An efficient synthesis of 4-oxo-2-thioxohexahydropyrimidines

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Several 4-oxo-2-thioxohexahydropyrimidines have been synthesised in very good yields from ethyl 2-cyanopropenoates and thiourea in sodium methoxide–methanol medium

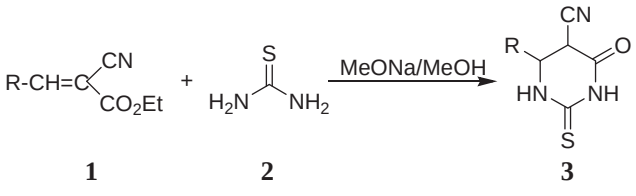
Keywords: 4-oxo-2-thioxohexahydropyrimidines, ethyl 2-cyanopropenoates, thiourea, sodium methoxide, synthesis

4-Oxo-2-thioxohexahydropyrimidines (dihydro-2-thiouracils) are interesting compounds both from a biochemical and a structural point of view.[1,2] The reaction of ethyl 2-cyanopropenoates with thiourea in the presence of sodium ethoxide has been reported to give 4-oxo-2-thioxohexahydropyrimidines.[3] This method suffered from drawbacks such as long reaction times (24 h) and low to moderate yields.

Recently we became interested in synthesis of pyrimidine derivatives[4] and this prompted us to reinvestigate the reaction of ethyl 2-cyanopropenoates **1** with thiourea **2**. Surprisingly the potential of sodium methoxide as a catalyst has not, hitherto, been studied in the cyclocondensation of ethyl 2-cyano-3-substituted-propenoates with thiourea. We have found this common commercially available reagent can catalyse the reaction to produce the corresponding 4-oxo-2-thioxohexahydropyrimidines **3** in good to excellent yields.

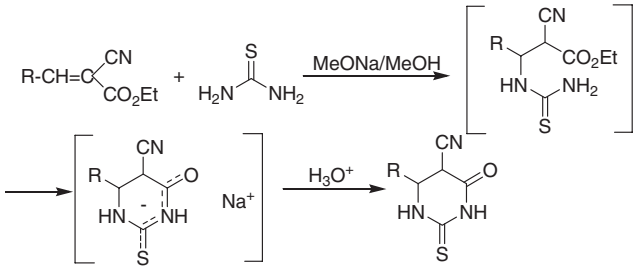
4-Oxo-2-thioxohexahydropyrimidines **3** were prepared by stirring an equimolar mixture of the corresponding ethyl 2-cyanopropenoates **1** and thiourea **2** in methanol at room temperature in the presence of two equivalents of sodium methoxide. The products were isolated by removal of the solvent and precipitation with 5% aqueous acetic acid. The results are reported in Table 1. The formation of 4-oxo-2-thioxohexahydropyrimidines can be explained through condensation of thiourea **2** with ethyl 2-cyanopropenoates **1**, and subsequent cyclisation of the adduct by attack of the amidic nitrogen to the ethoxycarbonyl group, according the process depicted in Scheme 2. In all cases the cyclisation of the intermediate Michael type adduct occurs regioselectively by attack of the nitrogen to the ethoxycarbonyl group. So compounds **3** contain *cis*-isomers and *trans*-isomers. It should be pointed out that in the reaction the formation of products through cyclization of the amidic nitrogen with the cyano group has not been observed.

The reaction of ethyl 2-cyano-3-(2-hydroxyphenyl) propenoate with thiourea under the same conditions as in the preceding cases did not lead to the corresponding 4-oxo-2-thioxohexahydropyrimidine. The phenolic hydroxyl group firstly reacted with MeONa to form phenolic sodium salt which can not react with thiourea. In addition we found that the substrates carrying a nitro group could not react as well as those without a nitro group. The reason was unclear.



