Reaction of 2-Alkylthiomethyl-3-alkylthioacrylophenones with Hydrazine, Guanidine, and Amines: Synthesis of Novel Pyrazoles, Pyrimidines, and Enaminoketones[1]

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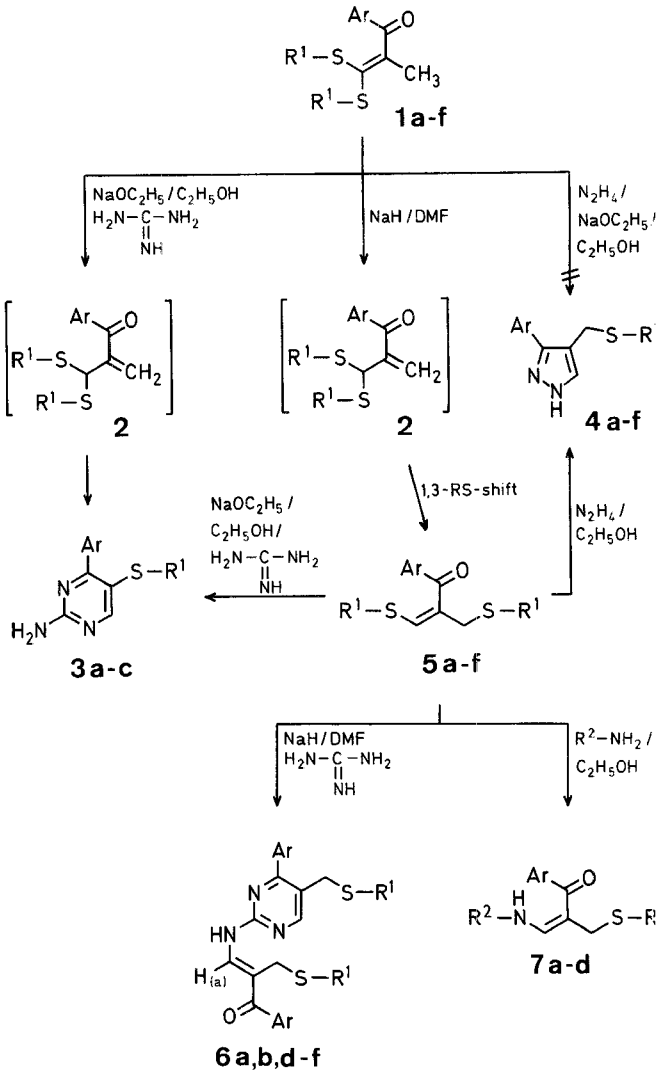
We had reported earlier[2] that the α-methyl-α-ketoketene dithioacetal **1a** reacts with guanidine in the presence of sodium ethoxide in refluxing ethanol to give 2-amino-4-phenyl-5-methylthiomethylpyrimidine **(3a)** in good yield. The formation of **3a** was believed to have involved an intermediate **2** which is formed from **1a** through a 1,3-proton shift in the presence of a base. We considered that a similar reaction of **1** with hydrazine in the presence of sodium ethoxide would yield the hitherto inaccessible pyrazoles **4.** However, the reaction of **1a** with hydrazine in the presence of sodium ethoxide in refluxing ethanol did not yield the desired pyrazole **4a.** In continuation with this work, we had further observed that ketene dithioacetals **1a-f** undergo interesting rearrangements in the presence of sodium hydride in dimethylformamide to yield the novel three carbon fragments **5a-f** with alkylthiomethyl side chains[3]. The formation of **5** from **1** was rationalised through intermediacy of **2** which undergoes a subsequent 1,3-alkylthio shift to give **5** in moderate to good yields.

In the present communication, we report the reaction of **5** with hydrazine, guanidine, and amines, which give novel pyrazoles, pyrimidines, and enaminoketones, respectively, in good yields. When **5a** was reacted with hydrazine in refluxing ethanol, the desired pyrazole **4a** was obtained in 85% yield. The pyrazoles **4b-f** were similarly obtained from **5b-f** in 70–93% overall yields. The reaction of **5a** with guanidine in the presence of sodium ethoxide in refluxing ethanol yielded the pyrimidine **3a** (m.p., m.m.p., I.R., ^{1}H-N.M.R.). The pyrimidines **3b** and **3c** were similarly obtained in 70% and 75% yields, respectively.



However, when the reaction of **5a** with guanidine was carried out in the presence of sodium hydride in dimethylformamide, the product isolated was characterised as the pyrimidine **6a** which is formed by further reaction of pyrimidine **3a** with **5a.** The compounds, **6b-e** were similarly obtained in 56–65% overall yields. The structure of **6a** was further confirmed from the observation that, when the pyrimidine **3a** was reacted with **5a** in the presence of sodium hydride in dimethylformamide under similar conditions, **6a** was obtained in 70% yield. Attempts to isolate the intermediate pyrimidines **3** were not successful.

