (5)	561	-238	247	2.5
H (N6)	604	-108	514	2.2
H (8A)	842	89	611	2.8
H (8B)	962	-4	595	2.8
H (8C)	830	-47	642	2.8
H (10)	132	125	170	2.8
H (11)	-50	251	18	3.2
H (12)	-54	263	-190	3.1
H (13)	126	158	-245	3.1
H (14)	306	29	-95	2.7

An ORTEP diagram is provided in Figure 1.

The *N*-oxide oxygen participates in 2 hydrogen bonds; it accepts a hydrogen from the secondary amine in the molecule related by 1-x, -y, 1-z (O - N distance: 2.812(2)Å), and also accepts a hydrogen from the ring CH carbon in the molecule related by 1-x, y+1/2, 1/2-z, (O - C distance: 3.010(2)Å; O - H distance: 2.11Å). The latter C-H - - O hydrogen bond is unusual; Taylor and Kennard [16] have surveyed similar short carbon- oxygen contacts found in crystal structures in the Cambridge Crystallo-

Table 3

Bond Lengths (Å), Angles (°), and Torsion Angles (°) for *N*-(4-Cyano-3-phenyl1*H*-pyrazol-1-yl)acetamide *N*-Oxide **20a**

N (1)	N (2)			1.395 (2)	N (6)	C (7)	1.384 (2)
N (1)	C (5)			1.339 (2)	C (7)	O (7)	1.210 (2)
N (1)	N (6)			1.369 (2)	C (7)	C (8)	1.498 (2)
N (2)	O (2)			1.293 (2)	C (9)	C (10)	1.388 (2)
N (2)	C (3)			1.342 (2)	C (9)	C (14)	1.400 (2)
C (3)	C (4)			1.422 (2)	C (10)	C (11)	1.388 (3)
C (3)	C (9)			1.468 (2)	C (11)	C (12)	1.390 (3)
C (4)	C (N4)			1.427 (3)	C (12)	C (13)	1.375 (2)
C (4)	C (5)			1.368 (2)	C (13)	C (14)	1.386 (2)
N (4)	C (N4)			1.144 (2)			
N (2)	N (1)	C (5)		109.4 (1)	N (1)	C (5)	C (4) 107.4 (1)
N (2)	N (1)	N (6)		119.8 (1)	N (1)	N (6)	C (7) 116.6 (1)
C (5)	N (1)	N (6)		127.8 (1)	N (6)	C (7)	O (7) 121.1 (2)
N (1)	N (2)	O (2)		120.2 (1)	N (6)	C (7)	C (8) 113.4 (1)
N (1)	N (2)	C (3)		108.3 (1)	O (7)	C (7)	C (8) 125.5 (1)
O (2)	N (2)	C (3)		131.4 (1)	C (3)	C (9)	C (10) 121.9 (1)
N (2)	C (3)	C (4)		106.4 (1)	C (3)	C (9)	C (14) 118.7 (1)
N (2)	C (3)	C (9)		123.2 (1)	C (10)	C (9)	C (14) 119.3 (1)
C (4)	C (3)	C (9)		130.4 (1)	C (9)	C (10)	C (11) 120.4 (2)
C (3)	C (4)	C (N4)		126.7 (2)	C (10)	C (11)	C (12) 120.0 (1)
C (3)	C (4)	C (5)		108.4 (1)	C (11)	C (12)	C (13) 119.8 (2)
C (N4)	C (4)	C (5)		124.9 (2)	C (12)	C (13)	C (14) 120.8 (2)
C (4)	C (N4)	N (4)		179.3 (2)	C (9)	C (14)	C (13) 119.8 (1)
C (5)	N (1)	N (2)	O (2)	-175.9 (1)	N (2)	C (3)	C (9) C (10) -37.0 (2)
C (5)	N (1)	N (2)	C (3)	2.9 (1)	N (2)	C (3)	C (9) C (14) 144.9 (1)
N (6)	N (1)	N (2)	O (2)	-13.8 (2)	C (4)	C (3)	C (9) C (10) 142.9 (2)
N (6)	N (1)	N (2)	C (3)	165.0 (1)	C (4)	C (3)	C (9) C (14) -35.2 (2)
N (2)	N (1)	C (5)	C (4)	-2.7 (1)	C (3)	C (4)	C (5) N (1) 1.5 (2)
N (6)	N (1)	C (5)	C (4)	-162.9 (1)	C (N4)	C (4)	C (5) N (1) -177.6 (1)
N (2)	N (1)	N (6)	C (7)	-74.9 (2)	N (1)	N (6)	C (7) O (7) -7.6 (2)
C (5)	N (1)	N (6)	C (7)	83.5 (2)	N (1)	N (6)	C (7) C (8) 173.4 (1)
N (1)	N (2)	C (3)	C (4)	-1.9 (1)	C (3)	C (9)	C (10) C (11) -177.6 (2)
N (1)	N (2)	C (3)	C (9)	178.1 (1)	C (14)	C (9)	C (10) C (11) 0.5 (3)
O (2)	N (2)	C (3)	C (4)	176.7 (1)	C (3)	C (9)	C (14) C (13) 178.2 (2)
O (2)	N (2)	C (3)	C (9)	-3.3 (2)	C (10)	C (9)	C (14) C (13) 0.1 (2)
N (2)	C (3)	C (4)	C (N4)	179.3 (1)	C (9)	C (10)	C (11) C (12) -0.5 (3)
N (2)	C (3)	C (4)	C (5)	0.3 (2)	C (10)	C (11)	C (12) C (13) -0.1 (3)
C (9)	C (3)	C (4)	C (N4)	-0.6 (2)	C (11)	C (12)	C (13 C (14) 0.6 (3)
C (9)	C (3)	C (4)	C (5)	-179.7 (1)	C (12)	C (13)	C (14) C (9) -0.7 (3)