1 **2** **3**

Scheme 1



Scheme 2

In conclusion, this report discloses a new and simple modification of the cyclocondensation of ethyl 2-cyano-propenoates with thiourea. By using sodium methoxide as a catalyst, the yield of 4-oxo-2-thioxohexahydropyrimidines can be increased from 30-82% to 50-98%, while the reaction time was shortened from 24 h to 30 min (or 1 h). This method for synthesis of 4-oxo-2-thioxohexahydropyrimidines therefore is a simple high yielding and time saving process.

Table 1 Synthesis of 4-oxo-2-thioxohexahydropyrimidines catalysed by MeONa

No.	R	*t*/h	Yield/% (lit.[a])	m.p./°C (lit.[3])	*cis:trans*[b]
a	C_6H_5	0.5	97(65)	238-240(239-240)	38:62
b	2-ClC_6H_4	0.5	94	200-202	25:75
c	3-ClC_6H_4	0.5	91	208-210	30:70
d	4-ClC_6H_4	0.5	93	220-222	35:65
e	2,4-$Cl_2C_6H_3$	0.5	98	160-161	20:80
f	4-$CH_3C_6H_4$	0.5	98(82)	248-250(244-245)	40:60
g	4-$CH_3OC_6H_4$	0.5	96(50)	230-232(231-233)	35:65
h	3,4-$(OCH_2O)C_6H_3$	0.5	95	228-230	30:70
i	4-$(CH_3)_2NC_6H_4$	0.5	94	207-209	40:60
j	2-$O_2NC_6H_4$	1.0	50	214-216	27:73
k	3-$O_2NC_6H_4$	1.0	57(30)	219-221(220-221)	27:73
l	4-$O_2NC_6H_4$	1.0	60	210-212	30:70

[a]Conditions reported in literature[3]: EtONa in EtOH, stirred for 24 h at room temperature.
[b]The ratios of *cis/trans* were determined by ^{1}H NMR.

* Correspondence.

Experimental

Melting points are uncorrected. IR spectra were recorded on a Bio-Rad FTS-40 spectrometer (KBr). ^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker AVANCE (400 MHz) spectrometer using TMS as the internal standard and DMSO as a solvent. MS were determined on a VG-7070E spectrometer (EI, 70 eV). Elemental analyses were measured on a HERAEUS (CHNO, Rapid) analyser.

General procedure for preparation of 4-oxo-2-thioxohexahydropyrimidines **3**: To a solution of sodium methoxide (2 mmol) in absolute methanol (5 mL), thiourea (1 mmol) and ethyl 2-cyanopropenoate (1 mmol) were added. After stirring at room temperature for a period as indicated in the Table 1, the solvent was removed and the residue was dissolved in water. The solution was acidified with 5% acetic acid and the resulting precipitate was collected, washed with water and recrystallised from 95% ethanol. All the products were confirmed by their m.p., IR, MS, ^{1}H NMR, ^{13}C NMR spectra data. Among of them, compounds **3b–3e, 3h–3j** and **3l** have not been reported.

3a: White needle; m.p. 238–240 °C; ^{1}H NMR (DMSO-d_6) δ: 10.50 (s, 0.38H, NH-1), 10.23 (s, 0.62H, NH-1), 7.24–7.45 (m, 5H, arom.), 5.29 (d, 0.38H, H-6, *J*=8 Hz), 5.21 (d, 0.62H, H-6, *J*=12 Hz), 5.19 (d, 0.38H, H-5, *J*=8 Hz), 5.01 (d, 0.62H, H-5, *J*=12 Hz); ^{13}C NMR (DMSO-d_6) 179.55, 179.15, 161.00, 160.75, 136.95, 136.50, 130.10, 129.90, 129.83, 129.68, 128.62., 127.51, 115.40, 115.10, 56.94, 54.80, 41.42, 41.02; IR (KBr) ν: 3250, 3130, 2890, 1720, 1550, 1230 cm^{-1}; MS *m/z* (%): 231 (M$^+$, 43), 171 (100), 157 (82), 128 (51), 115 (60), 105 (57), 77 (73); Anal. calcd. for $C_{11}H_9N_3OS$: C 57.14, H 3.90, N 18.18; found C 57.04, H 3.91, N 18.16.

