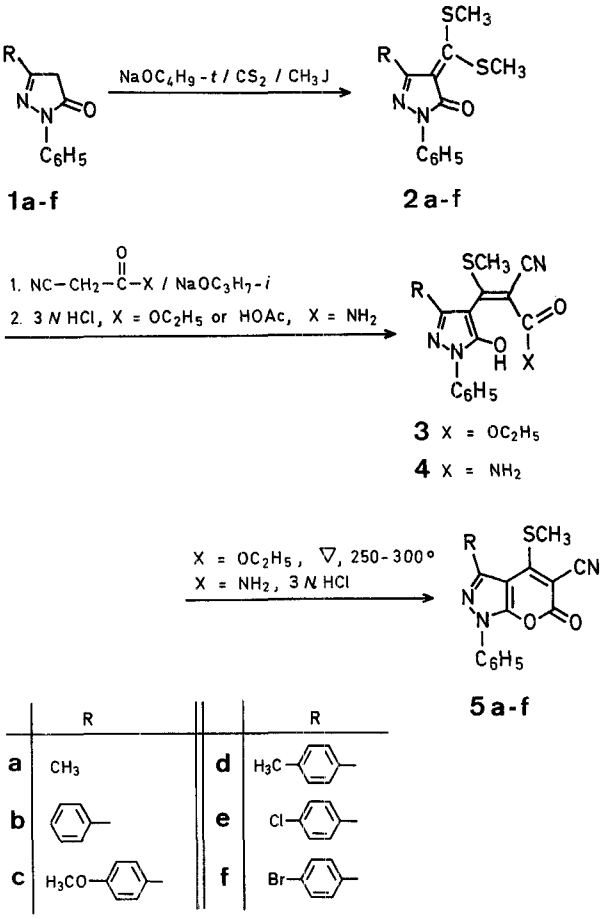

A New General Method for the Synthesis of 1,3-Disubstituted 5-Cyano-4-methylthio-6-oxo-1,6-dihydropyrano[2,3-*c*]pyrazoles Using α-Ketoketene *S,S*-Acetals[1]

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There are only two methods described in the literature for the synthesis of compounds containing the 6-oxo-1,6-dihydropyrano-[2,3-*c*]pyrazoles skeleton. The reaction of the pyrazoline-5-one (**1a**) with carbon suboxide is reported to yield the corresponding 4-hydroxy-6-oxo-1,6-dihydropyrano[2,3-*c*]pyrazole in good yield[2]. The other method involves the thermolysis of acetylhydrazones of ethyl acetoacetate to yield the corresponding 4-methyl-6-oxo-1,6-dihydropyrano[2,3-*c*]pyrazole in poor yield[3]. In continuation of our studies[4] on the synthetic utility of α-ketoketene *S,S*-acetals, we now wish to report a facile new general method for the synthesis of 5-cyano-4-methylthio-1,3-disubstituted-6-oxo-1,6-dihydropyrano[2,3-*c*]pyrazoles (**5a–f**) in excellent yields in one step from **2a–f**.

The previously undescribed ketene *S,S*-acetals (**2a–f**) required in the present investigation were conveniently prepared by reacting **1a–f** with carbon disulphide in the presence of sodium *t*-butoxide followed by *in situ* alkylation with methyl iodide to give **2** in one step in 65–76% overall yields. The I.R. and N.M.R. data of these compounds were fully consistent with the assigned structures (Table, products **2a–f**).

On treatment of **2a** with the sodio derivative of cyanoacetamide (X = NH_2) in boiling isopropanol and subsequent addition of hydrochloric acid, followed by refluxing gave **5a** in 65% yield. The other compounds **5b–f** were similarly prepared in 68–86% yields (Table). The structural proof of **5a–f**, was accomplished by an alternate synthesis of one of these compounds **5b**. Thus **2b**, was treated with ethyl cyanoacetate (X = OC_2H_5) in the presence of sodium isopropoxide, when only an open chain compound **3b** (X = OC_2H_5) was obtained in 69% yield after work-up as described above. However, **3b** underwent cyclization on thermolysis (250–300°) to yield **5b** in 86% yield (m.p., mixture m.p., I.R., and N.M.R.). Also, an open chain compound **4e** (X = NH_2) from the reaction of cyanoacetamide with **2e** was isolated by treating the intermediate sodium salt with dilute acetic acid, which on further refluxing with ethanolic hydrochloric acid (10 min) gave **5e** in identical yields (m.p. and mixture m.p.).

Apparently the cyanoacetamide route is better, as it involves milder reaction conditions and does not necessitate the isolation of either of the intermediates **3** or **4**.

