The Mechanism of the Thermolytic Ring Opening of 5-Azido-4-formyl-3-methyl-1-phenylpyrazole

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Thermolysis of 5-azido-4-formyl-3-methyl-1-phenylpyrazole **4** produces the (4-cyanopyrazol-3-ylmethyl))pyrazoles **3** and **6**. 2-Cyano-3-phenylazo-2-butenal **2** was detected by ^{1}H NMR spectroscopy during the reaction. The products **3** and **6** and other rearrangement products obtained when 5-chloro-4-formylpyrazoles are reacted with azide ion all seem to be formed by a common mechanism, via substituted 2-cyano-3-azo propenals or a zwitterionic intermediate. The nature of the products is determined by the position of nucleophilic attack at the intermediate. Structural characterization of the products has been obtained by NMR spectroscopy and single-crystal X-ray crystallography.

o-Chloroformylhetarenes react with azide ion at low temperature by replacement of the halogen with azide. At elevated temperatures the azido substituted hetarenes may undergo ring opening followed by secondary reactions such as rearrangements.[1-6] In the triazole and the pyrazole series the ring opening may take place via a nitrene. Related ring cleavage has been reported in the thiophene[7-9] benzothiophene[10-12] and indole[13] series. In 2-azidobenzo[*b*]thiophene and 2-azidoindole, ring opening takes place via an *ortho*-quinoidal intermediate which could be trapped with dienophiles. Ring opening may be followed by recyclization with concomitant *tele*-substition or with formation of an *o*-cyano-hydroxy substituted azole. The former route was followed when 5-chloro-4-formyl-1,3-dimethylpyrazole was treated with an excess of sodium azide to give **8**.[14,15] Under similar conditions, 5-chloro-4-formyl-3-methyl-1-phenylpyrazole **1** reacted according to the latter course to produce 4-cyano-5-hydroxy-3-methyl-1-phenylpyrazole **5**[16] since the phenyl group makes *tele*-substitution impossible (Scheme 1). In the present study thermolysis of the intermediate 5-azido-4-formyl-3-methyl-1-phenylpyrazole **4** has been investigated in order to trap the intermediates and elucidate the mechanism of the ring opening.

Results and discussion

The thermolysis of 5-azido-4-formyl-3-methyl-1-phenylpyrazole **4**, prepared in 75% yield by treatment of 5-chloro-4-formyl-3-methyl-1-phenylpyrazole **1** with sodium azide in dimethyl sulfoxide at 20°C,[17] was studied in different solvents. In toluene, the expected 4-cyano-5-hydroxy-3-methyl-1-phenylpyrazole **5** was the final product while in dimethyl sulfoxide a complicated mixture was
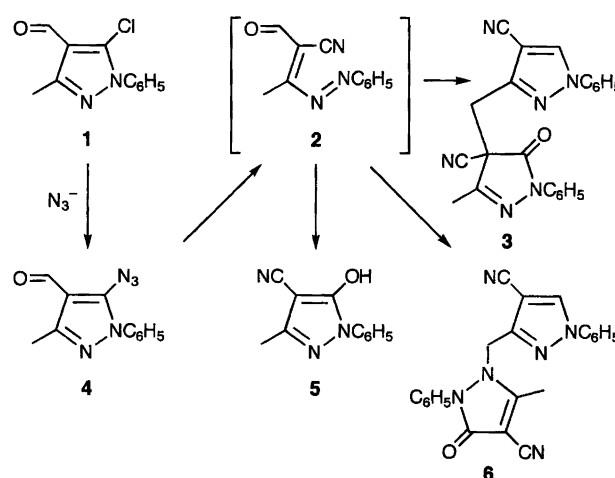
Scheme 1.

