SYNTHESIS OF ALKYL- AND PHENYL-2-THIOURACILS AND 1,3-THIAZIN-4-ONES BY NUCLEOPHILIC SUBSTITUTION OF UNSYMMETRICAL THIOUREAS WITH 3-CHLOROPROPENOATES

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Unsymmetrically substituted thioureas and ethyl (*E*)- and (*Z*)-3-aryl-3-chloro-2-cyanopropenoates (**1a**) and (**1b**) gave after nucleophilic vinylic substitution and cyclisation two isomers of 1,3-disubstituted 6-aryl-5-cyano-2-thiouracil derivatives, **3a**–**3i** and **4a**–**4i**. Substituted 1,3-thiazin-4-ones **5a**–**5d** were formed in moderate to good yields when monosubstituted thioureas were allowed to react under similar conditions.

Key words: 2-Thiouracils; 1,3-Thiazin-4-ones; Thioureas; Cyclization; Nucleophilic substitutions; Pyrimidines.

Some aminouracil derivatives display antitumor activity[1–3] and certain pyrimidines and bridgehead nitrogen heterocycles exhibit antileishmanial activity[4–7]. The synthesis of some 2-thiouracil derivatives has previously been reported[8–13].

We have previously reported the synthesis of 1,3-thiazinones obtained in the reaction between ethyl (*E*)- and (*Z*)-3-aryl-3-chloro-2-cyanopropenoates and thioureas containing at least one NH_2 group. We have also reported the synthesis of 2-thiouracil derivatives starting from the same ethyl 3-chloropropenoates and symmetrically substituted thioureas[14].

The present investigation was undertaken to elucidate the regioselectivity of reactions between ethyl 3-chloropropenoates (**1a** and **1b**) and unsymmetrically substituted thioureas. It was of interest to study the effect of diverse substituents in unsymmetrically substituted thioureas on the nucleophilic substitution partly at the chloro substituted β-carbon and partly at the carbonyl carbon of the ethoxycarbonyl group. This study was not possible with the previously studied symmetrically substituted thioureas. We also report the results of the reactions between **1a**, **1b** and allyl- and phenylthioureas.

Some of the previously synthesized 1,3-thiazin-4-ones have been screened in an antituberculosis activity testing program. However, no notable activity was found. We are therefore now concentrated on the synthesis of new pyrimidin derivatives.

EXPERIMENTAL

Methods

Melting points are uncorrected. IR spectra were measured in KBr discs and are reported in cm^{-1}. ^1H NMR spectra were measured at 400 MHz on a JEOL JNM-LA400 spectrometer and ^{13}C NMR spectra on the same instrument at 100.4 MHz in $CDCl_3$. Coupling constants *J* are given in Hz, chemical shifts are expressed in ppm (δ-scale) 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 mass spectra (EI MS) and high-resolution mass spectra (HR MS) 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**) ($E : Z \approx 1 : 1$) and ethyl 3-chloro-2-cyano-3-(4-methylphenyl)propenoate (**1b**) ($E : Z \approx 1 : 1$) were prepared as described earlier[15]. The thioureas were prepared from appropriate isothiocyanates and amines[16].

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

A solution of **1a** or **1b** (2 mmol) and the corresponding 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 extracted with water and dichloromethane. The organic phase was treated with Na_2CO_3 solution, dried with Na_2SO_4 and evaporated under reduced pressure. The residue was repeatedly recrystallized from ethanol to separate isomers **3** and **4**. Isomer **4** crystallized first and was easier to purify. The purification of **3** was generally achieved by repeated recrystallisation from a mixture of ethanol and methyl *tert*-butyl ether except of **3e** which was isolated by HPLC with acetonitrile–water (70 : 30) as eluent.

