The Selective Synthesis of Unsymmetrical 1-Substituted 2(1*H*)-Pyrimidinones and -thiones

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The synthesis of 2(1*H*)-pyrimidinones and -thiones is of considerable practical interest because of the biological activities exhibited by many of these compounds[1,2]. Further 1,4,6-trisubstituted derivatives are useful synthons for the preparation of various heterocyclic compounds[3,4,5]. Therefore, it is quite valuable to synthesize unsymmetrical 1-substituted 2(1*H*)-pyrimidinones and -thiones having different substituents at C-4

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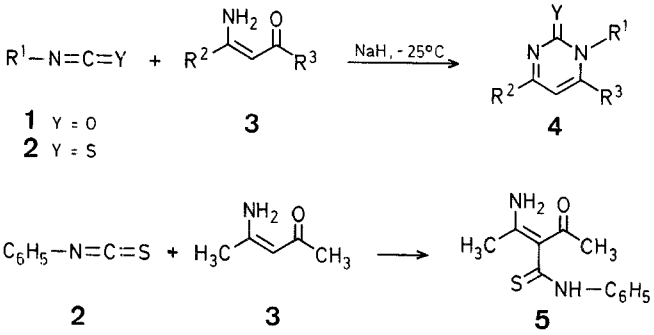
and C-6 of the pyrimidine ring. However, the ordinarily employed methods[5-8] are cumbersome, and there is no general preparative method for the synthesis of unsymmetrical 1-substituted 2(1*H*)-pyrimidinones and -thiones.

It was reported that 2-methyl-3-aminopropenal reacted with phenyl isothiocyanate in acetonitrile under reflux for 5 h to afford 5-methyl-1-phenyl-2(1*H*)-pyrimidinethione in 51% yield[9]. This result suggests that 1-substituted 2(1*H*)-pyrimidinones and -thiones **4** may be obtained by the reaction of isocyanate **1** and isothiocyanate **2** with *β*-amino-*α*,*β*-unsaturated ketones **3**[10] instead of 2-methyl-3-aminopropenal. Although 4-amino-3-penten-2-one **(3a)** reacted with phenyl isothiocyanate under the conditions described, the yield of the expected 4,6-dimethyl-1-phenyl-2(1*H*)-pyrimidinethione **(4a)** was only 3%, and 3-(*N*-phenylamino-thiocarbonyl)-4-amino-3-penten-2-one **(5)** was obtained as the main product. Kashima et al.[11] reported that compounds **3a, 3b,** and **3e** reacted with acyl chloride at 0 °C to give not *C*-acylated but *N*-acylated products in high yields. Therefore, the reaction was carried out at a low temperature in the presence of a base. When compound **3a** was reacted with phenyl isothiocyanate in *N*,*N*-dimethylformamide in the presence of sodium hydride in an ice/methanol bath (~ −25 °C), the formation of compound **5** was not detected, and compound **4a** was obtained in 53% yield.

Under the same conditions, the synthesis of unsymmetrical 1-substituted 2(1*H*)-pyrimidinones and -thiones was attempted (Table).



Sodium hydride is superior to other bases in the following points: (a) a strong base is required in the cyclization step; (b) it is the most suitable base for quenching the resulting water; (c) the direct *N*-methylation of **3e**[12] is carried out in the presence of sodium hydride. Also the reaction at a low temperature is responsible for the attack at nitrogen in preference to carbon of compounds **3** by isocyanates **1** or isothiocyanates **2**. As the result of these reaction conditions, the selective synthesis of unsymmetrical 1-substituted 2(1*H*)-pyrimidinones and -thiones **4** is possible.

Table. 1,4,6-Trisubstituted 2(1*H*)-Pyrimidinones **4b–g** (Y = O) and 2(1*H*)-Pyrimidinethiones **4h–l** (Y = S) prepared

