Synthesis and Structure of 3-Methyl-1-phenyl-4-sulfhydrylbenzylidene-5-thiopyrazolone

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The synthesis of 3-methyl-1-phenyl-4-sulfhydrylbenzylidene-5-thiopyrazolone (**4**) is reported. It is a potential sequestering agent as well as a new example of a β-dithiocarbonyl compound. The structure of **4** is unambiguously established by conversion to 4-benzoyl-3-methyl-1-phenyl-5-pyrazolethiol (**3**).

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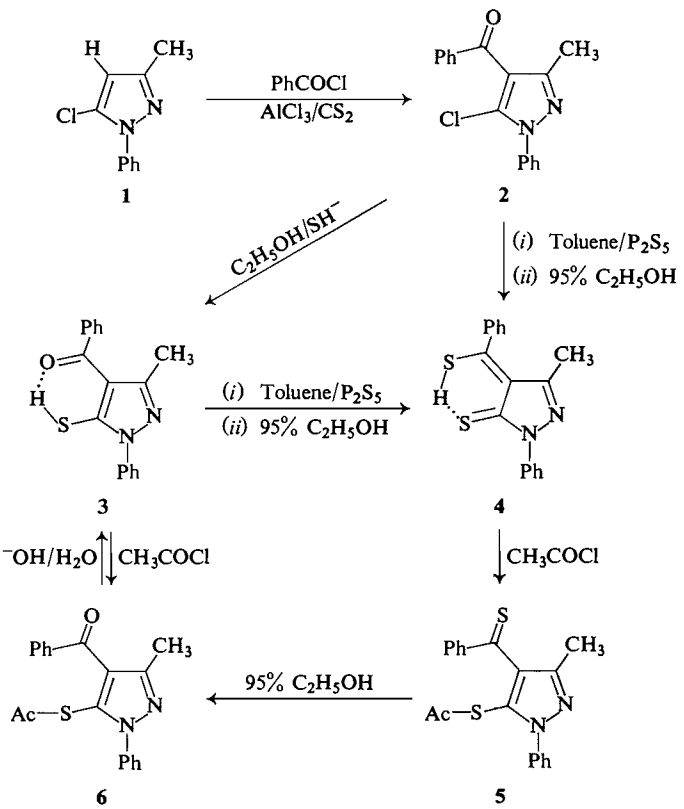
In recent years, there has been an increasing interest in the application of sulfur-containing ligands to trace-metal analysis. A number of successful syntheses of both monothio (1–4) and dithio analogs (5–7) of the β-dicarbonyl chromophore have been reported. I now report the preparation of a new β-dithiocarbonyl system.

A 4-acyl pyrazole substrate was selected because of the well established value of these systems as sequestering agents (8, 9).

Treatment of 4-benzoyl-5-chloro-3-methyl-1-phenylpyrazole (**2**) or 4-benzoyl-3-methyl-1-phenyl-5-pyrazolethiol (**3**) with phosphorus pentasulfide in hot toluene gives 3-methyl-1-phenyl-4-sulfhydrylbenzylidene-5-thiopyrazolone (**4**) in 10 and 15% yields respectively (see Scheme 1).

The i.r. spectrum of **4** exhibits a broad, weak absorption band at 2400 cm^{-1} which does not change upon dilution, in accord with an intramolecularly H-bonded thiol. The n.m.r. spectrum displays a sharp singlet at -0.1 τ (1H) which is



SCHEME 1

readily removed from the spectrum when the sample is shaken with D_2O, thus further substantiating the thiol moiety. Also evident in the n.m.r. are a broad signal centered at 2.4 τ (10H) and a singlet at 8.2 τ (3H) assigned to the two phenyl rings and the C-3 methyl group respectively.