1-Benzyl-5-cyano-3-methyl-6-phenyl-2-thiouracil (**3a**). Yield 140 mg (21%), purity >99% (GC), m.p. 189–191 °C. IR: 2 210, 1 680. EI MS, *m/z* (rel.%): 333 (M^+, 35), 332 (7), 300 (8), 104 (7), 92 (8), 91 (100), 77 (9), 65 (11). ^1H NMR: 7.13–7.53 (m, 10 H); 6.84 (m, 2 H); 3.83 (s, 3 H). ^{13}C NMR: 177.93, 162.12, 156.52, 134.67, 131.41, 130.46, 129.19, 128.64, 127.80, 127.14, 126.03, 112.90, 94.51, 56.86, 36.53. HR MS calculated for $C_{19}H_{15}N_3OS$ 333.0936; found 333.0937.

3-Benzyl-5-cyano-1-methyl-6-phenyl-2-thiouracil (**4a**). Yield 273 mg (41%), purity >99% (GC), m.p. 149–151 °C. IR: 2 220, 1 690. EI MS, *m/z* (rel.%): 333 (M^+, 68), 300 (32), 242 (23), 148 (12), 118 (21), 91 (100), 77 (21), 65 (19). ^1H NMR: 7.26–7.63 (m, 10 H); 5.77 (s, 2 H); 3.55 (s, 3 H). ^{13}C NMR: 177.58, 161.75, 156.94, 134.92, 131.78, 130.92, 129.82, 129.27, 128.35, 128.01, 127.19, 119.05, 94.11, 51.28, 43.71. HR MS calculated for $C_{19}H_{15}N_3OS$ 333.0936; found 333.0935.

1-Benzyl-5-cyano-3-methyl-6-(4-methylphenyl)-2-thiouracil (**3b**). Yield 153 mg (22%), purity >98% (GC), m.p. 162–164 °C. IR: 2 210, 1 690. EI MS, *m/z* (rel.%): 347 (M^+, 43), 346 (12), 314 (10), 256 (8), 92 (8), 91 (100), 74 (7) 65 (12). ^1H NMR: 7.04–7.40 (m, 9 H); 6.88 (m,

2 H); 3.83 (s, 3 H); 2.38 (s, 3 H). ^{13}C NMR: 177.86, 162.49, 156.61, 142.03, 134.79, 129.89, 128.64, 127.75, 127.62, 127.08, 126.04, 113.10, 94.53, 56.80, 36.49, 21.49. HR MS calculated for $C_{20}H_{17}N_3OS$ 347.1092; found 347.1093.

3-Benzyl-5-cyano-1-methyl-6-(4-methylphenyl)-2-thiouracil (**4b**). Yield 257 mg (37%), purity >98% (GC), m.p. 135–137 °C. IR: 2 240, 1 670. EI MS, *m/z* (rel.%): 347 (M^+, 81), 346 (12), 314 (42), 256 (26), 148 (12), 132 (18), 91 (100), 65 (22). ^{1}H NMR: 7.19–7.58 (m, 9 H); 5.81 (s, 2 H); 3.55 (s, 3 H); 2.44 (s, 3 H). ^{13}C NMR: 177.57, 162.03, 156.96, 142.32, 134.74, 130.31, 129.07, 128.24, 127.89, 127.83, 127.11, 113.33, 93.92, 51.16, 43.69, 21.49. HR MS calculated for $C_{20}H_{17}N_3OS$ 347.1092; found 347.1093.

5-Cyano-3-methyl-1,6-diphenyl-2-thiouracil (**3c**). Yield 89 mg (14%), purity >99% (GC), m.p. 217–219 °C. IR: 2 210, 1 680. EI MS, *m/z* (rel.%): 319 (M^+, 100), 318 (56), 210 (22), 180 (42), 91 (19), 83 (33) 77 (72), 51 (32). ^{1}H NMR: 7.01–7.31 (m, 10 H); 3.84 (s, 3 H). ^{13}C NMR: 178.25, 161.65, 156.86, 130.67, 130.62, 129.35, 129.19, 128.67, 128.57, 128.09, 113.11, 93.77, 35.99. HR MS calculated for $C_{18}H_{13}N_3OS$ 319.0779; found 319.0779.

