The Reaction of Cyclohexanone Azine with Cyanoacetic Acid–Acetic Anhydride

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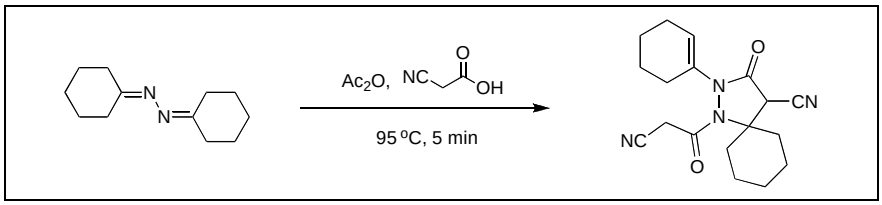

The reaction of cyclohexanone azine with a reagent produced by brief heating of cyanoacetic acid with acetic anhydride produced a highly substituted dihydropyrazolone.

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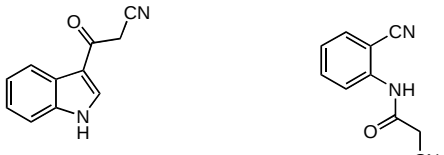
INTRODUCTION

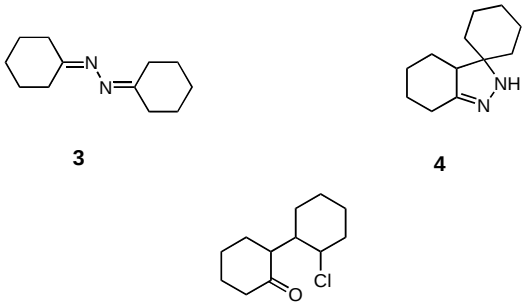
The reagent which can quickly be prepared from cyanoacetic acid and acetic anhydride (10 min, 95 °C) has been demonstrated to be a powerful means for *N*- and *C*-cyanoacetylation [1,2]. Thus, molecules like **1** (from indole) and **2** (from 2-cyanoaniline) can readily be prepared (Figure 1).



1 **2**

Figure 1

Currently there is a strong interest in the synthesis and biological properties of pyrazoles [3-6], and in this context we contemplated hydrazones and azines as readily available precursors to such systems. As a first probe, the azine **3** of cyclohexanone was selected because this molecule is known to be convertible into the hexahydro-indazole derivative **4** (a 4,5-dihydropyrazole) by reaction with oxalic acid, as was first reported by Stollé and Hanusch in 1930 [7]. The structure of **4** was later confirmed by Kost and Grandberg [8] and it was also independently prepared from **5** [9] (Figure 2).



3 **4**

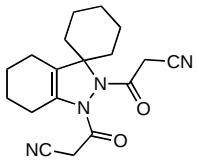
5

Figure 2

RESULTS AND DISCUSSION

Exposure of the azine **3** to the standard reagent (cyanoacetic acid dissolved for 5 min in acetic anhydride at 95 °C) at 40 °C gave, after work-up, a product, $C_{18}H_{22}N_4O_2$, in 40-80% yield (depending on the conditions), where clearly two units of the reagent had been incorporated. Bearing in mind the conversion of **3** into **4** on acid treatment, we initially considered structure **6** for this product. However since the ^{1}H NMR spectrum revealed the presence of a typical alkenic CH-signal, this assignment was reconsidered and structure **7** was considered as a possible structure. Further NMR analysis contradicted even this hypothesis and the molecule was therefore subjected to an X-ray analysis which gave conclusive evidence for the 4,5-dihydro-5*H*-pyrazol-3-one structure **8** (Figure 3). Details of the structural analysis are given in the Experimental Section and a Chem3D representation of the molecule is shown in Figure 4. There are several intriguing features of the structure which merit comment.