Table 4

Close Intermolecular Contacts Between Non-hydrogen Atoms for *N*-(4-Cyano-3-phenyl-1*H*-pyrazol-1-yl)acetamide *N*-Oxide **20a**

Related atom.....Atom	Symmetry	Distance(Å)
C (8).....C (13)	x-1, y, z-1	3.482 (2)
N (1).....N (4)	x, -y-1/2, z-1/2	3.165 (2)
C (5).....N (4)	x, -y-1/2, z-1/2	3.353 (2)
N (6).....N (4)	x, -y-1/2, z-1/2	3.487 (2)
O (7) .....C (13)	1-x, -y, -z	3.479 (2)
O (2).....N (6)	1-x, -y, 1-z	2.812 (2)
O (2).....C (8)	1-x, -y, 1-z	3.283 (2)
N (6).....N (6)	1-x, -y, 1-z	3.499 (1)
O (7).....C (8)	2-x, -y, 1-z	3.402 (2)
O (2).....C (N4)	1-x, y-1/2, 1/2-z	3.390 (2)
O (2).....C (5)	1-x, y-1/2, 1/2-z	3.010 (2)
C (8).....N (4)	1-x, y-1/2, 1/2-z	3.444 (2)

graphic Database, and they concluded that such hydrogen bonds are likely to occur in molecules deficient in proton donors, and with carbons immediately adjacent to neutral or positively charged nitrogen atoms.

The atomic coordinates and thermal parameters are deposited at the Cambridge Crystallographic Data Centre.

Table 5

Hydrogen Bonds for *N*-(4-Cyano-3-phenyl-1*H*-pyrazol-1-yl)acetamide *N*-Oxide **20a**

D	A	A AT	D....A	H....A	<,D-H....A
N (6)	O (2)	1-x, -y, 1-z	2.812 (2)	1.93	158
C (5)	O (2)	1-x, y-1/2, 1/2-z	3.010 (2)	2.11	146

D represents donor, A acceptor; distances are in Å and angles are in °. Standard deviations are in parentheses.

Table 6

Anisotropic Thermal Parameters (x10^4) for *N*-(4-Cyano-3-phenyl-1*H*-pyrazol-1-yl)acetamide *N*-Oxide **20a**

	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
N (1)	65 (2)	34 (1)	35 (1)	10 (3)	25 (3)	0 (2)
N (2)	64 (2)	28 (1)	36 (1)	-1 (3)	36 (3)	-3 (2)
O (2)	86 (2)	30 (1)	36 (1)	-4 (2)	41 (2)	-16 (2)
C (3)	58 (2)	39 (1)	32 (1)	-13 (3)	32 (3)	-9 (2)
C (4)	68 (2)	37(1)	42 (2)	-4 (3)	47 (3)	-15 (2)
N (4)	132 (3)	62 (2)	56 (2)	4 (4)	51 (4)	-40 (3)
C (N4)	81 (3)	44 (2)	53 (2)	6 (4)	45 (4)	-15 (3)
C (5)	70 (2)	35 (1)	52 (2)	4 (3)	56 (4)	- 13 (3)
N (6)	58 (2)	49 (1)	28 (1)	-7 (3)	27 (3)	8 (2)
C (7)	62 (2)	47 (2)	47 (2)	12 (4)	44 (4)	9 (3)
O (7)	80 (2)	89 (1)	49 (1)	-19 (3)	60 (3)	29 (2)
C (8)	66 (2)	60 (2)	46 (2)	-6 (4)	30 (3)	1 (3)
C (9)	55 (2)	35 (1)	39 (1)	-12 (3)	31 (3)	-10 (3)
C (10)	83 (3)	51 (2)	44 (2)	9 (4)	48 (4)	-6 (3)
C (11)	80 (3)	57 (2)	66 (2)	29 (4)	33 (4)	-10 (3)
C (12)	86 (3)	53 (2)	54 (2)	3 (4)	-13 (4)	9 (3)
C (13)	104 (3)	60 (2)	40 (2)	-13 (4)	24 (4)	6 (3)
C (14)	79 (3)	50 (2)	43 (2)	-8 (4)	47 (4)	-3 (3)