5-Cyano-1-methyl-3,6-diphenyl-2-thiouracil (**4c**). Yield 307 mg (48%), purity >98% (GC), m.p. >280 °C. IR: 2 230, 1 680. EI MS, *m/z* (rel.%): 319 (M^+, 64), 318 (100), 183 (9), 135 (26), 118 (43), 91 (8), 77 (42), 51 (15). ^{1}H NMR: 7.21–7.68 (m, 10 H); 3.60 (s, 3 H). ^{13}C NMR: 177.55, 161.43, 155.66, 130.57, 129.93, 128.64, 128.59, 127.83, 126.69, 126.13, 112.19, 93.46, 42.24. HR MS calculated for $C_{18}H_{13}N_3OS$ 319.0779; found 319.0775.

5-Cyano-3-methyl-6-(4-methylphenyl)-1-phenyl-2-thiouracil (**3d**). Yield 67 mg (10%), purity >98% (GC), m.p. 221–223 °C. IR: 2 230, 1 660. EI MS, *m/z* (rel.%): 333 (M^+, 100), 332 (51), 224 (17), 194 (42), 91 (27), 83 (49), 77 (68), 51 (27). ^{1}H NMR: 6.93–7.21 (m, 9 H); 3.75 (s, 3 H); 2.18 (s, 3 H). ^{13}C NMR: 178.31, 161.94, 156.92, 141.11, 140.75, 129.91, 129.32, 129.20, 129.15, 128.02, 127.65, 113.32, 93.83, 36.02, 21.38. HR MS calculated for $C_{19}H_{15}N_3OS$ 333.0936; found 333.0936.

5-Cyano-1-methyl-6-(4-methylphenyl)-3-phenyl-2-thiouracil (**4d**). Yield 347 mg (52%), purity >98% (GC), m.p. 263–265 °C. IR: 2 220, 1 690. EI MS, *m/z* (rel.%): 333 (M^+, 65), 332 (100), 197 (9), 135 (15), 132 (44), 91 (11), 77 (19), 51 (7). ^{1}H NMR: 7.12–7.51 (m, 9 H); 3.55 (s, 3 H); 2.40 (s, 3 H). ^{13}C NMR: 178.89, 162.70, 156.64, 142.51, 139.20, 130.45, 129.93, 129.16, 128.04, 127.71, 127.20, 113.11, 94.87, 43.46, 21.57. HR MS calculated for $C_{19}H_{15}N_3OS$ 333.0936; found 333.0934.

5-Cyano-1-ethyl-3-methyl-6-phenyl-2-thiouracil (**3e**). Yield 109 mg (20%), purity >98% (GC), m.p. 149–151 °C. IR: 2 240, 1 680. EI MS, *m/z* (rel.%): 271 (M^+, 77), 270 (100), 243 (13), 242 (15), 197 (15), 104 (32), 77 (18), 74 (23). ^{1}H NMR: 7.40–7.64 (m, 5 H); 4.32 (q, 2 H, J = 7.0); 3.80 (s, 3 H); 1.20 (t, 3 H, J = 7.0). ^{13}C NMR: 176.71, 161.62, 156.52, 131.40, 130.94, 129.63, 127.16, 113.00, 94.22, 49.40, 36.09, 13.24. HR MS calculated for $C_{14}H_{13}N_3OS$ 271.0779; found 271.0774.

5-Cyano-3-ethyl-1-methyl-6-phenyl-2-thiouracil (**4e**). Yield 157 mg (29%), purity >98% (GC), m.p 155–156 °C. IR: 2 210, 1 670. EI MS, *m/z* (rel.%): 271 (M^+, 100), 270 (76), 242 (42), 238 (32), 211 (27), 118 (39), 83 (22), 77 (23). ^{1}H NMR: 7.38–7.63 (m, 5 H); 4.60 (q, 2 H, J = 7.0); 3.57 (s, 3 H); 1.35 (t, 3 H, J = 7.0). ^{13}C NMR: 177.22, 161.55, 156.21, 131.64, 129.71, 127.14, 126.90, 113.18, 93.96, 44.35, 43.40, 10.88. HR MS calculated for $C_{14}H_{13}N_3OS$ 271.0779; found 271.0776.