General Method for the Preparation of Ketene *S,S*-Acetals (2a–f): A solution of **1** (0.05 mol) and carbon disulphide (3.8 g, 0.05 mol) in dry dimethylformamide (50 ml) was added dropwise with stirring to an ice cold mixture of sodium *t*-butoxide [prepared by dissolving sodium (2.3 g, 0.1 mol) in *t*-butanol (25 ml) and benzene (100 ml)] and the reaction mixture was allowed to stand at room temperature for 6 h. Methyl iodide (14.2 g, 0.1 mol) was then added with continuous stirring and cooling and the contents were allowed to stand at room temperature for 6 h. The solvents were removed under reduced pressure, and the dry residual solid was treated with cold water to give red, syrupy semisolid which was purified by crystallization from ethyl acetate/hexane.

General Method for the Preparation of Pyrano[2,3-*c*]pyrazoles (3a–f):

To a boiling solution of the sodio derivative of cyanoacetamide, [prepared by dissolving sodium (0.057 g, 0.028 mol) in isopropanol

Table. Preparation of 3-Substituted 4-Bis[methylthio]methylene-5-oxo-1-phenyl-4,5-dihydropyrazoles (**2a–f**) and 3-Substituted 5-Cyano-4-methylthio-6-oxo-1-phenyl-1,6-dihydropyrano[2,3-*c*]pyrazoles (**5a–f**)

Product	Yield (%)	m.p.[a]	Empirical formula[b]	I.R. (KBr)[c] ν_{max} cm^{-1}	^{1}H-N.M.R. ($CDCl_3$)[d] δ ppm	Mass spectrum[e] *m/e* ($M^{\oplus}$)
2a	65	62.3°	$C_{13}H_{14}N_2OS_2$ (278.3)	1650 (C=O)	2.48 (s, 3H, CH_3), 2.60 (s, 3H, SCH_3), 2.71 (s, 3H, SCH_3), 7.29 (m, 3H$_{arom}$), 8.01 (m, 2H$_{arom}$)	–
2b	65	150°	$C_{18}H_{16}N_2OS_2$ (340.3)	1655 (C=O)	2.13 (s, 3H, SCH_3), 2.71 (s, 3H, SCH_3), 7.41 (m, 8H$_{arom}$), 8.10 (m, 2H$_{arom}$)	–
2c	68	147°	$C_{19}H_{18}N_2O_2S_2$ (370.4)	1665 (C=O)	2.10 (s, 3H, SCH_3), 2.76 (s, 3H, SCH_3), 3.81 (s, 3H, OCH_3), 7.28 (m, 7H$_{arom}$), 8.08 (m, 2H$_{arom}$)	–
2d	67	116°	$C_{19}H_{18}N_2OS_2$ (354.4)	1643 (C=O)	2.20 (s, 3H, SCH_3), 2.38 (s, 3H, CH_3), 2.61 (s, 3H, SCH_3), 7.29 (m, 7H$_{arom}$), 8.1 (m, 2H$_{arom}$)	–
2e	72	149–150°	$C_{18}H_{15}ClN_2OS_2$ (374.7)	1655 (C=O)	2.23 (s, 3H, SCH_3), 2.81 (s, 3H, SCH_3), 7.53 (m, 7H$_{arom}$), 8.17 (m, 2H$_{arom}$)	–
2f	76	121°	$C_{18}H_{15}BrN_2OS_2$ (419.2)	1655 (C=O)	2.23 (s, 3H, SCH_3), 2.78 (s, 3H, SCH_3), 7.18 (m, 7H$_{arom}$), 8.16 (m, 2H$_{arom}$)	–
5a	65	167–168°	$C_{15}H_{11}N_3O_2S$ (297.3)	2208 (C≡N) 1743 (C=O)	2.58 (s, 3H, CH_3), 3.08 (s, 3H, S—CH_3), 7.55 (m, 3H$_{arom}$), 7.81 (m, 2H$_{arom}$)	297
5b	81	218–219°	$C_{20}H_{13}N_3O_2S$ (359.3)	2216 (C≡N) 1745 (C=O)	2.80 (s, 3H, SCH_3), 7.56 (m, 8H$_{arom}$), 7.88 (m, 2H$_{arom}$)	359
5c	77	242°	$C_{21}H_{15}N_3O_3S$ (389.4)	2210 (C≡N) 1755 (C=O)	2.83 (s, 3H, SCH_3), 3.89 (s, 3H, OCH_3), 7.16 (m, 7H$_{arom}$), 7.90 (m, 2H$_{arom}$)	389
5d	86	219–220°	$C_{21}H_{15}N_3O_2S$ (373.4)	2205 (C≡N) 1758 (C=O)	2.45 (s, 3H, CH_3), 2.81 (s, 3H, SCH_3), 7.51 (m, 7H$_{arom}$), 7.85 (m, 2H$_{arom}$)	373
5e	70	196–197°	$C_{20}H_{12}ClN_3O_2S$ (393.7)	2190 (C≡N) 1725 (C≡O)	2.86 (s, 3H, SCH_3), 7.60 (m, 7H$_{arom}$), 8.10 (m, 2H$_{arom}$)	393.5
5f	68	198°	$C_{20}H_{12}BrN_3O_2S$ (438.2)	2205 (C≡N) 1735 (C=O)	2.88 (s, 3H, SCH_3), 7.61 (m, 7H$_{arom}$), 7.96 (m, 2H$_{arom}$)	438