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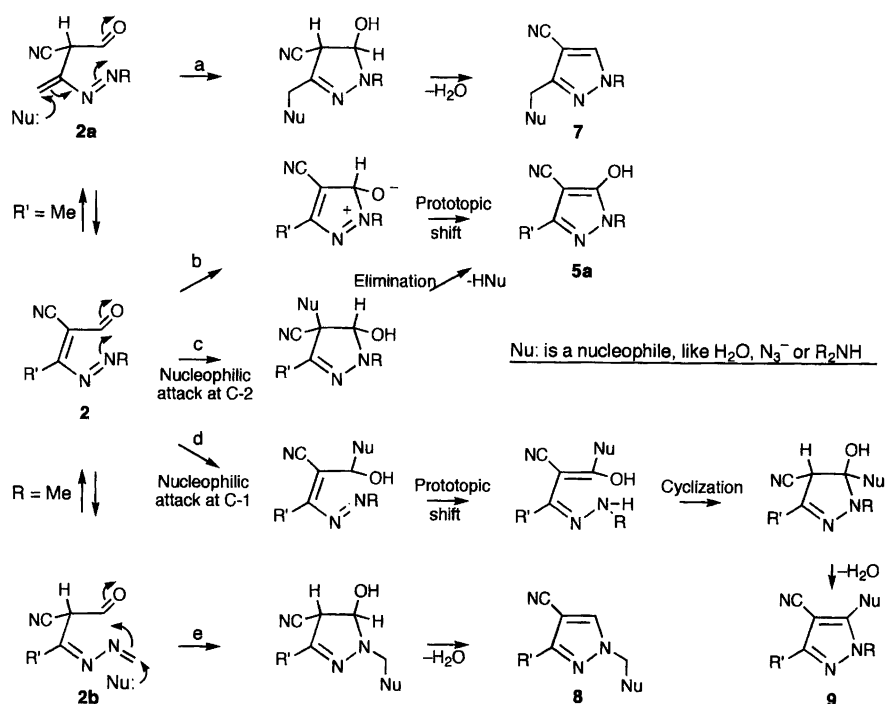
Scheme 2. The five possible routes for nucleophilic attack on the intermediate alkylazocyanoaldehyde.

formed. Heating to reflux in acetonitrile for 36 h gave, however, two new products. These were also formed in other solvents, such as *N,N*-dimethylformamide (DMF), although in lower yields along with other compounds in a less clean reaction.

The thermolysis of **4** in refluxing acetonitrile was followed by ^{1}H NMR spectroscopy. First, the phenylazo cyanoaldehyde **2** appeared, its yield amounting to a maximum of 20% after 8 h. This compound was identified through its ^{1}H NMR spectrum showing close similarity with that of the isolated and characterized intermediate from the thermolysis of the ethoxycarbonylhydrazone derivative of **2**.[18] Next, two new products appeared almost

simultaneously. Work up after 36 h afforded 59% of the less polar **3** and 20% of the more polar **6**. The structures of compound **3** and **6** were elucidated by using NMR spectroscopy involving H–C–C correlated (COLOC-spectra) (see below). The crystal structure of compound **3** was determined by X-ray crystallography.