5-Cyano-1-ethyl-3-methyl-6-(4-methylphenyl)-2-thiouracil (**3f**). Yield 126 mg (22%), purity >98% (GC), m.p. 175–177 °C. IR: 2 220, 1 690. EI MS, *m/z* (rel.%): 285 (M^+, 75), 284 (100), 257 (12), 256 (13), 211 (15), 140 (11), 118 (23), 74 (18). ^{1}H NMR: 7.28–7.40 (m, 4 H); 4.33 (q, 2 H, J = 6.9); 3.78 (s, 3 H); 2.45 (s, 3 H); 1.19 (t, 3 H, J = 6.9). ^{13}C NMR: 176.69, 161.93,

156.56, 141.81, 130.17, 127.88, 126.77, 113.14, 94.17, 49.31, 35.99, 21.43, 13.19. HR MS calculated for $C_{15}H_{15}N_3OS$ 285.0936; found 285.0935.

5-Cyano-3-ethyl-1-methyl-6-(4-methylphenyl)-2-thiouracil (**4f**). Yield 177 mg (31%), purity >99% (GC), m.p. 197–199 °C. IR: 2 230, 1 680. EI MS, *m/z* (rel.%): 285 (M^+, 100), 284 (79), 256 (45), 252 (36), 225 (34), 132 (40), 86 (21), 83 (39). ^{1}H NMR: 7.27–7.40 (m, 4 H); 4.59 (q, 2 H, *J* = 6.9); 3.58 (s, 3 H); 2.45 (s, 3 H); 1.35 (t, 3 H, *J* = 6.9). ^{13}C NMR: 177.31, 161.86, 156.30, 142.27, 130.32, 128.00, 127.14, 113.36, 93.96, 44.33, 43.46, 21.50, 10.90. HR MS calculated for $C_{15}H_{15}N_3OS$ 285.0936; found 285.0931.

5-Cyano-3-ethyl-1,6-diphenyl-2-thiouracil (**3g**). Yield 107 mg (16%), purity >98% (GC), m.p. 219–221 °C. IR: 2 230, 1 670. EI MS, *m/z* (rel.%): 333 (M^+, 100), 332 (24), 304 (30), 247 (28), 180 (52), 105 (33), 77 (96), 51 (27). ^{1}H NMR: 7.01–7.44 (m, 10 H); 4.61 (q, 2 H, *J* = 7.0); 1.40 (t, 3 H, *J* = 7.0); ^{13}C NMR: 177.80, 161.60, 156.37, 140.63, 130.56, 130.10, 129.35, 129.09, 128.49, 128.02, 127.14, 113.10, 94.08, 44.43, 10.99. HR MS calculated for $C_{19}H_{15}N_3OS$ 333.0936; found 333.0931.

5-Cyano-1-ethyl-3,6-diphenyl-2-thiouracil (**4g**). Yield 307 mg (46%), purity >99% (GC), m.p. 220–222 °C. IR: 2 210, 1 690. EI MS, *m/z* (rel.%): 333 (M^+, 71), 332 (100), 304 (27), 135 (21), 132 (11), 104 (24), 77 (44), 51 (14). ^{1}H NMR: 7.19–7.65 (m, 10 H); 4.32 (q, 2 H, *J* = 7.0); 1.21 (t, 3 H, *J* = 7.0). ^{13}C NMR: 177.88, 162.47, 156.36, 139.26, 131.48, 130.90, 129.87, 129.69, 129.07, 127.70, 126.92, 112.76, 95.43, 49.48, 13.28. HR MS calculated for $C_{19}H_{15}N_3OS$ 333.0936; found 333.0933.