Estimated standard deviations are in parentheses. The expression is of the form: $\exp(-B_{11}h^2-B_{22}k^2-B_{33}l^2-B_{12}hk-B_{13}hl-B_{23}kl)$.

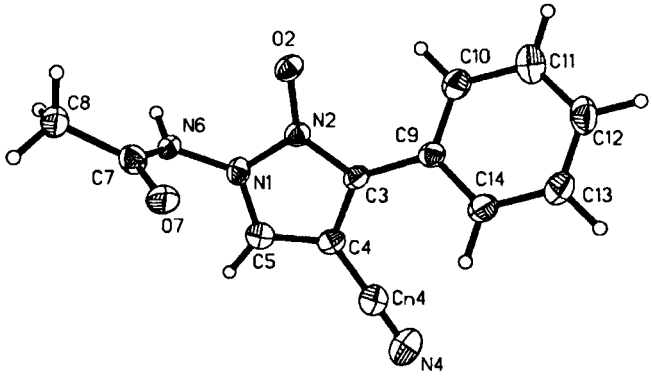


Figure 1. ORTEP Diagram of **20a**.

EXPERIMENTAL

5-Azido-3-phenyl-4-isoxazolecarboxaldehyde (**2**).

A mixture of chloroaldehyde **1** (62.5 g, 0.3 mole) and sodium azide (22.0 g, 0.338 mole) in DMF (300 ml) was stirred at room temperature for 1.5 hours then poured slowly into ice-water (2.5 l). The precipitate was filtered and the damp filter cake dissolved in methylene chloride (200 ml), washed with water (300 ml) and dried (sodium sulfate). Removal of the solvent gave a tan solid which was recrystallized from ether-hexane and isolated as short tan needles (47.4 g, 73%), mp 49.5-51.0°; ir (Nujol): 2176 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.40-7.65 (m, 3H), 7.65-7.85 (m, 2H), 9.77 (s, 1H).

Anal. Calcd. for $C_{10}H_6N_4O_2$: C, 56.07; H, 2.82; N, 26.16. Found: C, 56.19; H, 2.99; N, 25.79.

3-Phenylisoxazolo[5,4-*c*]isoxazole (**3**).

The azidoaldehyde **2** (5.0 g, 23.35 mmoles) was refluxed for 1 hour in toluene (100 ml) then the solvent removed. The residue was chromatographed over silica gel eluting with methylene chloride to afford yellow prisms (2.79 g, 64%) from methanol, mp 146-147°; ir (Nujol): 3114 (shp) cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.45-7.75 (m, 3H), 7.75-8.05 (m, 2H), 8.74 (s, 1H); ms: m/z 186.

Anal. Calcd. for $C_{10}H_6N_2O_2$: C, 64.52; H, 3.25; N, 15.05. Found: C, 64.41; H, 3.51; N, 15.00.

(*E*)-3-(5-Chloro-3-phenyl-4-isoxazolyl)-2-propenoic Acid Ethyl Ester (**5**).

The chloroaldehyde **1** (12.6 g, 60.7 mmoles) was dissolved in methylene chloride (100 ml) and carbethoxymethylene triphenylphosphorane **4** (21.0 g, 60.3 mmoles) was added portion wise over 5 minutes. The mixture was stirred for 18 hours then the solvent evaporated. The residue was chromatographed over silica gel (500 g) eluting with methylene chloride. An amber oil was obtained which crystallized on cooling. Recrystallization from hexane gave white flakes (15.35 g, 91%), mp 62-63°; ir (Nujol): 1718 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.30 (t, J = 7.0 Hz, 3H), 4.23 (q, J = 7.0 Hz, 2H), 6.43 (d, J = 16.5 Hz, 1H), 7.42 (d, J = 16.5 Hz, 1H), 7.57 (s, 5H); ms: m/z 277.

Anal. Calcd. for $C_{14}H_{12}ClNO_3$: C, 60.55; H, 4.35; N, 5.04; Cl, 12.77. Found: C, 60.29; H, 4.38; N, 4.97; Cl, 12.96.

