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Note

Synthesis of novel 3-cyano-4-methylthio-6-(arylcyclopropyl)-3-(1*H*)-pyridones and 5(3)-methylthio-3(5)-(arylcyclopropyl)pyrazoles

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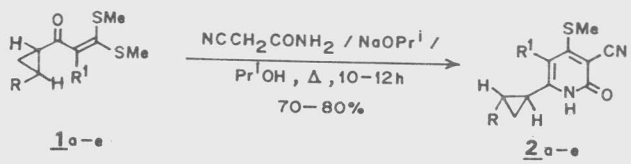
Reactions of cyclopropyl compounds **1** with cyanoacetamide in the presence of sodium isopropoxide in refluxing isopropanol afford the novel pyridones **2**. Similarly, when compounds **1** are reacted with hydrazine hydrate in refluxing ethanol, novel 5(3)-methylthio-3(5)-cyclopropylpyrazoles **3** are obtained in high yields.

α-Oxoketene dithioacetals have been proved to be the useful intermediates in organic synthesis[1-3]. In this area, cyclopropyl substituted ketene dithioacetals **1** have been extensively used in Lewis acid assisted rearrangements for the synthesis of functionalised cyclopentanones[4-6]. Research in the cyclopropane compounds and their Lewis acid or thermal rearrangements has been of increasing interest over the past years[7,8]. Prompted by these studies and in connection with a programme devoted to the preparation of biologically active heterocyclces we report herein a convenient method to prepare various cyclopropyl substituted heterocycles. The present method provides a general route to cyclopropylpyridones **2** and pyrazoles **3** by reacting the α-bis(methylthio)methylene cyclopropyl ketones **1** with cyanoacetamide and hydrazine hydrate, respectively.

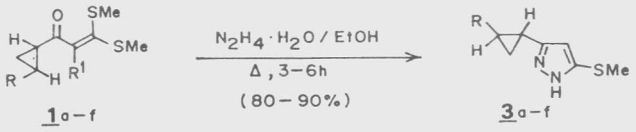
In a typical experiment, when **1a** (R′=H, R=C_6H_5) was reacted with cyanoacetamide in the presence of sodium isopropoxide in isopropanol, work-up of the reaction mixture afforded the corresponding 3-cyano-4-methylthio-6-phenylcyclopropyl-2(1*H*)-pyridone **2a** in 75% yield. Similarly, other substituted 6-(arylcyclopropyl)-2(1*H*)-pyridones **2b-e**



1a-e 2a-e

1, 2, a, R = C_6H_5, R^1 = H
b, R = 4-MeOC_6H_4, R^1 = H
c, R = 3,4-$(MeO)_2C_6H_3$, R^1 = H
d, R = 4-ClC_6H_4, R^1 = H
e, R = 4-MeC_6H_4, R^1 = H

Scheme I



1a-f 3a-f

1, 3, a R = C_6H_5, R^1 = H
b, R = 4-MeOC_6H_4, R^1 = H
c, R = 3,4-$(MeO)_2$ C_6H_3, R^1 = H
d, R = 3,4,5-$(MeO)_3$ C_6H_3, R^1 = H
e, R = 4-ClC_6H_4, R^1 = H
f, R = 4-MeC_6H_4, R^1 = H

Scheme II

were obtained from α-bis(methylthio)methylene cyclopropyl ketones **1b-e** under identical conditions in 70-80% overall yields (Scheme I). In an another experiment, when **1a** was refluxed with hydrazine hydrate in ethanol the corresponding 5(3)-methylthio3(5)-(phenylcyclopropyl)pyrazole **3a** in 90% yield. The α-bis(methylthio) arylcyclopropyl ketones **1b-f** similarly afforded the corresponding pyrazoles **3b-f** (Scheme II) in 86-92% overall yields.