5-Cyano-3-ethyl-6-(4-methylphenyl)-1-phenyl-2-thiouracil (**3h**). Yield 104 mg (15%), purity >99% (GC), m.p. 206–208 °C. IR: 2 210, 1 700. EI MS, *m/z* (rel.%): 347 (M^+, 100), 346 (22), 318 (34), 270 (30), 261 (26), 194 (46), 105 (31), 77 (77). ^{1}H NMR: 7.01–7.46 (m, 9 H); 4.61 (q, 2 H, *J* = 7.0); 2.25 (s, 3 H); 1.39 (t, 3 H, *J* = 7.0). ^{13}C NMR: 177.83, 161.86, 156.43, 140.95, 140.69, 129.31, 129.09, 129.01, 128.95, 127.93, 127.64, 113.27, 94.04, 44.36, 21.26, 10.94. HR MS calculated for $C_{20}H_{17}N_3OS$ 347.1092; found 347.1093.

5-Cyano-1-ethyl-6-(4-methylphenyl)-3-phenyl-2-thiouracil (**4h**). Yield 250 mg (36%), purity >98% (GC), m.p. 210–212 °C. IR: 2 220, 1 680. EI MS, *m/z* (rel.%): 347 (M^+, 75), 246 (100), 318 (26), 146 (10), 135 (15), 118 (23), 91 (9), 77 (22). ^{1}H NMR: 7.18–7.56 (m, 9 H); 4.33 (q, 2 H, *J* = 7.0); 2.46 (s, 3 H); 1.22 (t, 3 H, *J* = 7.0). ^{13}C NMR: 177.94, 162.80, 156.41, 141.95, 140.74, 130.29, 129.82, 129.36, 129.06, 127.70, 126,82, 112.90, 95.49, 49.41, 21.50, 13.28. HR MS calculated for $C_{20}H_{17}N_3OS$ 347.1092; found 347.1095.

1-Allyl-5-cyano-3-ethyl-6-(4-methylphenyl)-2-thiouracil (**3i**). Yield 237 mg (14%), purity >98% (GC), m.p. 214–216 °C. IR: 2 210, 1 680. EI MS, *m/z* (rel.%): 311 (M^+, 100), 310 (32), 296 (8), 282 (18), 183 (7), 140 (6), 118 (7), 86 (8). ^{1}H NMR: 7.35 (d, 2 H, *J* = 7.8); 7.26 (d, 2 H, *J* = 7.8); 5.8 (m, 1 H); 5.21 (m, 2 H); 4.83–4.92 (m, 2 H); 4.57 (q, 2 H, *J* = 6.8); 2.45 (s, 3 H); 1.35 (t, 3 H, *J* = 6.8). ^{13}C NMR: 176.69, 162.22, 156.01, 141.97, 130.55, 130.21, 127.93, 127.62, 118.90, 113.08. 94.63, 55.73, 44.49, 21.47, 10.89. ^{15}N NMR: –142.20, 217.74, –245.12. HR MS calculated for $C_{17}H_{17}N_3OS$ 311.1092; found 311.1096.

2-Allylamino-5-cyano-6-phenyl-4H-1,3-thiazin-4-one (**5a**). Yield 285 mg (53%), purity >98% (GC), m.p. >280 °C. IR: 2 210, 1 670. EI MS, *m/z* (rel.%): 269 (84), 187 (64), 159 (100), 132 (28), 121 (52), 82 (24), 77 (21), 41 (21). ^{1}H NMR: 9.53 (t, 1 H, *J* = 4.5); 7.67–7.57 (m, 5 H); 5.88 (m, 1 H); 5.25 (qd, 1 H, *J* = 15.6 and 1.6); 5.17 (qd, 1 H, *J* = 10.4 and 1.6); 4.06 (t, 2 H, *J* = 5.0). ^{13}C NMR: 165.25, 161.35, 160.18, 133.15, 133.01, 132.13, 129.38, 127.98, 117.06 (qt, *J* = 149.5 and 5.3), 114.83, 102.14, 44.13 (quintet of tripl., *J* = 140.3 and 4.5). HR MS calculated for $C_{14}H_{11}N_3OS$ 269.0623; found 269.0624.