There are two amide units in the structure **8** but they are quite different. The nitrogen of the five-membered ring amide is, as one would anticipate, essentially planar, with the sum of the angles around the nitrogen being 357.8°. However, the adjacent cyanoacetamide nitrogen is far



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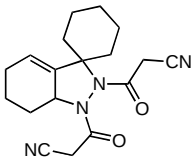

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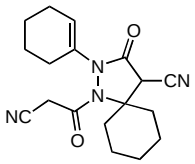


8

Figure 3

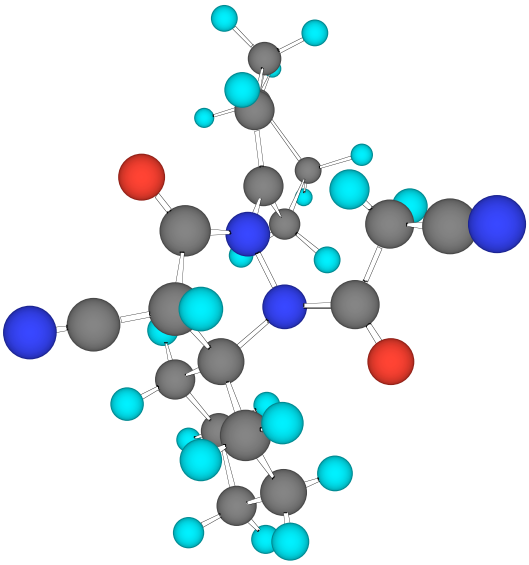
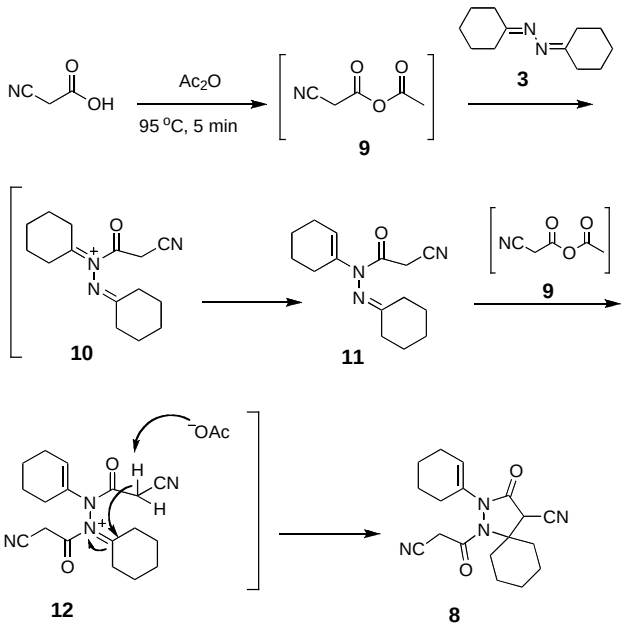


Figure 4 Chem3D representation of compound **8** using the atomic co-ordinates established by X-ray analysis.

from planar, with the sum of its angles being 344.7° – substantially pyramidalised. There are two copies of the molecule in the asymmetric unit, which from the choice made are an enantiomorphic pair. The five-membered dihydropyrazolone ring takes an envelope conformation, with the spiro carbon being 0.634 and 0.621 Å out of the average plane of the other four atoms in the two forms.

Scheme 1 shows a plausible mechanism for the formation of pyrazolone derivative **8**. Imine *N*-acylation of azine **3** by the reagent **9** which is prepared from cyanoacetic acid and acetic anhydride, produces the iminium salt **10**, which by deprotonation, would then give an intermediate enamide of structure **11**. A second *N*-acylation of the remaining imine **11** followed by intramolecular cyclisation due to the acidity of the cyanoacetamide hydrogen (arrows on **12**) would lead to **8**. In this context, the reported formation of 4-cyano-3-pyrazolidone from the corresponding hydrazone [10] and also the purported formation of 3-aryl-4,5,6,7-tetra-hydroindazoles upon treatment of *N*-cyclohexylidene-cyanoacetyl hydrazide with benzaldehyde derivatives [11] is of considerable interest.

