SYNTHESIS OF 1,3-DIALKYL- AND 1,3-DIPHENYL-5-CYANO-2-THIOURACIL 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, antipyretic and antiinflammatory agents. Synthesis of some 5-cyano-2-thiouracil derivatives has previously been reported. 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. 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 from the reactions of 1a and 1b with symmetrically substituted thioureas.

<table>
<thead>
<tr>
<th></th>
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<th>R</th>
<th>R'</th>
<th>Yield (%)</th>
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<tbody>
<tr>
<td>a</td>
<td>H</td>
<td>CH₃</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>b</td>
<td>CH₃</td>
<td>CH₃</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>c</td>
<td>H</td>
<td>Ph</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>d</td>
<td>CH₃</td>
<td>Ph</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>e</td>
<td>H</td>
<td>C₂H₅</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>f</td>
<td>CH₃</td>
<td>C₂H₅</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>g</td>
<td>H</td>
<td>Allyl</td>
<td>71</td>
<td></td>
</tr>
<tr>
<td>h</td>
<td>CH₃</td>
<td>Allyl</td>
<td>67</td>
<td></td>
</tr>
</tbody>
</table>

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 thio-carbonyl group to form 1,3-thiazinones, as was the case in the reactions with thioureas bearing at least one -NH₂ group.

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, ¹³C, ¹⁵N 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 $\delta = 3.75$ and 3.59 ppm, respectively. This clearly shows the presence of two N-CH₃ groups and not one N-CH₃ and one S-CH₃ group, since the S-CH₃ signal should appear at approximately $\delta = 2.65$ ppm as in the spectrum of 5-cyano-3-methyl-2-methylthio-6-phenyl-4-pyrimidone.

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) ($\delta$=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 ($\delta$=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 (\(\delta\)) 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\(_2\)SO\(_4\)) 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, 3 H), 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\(_3\)OS 257.0623, found 257.0619. Anal. Calcd for C\(_{13}\)H\(_{11}\)N\(_3\)OS: 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\(_3\)OS 271.0779, found
271.0772: Anal. Calcd for C_{14}H_{13}N_{3}O_{2}: 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); \( ^1H \) NMR 7.30-7.70 (m, 15 H); \( ^13C \) 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, 114.32, 94.53; \( ^15N \) NMR -140.53, -214.75, -234.51; HRMS calcd for C_{23}H_{15}N_{3}O_{2} 381.0936, found 381.0932. Anal. Calcd for C_{23}H_{15}N_{3}O_{2}: 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 m/z (M\(^+\)) 395 (92), 394 (46), 286 (100), 194 (26), 145 (35), 91 (7), 77 (46); \( ^1H \) NMR 7.20-7.80 (m, 14 H), 2.30 (s, 3 H); \( ^13C \) 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; \( ^15N \) NMR -140.96, -214.73, -234.19; HRMS calcd for C_{24}H_{17}N_{3}O_{2} 395.1092, found 395.1396. Anal. Calcd for C_{24}H_{17}N_{3}O_{2}: 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 m/z (M\(^+\)) 285 (50), 284 (100), 256 (49), 252 (28), 204 (41), 86 (31), 77 (27), 60 (25); \( ^1H \) 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, 3 H, J=7.0 Hz), 1.19 (t, 3 H, J=6.8 Hz); \( ^13C \) 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; \( ^15N \) NMR -141.99, -218.04, -240.61; HRMS calcd for C_{15}H_{15}N_{3}O_{2} 285.0936 found, 285.0931. Anal. Calcd for C_{15}H_{15}N_{3}O_{2}: 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 m/z (M\(^+\)) 299 (96), 298 (100), 270 (40), 266 (26), 239 (23), 118 (25), 86 (24); \( ^1H \) 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); \( ^13C \) 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); \( ^15N \) 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); \( ^13C \) 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); \( ^15N \) 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); \( ^13C \) 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); \( ^15N \) 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).
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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_{3}O_{5}S: 309.3941 found, 309.3937. Anal. Calcd for C_{17}H_{15}N_{3}O_{5}S: 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; EI-MS 323 (M+41), 322(100), 282 (55), 250 (22), 140 (19), 98 (22), 87 (22), 73 (25); 1H 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); 13C 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_{3}O_{5}S 323.4212, found 323.421. Anal. Calcd for C_{18}H_{17}N_{3}O_{5}S: 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.

REFERENCES


Received, 16th June, 1997