Reaction of **5a** with methylamine in refluxing ethanol yielded the novel enaminoketone **7a** in 80% yield. The enaminoketones **7b-d** were similarly obtained from the respective amines and **5** in 75–83% overall yields. However, **5a** failed to react with aromatic amines under similar conditions or at higher temperatures.

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Table 1. Physical and Spectral Data of 3-Aryl-4-alkylthiomethylpyrazoles **(4a–f)**

Product No.	Ar	R^1	Yield[a] [%]	m.p. [°C] (solvent)	Molecular formula[b]	M.S. *m/e* (M^+)	I.R. (neat) ν [cm^{-1}]	^{1}H-N.M.R. (CCl_4) δ [ppm]
4a	C_6H_5	CH_3	85	Viscous liquid	$C_{11}H_{12}N_2S$ (204.3)	204	3165 (NH)	1.94 (s, 3H, CH_2SCH_3); 3.53 (s, 2H, CH_2SCH_3); 7.20–7.60 (m, $5H_{arom}$ + H-5); 11.80 (br s, 1H, NH)
4b	C_6H_5	C_2H_5	70	Viscous liquid	$C_{12}H_{14}N_2S$ (218.3)	218	3160 (NH)	1.20 (t, 3H, SCH_2CH_3); 2.45 (q, 2H, SCH_2CH_3); 3.65 (s, 2H, $CH_2SCH_2CH_3$); 7.30–7.75 (m, $5H_{arom}$ + H-5); 11.70 (br s, 1H NH)
4c	4-Cl—C_6H_4	CH_3	76	82–83° (hexane)	$C_{11}H_{11}ClN_2S$ (238.7)	238.5	3150 (NH)[c]	1.98 (s, 3H, SCH_3); 3.50 (s, 2H, CH_2SCH_3); 7.20–7.50 (m, 5H, $4H_{arom}$ + H-5); 12.3 (br s, 1H, NH)
4d	4-H_3C—C_6H_4	CH_3	80	Viscous liquid	$C_{12}H_{14}N_2S$ (218.3)	218	3150 (NH)	1.95 (s, 3H, SCH_3); 2.34 (s, 3H, CH_3); 3.55 (s, 2H, CH_2SCH_3); 7.03–7.50 (dd, $4H_{arom}$ + H-5); 11.6 (br s, 1H, NH)
4e	4-H_3CO—C_6H_4	CH_3	93	67–68° (hexane)	$C_{12}H_{14}N_2OS$ (234.3)	234	3150 (NH)[c]	1.95 (s, 3H, CH_2SCH_3); 3.52 (s, 2H, CH_2SCH_3); 3.70 (s, 3H, OCH_3); 6.75 (d, $2H_{arom}$); 7.20 (s, 1H, H-5); 7.42 (d, $2H_{arom}$); 11.20 (br s, 1H, NH)
4f	4-H_3CO—C_6H_4	C_2H_5	90	52–53° (hexane)	$C_{13}H_{16}N_2OS$ (248.3)	248	3150 (NH)[c]	1.20 (t, 3H, SCH_2CH_3); 2.45 (q, 2H, SCH_2CH_3); 3.60 (s, 2H, $CH_2SCH_2CH_3$); 3.80 (s, 3H, OCH_3); 6.70 (d, $2H_{arom}$); 7.40 (s, 1H, H-5); 7.50 (d, $2H_{arom}$); 11.70 (br s, 1H, NH)

[a] Yield of pure, isolated product.
[b] Satisfactory microanalyses obtained: C ±0.48, H ±0.45, N ±0.45.
[c] Nujol mull.