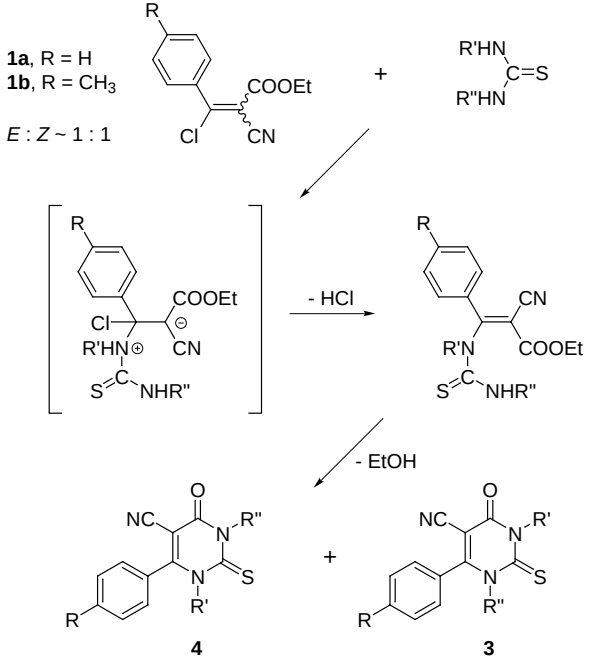
2-Allylamino-5-cyano-6-(4-methylphenyl)-4H-1,3-thiazin-4-one (**5b**). Yield 261 mg (46%), purity >98% (GC), m.p. >280 °C. IR: 2 210, 1 670. EI MS, *m/z* (rel.%): 283 (M^+, 77), 282 (10), 201 (53), 173 (100), 141 (27), 135 (43), 128 (18), 91 (23). ^{1}H NMR: 7.32–7.59 (m, 4 H); 5.80–5.91 (m, 1 H); 5.39–5.19 (m, 2 H); 4.15–4.22 (m, 2 H); 2.46 (s, 3 H). ^{13}C NMR: 169.17, 165.15, 160.51, 145.24, 130.43, 130.26, 128.00, 120.61, 118.68, 116.38. 113.53, 103.29, 46.49, 21.69. HR MC calculated for $C_{15}H_{13}N_3OS$ 283.0779; found 283.0775.

5-Cyano-6-phenyl-2-(phenylamino)-4H-1,3-thiazin-4-one (**5c**). Yield 373 mg (61%), purity >98% (GC), m.p. 240–242 °C. IR: 2 210, 1 670. EI MS, *m/z* (rel.%): 305 (M^+, 44), 187 (7), 159 (13), 121 (12), 118 (100), 91 (10), 77 (22), 51 (14). ^{1}H NMR: 10.85 (1 H, s); 7.18–7.52 (m, 10 H). ^{13}C NMR: 167.45, 160.41, 156.13, 131.56, 130.76, 127.85, 127.50, 127.32, 127.20, 126.38, 123.98, 112.83, 101.54. HR MS calculated for $C_{17}H_{11}N_3OS$ 305.0623; found 305.0624.

5-Cyano-6-(4-methylphenyl)-2-(phenylamino)-4H-1,3-thiazin-4-one (**5d**). Yield 422 mg (66%), purity >98%, m.p. 257–259 °C. IR: 2 230,1 680. EI MS, *m/z* (rel.%): 319 (M^+, 60), 202 (10), 173 (14), 135 (15), 119 (9), 118 (100), 91 (8), 77 (8). ^{1}H NMR: 10.87 (s, 1 H); 7.11–7.70 (m, 9 H); 2.44 (s, 3 H). ^{13}C NMR: 164.84, 160.81, 156.92, 141.80, 136.49, 128.94, 128.72, 127.79, 126.54, 124.20, 120.74, 113.25, 101.17, 20.19. HR MS calculated for $C_{18}H_{13}N_3OS$ 319.0779; found 319.0780.