Scheme 1



The ^{13}C-NMR spectrum of **8** indicated that it is unstable in solution, because the spectrum of **8** in DMSO solution changed with time. Thus the 18 original signals were slowly replaced by a new set of 18 signals. Thus, for instance, the signal for the spirocyclic carbon atom in **8** at 73.1 ppm was slowly replaced by a new signal at 60.2 ppm.

The same changes were observed in an ethanol solution, but over a longer period of time. However, with the addition of water to the ethanol solution these changes occurred faster. The conversion could be completed by heating an aqueous alcoholic solution of **8** to 75 °C when cooling resulted in precipitation of a product in 80% yield. The changed product was shown to have the elemental composition $C_{15}H_{21}N_3O$ and was assigned structure **13** (Figure 5). Thus, the NMR spectrum of **13** showed that the cyanoacetyl unit was absent, but rather surprisingly, the enehydrazide functionality was intact – it had not been hydrolysed.

Heating compound **8** at reflux in aqueous ethanol for a longer period did bring about further hydrolysis and the resulting bicyclic hydrazide **14** could be isolated in 70% yield. The structure was initially established by a consideration of spectroscopic data – for example, the

spirocyclic carbon atom resonated at 63.3 ppm and the corresponding carbon in **15** [12] resonated at 62.3 ppm (Figure 5). The structure of **14** was confirmed by an X-ray analysis, the details of which are given in the Experimental Section and a Chem3D representation of the molecule is shown in Figure 6. Here again, there is interest in the three different nitrogen situations: in addition to the nitrile nitrogen, there is a five-membered amide nitrogen and a hydrazine nitrogen in a five-membered ring. The amide nitrogen is perfectly planar, with the sum of angles being 360.1°. The hydrazine nitrogen has three angles (107.4°, 106.9° and 103.8°) which are very close to those around ammonia (107°), the smallest being the internal ring angle.

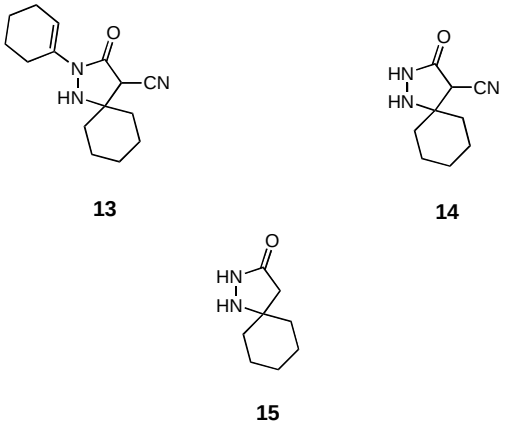


Figure 5

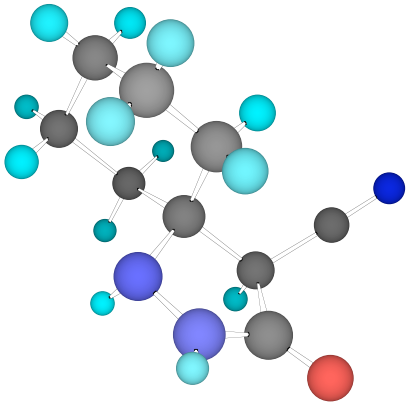


Figure 6 Chem3D representation of compound **14** using the atomic co-ordinates established by X-ray analysis.

EXPERIMENTAL

NMR data were recorded on a Bruker DPX at 300.1 MHz for ^{1}H and 75.5 MHz for ^{13}C, respectively. IR spectra were acquired on a Perkin-Elmer FT-IR 1600 spectrophotometer. Elemental analyses were performed by LSM Lab, Uppsala, Sweden. Melting points were determined on a Leica Kofler hot stage or a Büchi B-545 capillary melting point apparatus and are uncorrected. Data for the two X-ray analyses have been deposited at the Cambridge Crystallographic Data Centre under the CCDC numbers 669439 (compound **8**) and 669440 (compound **14**) and can be obtained free of charge *via* www.ccdc.cam.ac.uk/data_request/cif.