Experimental Section

Melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 297 and 983 spectrometer (ν_{max} in cm^{-1}), PMR spectra on a Varian EM-390 spectrometer using TMS as internal standard (chemical shifts in δ, ppm) and mass spectra on a Jeol-D 300 mass to a solution of the appropriate S, S-acetal **1** (5 mmoles) in distilled ethanol (20 mL) and the reac-

Table I—Characterization data of 3-cyano-4-methylthio-6-(aryl cyclopropyl)-2 (IH)-pyridones **2a-e** and 5(3)-methylthio-3(5)-(arylcyclopropyl)pyrazoles **3a-f**

Compd.	Mol. formula (Mol. wt)	m.p. (°C)	Yield (%)	Found (Calcd) (%) C	H	N	IR(KBr/CCL_4) (cm^{-1})	^{1}H NMR (Solvent)) δ, ppm
2a	$C_{16}H_{14}N_2OS$ (282)	151	75	68.32 (68.5	4.6 4.6	9.9 9.6)	(KBr):3290 (νNH), 2201 (νC≡N), 1670, 1596	(DMSO-d_6): 1.29-1.56(m, 2H, CH_2),1.67-1.71(m,1H, 2CH), 1.98-2.40 (m, 1H,CH), 2.50(s,3H SCH_3) 5.98 (s,1H,H-5), 7.05-7.21 (m, 5H, ArH).
2b	$C_{17}H_{16}N_2O_2S$ (312)		74	65.38 (65.40	5.12 5.01	8.97 8.99)	3292, 2209 (νCN), 1632, 1586, (νCO and pyridone ring)	1.25-1.50(m, 2H, CH_2), 1.56-1.65(m, 1H, CH), 1.90-2.25(m, 1H, CH),2.43,(s, 3H, SCH_3), 3.65 (s, 3H, OCH_3), 5.90(s, 1H,H-5),6.70 (d, 2H, *J*=9Hz, ArH), 7.00 (d, 2H, *J*=9Hz, ArH).
2c	$C_{18}H_{18}N_2O_3S$ (342)	140	75	63.1 (62.6	5.21 5.3	8.18 8.05)	3298, 2209,1659, 1589	1.35-1.65 (m, 1H, CH), 1.85-2.10 (m, 1H, CH), 2.28-2.51 (m, 1H,CH), 3.80 (s, 6H,2OCH_3), 6.10 (s,1H, H-5) 6.90 (m,3H, ArH).
2d	$C_{16}H_{13}N_2SCl$ (300.5)	150	80	64.5 (64	4.3 4.1	9.33 9.2)	3294, 2213, 1652, 1597	1.35-1.60 (m, 2H, CH_2), 1.70-1.89 (m,1H,CH), (m,1H,CH), 2.59 (s, 3H, SCH_3), 6.10(s, 1H, H-5), 7.20-7.50 (m, 4H, ArH).
2e	$C_{17}H_{16}N_2OS$ (296)	145	70	68.91 (68.85	5.40 5.30	9.45 9.5)	3128, 2210, 1651, 1595	1.35-1.65 (m, 2H, CH_2), 1.80-2.01 (m, 1H, CH), 2.25-2.45 (m, 1H, CH), 2.50 (s, 3H, CH_3),2.68(s, 3H, SCH_3), 6.20 (s, 1H, H-5), 7.20-7.45 (m, 4H, Ar).
3a	$C_{13}H_{14}N_2S$ (230	Oil	90	67.8 (66.7	6.08 6.6	12.1 11.9)	(CCl_4):3156(νNH),1587 (νC=N), 1430	($CDCl_3$):1.10-1.25(m, 2H, CH_2). 1.85-2.0 (m, 2H, 2CH), 2.29(s, 3H, SCH_3), 5.85(s, 1H, H-4), 7.0-7.30(m, 5H, ArH).
3b	$C_{14}H_{16}N_2OS$ (260)	Oil	92	64.45 (62.0	6.3 6.1	10.51 10.76)	3176, 3130, 1609, 1510	1.20(m, 2H, CH_2), 2.1(m, 2H, 2CH), 2.3 (s, 3H, SCH_3), 3.70 (s, 3H, OCH_3), 5.90(s, 1H, H-4), 6.75(d, 2H, *J*=9Hz, ArH), 6.95 (d, 2H, *J*=9 Hz, ArH)
3c	$C_{15}H_{18}N_2OS$ (260)	Oil	91.3	62.06 (62.0	6.20 6.16	9.65 9.70)	3155, 1590, 1280	1.20(m, 2H, CH), 2.0(m, 2H, 2CH), 2.23(s, 3H, SCH_3), 3.65 (s, 3H, OCH_3), 5.85(s, 1H, H-4), 6.50-6.65(m, 3H, ArH).

