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Synthesis, characterisation and crystal structure of 3,5-dimethylpyrazole-1-carbothioic acid amide

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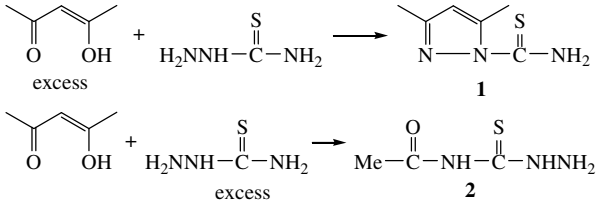
3,5-Dimethylpyrazole-1-carbothioic acid amide was obtained (along with acetyl thiosemicarbazide) by the condensation of acetylacetone with thiosemicarbazide and characterised through X-ray diffraction and spectral studies.

Thiosemicarbazones and their metal complexes have attracted considerable attention because of their pharmacological applications.[1] Monothiosemicarbazones (monotsc) $(RR^1)C{=}N{-}NH{-}C(=S)NH_2$ (where R and R^1 are H, substituted or non-substituted alkyl or aryl) have been synthesised by a reaction of thiosemicarbazide (tsc) with a desired aldehyde or ketone.[2] However, attempts to prepare dithiosemicarbazones (ditsc) of 1,3-dicarbonyls through similar reactions were unsuccessful. A mixture of products (acyl thiosemicarbazide, monotsc, ditsc and pyrazole derivative) were formed,[3] which were poorly characterised because of their low solubility.

We reinvestigated the reaction of acetylacetone with tsc. Earlier, Gingras and coworkers[3] identified only acetylthiosemicarbazide **2** from the same reaction. The product is expected to be formed from the cleavage of acetylacetone. However, no mono, ditsc or pyrazole derivative could be obtained. Simply by reversing the mode of mixing of reactants, we isolated two products: new cyclic five-membered **1** and already known **2** (Scheme 1)† from the reaction of acetylacetone with tsc. These compounds were characterised by elemental and spectral analysis. The structure of **1** was confirmed by X-ray crystallography.

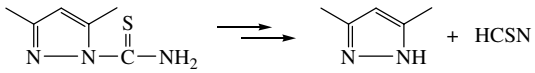
The hot solution of tsc in dilute HCl on addition to a methanolic solution of acetylacetone gave white crystalline product, mp 160 °C. As studied by ^{1}H NMR ($CDCl_3$) **1** was found to hydrolyse in solution to **3** (Scheme 2). A freshly prepared solution of **1** exhibits two singlets at δ 2.18 (3H, Me) and 2.73 (3H, Me), one singlet at δ 5.99 (1H, =CH) along with two exchangable broad singlets at δ 7.26 and 8.62 due to NH_2 protons in its ^{1}H NMR spectrum. The ^{1}H NMR spectrum of this compound changes on long standing. A new singlet also appeared in the centre of two methyl signals at δ 2.41 (< 3%).



Scheme 1

After two days, the intensity of a new signal at δ 2.41 was significantly enhanced at the expense of original Me protons. However, total methyl protons to olefinic proton ratio is retained at 6:1. Finally, during the period of one week, both the methyl signals merge into the central signal, strongly indicating the equivalence of both the methyl protons.

It is expected that **1** undergoes hydrolysis to pyrazole derivative **3** and HNCS on long standing in solution (Scheme 2). The



Scheme 2

formation of HNCS from tsc is already known.[4] The cleavage of tsc to a pyrazole derivative has also been observed earlier. The reaction of 1,3-diphenyl-1,3-propanedione with tsc yields 3,5-diphenylpyrazole along with monotsc.[3] Similarly, pyrazoles are also obtained from the reaction of 1,3-dicarbonyl compounds with semicarbazides.[3,5]

It was shown by X-ray diffraction analysis of **1**‡ that there are two crystallographically independent molecules in the unit cell. They slightly differ from each other in bond distances and bond angles, specially, for C–S and C–N (amine) distances.

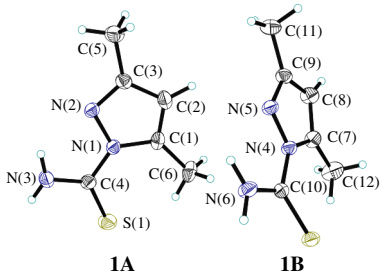


Figure 1 ORTEP drawing of two independent molecules of **1** showing their labelling scheme.

† *Synthesis of* **1**. A hot solution of tsc (0.92 g, 10 mmol) in dilute HCl (2 M, 10 ml) was slowly added to a methanolic solution (10 ml) of acetylacetone (0.51 ml, 5.0 mmol). White crystalline X-ray quality product separated out after standing overnight in a refrigerator, which was filtered at the pump washed with cold water and ethanol and dried in a vacuum. Yield 40%, mp 160 °C. ^{1}H NMR ($CDCl_3$) δ: 2.18 (s, 3H, Me), 2.73 (s, 3H, Me), 5.99 (s, 1H, =CH), 7.26 (1H, NH, exchanges with D_2O) and 8.62 (1H, NH, exchanges with D_2O). IR (KBr, ν/cm^{-1}): 3386, 3242 and 3153 (N–H stretching), 1598, 1571 ($\nu_{C=C}$, $\nu_{C=N}$ and δ_{N-H}), 800 ($\nu_{C=S}$). Found (%): C, 46.4; H, 5.2; N, 26.6. Calc for $C_6H_9N_3S$ (%): C, 46.5; H, 5.8; N, 27.1.