RESULTS AND DISCUSSION

Two equivalents of unsymmetrically substituted thioureas were allowed to react with 3-chloropropenoates **1a** and **1b** for 15 h at 60 °C in THF (Scheme 1).



SCHEME 1

The reaction starts with a nucleophilic attack at C-3 followed by elimination of HCl. The intermediate formed could not be isolated, which shows that the cyclisation step is fast. In an earlier study[17] we reacted the same 3-chloropropenoates (**1a** and **1b**) with diverse amines giving always only one 3-aminopropenoate isomer. This shows that it is a nucleophilic reaction and that the reaction starts with an attack at C-3 followed by elimination of HCl. The starting esters consist of *E*- and *Z*-isomers (≈1 : 1). The intermediate shown in Scheme 1 has a single bond character which allows for conformational changes and the formation of thiouracils from both isomers. Since the thioureas are unsymmetrically substituted, two isomers (**3** and **4**) were formed. The proportion of **3** and **4** varied from 16 : 84 to 42 : 58% (Table I). The highest difference was with *N*-methyl- *N*'-phenylthiourea.

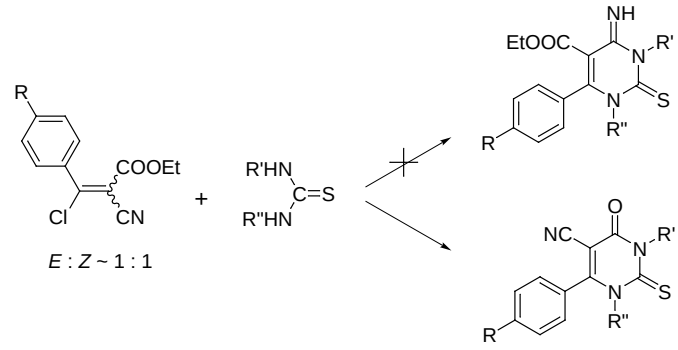
The distribution of the isomers is determined by the first reaction step. The higher yields of **4c** and **4d** can be attributed to electronic effects. The methyl substituted nitrogen atom is more reactive because the nonbonding electrons of the phenyl substituted nitrogen can be delocalized in the phenyl ring. The methyl group has an opposite effect owing to its positive inductive effect. The higher yields of **4g** and **4h** indicate a similar effect. In all reactions with a methylamino group of thiourea, higher yields of isomer **4** were generally attained.

TABLE I
Yields of reaction products (**3a–3i**) and (**4a–4i**) in the reactions of **1a** and **1b** with unsymmetrically substituted thioureas

3,4	R	R′	R″	Yields[a] of **3**, %	Yields[a] of **4**, %	Ratio[b] of **3** : **4**, %
a	H	CH_3	$PhCH_2$	21	41	32 : 68
b	CH_3	CH_3	$PhCH_2$	22	37	37 : 63
c	H	CH_3	Ph	14	48	23 : 77
d	CH_3	CH_3	Ph	10	52	16 : 84
e	H	CH_3	CH_3CH_2	20	29	37 : 63
f	CH_3	CH_3	CH_3CH_2	22	31	42 : 58
g	H	CH_3CH_2	Ph	16	46	27 : 73
h	CH_3	CH_3CH_2	Ph	15	36	30 : 70
i	CH_3	CH_3CH_2	allyl	14	–	31 : 69

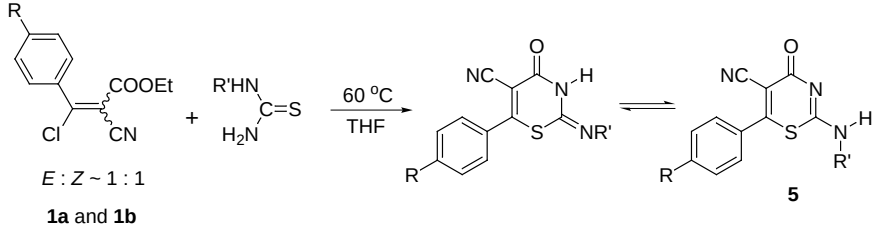
[a] Isolated yields. [b] Determined by GC.