3b: White needle; m.p. 200–202 °C; ^{1}H NMR (DMSO-d_6) δ: 12.03 (s, 0.25H, NH-3), 11.78 (s, 0.75H, NH-3), 10.40 (s, 0.25H, NH-1), 10.13 (s, 0.75H, NH-1), 7.66–7.21 (m, 4H, arom.), 5.68 (d, 0.75H, H-6, *J*=12 Hz), 5.56 (d, 0.25H, H-6, *J*=8 Hz), 5.32 (d, 0.25H, H-5, *J*=8 Hz), 5.11 (d, 0.75H, H-5, *J*=12 Hz); ^{13}C NMR (DMSO-d_6) 179.51, 179.17, 160.80, 160.15, 134.75, 134.18, 133.61, 131.83, 131.08, 130.69, 130.30, 129.23, 128.80, 127.95, 115.02, 114.47, 53.42, 51.76, 40.60, 40.28; IR (KBr) ν: 3287, 2891, 2266, 1734, 1554, 1447, 1352, 1239, 1155 cm^{-1}; MS *m/z* (%): 267 (M+2, 18), 265 (M$^+$, 55), 233 (29), 189 (10), 180 (20), 162 (10), 138 (100), 128 (19), 102 (16), 77 (34); Anal. calcd. for $C_{11}H_8ClN_3OS$: C 49.72, H 3.01, N 15.82; found C 49.60, H 3.30, N 15.64.

3c: White needle; m.p. 208–210 °C; ^{1}H NMR (DMSO-d$_6$) δ: 11.95 (s, 0.3H, NH-3), 11.84 (s, 0.7H, NH-3), 10.51 (s, 0.3H, NH-1), 10.25 (s, 0.7H, NH-1), 7.78–7.21 (m, 4H, arom.), 5.33 (d, 0.3H, H-6, J=4 Hz), 5.29 (d, 0.3H, H-5, J=4 Hz), 5.26 (d, 0.7H, H-6, J=12 Hz), 5.08 (d, 0.7H, H-5, J=12 Hz); ^{13}C NMR (DMSO-d$_6$) 179.55, 179.28, 160.83, 160.53, 139.23, 138.75, 134.32, 134.23, 131.91, 131.59, 130.20, 129.96, 128.64, 127.62, 126.03, 115.21, 114.96, 56.34, 54.02, 41.15, 40.93; IR (KBr) ν: 3188, 2885, 2258, 1730, 1551, 1440, 1353, 1233, 1159 cm^{-1}; MS m/z (%): 267 (M+2, 30), 265 (M$^+$, 82), 233 (23), 162 (25), 138 (100), 128 (37); Anal. calcd. for $C_{11}H_8ClN_3OS$: C 49.72, H 3.01, N 15.82 ; found C 49.51, H 3.00, N 16.08.

3d: White needle; m.p. 220–222 °C; ^{1}H NMR (DMSO-d_6) δ: 11.92 (s, 0.35H, NH-3), 11.81 (s, 0.65H, NH-3), 10.49 (s, 0.35H, NH-1), 10.21 (s, 0.65H, NH-1), 7.70–7.26 (m, 4H, arom.), 5.29 (d, 0.35H, H-6, *J*=8 Hz), 5.26 (d, 0.35H, H-5, *J*=8 Hz), 5.16 (d, 0.65H, H-6, *J*=12 Hz), 5.03 (d, 0.65H, H-5, *J*=12 Hz); ^{13}C NMR (DMSO-d_6) 179.53, 179.16, 160.92, 160.56, 135.86, 135.40, 134.77, 134.62, 130.66, 129.92, 129.73, 129.40, 115.25, 115.02, 56.24, 54.03, 41.27, 40.95; IR (KBr) ν: 3299, 3160, 2898, 2265, 1743, 1555, 1448, 1350, 1235, 1158 cm^{-1}. MS *m/z* (%): 267 (M+2, 20), 265 (M$^+$, 65), 233 (33), 162 (25), 138 (100), 128 (15), 101 (8), 77 (11); Anal. calcd. for $C_{11}H_8ClN_3OS$: C 49.72, H 3.01, N 15.82; found C 49.75, H 3.02, N 15.67.