Cyclohexanone azine (3). This compound was prepared according to ref. [13], as yellow crystals, mp 33-34 °C (lit [13] 35 °C); IR (neat) 2935, 2919, 2850, 1630, 1436, 1313, 1130, 988 cm^{-1}.

4-Cyano-1-cyanoacetyl-2-(cyclohexen-1-yl)-1,2-diazaspiro-[4.5]decan-3-one (8). Cyanoacetic acid (6.2 g, 72.9 mmol) and Ac_2O (20 mL) were heated to 95 °C for 5 min. The solution was cooled to 40 °C and cyclohexanone azine [13] (7 g, 36.5 mmol) was added. The reaction mixture was heated to 70 °C for 15 min. After leaving at rt overnight the product had formed as a precipitate which was collected, washed with a small volume of acetic acid, and dried at room temperature in the air to yield **8** (5.2 g, 44%) as a white solid, mp 152-153 °C; IR (neat) 2933, 2864, 2257, 2250, 1714, 1664, 1324, 1207 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 5.77-5.71 (m, 1H, CH), 4.89 (s, 1H, CH), 3.98 (d, J_{AB}=19.3 Hz, 1H, CH_A), 3.80 (d, J_{AB}=19.3 Hz, 1H, CH_B), 2.44-1.21 (m, 18H, 9 CH_2); ^{13}C NMR (DMSO-d_6) δ 168.1 (s), 164.2 (s), 133.9 (s), 119.4 (d), 115.4 (s), 114.1 (s), 73.1 (s), 46.8 (d), 31.5 (t), 31.4 (t), 28.2 (t), 24.3 (t), 24.2 (t), 23.6 (t), 22.5 (t), 21.8 (t), 21.7 (t), 21.0 (t). Calcd for $C_{18}H_{22}N_4O_2$: C, 66.24; H, 6.79; N, 17.16%. Found: C, 66.20; H, 6.79; N, 17.25%.

Crystal structure determination. Data were collected on a Bruker Smart Apex CCD diffractometer. Wavelength: 0.71073 Å; Temperature: 100(2) K; Reflections collected/unique: 26285/6927 [R(int) = 0.0759]; Completeness to theta = 26.37: 99.7%; Space group: C2/c; a = 27.216(2) Å; b = 9.5770(9) Å β = 103.073(2) deg.; c = 26.798(2) Å; V= 6803.8(11) Å^3; Z=16; R indices [I>2σ(I)]: R1 = 0.0548, wR2 = 0.1020; R indices (all data): R1 = 0.1020, wR2 = 0.1151.

The structure was solved with SIR2004 [14] and refined with SHELXL97 [15]. There were two molecules in the asymmetric unit.

2-Cyclohex-1-enyl-3-oxo-1,2-diaza-spiro[4.5]decane-4-carbonitrile (13). Compound **8** (2.0 g), ethanol (35 mL) and H_2O (5 mL) were heated to 75 °C for 5 min. After 6 h at rt the product had formed as white crystals which were collected, washed with chilled ethanol and dried at room temperature to yield **13** (1.3 g, 80%), mp 113-115 °C; IR (neat) 3212, 2921, 2858, 2249, 2235, 1686, 1673, 1378 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 5.97 (s, 1H, NH), 5.82-5.77 (m, 1H, CH), 4.15 (s, 1H, CH), 2.45-1.14 (m, 18H, 9 CH_2); ^{13}C NMR (DMSO-d_6) δ 163.9 (s), 134.6 (s), 115.6 (s), 114.8 (d), 60.2 (s), 47.5 (d), 33.2 (t), 30.2 (t), 25.3 (t), 24.8 (t), 23.5 (t), 22.0 (t), 21.4 (t), 21.3 (t), 21.3 (t). Calcd for $C_{15}H_{21}N_3O$: C, 69.47; H, 8.16; N, 16.20%. Found: C, 69.15; H, 8.16; N, 16.21%.