As pointed out previously,[14] the ring opening of the starting material **4** to give the phenylazo cyanoaldehyde **2** most likely proceeds with a nitrene or a zwitterionic species as an intermediate. The phenylazo cyanoaldehyde **2** may cyclize directly (route b, Scheme 2) or upon nucleophilic addition. This can take place at four different positions. If the intermediate phenylazo cyanoaldehyde **2**
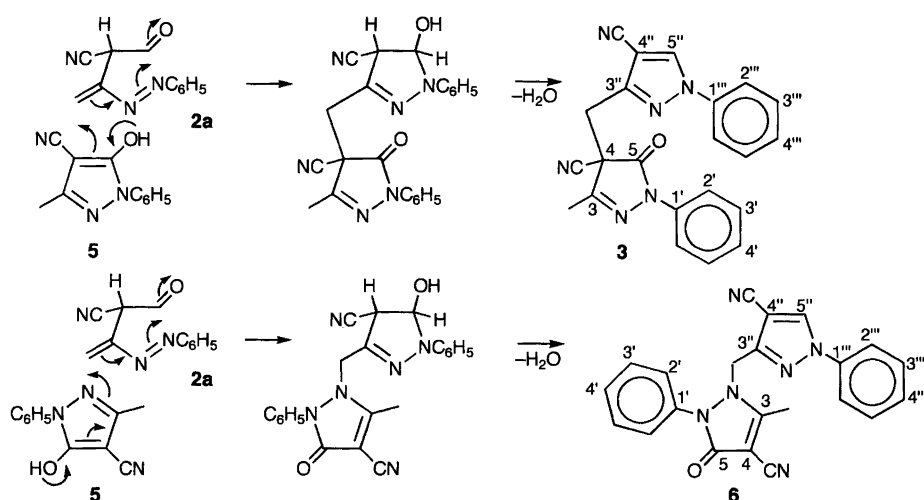
Scheme 3. Formation of cyanopyrazolylpyrazolinones from alkylazocyanoaldehydes.

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is devoid of α-protons at the nitrogen and C-3, proto-tropy is impossible and C-2 or C-1 is attacked (route c or d). Attack at C-2 leads to cyclization. Subsequent elimination produces a 5-hydroxypyrazole **5a** as observed when **2** is generated directly in dimethyl sulfoxide in the presence of azide ions.[14] Alternative attack at C-1 (route d) followed by a prototropic shift, cyclization and elimi-nation affords a 5-substituted 4-cyanopyrazole **9**.

When the substituent at the nitrogen of compound **2** possesses a hydrogen atom prototropy gives rise to tau-tomer **2b** which is attacked at the α-position of the *N*-sub-stituent resulting in formation of a 1-alkyl-4-cyanopyra-zole **8** (route e). This course is observed when the *N*-methylazo cyanoaldehyde **2**, R' = Me is generated in dimethyl sulfoxide in the presence of azide ions.[16]

In the present case the intermediate phenylazo cy-anoaldehyde **2** possesses a 3-substituent with an α-pro-ton. Prototropy now gives rise to the tautomer **2a** which is attacked at the α-position of the C-3 substituent pro-ducing a 3-alkyl-4-cyanopyrazole such as **7**, **3** or **6** which is observed when phenylazo cyanoaldehyde **2** is gener-ated in acetonitrile (route a). This nucleophile may be water which is required in only catalytic amounts since it is regenerated in the aromatization step.

The nucleophile producing **3** and **6** is the hydroxypyra-zole **5** formed initially via route b or c. The hydroxy-pyrazole is acting as an ambident nucleophile. C-4 or N-2 may act as the attacking nucleophilic center yielding **3** and **6**, respectively (Scheme 3). The oxygen of the hy-droxypyrazole **5** may also act as the nucleophilic center, however, the resulting product was not observed.

Identification of products

The crystal structure of **3** verified the chemical compo-sition of the compound. It is illustrated by the ORTEP drawing in Fig. 1. Each of the two five-membered rings are planar to within the experimental accuracy and are almost coplanar with their substituted phenyl group. The interplanar angle is 108.8° between the two least-squares planes calculated for the pyrazole and pyrazolinone ring systems. The relative magnitude of the bond lengths in the pyrazolinone ring corresponds to localized bonds. The conformation of compound **3** is characterized by the following features: (*i*) The CH$_2$ group is staggered with respect to the heteroaromatic ring. (*ii*) The pyrazoline ring is situated opposite the hydrogen and not to the cyano group of the heteroaromatic ring. (*iii*) The distance be-tween one of the CH$_2$-hydrogens and the oxygen (2.86 Å) is similar to the distance between the second CH$_2$-hy-drogen and the methyl H (2.52 Å).

