SYNTHESIS OF 1,3-DIALKYL- AND 1,3-DIPHENYL-5-CYANO-2-THIO-URACIL DERIVATIVES

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Abstract- Nucleophilic vinylic substitutions of ethyl (*E*)- and (*Z*)-3-aryl-3-chloro-2-cyanopropenoates (**1a**) and (**1b**) with symmetrically substituted thioureas afforded, after spontaneous cyclisation, 1,3-dialkyl- and 1,3-diphenyl-5-cyano-2-thiouracil derivatives (**3a-3h**) in moderate to good yields

Pyrimidine derivatives have proven to be active antitumor,[1-4] antipyretic and antiinflammatory agents.[5-8] Synthesis of some 5-cyano-2-thiouracil derivatives has previously been reported. [9-11]

Recently we reported the synthesis of 1,3-thiazin-4-one derivatives obtained by reacting ethyl (*E*)- and (*Z*)-3-aryl-3-chloro-2-cyanopropenoates with thioureas bearing at least one primary amino group.[12] In this article we report the synthesis of 2-thiouracils (**3a-3h**) starting from the same substrates (**1a, 1b**) as in the above mentioned 1,3-thiazin-4-one synthesis but now by using symmetrically substituted thioureas as reagents. (Scheme 1, Table 1).

Scheme 1

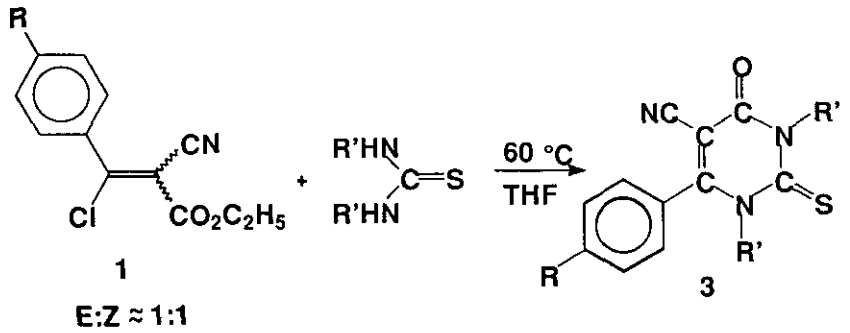

Table 1. Reaction products (**3a-3h**) and yields[a] from the reactions of **1a** and **1b** with symmetrically substituted thioureas.

	3				3		
R	R	R'	Yield (%)		R	R'	Yield (%)
a	H	CH_3	68	**e**	H	C_2H_5	82
b	CH_3	CH_3	65	**f**	CH_3	C_2H_5	79
c	H	Ph	62	**g**	H	Allyl	71
d	CH_3	Ph	82	**h**	CH_3	Allyl	67

In the reactions with the thioureas studied in the present work, substitution of chlorine proceeded by an attack from the amino group forming 2-thiouracils (**3a-3h**) and not from the thiocarbonyl group to form 1,3-thiazinones, as was the case in the reactions with thioureas bearing at least one -NH_2 group.[12]

The thiouracils (**3a-3h**) were formed at 60 °C in THF independent of the *E* :*Z* configuration of the starting esters (**1a**) and (**1b**). The method is advantageous since both isomers can be used and the troublesome separation of *E*- and *Z*-isomers is avoided. The amino group reacted exclusively with the carbethoxy group to form the imide carbonyl group at C-4 after expulsion of the ethoxy group. Cyclisation to the cyano group to form an imino group at C-4 was not observed in the present investigation. The structures of the thiouracils were deduced from their ^1H, ^{13}C, ^{15}N NMR and MS spectra. Typical fragmentations in all MS spectra are abundant M^+-1 ions, which were the base peaks, except for the spectra of the diphenyl derivatives (**3c-d**). In the ^1H NMR spectrum of **3a** the methyl signals appear at δ = 3.75 and 3.59 ppm, respectively. This clearly shows the presence of two N-CH_3 groups and not one N-CH_3 and one S-CH_3 group, since the S-CH_3 signal should appear at approximately δ = 2.65 ppm as in the spectrum of 5-cyano-3-methyl-2-methylthio-6-phenyl-4-pyrimidone.[13]

Further evidence for the thiouracil structure was obtained from the $^3J_{CH}$-coupling between the thiocarbonyl carbon and the methylene protons of the allyl groups at positions 1 and 3, respectively, of product (**3h**) (δ=176.68, quintet, $^3J_{CH}$ =5.3 Hz). The $^3J_{CH}$-coupling between the carbonyl carbon and the methylene protons of the allyl group at position 3 appeared as a triplet (δ=155.99, t, $^3J_{CH}$=2.7 Hz).