The reactions are regioselective, *i.e.*, the cyclisation proceeds exclusively by attack of nitrogen on the ethoxycarbonyl group and not on the cyano group (Scheme 2). These syntheses are advatageous since both isomers cyclize to thiouracils and the troublesome separation of *E*- and *Z*-isomers is



SCHEME 2

avoided. In the reaction with the monosubstituted thioureas, the substitution of chlorine proceeds by a nucleophilic attack from the nonbonded electrons on nitrogen and not from sulfur in the thiocarbonyl group leading to 1,3-thiazin-4-ones, which are the only products formed in the reaction with thioureas bearing at least one NH_2 group (Scheme 3)[18].



SCHEME 3

Two reactions with phenylthiourea were carried out to elucidate if 1,3-thiazin-4-ones are also formed in reactions with aromatic thioureas with one NH_2 group. These reactions gave exclusively 1,3-thiazin-4-ones. The same results were achieved with allylthiourea (Table II).

The structures of the thiouracils and thiazinones were deduced from their ^1H, ^{13}C and ^{15}N NMR and mass spectra. An abundant $M^+ - 1$ ion was typical for the fragmentation of the thiouracils and it was also the base peak in six of the thiouracil spectra. The fragmentation pattern giving rise to the most abundant ions common for 1,3-thiazin-4-ones is presented in Fig. 1.

The identification of compounds **3** and **4** was among other evidences deduced from $^3J_{CH}$ coupling patterns. For example **3a**, **3b**, **4a** and **4b** were unambiguously identified by the $^3J_{CH}$ coupling between the carbonyl carbon (C-4) and the methyl or benzyl protons at position 3 and, furthermore, by the $^3J_{CH}$ coupling between C-6 and the methyl or benzyl protons at position 1. This can be exemplified by the C–H coupled NMR spectra of **3a** and **4a**. The $^3J_{CH}$ coupling of **3a** between the carbonyl carbon at position 4 (δ 157.36) and the protons in the methylamino group at position 3 gave a quartet and C-6 (δ 163.02) gave a triplet due to the coupling with the methylene protons in the benzyl group at position 1. In **4a** the methyl group and the benzyl group are in opposite positions compared with **3a** and consequently the coupling pattern is changed. In **4a** the carbonyl carbon (C-4) at δ 156.90 gave a triplet ($^3J_{CH}$ = 2.44) and C-6 at δ 161.73 gave a quartet ($^3J_{CH}$ = 2.44) due to the coupling with the methyl group. The fact that the thiazinones **5** exist in a 2-amino form and not in a 2-imino form was proved by their ^{1}H NMR and C–H coupled NMR spectra. In the ^{1}H NMR spectra of **5a** the amino pro-

TABLE II
Yields of reaction products **5a**–**5d** in the reactions of **1a** and **1b** with phenyl- and allylthioureas

5	R	R′	Yields[a], %
a	H	allyl	53
b	CH_3	allyl	46
c	H	phenyl	61
d	CH_3	phenyl	66

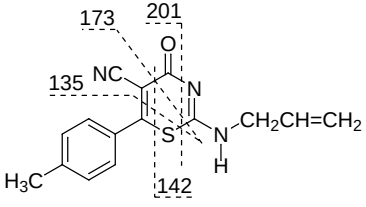


FIG. 1
Fragmentation patterns of 1,3-thiazin-4-ones **5**

ton gave a triplet due to the coupling to the methylene protons of the allyl group. The methylene protons neighboring the amino nitrogen at δ 4.06 appeared as a triplet (J = 5.0) and the methylene carbon at δ 44.13 appeared as a quintet of triplets due to $^1J_{CH}$, $^2J_{CH}$ and $^3J_{CH}$ couplings.

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