Product No.	R^1	R^2	R^3	Yield [%]	m.p. [°C]	Molecular formula[a] or Lit. m.p. [°C]	I.R. (KBr) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]
4b	C_6H_5	CH_3	C_2H_5	20	159–160°	$C_{13}H_{14}N_2O$ (214.3)	1650, 1530, 790, 770, 700	1.03 (t, 3H, J = 8 Hz); 2.23 (q, 2H, J = 8 Hz); 2.38 (s, 3H); 6.28 (s, 1H); 7.1–7.6 (m, 5H)
4c	C_6H_5	C_2H_5	CH_3	38	197–197.5°	$C_{13}H_{14}N_2O$ (214.3)	1650, 1530, 770, 700	1.28 (t, 3H, J = 8 Hz); 1.94 (d, 3H, J = 0.7 Hz); 2.63 (q, 2H, J = 8 Hz); 6.20 (q, 1H, J = 0.7 Hz); 7.0–7.6 (m, 5H)
4d	4-Cl—C_6H_4	CH_3	C_2H_5	29	146–146.5°	$C_{13}H_{13}ClN_2O$ (248.7)	1650, 1605, 1525, 785	1.07 (t, 3H, J = 8 Hz); 2.23 (q, 2H, J = 8 Hz); 2.40 (s, 3H); 6.23 (s, 1H); 7.1–7.6 (m, 4H)
4e	C_6H_5	CH_3	*n*-C_3H_7	34	126–127.5°	$C_{14}H_{16}N_2O$ (228.3)	1650, 1520, 1325, 780, 760, 695	0.82 (t, 3H, J = 7 Hz); 1.2–1.7 (m, 2H); 2.0–2.3 (m, 2H); 2.41 (s, 3H); 6.20 (s, 1H); 7.1–7.6 (m, 5H)
4f	4-Cl—C_6H_4	CH_3	*n*-C_3H_7	36	205–206°	$C_{14}H_{15}ClN_2O$ (262.7)	1650, 1530, 1060, 820, 780	0.83 (t, 3H, J = 7 Hz); 1.2–1.7 (m, 2H); 2.1–2.4 (m, 2H); 2.43 (s, 3H); 6.22 (s, 1H); 7.1–7.6 (m, 4H)
4g	4-Cl—C_6H_4	C_6H_5	CH_3	65	249–250°	$C_{17}H_{13}ClN_2O$ (296.8)	1650, 1345, 1080, 825, 765	2.06 (d, 3H, J = 0.7 Hz); 6.80 (q, 1H, J = 0.7 Hz); 7.0–7.5 (m, 7H); 8.0–8.2 (m, 2H)
4h	C_6H_5	CH_3	C_2H_5	58	171.5–172°	$C_{13}H_{14}N_2S$ (230.3)	1600, 1510, 1225, 755, 690	1.08 (t, 3H, J = 8 Hz); 2.27 (q, 2H, J = 8 Hz); 2.45 (s, 3H); 6.58 (s, 1H); 7.1–7.7 (m, 5H)
4i	C_6H_5	C_2H_5	CH_3	50	179.5–180.5°	$C_{13}H_{14}N_2S$ (230.3)	1600, 1510, 1350, 1265, 1235, 1225	1.29 (t, 3H, J = 8 Hz); 1.98 (d, 3H, J = 0.7 Hz); 2.67 (q, 2H, J = 8 Hz); 6.61 (q, 1H, J = 0.7 Hz); 7.0–7.6 (m, 5H)
4j	C_6H_5	C_6H_5	CH_3	65	213.5–215°	$C_{17}H_{14}N_2S$ (278.4)	1600, 1490, 1345, 1275, 730, 690	2.08 (d, 3H, J = 0.7 Hz); 7.09 (q, 1H, J = 0.7 Hz); 7.2–7.6 (m, 8H); 8.1–8.3 (m, 2H)
4k	C_6H_5	CH_3	C_6H_5	68	214° (dec)	217° (dec)[8]	1600, 1260, 760, 740	2.49 (s, 3H); 6.60 (s, 1H); 7.1–7.4 (m, 10H)
4l[b]	C_2H_5	CH_3	C_6H_5	48	143–143.5°	$C_{13}H_{14}N_2S$ (230.3)	1590, 1520, 1350, 1250, 1140	1.28 (t, 3H, J = 7 Hz); 2.40 (s, 3H); 4.51 (q, 2H, J = 7 Hz); 6.44 (s, 1H); 7.2–7.7 (m, 5H)

[a] Satisfactory microanalyses obtained: C ±0.32; H, ±0.07; N, ±0.14.

[b] Dimethylformamide/tetrahydrofuran (1 : 1) as solvent in a Dry Ice/ethanol bath.

1,4,6-Trisubstituted 2(1*H*)-Pyrimidinones (4b–g) and -thiones (4h–l); General Procedure:

Compound **3** (1 mmol) in dry dimethylformamide (10 ml) is stirred for 1 h at room temperature in the presence of sodium hydride (60% suspension in oil, 17.5 mmol), isocyanate **1** or isothiocyanate **2** (1 mmol) in dimethylformamide (5 ml) is then added dropwise to the mixture cooled in an ice/methanol bath with stirring for 2 h. After 1.5 h at room temperature, the reaction mixture is poured on ice (20 g). The resulting solution is extracted with dichloromethane (40 ml). The organic layer is washed with water (7 × 80 ml) to remove the dimethylformamide, dried with anhydrous magnesium sulfate, and evaporated. The crude products **4b–g** (Y = O) or **4h–l** (Y = S) are recrystallized from benzene/hexane or ethanol/hexane, respectively.

3-(*N*-Phenylamino-thiocarbonyl)-4-amino-3-penten-2-one (5):

A mixture of 4-amino-3-penten-2-one (**3**; $R^2 = R^3 = CH_3$; 0.149 g, 1.5 mmol) and phenyl isothiocyanate (**2**; $R^1 = C_6H_5$; 0.203 g, 1.5 mmol) in dry acetonitrile (5 ml) is refluxed for 5 h. The solvent is evaporated, and the residue is chromatographed with chloroform/acetone/ethanol (50:5:1) on silica gel; yield: 0.074 g (21%); m.p. 142–143 °C (ethyl acetate/hexane).

$C_{12}H_{14}N_2OS$	calc.	C 61.51	H 6.02	N 11.95
(234.3)	found	61.62	6.04	11.91

I.R. (KBr): $\nu = 3360, 3220, 3180, 1615\ cm^{-1}$.

^{1}H-N.M.R. (CD_3OD): $\delta = 2.21$ (s, 3H); 2.22 (s, 3H); 3.92 (br. s, 2H); 7.2–7.9 (m, 5H); 11.1 ppm (br. s, 1H).

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