[a] Melting points were determined, on a Townson and Mercer (England) apparatus (Capillary method) and are uncorrected.
[b] All compounds gave satisfactory elemental analyses (C ±0.58%, H ±0.36%, N ±0.39%).
[c] The I.R. spectra were recorded with a Perkin-Elmer 337 and 137 spectrophotometers.
[d] The N.M.R. spectra were recorded on a Varian A-60-D Spectrometer using TMS, as an internal standard.
[e] The mass spectra were recorded on a Hitachi RMU-6E mass spectrometer fitted with a direct inlet system.

(25 ml), followed by addition of cyanoacetamide (0.21 g, 2.5 mmol)] was added **2** (2.5 mmol) and the contents were refluxed for 45 minutes. After cooling the reaction flask under tap water, 3*N* hydrochloric acid (0.3 ml) was added and the refluxing was continued for another 10 minutes. The solvent was distilled off and the residue was treated with cold water to give **3a–f** which were crystallized from ethylacetate/ethanol.

Ethyl 1-Cyano-2-(1,3-diphenyl-5-hydroxypyrazol-4-yl)-2-methylthio-acrylate (3b):
To a boiling sodium isopropoxide solution [prepared by dissolving sodium (0.057 g, 2.5 mmol) in isopropanol (25 ml)] ethylcyanoacetate (0.28 g, 2.5 mmol) was added followed by the addition of **2b** (0.85 g, 2.5 mmol) and the reaction mixture was refluxed for 1 h. Work up as described above gave **3b** as light yellow needles; yield: 0.7 g (69%); m.p. 201° (from ethanol).

$C_{22}H_{19}N_3O_3S$ (405.4)	calc.	C 65.18	H 4.69	N 10.37
	found	65.30	4.91	10.46

I.R. (KBr) ν = 2200 (CN), 1685 cm^{-1} (—CO—OC_2H_5).

^{1}H-N.M.R.: ($CDCl_3$ + DMSO-d_6) δ = 1.25 (t, 3H, —O—CH_2—CH_3), 2.06 (s, 3H, —SCH_3), 4.23 (q, 2H, —OCH_2CH_3), 7.51 ppm (m, 10 H$_{arom}$).

Thermal Cyclization of 3b to 5b:
In a pyrex test tube **3b** (0.5 g, 1.2 mmol) was held on an open flame (~250–300°) for 5 minutes and the contents were cooled and crystallized as light yellow needles from ethyl acetate/ethanol (9:1); yield: 0.38 g (86%); m.p. and m.m.p. with **5b**: 218–219°.

1-Cyano-2-methylthio-2-[1-phenyl-3-(4-chlorophenyl)-5-hydroxypyrazole-4-yl]acrylamide (4e):
Cyanoacetamide (0.21 g, 2.5 mmol) in sodium isopropoxide [from sodium (0.057 g, 2.5 mmol) dissolved in isopropanol (25 ml)] was treated with **2e** (0.93 g, 2.5 mmol) as described above and the solvent was distilled off to give the sodium salt of **4e**, which on acidification with dilute (5%) acetic acid (10 ml) gave **4e** as light yellow needles; yield: 0.80 g (78%); m.p. 167–168° (from ethanol).

$C_{20}H_{15}ClN_4O_2S$ (410.8)	calc.	C 58.44	H 3.65	N 13.65
	found	58.09	3.88	13.31

I.R. (KBr): ν = 3205 (NH_2), 2175 (CN), 1658 cm^{-1} (—CO—NH_2).

^{1}H-N.M.R. ($CDCl_3$ + DMSO-d_6): δ = 2.07 (s, 3H, —SCH_3), 7.41 (s, 2H, NH_2), 7.55 (m, 7H$_{arom}$), 7.93 ppm (m, 2H$_{arom}$).

Cyclization of 4e to 5e in Ethanolic Hydrochloric Acid:
Compound **4e** (0.51 g, 1.5 mmol) was dissolved in ethanolic hydrochloric acid (3*N*, 0.2 ml of conc. hydrochloric acid dissolved in 20 ml ethanol) and the reaction mixture was refluxed for 10 minutes. The solvent was distilled off to give **5e** as light yellow needles; yield: 0.4 g (82%); m.p. and mixture m.p. with **5e**: 196–197° (from ethyl acetate/ethanol, 9:1).

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