(*E*)-3-(5-Azido-3-phenyl-4-isoxazolyl)-2-propenoic Acid Ethyl Ester (**6**).

The chloroolefin **5** (13.0 g, 46.8 mmoles) and sodium azide (6.1 g, 93.8 mmoles) were stirred in acetonitrile (200 ml) for 24 hours at 25°. The mixture was filtered and the filtrate evaporated. The residue was chromatographed over silica gel (500 g) eluting with methylene chloride. Recrystallization from ether-hexane gave bright yellow needles (7.52 g, 56%), mp 57-59° dec; ir (Nujol): 2200, 2141, 1713 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.27 (t, J = 7.0 Hz, 3H), 4.18 (q, J = 7.0 Hz, 2H), 6.29 (d, J = 16.5 Hz, 1H), 7.28 (d, J = 16.5 Hz, 1H), 7.53 (s, 5H); ms: m/z 284.

Anal. Calcd. for $C_{14}H_{12}N_4O_3$: C, 59.15; H, 4.26; N, 19.71. Found: C, 58.90; H, 4.39; N, 19.65.

4-Cyano-1-hydroxy-5-phenyl-1*H*-pyrrole-2-carboxylic Acid Ethyl Ester (**8**).

The azidoolefin **6** (0.5 g, 1.75 mmoles) was heated under reflux in toluene (25 ml) for 2 hours. Removal of the solvent gave a brown oil. Chromatography on silica gel (50 g) eluting with methylene chloride afforded the pyrrole as white plates (0.14 g, 30%) from hexane, mp 129.5-131.0°; ir (Nujol): 3297, 3143, 2222 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.38 (t, J = 7.5 Hz, 3H), 4.38 (q, J = 7.5 Hz, 2H), 7.07 (s, 1H), 7.30-7.60 (m, 3H), 7.65-7.90 (m, 2H), 12.26 (s, OH); ms: m/z 256.

Anal. Calcd. for $C_{14}H_{12}N_2O_3$: C, 65.61; H, 4.72; N, 10.93. Found: C, 65.44; H, 4.65; N, 10.75.

5-Azido-3-phenyl-4-isoxazolecarboxaldehyde Oxime (**9**).

The azidoaldehyde **2** (5.0 g, 23.3 mmoles) and hydroxylamine hydrochloride (2.5 g, 35.9 mmoles) were stirred in pyridine (25 ml) for 1 hour and then poured into ice-water (200 ml). The precipitate was filtered and recrystallized from acetone-hexane to give short orange needles (3.67 g, 68%), mp 130° dec; ir (Nujol): 3282, 2303, 2212, 2148 cm^{-1}; ^1H nmr (DMSO-d_6): δ

7.62 (m, 5H), 7.84 (s, 1H), 11.60 (s, OH); ms: m/z 229.

Anal. Calcd. for $C_{10}H_7N_5O_2$: C, 52.40; H, 3.08; N, 30.57. Found: C, 52.31; H, 3.22; N, 30.44.

1-Hydroxy-5-phenyl-1*H*-pyrazole-4-carbonitrile 2-Oxide (**11**).

The azidooxime **9** (3.7 g, 16 mmoles) was heated under reflux in toluene (75 ml) for 1.5 hours. Upon cooling, the resulting precipitate was filtered and recrystallized from methanol-acetone as white fluffy needles (1.66 g, 51%), mp 204° dec; ir (Nujol): 3152, 2240 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.45-7.70 (m, 3H), 7.80-8.10 (m, 2H), 8.47 (s, 1H); ms: m/z 201.

Anal. Calcd. for $C_{10}H_7N_3O_2$: C, 59.70; H, 3.51; N, 20.89. Found: C, 59.55; H, 3.58; N, 20.93.

3-Phenyl-1*H*-pyrazole-4-carbonitrile (**12**).

A mixture of the *N*-oxide **11** (0.20 g, 1.0 mmole) and zinc dust (0.80 g, 12.2 mmoles) in acetic acid (5 ml) was heated under reflux for 2 hours. After cooling, the reaction was filtered and the solvent evaporated. The residue was chromatographed over silica gel (50 g) eluting with 1% methanol-methylene chloride. Recrystallization from methylene chloride-hexane gave fine white needles (0.11 g, 65%), mp 134.0-135.5° (lit [11] 133-134°); ir (Nujol): 3329, 3135, 2237 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.30-7.75 (m, 3H), 7.75-8.10 (m, 2H), 8.52 (s, bd, 1H), 13.90 (s, bd, NH); ms: m/z 169.

Anal. Calcd. for $C_{10}H_7N_3$: C, 70.99; H, 4.17; N, 24.84. Found: C, 71.07; H, 4.33; N, 24.73.