The mass spectrum of compound **3** exhibits a molecu-lar ion peak at *m/z* 380 corresponding to condensation of 2 mol of starting material with loss of water. This is sup-ported by the elemental analysis. The base peak is situ-ated at *m/z* 182 which may be due to the 1-phenyl-4-cyano-5-methylene radical cation. The most prominent
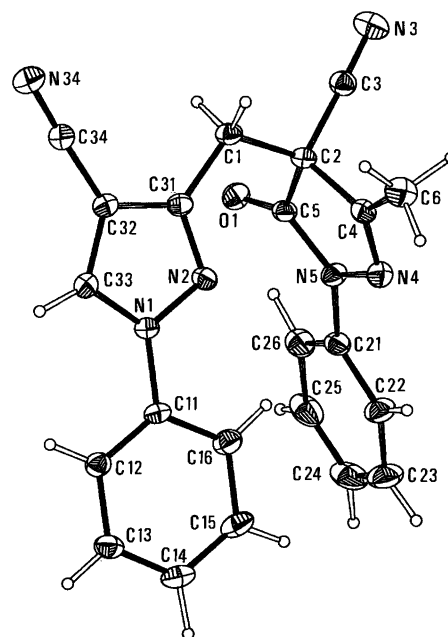

Fig. 1. ORTEP drawing of **3**. The thermal ellipsoids enclose 50% probability, the hydrogen atoms are drawn as spheres with a fixed radius. Some selected bond lengths (Å) and angles (deg): C1–C2 1.545(2), C1–C31 1.495(2), C2–C5 1.549(2), C5–N5 1.361(2), N5–N4 1.413(2), N4–C4 1.282(2), C4–C2 1.520(2), C31–C32 1.417(2), C32–C33 1.377(2), C33–N1 1.354(2), N1–N2 1.365(1), N2–C31 1.322(2), C2–C1–C31 113.0(1), C4–C2–C5 100.2(1), C4–N4–N5 108.4(1), N4–N5–C5 113.2(1), N5–C5–C2 105.2(1), N2–C31–C32 110.8(1), C31–N2–N1 105.5(1), N2–N1–C33 111.9(1), N1–C33–C32 106.5(1), C33–C32–C31 105.3(1).

features of the IR spectrum are a cyano-group absorption at 2235 cm^{-1} and a carbonyl absorption at 1728 cm^{-1}. The ^{1}H NMR spectrum (see Table 1) shows one het-eroaromatic proton, two phenyl groups, one with low field *o*-protons, a CH$_2$-group with diastereotopic protons and a methyl group situated on an sp^2-carbon atom. The ^{13}C NMR spectrum (see Table 1) exhibits characteristic sig-nals for an amide carbon, three imine or pyrazole C-3 or C-5 carbon atoms, two cyano groups, and one pyrazole C-4 carbon atom. The H,H- and C,H-correlated spectra reveal the connectivities. However, detailed information comes from the two- and three-bond C–H couplings and the C,C,H-correlated (COLOC) spectrum (Table 1). The latter demonstrates the central position of the CH$_2$ group, exhibiting long-range connectivities to the amide carbon, the imine or pyrazole ring carbon atoms at 152.9 and 147.2 ppm, the nitrile carbon atom at 112.7 ppm, and the pyrazole C-4 carbon atom. The two and three bond C–H coupling constants are characteristic of those observed in substituted pyrazoles.[19] The couplings from C-3 and C-5 of the pyrazolinone ring to each of the diastereotopic CH$_2$-protons are different. This indicates that the C-5–C-4–CH$_2$^{a} and the C-5–C-4–CH$_2$^{b} angles are different, as are the C-3–C-4–CH$_2$^{a} and C-3–C-4–CH$_2$^{b} angles.