3e: White needle; m.p. 160–161 °C; ^{1}H NMR (DMSO-*d6*) δ: 12.06 (s, 0.2H, NH-3), 11.80 (s, 0.8H, NH-3), 10.38 (s, 0.2H, NH-1), 10.10 (s, 0.8H, NH-1), 7.78–7.21 (m, 3H, arom.), 5.70 (d, 0.8H, H-6, *J*=12 Hz), 5.54 (d, 0.2H, H-6, *J*=8 Hz), 5.30 (d, 0.2H, H-5, *J*=8 Hz), 5.14(d, 0.8H, H-5, *J*=12 Hz); ^{13}C NMR (DMSO-d_6) 179.52, 179.33, 160.68, 159.96, 135.56, 135.30, 134.23, 134.10, 132.90, 131.83, 130.55, 130.10, 129.43, 129.08, 114.93, 114.25, 52.91, 51.41, 39.69, 38.99; IR(KBr) ν: 3190, 2890, 2260, 1730, 1555, 1471, 1351, 1237, 1155 cm^{-1}; MS *m/z* (%): 299 (M$^+$, 100), 267 (28), 223 (18), 199 (20), 172 (68), 147 (26), 128 (24); Anal. calcd. for $C_{11}H_7Cl_2N_3OS$: C 44.00, H 2.33, N 14.00; found C 43.85, H 2.38, N 14.29.

3f: White needle; m.p. 248–250 °C; ^{1}H NMR (DMSO-d_6)δ: 11.84 (s, 0.4H, NH-3), 11.75 (s, 0.6H, NH-3), 10.45 (s, 0.4H, NH-1), 10.15 (s, 0.6H, NH-1), 7.59–7.12 (m, 4H, arom.), 5.23 (d, 0.4H, H-6, *J*=8 Hz), 5.14 (d, 0.6H, H-6, *J*=12 Hz), 5.12 (d, 0.4H, H-5, *J*=8 Hz), 4.95 (d, 0.6H, H-5, *J*=12 Hz), 2.33 (s, 1.8H, CH_3), 2.31 (s, 1.2H, CH_3); ^{13}C NMR (DMSO-d_6) 179.44, 178.99, 161.10, 160.81, 139.56, 139.42, 133.89, 133.43, 130.34, 130.22, 128.49, 127.36, 115.43, 115.14, 56.67, 54.59, 41.46, 40.85, 21.64, 21.54; IR (KBr) ν: 3150, 2944, 2362, 1715, 1560, 1445, 1357, 1241, 1158 cm^{-1}; MS *m/z* (%): 245 (M$^+$, 85), 185 (45), 143 (27), 128 (50), 113 (100), 102 (49), 91 (95); Anal. calcd. for $C_{12}H_{11}N_3OS$: C 58.78, H 4.49, N 17.14; found C 58.66, H 4.60, N 17.04.

3g: White needle; m.p. 230–232 °C; ^{1}H NMR (DMSO-d_6) δ: 10.45 (s, 0.35H, NH-1), 10.14 (s, 0.65H, NH-1), 7.36 (d, 1.3H, arom., *J*=8 Hz), 7.16 (d, 0.7H, arom., *J*=8 Hz), 7.00 (d, 2H, arom., *J*=8 Hz), 5.23 (d, 0.35H, H-6, *J*=8 Hz), 5.14 (d, 0.65H, H-6, *J*=12 Hz), 5.12 (d, 0.35H, H-5, *J*=8 Hz), 4.98 (d, 0.65H, H-5, *J*=12 Hz), 3.78 (s,1.95H, OCH_3), 3.77 (s, 1.05H, OCH_3); ^{13}C NMR (DMSO-d_6) 179.36, 178.90, 161.23, 160.86, 160.65, 160.45, 129.98, 128.78, 128.25, 115.46, 115.15, 114.99, 56.40, 56.06, 54.30, 41.58, 40.96; IR (KBr) ν: 3135, 2903, 2600, 2266, 1725, 1565, 1447, 1357, 1247, 1166 cm^{-1}; MS *m/z* (%): 262 (M+1, 95), 261 (M$^+$, 30), 161 (75), 136 (53), 121 (100), 105 (50); Anal. calcd. for $C_{12}H_{11}N_3O_2S$: C 55.17, H 4.21, N 16.09; found C 55.26, H 4.46, N 15.94.