1-Hydroxy-5-phenyl-1*H*-pyrazole-4-carbonitrile (**13**).

The *N*-oxide **11** (0.40 g, 2 mmoles) was added in portions to a stirred solution of sodium hydrosulfite (1.60 g, 9.2 mmoles) in water (50 ml) and the mixture heated under reflux for 7 hours. After cooling, the mixture was extracted with ethyl acetate (3 x 15 ml). The organic extracts were washed with water (100 ml), dried (sodium sulfate), filtered and evaporated to afford a brown solid. Two recrystallizations from acetone-hexane gave pinkish needles (0.05 g, 14%), mp 221-223° dec; ir (Nujol): 3144, 2240 cm^{-1}; ms: m/z 185.

Anal. Calcd. for $C_{10}H_7N_3O$: C, 64.86; H, 3.81; N, 22.69. Found: C, 64.57; H, 4.05; N, 22.80.

5-Azido-3-phenyl-4-isoxazolecarboxaldehyde-*O*-methyloxime (**15a**).

The azidoaldehyde **2** (5.0 g, 23.4 mmoles) and methoxylamine hydrochloride (2.2 g, 26.4 mmoles) were stirred in pyridine (25 ml) for 18 hours then poured into ice-water (500 ml). The resultant precipitate was filtered and chromatographed over silica gel (300 g) eluting with methylene chloride. Recrystallization from hexane gave yellow prisms (3.8 g, 67%), mp 67-71°; ir (Nujol): 2154 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.92 (s, 3H), 7.30-7.65 (m, 5H), 7.78 (s, 1H); ms: m/z 243.

Anal. Calcd. for $C_{11}H_9N_5O_2 \cdot 0.245H_2O$: C, 53.35; H, 3.86; N, 28.28. Found: C, 53.34; H, 3.87; N, 28.64.

5-Methoxy-3-phenyl-5*H*-pyrazolo[4,3-*d*]isoxazole (**17a**).

The azidomethyloxime **15a** (2.0 g, 8.2 mmoles) was heated under reflux in benzene (50 ml) for 6 hours. The solvent was removed and the residue chromatographed over silica gel (100 g) eluting with methylene chloride. An off-white solid was obtained which was recrystallized from acetone-hexane as cream colored plates (0.49 g, 28%), mp 129.5-131.5°; ir (Nujol): 3133, 3052 cm^{-1}; ^1H nmr (deuteriochloroform): δ 4.26 (s, 3H), 7.30-7.55 (m, 3H), 7.70 (s, 1H), 7.75-7.95 (m, 2H); ms: m/z 215.

Anal. Calcd. for $C_{11}H_9N_3O_2$: C, 61.39; H, 4.21; N, 19.53. Found: C, 61.01; H, 4.27; N, 19.41.

5-Azido-3-phenyl-4-isoxazolecarboxaldehyde-*O*-(phenylmethyl)oxime (**15b**).

A mixture of the azidoaldehyde **2** (4.28 g, 20 mmoles) and *O*-benzylhydroxylamine hydrochloride (3.51 g, 22 mmoles) was stirred in pyridine (20 ml) for 3 hours. After pouring into ice-water (500 ml), an orange gummy solid was obtained. Chromatography on silica gel (300 g) eluting with methylene chloride gave a pale yellow solid (5.5 g). Recrystallization from hexane gave pale yellow needles (4.3 g, 67%), mp 57-59°; ir (Nujol): 2144 cm^{-1}; ^1H nmr (deuteriochloroform): δ 5.04 (s, 2H), 7.05-7.65 (m, 5H), 7.27 (s, 5H), 7.80 (s, 1H); ms: m/z 319.

Anal. Calcd. for $C_{17}H_{13}N_5O_2$: C, 63.94; H, 4.10; N, 21.93. Found: C, 63.61; H, 4.20; N, 21.76.

3-Phenyl-5-(phenylmethoxy)-5*H*-pyrazolo[4,3-*d*]isoxazole (**17b**).

The azidobenzyloxime **15b** (3.8 g, 11.9 mmoles) was heated under reflux in heptane (100 ml) for 3 hours. Removal of the solvent gave a brown oil which was chromatographed over silica gel (300 g) using a 50-100% methylene chloride-hexane gradient. The title compound was isolated as a white solid which was recrystallized from ether-hexane as fine white needles (0.53 g, 15%), mp 118-120°; ir (Nujol): 3132 cm^{-1}; ^1H nmr (acetone-d_6): δ 5.47 (s, 2H), 7.25-7.60 (m, 8H), 7.75-8.00 (m, 2H), 8.07 (s, 1H); ms: m/z 291.