The high resolution mass spectrum of **4** shows the molecular ion at *m/e* 310.0586 ($C_{17}H_{14}N_2S_2$) and an abundant ion at *m/e* 121.0113 (C_7H_5S) in agreement with a thiobenzoyl group. Other abundant ions occur at *m/e* 309 ($M^{\cdot+}$-H), 277 ($M^{\cdot+}$-SH), 105 (PhN_2^+), 77 ($C_6H_5^+$), and 51 ($C_4H_3^+$) all of which were determined at low resolution. The loss of a hydrogen radical ($M^{\cdot+}$-1) and an ·SH radical ($M^{\cdot+}$-33) from the molecular ion are processes observed in the mass spectrum of enethiolphenone **3** and have been observed in other enethiol systems (1).

The u.v. spectrum of **4** exhibits maxima at 235 (ε 15 900), 310 (ε 5600), and 538 nm (ε 228), the latter of which shifts to 450 nm (ε 3480), in the presence of dilute sodium hydroxide. Hopefully, this base-induced hypsochromic shift will prove useful in characterizing other β-dithiocarbonyl compounds. No analogous shift is observed in the u.v. spectrum of enethiolphenone **3**.

When the red crystalline dithiopyrazole **4** is refluxed in acetyl chloride, the blue, oily monoacetate **5** is obtained. Its i.r. spectrum displays an intense enethiolacetate carbonyl bond (4) at 1720 cm^{-1}. The n.m.r. spectrum of this dithioacetate exhibits two sharp singlets (3H each) at 7.9 and 7.8 τ confirming monoacetylation.

The mass spectrum of the acetylated dithio adduct **5** does not show a molecular ion but is essentially identical to that of **4** with an additional ion at *m/e* 43 (CH_3CO^+). The u.v. spectrum displays maxima at 595 (ε 100), 310 (ε 10 000), and 232 nm (ε 20 000).

By momentarily refluxing the dithioacetate **5** in 95% ethanol a quantitative conversion to the colorless crystalline monothioacetate **6** is accomplished. The i.r. spectrum of **6** shows intense absorption bands at 1720 and 1660 cm^{-1} in agreement with enethiolacetate and enaminophenone functions respectively. The n.m.r. spectrum exhibits two methyl singlets at 7.9 and 7.7 τ. A high resolution mass spectrum established the molecular ion as 336.0929 a.m.u. ($C_{19}H_{16}N_2O_2S$) showing no ion at *m/e* 121 and displaying abundant ions at *m/e* 105 ($C_7H_5O^+$, $C_6H_5N_2^+$) and 43 (CH_3CO^+). The mass spectrum of **6** is essentially identical to that of **3** with an additional ion at *m/e* 43.

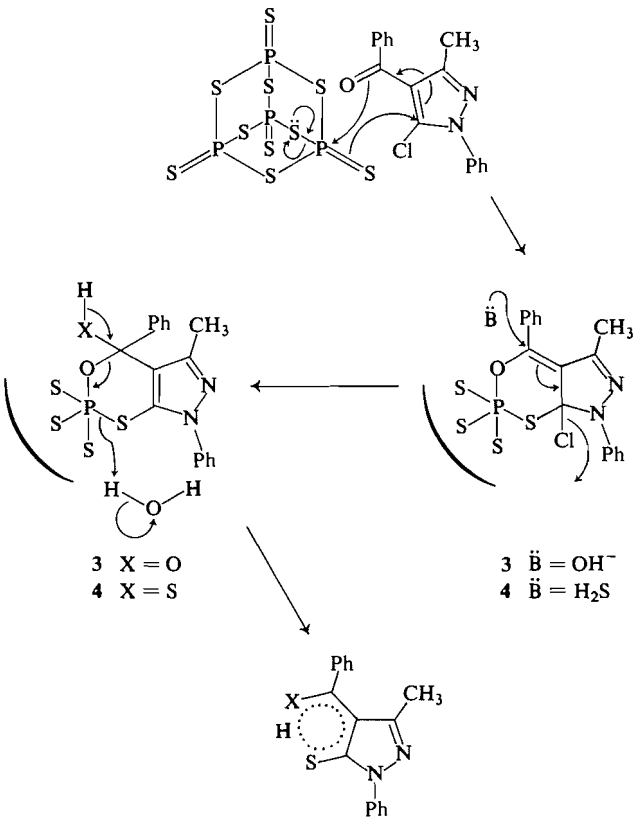
Since the instability of thioketones is well established (10), the mild hydrolysis of **5** to **6** lends chemical support to the formulation of **5** as a thiophenone.