3h: White needle; m.p. 228–230 °C; ^{1}H NMR (DMSO-d_6) δ: 11.86 (s, 0.3H, NH-3), 11.75 (s, 0.7H, NH-3),10.46 (s, 0.3H, NH-1), 10.13 (s, 0.7H, NH-1), 7.25–6.72 (m, 3H, arom.), 6.08 (s, 1.2H, OCH_2O), 6.07 (s, 2.8H, OCH_2O), 5.24 (d, 0.3H, H-6, *J*=4 Hz), 5.14 (d, 0.3H, H-5, *J*=4 Hz), 5.12 (d, 0.7H, H-6, *J*=12 Hz), 4.98 (d, 0.7H, H-5, *J*=12 Hz); ^{13}C NMR (DMSO-d_6) 179.33, 178.95, 161.17, 160.78, 148.78, 148.60, 148.41, 130.59, 129.99, 122.89, 121.00, 115.36, 115.12, 109.46, 109.13, 108.53, 107.68, 102.40, 102.29, 56.69, 54.46, 41.48, 40.95; IR (KBr) ν: 3193, 2897, 2265, 1723, 1554, 1446, 1353, 1238, 1153 cm^{-1}; MS *m/z* (%): 275 (M$^+$, 42), 216 (48), 201 (16), 173 (13), 148 (22), 135 (100), 129 (14), 87 (10), 59 (23); Anal. calcd. for $C_{12}H_9N_3O_3S$: C 52.36, H 3.27, N 15.27; found C 52.36, H 3.18, N 15.03.

3i: Yellow needle; m.p. 207–209 °C; ^{1}H NMR (DMSO-d_6) δ: 11.77 (s, 0.4H, NH-3), 11.68 (s, 0.6H, NH-3), 10.39(s, 0.4H, NH-1), 10.05(s, 0.6H, NH-1), 7.24–6.72 (m, 4H, arom.), 5.18 (d, 0.4H, H-6, *J*=4 Hz), 5.03 (d, 0.6H, H-6, *J*=12 Hz), 5.02 (d, 0.4H, H-5, *J*=4 Hz), 4.94 (d, 0.6H, H-5, *J*=12 Hz), 2.92 (s, 2.4H, $N(CH_3)_2$), 2.90 (s, 3.6H, $N(CH_3)_2$); ^{13}C NMR (DMSO-d_6) 179.27, 178.70, 161.43, 161.05, 151.65, 151.41, 129.29, 128.20, 123.63, 123.12, 115.62, 115.32, 112.98, 112.95, 56.60, 54.60, 41.67, 40.84; IR (KBr) ν: 3193, 2897, 2362, 1714, 1530, 1439, 1362, 1236, 1155 cm^{-1}; MS *m/z* (%): 274(M$^+$, 38), 215 (57), 200 (12), 196 (90), 171 (68), 134 (100), 72 (53), 59 (66); Anal. calcd. for $C_{13}H_{14}N_4OS$: C 56.93, H 5.11, N 20.44; found C 57.04, H 5.09, N 20.19.