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Table 1. ^{1}H and ^{13}C NMR data and ^{1}H–^{13}C connectivities [a] in the NMR spectra of compound **3**

Carbon atom	δ	Multiplicity ($^2J_{CH}$ and $^3J_{CH}$)	Proton signal δ (number of protons, multiplicity)	J_{CH}/Hz [d]	CH$_3$ 2.31 (3 H, s)	CH$_2$ 3.67 (1 H, d, J=15.57) and 3.83 (1 H, d, J=15.57)	H-4' 7.19 [b]	H-3''' 7.23 [b]	H-4''' 7.25 [b]	H-2'' 7.28 [b]	H-3' 7.33 (2 H, t)	H-2' 7.81 (2 H, d) [c]	H-5'' 8.18 (1 H, s)
5	165.4	s (dd)		CH$_2^a$: 2.59 CH$_2^b$: 7.16		•							
3	153.1	s (ddq)		CH$_3^a$: 1.90 CH$_2^b$: 7.10 CH$_3$: 7.93	•	•							
3''	147.4	s (dt)		H-5'': 6.08 CH$_2$: 7.01		•							•
1'''	137.9	s (br t)		H-3''': 6.88				•		•			
1'	137.0	s (dtt)		H-4': 1.31 H-2': 2.64 H-3': 9.36							•	•	
5''	132.4	d (s)		195.12									×•
3'''	129.5	d (d)		163.75 H-3''' [b]: 6.88				×•					
3'	128.9	d (d)		159.91 H-3' [b]: 8.11							×•	•	
4'''	128.2	d (tt)		162.94 H-2''': 4.20 H-3''': 6.08				•	×	•			
4'	126.0	d (dt)		161.49 H-3': 0.51 H-2': 7.54			×					•	

Position	δ(13C)	Mult.	δ(1H) / assignment								
2‴	119.2	d[e]	163.65[e]				X •	•			
2′	118.9	d[e]	164.18[e]		X •	•			•	X •	
4-CN	112.9	s (t)	CH₂: 3.50	•						•	
4″-CN	112.0	s (d)	H-5″: 1.43	•							
4″	94.2	s (dt)	H-5″: 7.11; CH₂: 2.67							•	
4	50.7	s (oct)	CH₃: 2.64; CH₂: 5.21							•	•
CH₂	30.4	dd (s)	Hᵃ: 136.2; Hᵇ: 137.78							X •	
CH₃	130.39	q (s)	X								

[a] X indicates C–H correlation and • indicates C–C–H or C–C–C–H correlation. [b] The proton chemical shift was determined from the C–H correlated spectra. [c] The signal shows additional fine structure. [d] If no one-bond couplings are specified the proton(s) to which coupling takes place is given. [e] The two- and three-bond coupling constants could not be extracted owing to signal overlap.

Table 2. Assignment of the $^3J_{CH}$ coupling constants of compound 3.

Atoms defining the dihedral angle[a]	The carbon atom to which coupling takes place[b]	Dihedral angle (°)	$^3J_{CH}$/Hz
24, 23, 1, 2	C=O	176.9	2.59
24, 23, 1, 3	C=O	62.8	7.16
39, 23, 1, 2	C—Me	61.3	1.90
39, 23, 1, 3	C—Me	178.4	7.10
44, 23, 1, 2	CN	63.6	3.50
44, 23, 1, 3	CN	56.7	3.50
5, 4, 1, 2	C-4″	64.0	2.67
5, 4, 1, 3	C-4″	56.0	2.67

[a] The numbers refer to Fig. 1. [b] The numbers refer to Scheme 3.

Thus, the pyrazolinone ring is not coplanar with the pyrazole ring in solution. The X-ray analysis indicates that this angle is 108.8° in the solid state. The magnitude of the $^3J_{CH}$ couplings (Table 2) indicates that compound 3 adopts similar conformations in solution and in the solid state. Six of the dihedral angles characterizing the conformation in the solid state are close to 60° while the remaining two dihedral angles are approximately 180°. Accordingly, six of the $^3J_{CH}$ couplings are in the range 1.9–2.7 Hz while the two remaining are 7.1–7.2 Hz as assigned in Table 2.