Contd.

Table I—Characterization data of 3-cyano-4-methylthio-6-(aryl cyclopropyl)-2 (IH)-pyridones **2a-e** and 5(3)-methylthio-3(5)-(arylcyclopropyl)pyrazoles **3a-f**—*Contd*

Compd.	Mol. formula (Mol.wt)	m.p. (°C)	Yield (%)	Found (Calcd) (%) C	H	N	IR(KBr/CCl_4) (cm^{-1})	^{1}H NMR (Solvent)) δ, ppm
3d	$C_{16}H_{20}N_2O_3S$ (320)	Oil	89	60.0 (60.3	6.25 6.3	8.75 8.65)	3133, 1576, 1499, 1232	1.20(m,2H,CH_2), 1.98-2.20(m,2H,2CH) 2.29(s,3H,SCH_3), 3.65(s, 3H,OCH_3),3.70(s,6H,2xOCH_3),5.83(s,1H,H-4), 6.22 (s, 2H, ArH).
3e	$C_{13}H_{13}N_2SCl$ (264.5)	Oil	90	58.97 (58.85	4.91 4.93	10.58 10.63)	3125, 1568, 1449, 1428	1.15-1.35 (m, 2H, CH_2), 2.01-2.20 (m, 2H, 2CH), 2.29 (s, 3H, SCH_3), 5.89 (s, 1H, H-4), 6.95 (d, 2H, *J*=9Hz, ArH), 7.20 (d, 2H,*J*=9Hz, ArH).
3f	$C_{14}H_{16}N_2S$ (249)	Oil	86	68.85 (68.86	6.55 6.75	11.47 11.37)	3129, 2919, 1565, 1430	1.20(m, 2H, CH_2), 2.0-2.11 (m,2H,2CH), 2.29(s, 3H, SCH_3), 5.86 (s, 1H, H-4), 6.90-6.99 (m, 4H, ArH).

MS(m/z,%) of **2b**:312(M^+,100), 297(M^+–15,40.1), 180(64.7). MS(m/z,%) of **3a**: 230(M^+,70), 215(M^+–15,60).

spectrometer. Elemental analyses (C, H, N) were carried out on a Heraus CHN-O Rapid Elemental analyser. The required α-bis(methylthio)methylene cyclopropyl ketones **1a-f** were prepared according to the earlier reported[1,4] procedure.

Preparation of 3-cyano-4-methylthio-6-(substituted arylcyclopropyl)-2(1*H*)-pyridones 2a-e: General procedure. To a solution of sodium isopropoxide [prepared by dissolving 0.23 g (0.01 mole) sodium in 40 mL of dry isopropanol] in isopropanol, cyanoacetamide (0.01 mole) was added and the mixture shaken for 5-10 min. The appropriate cyclopropyl ketene S, S-acetal (0.01 mole) was then added and the reaction mixture refluxed for 8-15 hr. Evaporation of the solvent yielded a bright orange sodium salt, which was diluted with water (20-30 mL) and filtered. The residue obtained was acidified with dil. HCl (30%) to give the corresponding crude pyridone **2** as a pale yellow amorphous solid which was crystallized from acetic acid.

The characterization data of pyridones **2a-e**, thus prepared, are given in Table I.

Preparation of 5(3)-alkylthio-3(5)-(aryl substituted cyclopropyl)-pyrazole 3a-f: General procedure. Hydrazine hydrate (6 mmoles) was added tion mixture refluxed for 3-4 hr (monitored by TLC). The solvent was removed under reduced pressure and the residue diluted with water (100 mL), extracted with chloroform (2×50 mL). The organic layer was washed with water (100 mL), dried (Na_2SO_4) and evaporated to give the corresponding crude pyrazole (**3a-f**; Table I) which was further purified by column chromatography over silica gel using hexane-ethyl acetate (20:1) as eluent.

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