The monothio acetate **6** may also be conveniently prepared by treating **3** with acetyl chloride, thus unambiguously establishing the skeleta of **6**, **5**, and **4** and conclusively establishing **4** as the desired dithioketo system.

The facile conversion of the monothioacetate **6** to the enethiolphenone **3** in dilute aqueous sodium hydroxide provides chemical evidence for the formulation of **6** (and therefore **5**) as an *S*-acetate, since this functional group is particularly unstable to base (11).

The n.m.r. resonance positions of the C-3 methyl group in the chlorophenone **2**, the enethiolphenone **3**, and the dithiopyrazole **4** are 7.5, 7.9, and 8.2 τ respectively. This can be interpreted to indicate progressively decreasing π-electron density along the C_4—C_5 bond of the pyrazole nucleus, thereby resulting in progressively lesser deshielding of the C-3 methyl group by the π-system of the ring. Hence, I have formulated the dithiopyrazole as tautomer **4**. Such a formulation is in accord with expectation. Tautomeric forms involving a thiophenone are essentially precluded by the instability of thioketones (10). Further, thioamides are generally quite stable (12) and the resonance energy of the pyrazole nucleus appears to be rather small (9) so that the ring itself provides little energy for enolization of the thiolactam thiocarbonyl.

If the residue from the reaction of chlorophenone **2** with phosphorus pentasulfide is recrystallized from 95% ethanol, excess reagent is hydrolyzed, generating H_2S *in situ*, and red crystals of **4** are obtained in 10% yield. If, however, the residue is washed with several aliquots of 2½% sodium hydroxide solution, no dithiopyrazole **4** is obtained but the enethiolphenone **3** is isolated from the wash solution in 10% yield. Since dissolution of pure dithiopyrazole **4** in aqueous sodium hydroxide does not result in the formation of any enethiolphenone **3**, it is reasonable to propose that some intermediate is formed between P_2S_5 and chlorophenone **2**, which is then decomposed upon work-up to give products



SCHEME 2

dependent upon the nucleophiles present in solution. A proposed mechanism is depicted in formula Scheme 2.

Experimental

General

The i.r. spectra were recorded on a Baird Associates Model 4-55 Double-beam spectrophotometer. The mass spectra were determined with a Bell and Howell/CEC 21-110B spectrometer. The n.m.r. spectra were obtained on a Varian A-60 instrument using TMS as internal standard. The u.v. spectra were recorded using a Coleman Model 124 Hitachi Double Beam spectrophotometer. Melting points were determined on a Fisher–Johns melting point apparatus and are uncorrected. The t.l.c. was carried out on plates of silica gel G (A. G. Merck).

Preparation of 4-Benzoyl-5-chloro-3-methyl-1-phenylpyrazole (2)

The chlorophenone **2** is prepared as described by Michaelis and Rojahn (13) from the chloropyrazole **1** (14). The preparation requires reflux of the appropriate compounds (*vide* formula Scheme 1), in CS_2 for 18 h. If the procedure is modified by allowing the CS_2 to evaporate after refluxing for 15 min, and heating the dry reaction mixture for 5–6 h at 70 °C, the yield, after basification and ether extraction, is 83% as opposed to the reported yield of 65–70%.