The mass and IR spectra of compound 6 confirm that it is isomeric with compound 3 possessing cyano as well as carbonyl groups. the ^1H NMR spectrum indicates the presence of a CH_3, a CH_2, and two phenyl groups as well as pyrazole 5-proton. The ^{13}C NMR spectrum exhibits the characteristic signals from two cyano groups and two pyrazole C-4 carbon atoms. The signals from C-5, C-1‴, C-3′ and C-3″, C-4′ and C-4‴, C-2‴ and C-4″ are assigned by comparison with the spectrum of compound 3. The difference between the chemical shifts of the meta- and para-carbons atoms of the two phenyl groups indicates that only the phenyl group represented by C-3‴ and C-2‴ is coplanar with the pyrazole ring.[20] The position of the CH_2 signal verifies that it is situated at a nitrogen atom and not an oxygen atom.

Experimental

General. Solvents were removed in vacuo by rotary evaporation. Flash chromatography was performed using silica gel Merck 60 (70–230 mesh). All new compounds were colorless, unless otherwise stated. The purity of all compounds was confirmed by thin layer chromatography. ^1H and ^{13}C NMR spectra were recorded at 200 and 50.32 MHz, respectively, on a Bruker AC-200 instrument. Elementary analysis were performed at Novo Nordisk A/S, Bagsværd, Denmark.

5-Azido-4-formyl-3-methyl-1-phenylpyrazole 4.[17] 5-Chloro-4-formyl-3-methyl-1-phenylpyrazole 1 (22.5 g) was dis-

solved in dimethyl sulfoxide (150 ml). Sodium azide (13.0 g) was added and the mixture was protected from light, stirred for 48 h and then poured into ice–water (500 ml). Stirring for 1 h and filtration afforded 20.35 g (89%) of 5-azido-4-formyl-3-methyl-1-phenylpyrazole 4, identical with the material described in Ref. 17.

Thermolysis of 5-azido-4-formyl-3-methyl-1-phenylpyrazole 4. A solution of 5-azido-4-formyl-3-methyl-1-phenyl-pyrazole 4 (2.27 g) in acetonitrile (50 ml) was heated to reflux for 36 h. The solvent was removed and the residue flash chromatographed [dichloromethane–methanol (20:1)] to give 1.13 g (59%) of 4-cyano-4-(4-cyano-1-phenyl-pyrazol-3-yl)-3-methyl-1-phenyl-4H-pyrazol-5(1H)-one 3 ($R_F = 0.80$), m.p. 159–160°C (chloroform–ether). Found: C, 69.0; H, 4.25; N, 21.75. Calc. for $C_{21}H_{16}N_6O$: C, 69.45; H, 4.25, N, 22.10%. MS [IP 70 eV; m/z (% rel. int.)]: 380 (9, M), 182 (100), 77 (40, C_6H_5). IR (KBr): 2235 (C≡N), 1728 (C=O), 1500, 1356, 760, 690 cm^{-1}. NMR data are given in Table 1. The column was then eluted with dichloromethane–methanol (5:1) to give 0.39 g (20%) of 4-cyano-1-(4-cyano-1-phenyl-pyrazol-3-ylmethyl)-5-methyl-1,2-dihydropyrazol-3-one 6 ($R_F = 0.4$), m.p. 213–214°C (chloroform). Anal. $C_{21}H_{16}N_6O$: C, H, N. MS [IP 70 eV; m/z (% rel. int.)]: 380 (9, M), 182 (100), 77 (39, C_6H_5). IR (KBr): 2232 (C≡N), 1684 (C=O), 1546, 1499, 762, 691 cm^{-1}. δ_H (DMSO-d_6) 9.28 (1 H, s, H-5″), 9.71 (2 H, d with fine structure, H-2‴), 7.57 (1 H, t, H-4‴), 7.48 (5 H, m, H-2′, H-3′ and H-4′), 7.26 (2 H, d with fine structure, H-3‴), 5.26 (2 H, s, CH_2), 2.64 (3 H, s, CH_3). δ_C (DMSO-d_6) 162.2 (C-3), 158.3 (C-5), 149.1 (C-3″), 138.1 (C-1‴), 135.5 (C-5″), 133.0 (C-1′), 129.9 (C-3′ or C-3‴), 129.5 (C-3‴ or C-3′), 129.1 (C-4′ or C-4‴), 128.2 (C-4‴ or C-4′), 127.0 (C-2′), 119.2 (C-2″), 113.9 (C≡N), 112.1 (C≡N); 92.2 (C-4″), 81.0 (C-4), 43.0 (CH_2N), 12.6 (CH_3).