Table 2. Physical and Spectral Data of Pyrimidines **6a–e**

Product No.	Ar	R^1	Yield[a] [%]	m.p. [°C] (solvent)	Molecular formula[b]	M.S. *m/e* (M^+)	I.R. (Nujol) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]
6a	C_6H_5	CH_3	65	143–144° (C_2H_5OH)	$C_{23}H_{23}N_3OS_2$ (421.6)	421	1640, 1610, 1585, 1550, 1460[c]	2.00 (s, 3H, SCH_3); 2.15 (s, 3H, SCH_3); 3.60 (s, 2H, CH_2SCH_3); 3.73 (s, 2H, CH_2SCH_3); 7.30–7.65 (m, $10H_{arom}$); 8.30 (br s, 2H, H_A + NH, exchangeable with D_2O); 8.43 (s, 1H, H-6)
6b	C_6H_5	C_2H_5	60	106–107° (C_2H_5OH)	$C_{25}H_{27}N_3OS_2$ (449.6)	449	1638, 1605, 1580, 1550, 1458[c]	1.17 (t, 3H, SCH_2CH_3); 1.30 (t, 3H, SCH_2CH_3); 2.43 (q, 2H, SCH_2CH_3); 2.57 (q, 2H, SCH_2CH_3); 3.63 (s, 2H, $CH_2SCH_2CH_3$); 3.77 (s, 2H, $CH_2SCH_2CH_3$); 7.30–7.70 (m, $10H_{arom}$); 8.30 (br s, 2H, H_A + NH, exchangeable with D_2O); 8.42 (s, 1H, H-6)
6c	4-H_3C—C_6H_4	CH_3	56	111–112° (C_2H_5OH)	$C_{25}H_{27}N_3OS_2$ (449.6)	449	1638, 1605, 1580, 1550, 1460[c]	2.00 (s, 3H, SCH_3); 2.10 (s, 3H, SCH_3); 2.40 [s, 6H, $(CH_3)_2$]; 3.60 (s, 2H, CH_2SCH_3); 3.72 (s, 2H, CH_2SCH_3); 7.10–7.60 (dd, 8 H_{arom}); 8.25 (br s, 2H, H_A + NH, exchangeable with D_2O); 8.38 (s, 1H, H-6)
6d	4-H_3CO—C_6H_4	CH_3	64	134–135° (C_2H_5OH)	$C_{25}H_{27}N_3O_3S_2$ (481.6)	481	1635, 1610, 1570, 1545, 1460[c]	2.00 (s, 3H, SCH_3); 2.08 (s, 3H, SCH_3); 3.60 (s, 2H, CH_2SCH_3); 3.70 (s, 2H, CH_2SCH_3); 3.83 [s, 6H, $(OCH_3)_2$]; 6.86 (dd, $4H_{arom}$); 7.60 (d, $4H_{arom}$); 8.25 (br s, 2H, H_A + NH exchangeable with D_2O); 8.33 (s, 1H, H-6)

Table 2. (Continued)

Product No.	Ar	R^1	Yield[a] [%]	m.p. [°C] (solvent)	Molecular formula[b]	M.S. m/e (M^+)	I.R. (Nujol) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]
6e	4-H_3CO—C_6H_4	C_2H_5	59	121° (C_2H_5OH)	$C_{27}H_{31}N_3O_3S_2$ (509.7)	509	1640, 1605, 1583, 1548, 1460[c]	1.30 [q, 6H, $(SCH_2CH_3)_2$]; 2.53 [t, 4H, $(SCH_2CH_3)_2$]; 3.68 (s, 2H, $CH_2SCH_2CH_3$); 3.78 (s, 2H, $CH_2SCH_2CH_3$); 3.87 [s, 6H, $(OCH_3)_2$]; 6.90 (q, $4H_{arom}$); 7.65 (q, $4H_{arom}$); 8.25 (br s, 2H, H_A + NH, exchangeable with D_2O); 8.38 (s, 1H, H-6)

[a] Yield of pure, isolated product.
[b] Satisfactory microanalyses obtained: C ±0.46, H ±0.47, N ±0.50.
[c] In $CHCl_3$, broad peak between 3220–3400 cm^{-1} was observed and there was no change in the position of other peaks.