3j: Light brown needle; m.p. 214–216 °C; ^{1}H NMR (DMSO-d_6) δ: 12.13 (s, 0.27H, NH-3), 11.84 (s, 0.73H, NH-3), 10.27 (s, 0.27H, NH-1), 10.24 (s, 0.73H, NH-1), 8.20–7.42 (m, 4H, arom.), 5.94 (d, 0.27H, H-6, *J*=8 Hz), 5.77 (d, 0.73H, H-6, *J*=12 Hz), 5.40 (d, 0.27H, H-5, *J*=8 Hz), 5.25 (d, 0.73H, H-5, *J*=12 Hz); ^{13}C NMR (DMSO-d_6) 179.34, 160.59, 159.90, 150.12, 148.50, 135.89, 134.95, 131.93, 131.67, 130.50, 130.21, 128.58, 126.70, 125.77, 115.04, 114.60, 51.86, 50.30, 39.88, 39.22; IR (KBr) ν: 3260, 2867, 2265, 1721, 1543, 1441, 1341, 1247, 1152 cm^{-1}; MS *m/z* (%): 276 (M$^+$, 100), 259 (12), 217 (8), 201 (18), 170 (21), 151 (43), 128 (30), 101 (26), 59 (45); Anal. calcd. for $C_{11}H_8N_4O_3S$: C 47.83, H 2.90, N 20.29; found C 47.89, H 2.87, N 19.93.

3k: Yellow needle; m.p. 219–221 °C; ^{1}H NMR (DMSO-d_6) δ: 12.05 (s, 0.27H, NH-3), 11.90 (s, 0.73H, NH-3), 10.58 (s, 0.27H, NH-1), 10.33 (s, 0.73H, NH-1), 8.42–7.73 (m, 4H, arom.), 5.50 (d, 0.27H, H-6, *J*=4 Hz), 5.46 (d, 0.73H, H-6, *J*=12 Hz), 5.38 (d, 0.27H, H-5, *J*=4 Hz), 5.20 (d, 0.73H, H-5, *J*=12 Hz); ^{13}C NMR (DMSO-d_6) 179.70, 179.48, 160.70, 160.34, 148.73, 138.88, 138.49, 135.69, 134.07, 131.72, 131.38, 125.18, 124.95, 123.80, 122.50, 115.08, 114.91, 56.16, 53.77, 41.05, 40.73; IR (KBr) ν: 3339, 3167, 3071, 2892, 2262, 1724, 1532 1445, 1355, 1236, 1153 cm^{-1}; MS *m/z* (%): 276 (M$^+$, 100), 259 (18), 201 (7), 193 (37), 170 (5), 151 (37), 128 (15), 101 (9), 77 (9), 59 (14); Anal. calcd. for $C_{11}H_8N_4O_3S$: C 47.83, H 2.90, N 20.29 ; found C 47.97, H 2.90, N 20.18.

3l: Brown needle; m.p. 210–212 °C; ^{1}H NMR (DMSO-d$_6$) δ: 12.02 (s, 0.3H, NH-3), 11.89 (s, 0.7H, NH-3), 10.55 (s, 0.3H, NH-1), 10.33 (s, 0.7H, NH-1), 8.36–7.53 (m, 4H, arom.), 5.47 (d, 0.3H, H-6, *J*=8Hz), 5.44 (d, 0.7H, H-6, *J*=12Hz), 5.38 (d, 0.3H, H-5, *J*=8Hz), 5.12 (d, 0.7H, H-5, *J*=12Hz); ^{13}C NMR (DMSO-d_6) 179.70, 179.36, 160.59, 160.32, 148.91, 148.72, 143.88, 143.59, 130.32, 129.07, 125.09, 124.83, 115.05, 114.90, 56.24, 54.00, 41.00, 40.73; IR (KBr) ν: 3307, 3106, 2880, 2362, 1715, 1552, 1462, 1350, 1237, 1154 cm^{-1}; MS *m/z* (%): 276 (M$^+$, 100), 217 (25), 201 (27), 175 (19), 170 (26), 155 (20), 151 (56), 128 (46), 101 (39), 77 (13), 59 (73); Anal. calcd. for $C_{11}H_8N_4O_3S$: C 47.83, H 2.90, N 20.29; found C 47.89, H 2.91, N 19.96.

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