Anal. Calcd. for $C_{17}H_{13}N_3O_2$: C, 70.09; H, 4.50; N, 14.42. Found: C, 69.84; H, 4.80; N, 14.24.

The column was washed with 5% methanol-methylene chloride to yield a brown oil (1.4 g) which was rechromatographed over silica gel (150 g) using 1% methanol-methylene chloride. 3-Phenyl-1*H*-pyrazole-4-carbonitrile **12** was obtained (0.51 g, 25%) as a white solid.

[(5-Azido-3-phenyl-4-isoxazolyl)methylene]acetic Acid Hydrazide (**19a**).

The azidoaldehyde **2** (1.0 g, 4.66 mmoles) and acethydrazide (0.70 g, 9.5 mmoles) were stirred in methylene chloride (20 ml) for 18 hours. The solvent was removed and the residue recrystallized twice from methanol to give flocculent yellow needles (0.35 g, 28%), mp 187-190° dec; ir (Nujol): 3100, 2202, 2163, 2139 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.88 and 1.93 (s, together 3H), 7.30-7.85 (m, 6H), 11.15 (bd, NH); ms: m/z 270.

Anal. Calcd. for $C_{12}H_{10}N_6O_2 \cdot 0.22H_2O$: C, 52.56; H, 3.84; N, 30.65. Found: C, 52.56; H, 3.99; N, 30.67.

N-(3-Phenyl-5*H*-pyrazolo[4,3-*d*]isoxazol-5-yl)acetamide (**21a**).

The azidohydrazone **19a** (2.57 g, 9.5 mmoles) was heated under reflux in toluene (100 ml) for 3 hours. The solvent was evaporated and the residue chromatographed over silica gel (350 g) eluting with 2% methanol-methylene chloride. The bicyclic compound was isolated as fine cream colored needles (0.225 g, 10%) from acetone-hexane, mp 198-200° dec; ir (Nujol): 3233, 3197, 3120, 1682 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.10 (s, 3H), 7.35-7.65 (m, 3H), 7.75-8.15 (m, 2H), 8.55 (s, 1H), 12.10 (bd, NH); ms: m/z 242.

Anal. Calcd. for $C_{12}H_{10}N_4O_2$: C, 59.50; H, 4.16; N, 23.13. Found: C, 59.23; H, 3.93; N, 22.98.

N-(4-Cyano-3-phenyl-1*H*-pyrazol-1-yl)acetamide *N*-Oxide

(**20a**).

Continued elution of the column afforded **20a** as white prisms (1.28 g, 56%) from methanol, mp 211-213° dec; ir (Nujol): 3113, 2237, 1733 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.16 (s, 3H), 7.30-7.65 (m, 3H), 7.85-8.15 (m, 2H), 8.58 (s, 1H), 11.70 (bd, NH); ms: m/z 242.

Anal. Calcd. for $C_{12}H_{10}N_4O_2 \cdot 0.315H_2O$: C, 58.14; H, 4.32; N, 22.60. Found: C, 58.15; H, 4.42; N, 22.58.

N-(4-Cyano-3-phenyl-1*H*-pyrazol-1-yl)acetamide (**22**).

The pyrazole *N*-oxide **20a** (0.30 g, 1.24 mmoles) and zinc dust (1.0 g, 15.3 mmoles) in acetic acid (10 ml) were heated under reflux for 4 hours. Filtration and evaporation of the filtrate gave a cream solid which was recrystallized from methylene chloride to give long white needles (0.21 g, 75%), mp 202-204°; ir (Nujol): 3218, 3133, 2235, 1681 cm^{-1}; ^1H nmr (DMSO-d_6): 2.07 (s, 3H), 7.30-7.65 (m, 3H), 7.65-8.00 (m, 2H), 8.72 (s, 1H); ms: m/z 226.

Anal. Calcd. for $C_{12}H_{10}N_4O$: C, 63.71; H, 4.46; N, 24.77. Found: C, 63.47; H, 4.65; N, 24.83.

Reaction of Azidoaldehyde **2** with *t*-Butyl Carbazate (**18b**).

(3-Phenyl-5*H*-pyrazolo[4,3-*d*]isoxazol-5-yl)carbamic Acid 1,1-Dimethyl Ester **21b**.

A mixture of the azidoaldehyde **2** (4.28 g, 20 mmoles) and *t*-butyl carbazate (2.65 g, 20 mmoles) was stirred in methylene chloride (25 ml) for 6 hours then cooled to 0°. The white precipitate (0.90 g, 15%) was filtered and recrystallized from methanol. This compound was obtained as white needles, mp 185-186° dec; ir (Nujol): 3195, 3111, 1728 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.50 (s, 9H), 7.30-7.55 (m, 3H), 7.72 (s, 1H), 7.75-7.95 (m, 2H), 8.07 (bd, NH); ms: m/z 300.