4-Cyano-1,2-diazaspiro[4.5]decan-3-one (14). Compound **8** (2.0 g), ethanol (35 mL) and H_2O (5 mL) were heated to reflux for 2.5 h. After leaving at rt overnight the product had formed as a precipitate which was collected, washed with ethanol, and dried at room temperature in the air to yield **14** (1.4 g, 70%) as a yellow solid, mp 92 °C; IR (neat) 3225, 3078, 2938, 2857, 2244, 1691, 1453, 910 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.62 (s, 1H, NH), 5.43 (s, 1H, NH), 3.88 (s, 1H, CH), 1.83-1.11 (m, 10H, 5 CH_2); ^{13}C NMR (DMSO-d_6) δ 168.6 (s), 115.9 (s), 63.3 (s), 45.3 (d), 33.6 (t), 30.5 (t), 24.8 (t), 21.3 (t), 21.3 (t). Calcd for $C_9H_{13}N_3O$: C, 60.32; H, 7.31; N, 23.45%. Found: C, 60.38; H, 7.31; N, 23.38%.

Crystal structure determination. Data were collected on a Bruker Smart Apex CCD diffractometer. Wavelength: 0.71073 Å; Temperature: 100(2) K; Reflections collected/unique: 14039/2132 [R(int) = 0.0491]; Completeness to theta = 25.00: 100.0%; Space group: C2/c; a = 8.0700(6) Å; b = 9.9362(8) Å; c = 22..0345(18) Å; V= 1766.8(2) Å^3; Z= 8; R indices [I>2σ(I): R1 = 0.0457, wR2 = 0.1058; R indices (all data): R1 = 0.0555, wR2 = 0.1108.

The structure was solved with SIR2004 [14] and refined with SHELXL97 [15].

REFERENCES

[1] Slaett, J.; Romero, I.; Bergman, J. *Synthesis* **2004**, 2760-2765.

[2] Slaett, J.; Janosik, T.; Wahlstroem, N.; Bergman, J. *J. Heterocycl. Chem.* **2005**, *42*, 141-145.

[3] Elgemeie, G. H.; Zaghary, W. A.; Amin, K. M.; Nasr, T. M. *Nucleos. Nucleot. Nucl.* **2005**, *24*, 1227-1247.

[4] Chornous, V. O.; Bratenko, M. K.; Vovk, M. V. *Zhur. Org. Farm. Khim.* **2003**, *1*, 35-50.

[5] Orth, R. E. *J. Pharm. Sci.* **1968**, *57*, 537-556.

[6] *See yearly reviews as chapter 5.4 in Prog. Heterocycl. Chem.*

[7] Stollé, R.; Hanusch, F. *Chem. Ber.* **1930**, *63*, 2211-2215.

[8] Kost, A. N.; Grandberg, I. I. *Zh. Obshch. Khim.* **1955**, *25*, 2064-2070.

[9] Terent'ev, A. P.; Kost, A. N.; Saltykova, Y. V.; Ershov, V. V. *Zh. Obshch. Khim.* **1956**, *26*, 2925-2928.

[10] Ovcharenko, V. V.; Terent'ev, P. B.; Avetisyan, A. A.; Kagramanyan, A. A. *Khim. Geterotsikl. Soedin.* **1995**, 1525-1530.

[11] Hussein, A. H. M. *Z Naturforsch., B.* **1998**, *53*, 488-494.

[12] Johnson, P. Y.; Hatch, C. E., III. *J. Org. Chem.* **1975**, *40*, 3502-3510.

[13] Perkin, W. H., Jr.; Plant, S. G. P. *J. Chem. Soc.* **1924**, *125*, 1503-1513.

[14] Burla, M. C.; Caliandro, R.; Camalli, M.; Carrozzini, B.; Cascarano, G. L.; De Caro, L.; Giacovazzo, C.; Polidori, G.; Spagna, R. *J. Appl. Cryst.* **2005**, *38*, 381-388.

[15] Sheldrick, G. M., (1997) SHELXS1997. Program for crystal structure solution. University of Göttingen, Germany.