Synthesis of **2**. Reversing the mode of addition of the reactants under analogous conditions resulted in the formation of **2**, mp 181 °C. IR (KBr, ν/cm^{-1}): 3384–3134 (br., ν_{N-H}), 1640–1620 ($\nu_{C=O}$),[6] 817 ($\nu_{C=S}$), 1545 ($\nu_{C=C}$ and $\nu_{C=N}$). Found (%): C, 27.3; H, 5.7; N, 31.9. Calc. for $C_3H_7N_3OS$ (%): C, 27.1; H, 5.3; N, 31.5.

Table 1 Important H-bonding interactions in compound **1**.

Type of interaction	X···Y	H···Y	∠X–H···Y
N(3)–H(31)···N(2)	2.594(5)	2.04	119
N(6)–H(61)···N(5)	2.618(4)	2.21	105
N(3)–H(31)···N(5i)	3.178(4)	2.56	127
N(6)–H(61)···N(2i)	3.158(4)	2.34	139
N(3)–H(32)···S(2ii)	3.459(4)	2.64	158
N(6)–H(62)···S(2iii)	3.441(3)	2.55	164

Molecule **1A** (lower atom numbers, Figure 1) has a C–S bond length 0.02 Å shorter and a C–N bond length 0.01 Å longer than the corresponding distances in molecule **1B** (higher atom numbers, Figure 1). All bond distances and bond angles are within the expected ranges. The two molecules are rotated by almost 50° with respect to each other. The heterocyclic rings in both the molecules are planar and make dihedral angles of 8° and 12° with their respective thioamide groups.

In the unit cell, the molecules of **1** are held to each other by strong inter- and intramolecular H-bonding interactions. Both the thioamide nitrogens N(3) and N(6) act as H-bond donors whereas S(2), N(2) and N(5) are behaving as H-bond acceptors (Figure 1). The amine nitrogen N(3) of molecule **1A** acts as a triple H-bond donor forming one intramolecular H-bond with the ring nitrogen N(2) and two intermolecular H-bonds with N(5) and S(2) of molecule **1B** (Figure 2, Table 1). Similarly, the amine nitrogen N(6) of molecule **1B** is behaving as a triple H-bond donor with one intramolecular bond to its ring nitrogen N(5) and one intermolecular H-bond to N(2) of molecule **1A**. However, its second intermolecular H-bond is also with the sulfur atom S(2) of its own thioamide group. Thus, S(1) of molecule **1A** is not undergoing any H-bonding interaction except for a weak intramolecular C(6)–H(6A)···S(1) interaction. The corresponding C(12)···S(2) interaction is also present there. These interactions

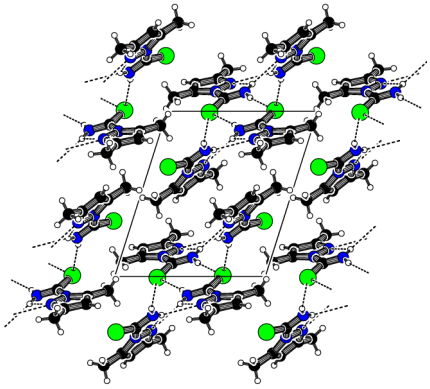


Figure 2 Important H-bonding interactions down the *a* axis.

‡ *X-Ray diffraction data for* **1**. At 293 K crystals of $C_6H_9N_3S$ (M = 155.22) are triclinic, space group *PI*, a = 8.461(5), b = 9.393(5) and c = 10.994(5) Å, α = 69.70(5)°, β = 73.21(5)° and γ = 76.85(5)°, V = 776.6(7) Å^3, Z = 2, d_{calc} = 1.328 g cm^{-3}; μ = 0.343 mm^{-1}. Crystal size, 0.15×0.19×0.10 mm. The data were collected on a Siemens P4 diffractometer with graphite monochromated MoKα radiation (λ = 0.71609 Å), 2.03 < θ < 25.0°, 0 < h < 9, –10 < k < 10. The structure was solved by direct methods and subsequent difference Fourier syntheses and refined by full-matrix least-squares on F^2 with SHELXLTL.[7] Lorentz and polarization corrections were applied, but no absorption correction was applied. All hydrogens were attached geometrically and were not refined. An anisotropic refinement for all the non-hydrogen atoms finally converged with a R factor of 0.0511 for observed and 0.0573 for all reflections. The H-bonding calculations, torsion and dihedral angles and plane were calculated using PARSI.[8]

CCDC 611159 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2007.

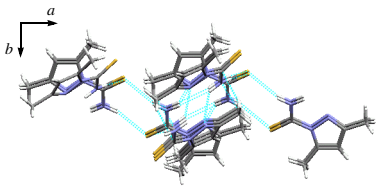


Figure 3 Formation of N(6)···S(2) H-bonded centrosymmetric layers and a cavity down the *c* axis.

[except for N(6)···S(2)] give rise to the formation of layers down the *c* axis. These layers are held to each other by the N(6)–H(62)···S(2) intermolecular interaction (Figure 3). In the centre of each layer, an H-bonded cavity is formed. Apart from these H-bonding interactions, two centrosymmetrically related molecules **1A** show face-to-face π–π interactions between them with a centre-to-centre distance of 3.77 Å. The closest distance between two centrosymmetric molecules **2** is 4.93 Å.

Therefore, the addition of acetylacetone to the hot solution provides a facile method for the synthesis of pyrazole-1-carbothioic acid amide.

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