EXPERIMENTAL

Melting points are uncorrected. IR spectra were measured in KBr discs and are reported in cm^{1}. NMR spectra were measured in $CDCl_3$. ^{1}H NMR spectra were determined at 400 MHz on a JEOL JNM-LA400 spectrometer and ^{13}C NMR on the same instrument at 100.4 MHz. Chemical shifts are expressed in ppm (δ) downfield from TMS. ^{15}N NMR spectra were measured at 50.55 MHz on a JEOL JNM-A500 spectrometer. Dimethylformamide was used as internal standard. Electron ionisation MS spectra (EIMS) and high resolution MS spectra (HRMS) were determined at 70 eV on a VG-7070E spectrometer equipped with a gas chromatograph (fused silica column DB-1). GLC analyses were performed on a similar column, temperature programming from 150 to 290 °C. Ethyl 3-chloro-2-cyano-3-phenylpropenoate (**1a**) (*E*:*Z*≈1:1) and ethyl 3-chloro-2-cyano-3-(4-methylphenyl)propenoate (**1b**) (*E*:*Z*≈1:1) were prepared as described earlier.[12] The thioureas were prepared from isothiocyanates and amines.[14]

General Procedure for the Reactions of **1a** and **1b** with Thioureas.

A solution of **1a** or **1b** (2 mmol) and thiourea (4 mmol) in THF (30 mL) was stirred for 15 h at 60 °C under argon atmosphere. The solvent was evaporated at reduced pressure. The residue was diluted with water and dichloromethane. The organic phase was dried (Na_2SO_4) and evaporated under reduced pressure. The resulting precipitate was generally recrystallized from ethanol except **3a** and **3b** which were recrystallized from dichloromethane.

5-Cyano-1,3-dimethyl-6-phenyl-2 thiouracil (3a). Yield 68 %; mp 128-130 °C; IR 2210, 1670; EIMS *m/z* (RA) 257 (M^+, 64), 256 (100), 183 (22), 127 (5), 118 (32), 77 (14), 74 (10), 51 (6); ^{1}H NMR 7.40-7.65 (m, 5 H), 3.79 (s, 3H), 3.59 (s, 3 H); ^{13}C NMR 177.77, 161.80, 156.82, 131.78, 131.02, 129.41, 127.28, 113.29. 93.80, 43.49, 36.12; ^{15}N NMR -142.45, -231.08, -254.21; HRMS calcd for $C_{13}H_{11}N_3OS$ 257.0623, found 257.0619. *Anal.* Calcd for $C_{13}H_{11}N_3OS$: C, 60.69; H, 4.31; N, 16.34; S, 12.44. Found: C, 60.04; H, 4.10; N, 15.84, S, 11.81.

5-Cyano-1,3-dimethyl-6-(4-methylphenyl)-2-thiouracil (3b). Yield 65 %; mp 173-175 °C; IR 2220, 1680; EIMS *m/z* (RA) 271 (M^+, 68), 270 (100), 197(18), 140 (8), 132 (24), 91 (8); ^{1}H NMR 7.39 (d, 2 H, *J*=8.2 Hz), 7.29 (d, 2 H, *J*=8.2 Hz), 3.79 (s, 3 H), 3.60 (s, 3 H), 3.45 (s, 3 H); ^{13}C NMR 177.92, 161.95, 156.88, 142.40, 130.44, 128.16, 127.28, 113.41, 93.83, 43.25, 36.12, 21.58; ^{15}N NMR -142.80, -218.07, -240.34; HRMS calcd for $C_{14}H_{13}N_3OS$ 271.0779, found

271.0772. *Anal.* Calcd for $C_{14}H_{13}N_3OS$: C, 61.97; H 4.83, N, 15.50; S, 11.79. Found: C, 62.04; H, 4.83, N, 15.14; S, 11.82.

5-Cyano-1,3,6-triphenyl-2-thiouracil (3c). Yield 62 %; mp 275-277 °C; IR 2230, 1695; EIMS *m/z* (RA) 381 (41), 380 (21), 272 (78), 180 (33), 145 (29), 77 (100); ^{1}H NMR 7.30-7.70 (m, 15 H); ^{13}C NMR 179.32, 162.64, 157.44, 140.97, 139.57, 136.03, 131.87, 131.48, 130.13, 129.54, 129.27, 128.67, 128.12, 127.97, 123.19, 122.28, 114.32, 94.53; ^{15}N NMR -140.53, -214.75 -234.51; HRMS calcd for $C_{23}H_{15}N_3OS$ 381.0936, found 381.0932. *Anal.* Calcd for $C_{23}H_{15}N_3OS$: C, 72.42; H, 3.97; N, 11.02, S, 8.39. Found: C, 69.14; H, 3.83; N, 10.73; S, 8.24.

5-Cyano-1,3-diphenyl-6-(4-methylphenyl)-2-thiouracil (3d). Yield 82 %; mp > 300 °C; IR 2220, 1705; EIMS 395 (M^+, 92), 394 (46), 286 (100), 194 (26), 145 (35), 91 (7), 77 (46); ^{1}H NMR 7.20-7.80 (m, 14 H), 2.30 (s, 3 H); ^{13}C NMR 179.21, 162.75, 157.28, 140.97, 139.83, 139.45, 129.43, 128.56, 127.97, 114.04, 94.16, 21.60; ^{15}N NMR -140.96, -214.73, -234.19; HRMS calcd for $C_{24}H_{17}N_3OS$ 395.1092, found 395.1396. *Anal.* Calcd for $C_{24}H_{17}N_3OS$: C, 72.89; H, 4.34; N, 10.63; S, 8.09. Found: C, 72.14; H, 4.50; N, 10.90; S, 8.40.