Table 3. Physical and Spectral Data of Enaminoketones, **7a–d**

Product No.	Ar	R^1	R^2	Yield[a] [%]	m.p. [°C] (solvent)	Molecular formula[b]	M.S. m/e (M^+)	I.R. (neat) ν [cm^{-1}]	^{1}H-N.M.R. (CCl_4) δ [ppm]
7a	4-H_3C—C_6H_4	CH_3	CH_3	80	Viscous yellow liquid	$C_{13}H_{17}NOS$ (235.3)	235	3300, 3275, 1638, 1575, 1540	1.90, 2.05 (2s, 3H, SCH_3); 2.38 (s, 3H, CH_3); 2.88, 3.10 (2d, 3H, NCH_3); 3.25, 3.55 (2s, 2H, CH_2SCH_3); 5.75 (m, 1H, NH); 6.80–7.40 (m, $4H_{arom}$ + $1H_{vinyl}$)[c]
7b	4-H_3C—C_6H_4	CH_3	C_6H_{11}	83	107–108° (hexane)	$C_{18}H_{25}NOS$ (303.5)	303	3265, 3220, 1625, 1540	1.20–1.85 (m, $10H_{cyclohexyl}$); 2.00 (s, 3H, SCH_3); 2.33 (s, 3H, CH_3); 2.93 (m, $1H_{cyclohexyl}$); 3.60 (s, 2H, CH_2); 5.55 (m, 1H, NH); 7.00–7.35 (m, $4H_{arom}$ + $1H_{vinyl}$)
7c	4-H_3CO—C_6H_4	CH_3	CH_3	75	Viscous yellow liquid	$C_{13}H_{17}NO_2S$ (251.3)	251	3310, 3250, 1640, 1605, 1580	1.92, 2.00 (2s, 3H, SCH_3); 2.90, 3.10 (2d, 3H, NCH_3); 3.30, 3.55 (2s, 2H, CH_2SCH_3); 3.80 (s, 3H, OCH_3); 5.65 (m, 1H, NH); 6.85–7.60 (m, $4H_{arom}$ + $1H_{vinyl}$)[c]
7d	4-H_3CO—C_6H_4	CH_3	C_6H_{11}	82	89–90° (hexane)	$C_{18}H_{25}NO_2S$ (319.6)	319	3270, 3225, 1630, 1540	1.15–1.90 (m, $10H_{cyclohexyl}$); 1.94 (s, 3H, SCH_3); 2.95 (m, $1H_{cyclohexyl}$); 3.50 (s, 2H, CH_2); 3.75 (s, 3H, OCH_3); 5.45 (m, 1H, NH); 6.65–7.40 (m, $4H_{arom}$ + $1H_{vinyl}$)

[a] Yield of pure, isolated product.
[b] Satisfactory microanalyses obtained: C ±0.44, H ±0.54, N ±0.51.
[c] Both geometrical isomers are present.

The experimental data for the preparation of **5a–f** and their spectral data are described in Ref.[3].

3-Aryl-4-alkylthiomethylpyrazoles 4a–f; General Procedure:
A solution of **5** (0.005 mol) and hydrazine hydrate (0.5 ml) in ethanol (15 ml) is refluxed for 1–2 h. Removal of solvent under reduced pressure gives the crude pyrazoles **4a–f**, which are further purified by column chromatography over neutral alumina using benzene as eluent (Table 1).

Reaction of 5 with Guanidine:

Method A, in sodium ethoxide/ethanol: To a solution of sodium ethoxide [prepared by dissolving sodium, (0.01 mol) in 20 ml of absolute alcohol], guanidine nitrate (0.6 g, 0.005 mol) is added and the reaction mixture is stirred for 10–15 min. The compound **5a** (1.2 g, 0.005 mol) is then added and the reaction mixture is refluxed for 5 h. The solvent is removed under reduced pressure and the residue is quenched over crushed ice (20 g). It is extracted with chloroform (3 × 20 ml), the extracts are washed with water (1 × 50 ml), dried, and evaporated to give the crude pyrimidine **3a** which is further purified by passing through a silica gel column using benzene/ethyl acetate (7:3) as eluent. The spectral and analytical data of **3a–c** are as reported in Ref.[2] (m.p., m.m.p., I.R., ^{1}H-N.M.R.).

Method B, in sodium hydride/dimethylformamide/benzene: To a stirred suspension of guanidine nitrate (0.6 g, 0.005 mol) and sodium hydride (1.5 g, 0.03 mol, 50% suspension) in dimethylformamide (15 ml) and benzene (10 ml), compound **5** (0.005 mol) dissolved in benzene (5 ml) is added and the temperature is raised with stirring to 80–85 °C. The reaction mixture is further stirred at 80–85 °C for 5–8 h and poured over crushed ice (200 g). The reaction mixture is neutralised with acetic acid (20%) and the benzene layer is separated. The aqueous layer is further extracted with chloroform (2 × 50 ml) and the combined organic layer is washed with water (5 × 50 ml), dried with sodium sulphate, and evaporated to give crude **6a–e**, which are further purified by column chromatography over silica gel using hexane/ethyl acetate (7:3) as eluent (Table 2).

3-Alkylamino-2-alkylthiomethyl-1-aryl-2-propen-1-ones (7a–d); General Procedure:
A solution of **5** (0.005 mol) and the respective amine (0.01 mol) in

ethanol (15 ml) is refluxed for 6–7 h (2 h in case of methylamine). Removal of solvent under reduced pressure gives the crude enaminoketones **7a–d**, which are further purified by column chromatography over neutral alumina using benzene/ethyl acetate (9:1) as eluent (Table 3).

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[1] Part 21, for part 20, see: G. Singh, S. S. Bhattacharjee, H. Ila, H. Junjappa, *Synthesis* **1982**, 693.

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