Anal. Calcd. for $C_{15}H_{16}N_4O_3$: C, 59.99; H, 5.37; N, 18.66. Found: C, 59.79; H, 5.51; N, 18.67.

(4-Cyano-3-phenyl-1*H*-pyrazol-1-yl)carbamic Acid 1,1-Dimethylethyl Ester *N*-Oxide (**20b**).

The reaction filtrate from the above reaction was evaporated to afford a yellow solid (6.0 g) which consisted of *ca.* 1:1 mixture of the expected azidohydrazone **19b** and the bicyclic compound **21b**. This mixture was heated under reflux in benzene (100 ml) for 5 hours then allowed to cool. Additional bicyclic compound **21b** was filtered (1.66 g, 28%). The filtrate was evaporated and the resultant solid recrystallized from acetone-hexane to give white prisms (1.10 g, 18%), mp 183-184° dec; ir (Nujol): 3138, 2238, 1755 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.33 (s, 9H), 7.33-7.55 (m, 3H), 7.60 (s, 1H), 7.95-8.20 (m, 2H), 9.96 (bd, NH); ms: m/z 300.

Anal. Calcd. for $C_{15}H_{16}N_4O_3$: C, 59.99; H, 5.37; N, 18.66. Found: C, 59.61; H, 5.65; N, 18.35.

1-Amino-3-phenyl-1*H*-pyrazole-4-carbonitrile 2-Oxide (**23**).

The pyrazole **20b** (0.50 g, 1.66 mmoles) and trifluoroacetic acid (5.0 ml) were stirred in methylene chloride (12 ml) for 3 hours. The solvent was evaporated and the residue dissolved in methylene chloride. The solution was washed with 5% sodium bicarbonate solution (25 ml), water (25 ml), dried (sodium sulfate) and evaporated to afford a tan solid. Recrystallization from methanol gave cream needles (0.25 g, 75%), mp 196-198° dec; ir (Nujol): 3297, 3147, 3067, 2239 cm^{-1}; ^1H nmr (DMSO-d_6): δ 6.40 (s, NH_2), 7.30-7.60 (m, 3H), 7.90-8.10 (m, 2H), 8.40 (s, 1H); ms: m/z 200.

Anal. Calcd. for $C_{10}H_8N_4O \cdot 0.15H_2O$: C, 59.20; H, 4.12; N, 27.61. Found: C, 58.97; H, 4.21; N, 27.98.

3-Phenyl-5*H*-pyrazolo[4,3-*d*]isoxazol-5-amine (**24**).

The bicyclic compound **21b** (1.0 g, 3.3 mmoles) and trifluoroacetic acid (10 ml) were stirred in methylene chloride (25 ml) for 3 hours then the solvent evaporated. The residue was dissolved in methylene chloride (50 ml) and washed with 5% sodium bicarbonate solution (50 ml), water (50 ml), dried (sodium sulfate) and evaporated. Recrystallization of the residue twice from ether gave cream needles (0.39 g, 57%), mp 181-182° dec; ir (Nujol): 3209, 3145, 3052 cm^{-1}; ^1H nmr (polysol D): δ 6.99 (s, NH_2), 7.40-7.70 (m, 3H), 7.70-8.05 (m, 2H), 8.25 (s, 1H); ms: m/z 200.

Anal. Calcd. for $C_{10}H_8N_4O \cdot 0.15H_2O$: C, 59.20; H, 4.12; N, 27.61. Found: C, 59.06; H, 4.09; N, 27.73.

X-ray Structure Determination of *N*-(4-Cyano-3-phenyl-1*H*-pyrazol-1-yl)acetamide *N*-Oxide **20a**.

$C_{12}H_{10}N_4O_2$, formula wt. = 242.2; monoclinic; space group P $2_1/c$; Z = 4; a = 9.505(3), b = 11.474(2), c = 11.577(2)Å, β = 113.08(3)°, V = 1161.5(2)$Å^3$; calculated density = 1.38 g cm^{-3}, absorption coefficient μ = 0.73 mm^{-1}. Intensity data were collected at low temperature (-155°) on a clear prism 0.07 x 0.08 x 0.10 mm mounted on a glass fiber on a Siemens P1bar diffractometer. Graphite monochromatized CuKα radiation was used, (λ(CuKα) = 1.5418Å), with 2θ max = 136°. Intensity data were measured at room temperature using θ/2θ scans with scan widths ≥ 3.4° and a scan rate of 1°/minute. The total time spent counting background, half at each end of the scan, was equal to the time spent scanning. Of 1659 unique reflections measured, 1325 had intensities >3σ. Ten reflections periodically monitored showed no trend towards deterioration; $\sigma^2(I)$ was approximated by $\sigma^2(I)$ from counting statistics + $(0.01I)^2$, where the coefficient of I was calculated from the variations in intensities of the monitored reflections. Cell parameters were determined by least squares fit of $K\alpha_1$ 2θ values (λ($K\alpha_1$) = 1.5402) for 25 high 2θ reflections [17]. An Lp correction appropriate for a monochromator with 50% perfect character was applied.