5-Cyano-1,3-diethyl-6-phenyl-2-thiouracil (3e). Yield 82 %; mp 161-163 °C; IR 2240, 1670; EIMS 285 (M^+, 97), 284 (100), 256 (49), 252 (28), 104 (41), 86 (31), 77 (27), 60 (25); ^{1}H NMR 7.39-7.61 (m, 5 H), 4.60 (q, 2 H, *J*=7.0 Hz), 4.31 (q, 2 H, *J*= 6.8 Hz), 1.36 (t, 3H, *J*=7.0 Hz), 1.19 (t, 3 H, *J*=6.8 Hz); ^{13}C NMR 176.30, 161.62, 156.01, 131.36, 130.92, 129.60, 126.90, 112.97, 94.52, 49.34, 44.42, 13.28, 10.92; ^{15}N NMR -141.99, -218.04, -240.61; HRMS calcd for $C_{15}H_{15}N_3OS$ 285.0936 found, 285.0931. *Anal.* Calcd for $C_{15}H_{15}N_3OS$: C, 63.14; H, 5.30; N, 14.74; S, 11.21. Found: C, 63.04; H, 5.23; N, 14.62; S, 11.30.

5-Cyano-1,3-diethyl-6-(4-methylphenyl)-2-thiouracil (3f). Yield 79 %: IR 2230, 1670; EIMS 299 (M^+ 96), 298 (100), 270 (40), 266 (26), 239 (23), 118 (25), 86 (24); ^{1}H NMR 7.20-7.34 (m, 4 H), 4.53 (q, 2 H, *J*=7.0 Hz), 4.26 (q, 2H, *J*=6.8 Hz), 2.39 (s 3 H), 1.29 (t, 3 H, *J*=7.0 Hz), 1.10 (t, 3 H, *J*=6.8 Hz); ^{13}C NMR 176.32, 161.91, 156.06, 141.75, 130.17, 127.99, 126.76, 113.12, 94.52, 49.25, 44.32, 21.42, 13.26, 10.88; ^{15}N NMR -142.71, -218.01, -240.43; HRMS calcd for $C_{16}H_{17}N_3OS$ 299.1092 found, 299.1090. *Anal.* Calcd for $C_{16}H_{17}N_3OS$: C 64.19; H, 5.73; N, 14.04; S, 10.69. Found: C, 64.14; H, 5.80; N, 14. 04; S, 11.00.

5-Cyano-1,3-diallyl-6-phenyl-2-thiouracil (3g). Yield 71 %; mp 134-136 °C; IR 2230, 1680; EIMS 309 (M^+ 32), 308 (100), 268 (35), 236 (22), 127 (16), 98 (26), 77 (17), 73 (18); ^{1}H NMR 7.37-7.58 (m, 5 H), 5.92-6.02 (m, 1 H), 5.73-5.83 (m, 1 H), 5.29-5.31 (dd, 1 H, *J* = 1.1 and 12.6 Hz), 5.39-5.44 (dd, 1 H, *J* = 1.2 and 18.4 Hz), 5.14-5.19 (m, 3 H), 4.80-4.87 (m, 3 H); ^{13}C NMR

176.65, 162.03, 155.96,131.46, 130.34, 130.26, 129.22, 129.17, 127.18, 120.01, 118.98, 112.81, 94.46, 55.87, 50.62; HRMS calcd for $C_{17}H_{15}N_3OS$ 309.3941 found, 309.3937. *Anal.* Calcd for $C_{17}H_{15}N_3OS$: C, 66.00; H, 4.89; N, 13.59; S, 10.34. Found: C, 65.44; H, 4.84; N, 13.33; S; 9.94.

5-Cyano-1,3-diallyl-6-(4-methylphenyl)-2-thiouracil (3h) Yield 67 %; mp 103-105 °C; IR 2230, 1670; EIMS 323 (M^+ 41), 322(100), 282 (55), 250 (22), 140 (19), 98 (22), 87 (22), 73 (25); ^{1}H NMR 7.22-7.39 (m, 4 H), 5.71-5.86 (m, 1 H), 5.88-6.04 (m, 1 H), 5.26-5.34 (m 1 H), 5.35-5.46 (m, 1 H), 5.11-5.22 (m, 3 H), 4.80-4.91 (m, 3 H), 2.43 (s, 3 H); ^{13}C NMR 176.68, 162.35, 155.99, 141.92. 130.37, 129.83, 129.21, 127.47, 127.07,119.89, 118.83, 112.94, 94.49, 55.77, 50.57, 21.40; HRMS calcd for $C_{18}H_{17}N_3OS$ 323.4212, found 323.421. *Anal.* Calcd for $C_{18}H_{17}N_3OS$: C, 66.85; H, 5.30; N, 13.00; S, 9.90. Found: C, 66.90; H, 5.25; N, 12.84; S, 9.73.

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