Similar results were obtained when deuteriobenzene was used as the solvent. When the reaction was followed by ^1H NMR spectroscopy, 2-cyano-3-phenylazo-2-butanol 2 was observed. The relative amount reached a maximum of 20% after 8 h. At this time the reaction mixture contained 40% of unchanged starting material 4 and 40% of a 3:1 mixture of 3 and 6. At this time the NMR data of 2 were as follows. δ_H(CDCl$_3$) 2.05 (s, 3 H, CH_3), 7.50 and 8.00 (m, 3 H and 2 H, C_6H_5), 9.95 (s, 1 H, CHO). δ_C (CDCl$_3$) 12.7 (CH_3), 113.1 (C≡N), 119.1 (C=CCH$_3$), 124.2, 128.5, 129.1, 137.7, 172.5 (C=CCH$_3$), 185.1 (CHO).

X-ray crystallography of 3. A single crystal 0.2 × 0.2 × 0.4 mm was selected for the diffraction study. An Enraf–Nonius CAD4 diffractometer was used for the data collection. The source was Mo Kα radiation obtained from a graphite monochromator. The crystal was cooled to 122(1) K during the data collection with an Enraf–Nonius gas flow low temperature device. The intensities were measured using an ω–2θ scan with scan

width $\Delta\omega = 0.8 + 0.35\tan\theta$ for reflections in the octants $h + k + l$ with $1° < \theta < 30°$. Unit cell parameters were determined from a least-squares refinement of the setting angles for 18 reflections in the θ range $14°$ to $20°$. The variations in the repeated measurements of three standard reflections were within 0.5%. Data reduction included corrections for Lorentz, polarization and background effects.

Crystal data. $C_{22}H_{16}N_6O$, $M_r = 380.408$, triclinic, space group $P\bar{1}$, $a = 13.253(2)$ Å, $b = 7.151(2)$ Å, $c = 10.417(5)$ Å, $\alpha = 75.48(3)°$, $\beta = 77.93(3)°$, $\gamma = 82.52(2)°$, $V = 931.4(5)$ Å^3, $D_c = 1.356$ g cm^{-3}, $Z = 2$.

A total of 3438 reflections with $|F|^2 > 2\sigma(|F|^2)$ were considered observed and used for the structure solution and refinement. The structure was solved by direct methods using SHELXS-86[21] and refined by least-squares minimizing $\Sigma w(|F_o|) - (|F_c|)^2$, $w^{-1} = \sigma_{cs}^2(F) + 0.0006$ $|F|^2$. After anisotropic displacement parameters had been introduced a $\Delta\rho$ map showed the positions of all the hydrogen atoms in the structure. The positional parameters for the H atoms were refined and they were given a fixed isotropic temperature factor of 2.0 Å^2. The final residuals were $R = 0.038$ and $R_w = 0.048$ for the 310 parameters $S = [\Sigma w\Delta F^2/(n - m)] = 1.34$ and max. shift $\times \sigma$.

The crystallographic computations were performed with the SDP-system.[22] Fractional coordinates for all atoms and anisotropic displacement parameters have been deposited at the Cambridge Crystallographic Data Centre.

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