Preparation of 3-Methyl-1-phenyl-4-sulfhydrylbenzylidene-5-thiopyrazolone (4)

Purified phosphorus pentasulfide[1] (10 g) (15) and either 4-benzoyl-5-chloro-3-methyl-1-phenylpyrazole (**2**) or 4-benzoyl-3-methyl-1-phenyl-5-pyrazolethiol (**3**) (6 g) (16, 17) were heated in distilled toluene (50 ml) for 3.5 h at 100 °C. The toluene was decanted, evaporated, and the residue recrystallized from 95% ethanol (25 ml). Red needles (650 mg) were obtained after recrystallization to constant m.p. (128–130 °C). The product was homogeneous on t.l.c. (R_F, 0.45) using benzene as eluant. The i.r. bands were present ($CHCl_3$) 2400 and 1600 cm^{-1}; λ_{max} (EtOH) 235 (ε 15 900), 310 (ε 5600) and 538 nm (ε 228). The n.mr. spectrum ($CDCl_3$) showed signals at τ −0.1 (1H, D_2O exchangeable), 2.4 (10H), and 8.2 (3H). The high resolution mass spectrum confirmed the formula as $C_{17}H_{14}N_2S_2$ (molecular ion *m/e* 310.0586).

Preparation of 5-Mercaptoacetyl-3-methyl-1-phenyl-4-thiobenzoylpyrazole (5)

The dithiopyrazole **4** (100 mg) was refluxed in freshly

[1]Reagent grade CS_2 should be used for the preparation of purified P_2S_5 as described in this reference.

distilled acetyl chloride (10 ml) for 1 h. The acetyl chloride was evaporated to give the blue, oily dithioacetate **5**. This oil exhibited two spots on t.l.c. The major spot (R_F, 0.60) using chloroform for elution was due to **5**. The secondary spot proved to be identical with authentic **6** when double spotted. The i.r. bands ($CHCl_3$) were present at 1720 and 1600 cm^{-1}; λ_{max} (EtOH) 232 (ε 20 000), 310 (ε 10 000) and 595 nm (ε 100).

The n.m.r. spectrum ($CDCl_3$) showed signals at τ 2.3 (10H), 7.8 (3H), and 7.9 (3H).

Preparation of 4-Benzoyl-5-mercaptoacetyl-3-methyl-1-phenylpyrazole (6)

Enethiolphenone **3** (100 mg) was refluxed in freshly distilled acetyl chloride (10 ml) for 1 h. Evaporation of the acetyl chloride, and recrystallization of the residue from benzene/low boiling petroleum ether gave colorless crystals (m.p. 114–115 °C).

The recrystallized product was homogeneous on t.l.c. (R_F, 0.45), using chloroform as eluant. The i.r. bands were present ($CHCl_3$) at 1720, 1660, and 1600 cm^{-1}; λ_{max} (EtOH) 210 (ε 22 000), 260 (ε 16 000) and 270 nm (ε 10 000). The n.m.r. spectrum ($CDCl_3$) displayed signals at τ 2.4 (10H), 7.7 (3H), and 7.9 (3H). The high resolution mass spectrum confirmed the formula as $C_{19}H_{16}N_2O_2S$ (molecular ion *m/e* 336.0929).

Hydrolysis of 5

5-Mercaptoacetyl-3-methyl-1-phenyl-4-thiobenzoylpyrazole (**5**) (44 mg) was heated in boiling 95% ethanol for 2 min. The ethanol was evaporated and the residue recrystallized from benzene/low boiling petroleum ether to give **6** (40 mg). Identity with authentic **6** (*vide supra*) was established by t.l.c., n.m.r., i.r., and a mass spectrum. No depression of m.p. was observed when the sample was admixed with authentic **6**.

Basic Hydrolysis of 6

4-Benzoyl-5-mercaptoacetyl-3-methyl-1-phenylpyrazole (**6**) (52 mg) was added to a solution of methanol (2 ml) – 2½% aqueous sodium hydroxide (8 ml) and the solution gently refluxed. As solid **6** dissolved, the solution turned yellow. After 1 h the solution was acidified and extracted with ether. The ether (dried over $MgSO_4$) was evaporated to give crude enethiolphenone **3** (42 mg).

After recrystallization from 95% ethanol, identity was established with authentic **3** by mixed m.p., t.l.c. and n.m.r. spectra.

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