The structure was solved by direct methods, using DIREC [18]. Hydrogen atoms were all found in a difference Fourier map at or near generated positions, except that the methyl hydrogens were rotated +37° from generated positions. Generated (and rotated) hydrogen coordinates were used in the refinement with isotropic temperature factors assigned as 0.5 units higher than attached atoms. Least squares refinement included coordinates and anisotropic thermal parameters for all nonhydrogen atoms. The function minimized in the refinement was $\Sigma w(Fo^2-Fc^{*2})^2$, where weights w were $1/\sigma^2(Fo^2)$ and Fc^{*2} was as defined by Larson [19]. In the final refinement cycle all shifts were ≤0.3σ. The final agreement index R was 0.042 for all 1659 reflections and 0.032 for the 1325 reflections having $Fo^2 \geq 3\sigma$. The standard deviation of fit was 2.5. Atomic form factors were from Doyle and Turner [20], and, for hydrogen, from Stewart, Davidson & Simpson [21]. The CRYM system of computer programs was used [18].

Acknowledgement.

The authors wish to recognize the expert technical assistance of the late Arlen J. Taylor and to thank Connie G. Chidester for collation of the X-ray data.

REFERENCES AND NOTES

‡ Christine Muchmore, present address: Department of Pharmacology and Biological Chemistry, Northwestern University School of Medicine, 303 E. Chicago Ave., Chicago, IL 60611.

[1] D. J. Anderson, *J. Org. Chem.*, **51**, 945 (1986).

[2] R. K. M. R. Kallury and P. S. U. Devi, *Tetrahedron Letters*, 3655 (1977).

[3] K. Ashok, G. Sridevi and Y. Umadevi, *Synthesis*, 623 (1993).

[4] W. Dehaen and J. Becher, *Acta Chem. Scand.*, **47**, 244 (1993) and references contained therein.

[5] G. Kumar, K. Rajagopalan, S. Swaminathan and K. K. Balasubramanian, *Tetrahedron Letters*, 4685 (1979).

[6] G. L'Abbé and F. Godts, *Bull. Soc. Chim. Belg.*, **96**, 229 (1987).

[7] S. Gronowitz, C. Westerlund and A-B. Hornfeldt, *Chem. Scripta*, **10**, 165 (1976).

[8] S. Gronowitz, C. Westerlund and A-B. Hornfeldt, *Acta Chem. Scand. B.*, **30**, 391 (1976).

[9] R. S. Gairns, C. J. Moody and C. W. Rees, *J. Chem. Soc., Chem. Commun.*, 1818 (1985).

[10] C. R. Muchmore, C. G. Chidester, D. J. Anderson and A. J. Taylor, *Abstr. Am. Cryst. Assoc.*, Seattle, Wash., Abs. PA 02, July, 1989.

[11] J. P. Freeman and E. Janiga, *J. Org. Chem.*, **39**, 2663 (1974) and references therein.

[12] I. I. Grandberg and N. I. Bobrova, *Khim. Geterotski. Soedin.*, 566 (1965); *Chem. Abstr.*, **64**, 3516g (1966).

[13] J. Becher, P. L. Jorgensen, K. Pluta, N. J. Krake and B. Falt-Hansen, *J. Org. Chem.*, **57**, 2127 (1992).

[14] T. L. Gilchrist, *Chem. Soc. Rev.*, **12**, 53 (1983).

[15] R. A. Abramovitch and C. Dupry, *J. Chem. Soc., Chem. Commun.*, 36 (1981).

[16] R. Taylor and O. Kennard, *J. Am. Chem. Soc.*, **104**, 5063 (1982).

[17] D. J. Duchamp, *ACS Symp. Ser.*, **46**, 98 (1977).

[18] D. J. Duchamp, DIREC, a direct methods program for solving crystal structures and CRYM, a system of crystallographic programs. The Upjohn Company, Kalamazoo, MI 49001, (1984).

[19] A. C. Larson, *Acta Crystallogr.*, **A23**, 664 (1967).

[20] P. A. Doyle and P. S. Turner, *Acta Crystallogr.*, **A24**, 390 (1968).

[21] R. F. Stewart, E. R. Davidson and W. T. Simpson, *J. Chem. Phys.*, **42**, 3175 (1965).