Short Communication

Synthesis of 4-Arylamino-1H-pyrazolo[3,4-d]pyrimidines

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4-Substituted pyrazolo[3,4-d]pyrimidines have long been known to possess antitumor activity.\(^1\),\(^2\) As early as 1956 Robins\(^3\) and later on Skipper et al.\(^4\) reported the synthesis and biological activity of 4-alkylaminopyrazolo[3,4-d]pyrimidines. Recently, the corresponding nucleosides have been shown to be antitumor agents.\(^5\) Therefore, it would be of interest to find an easy synthesis of 4-arylamino-1H-pyrazolo[3,4-d]pyrimidine derivatives as candidates for biological screening.

Commercially available 1H-pyrazolo[3,4-d]pyrimidine-4-ol (I) was treated with a mixture of triethylamine hydrochloride, phosphorus pentoxide, and an arylamine, at 150–200°C for 1.5–24 h to give the corresponding amino compounds (2) in 21–59% yield (see Table 1).

Correct microanalysis, mass, IR, \(^1\)H NMR and \(^13\)C NMR spectra were obtained for all new compounds.

The interpretation of the \(^13\)C NMR spectra was made by comparison with the spectra of other 4-substituted 1H-pyrazolo[3,4-d]pyrimidines\(^6\) and with \(^13\)C NMR spectra of anilines, and by inspection of undecoupled spectra.

**Experimental**

4-(3-Trifluoromethylenilino)1H-pyrazolo[3,4-d]pyrimidine (2e). Typical experiment. 3-Trifluoromethyleniline (0.16 mol) was added with stirring to a mixture of phosphorus pentoxide (27.2 g, 0.16 mol) and triethylamine hydrochloride (22.0 g, 0.16 mol) protected with a CaCl\(_2\) drying tube. The mixture was placed in a preheated oil bath at 200°C. When the mixture had turned into a homogeneous melt (15–30 min), (I) (5.44 g, 0.04 mol) was added and the mixture was stirred at 200°C for 24 h. The reaction mixture was allowed to cool to about 100°C, 2 M sodium hydroxide was added until a pH of 9–10 was reached and the mixture was stirred for 1 h at ambient temperature. The digested product was filtered off, washed with water and recrystallized from 96% ethanol to give 6.6 g (59%) of (2e). MS [m/z (% rel. int.)] 279 (79, M), 278 (100), 258 (12), 145 (19). \(^1\)H NMR (60 MHz; \[^{1}^\text{H}\]Me\(_2\)SO): \(\delta\) 7.42 (d, 1 H, \(J = 8\) Hz), 7.64 (t, 1 H, \(J = 8\) Hz), 8.20 (d, 1 H, \(J = 8\) Hz), 8.36 (s, 1 H), 8.57 (s, 1 H), 10.32 (NH), 13.76 (NH). \(^{13}\)C NMR

![Scheme 1](image)

Table 1. Preparation of (2a–g).

<table>
<thead>
<tr>
<th>Compound</th>
<th>Ar</th>
<th>Reaction</th>
<th>Time/h</th>
<th>Temp./°C</th>
<th>Yield/%</th>
<th>M.p./°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>(2a)</td>
<td>C₆H₅</td>
<td></td>
<td>1.5</td>
<td>150</td>
<td>21</td>
<td>253*</td>
</tr>
<tr>
<td>(2b)</td>
<td>4-ClC₆H₄</td>
<td></td>
<td>2.5</td>
<td>200</td>
<td>26</td>
<td>259</td>
</tr>
<tr>
<td>(2c)</td>
<td>3-ClC₆H₄</td>
<td></td>
<td>3</td>
<td>200</td>
<td>50</td>
<td>298–299</td>
</tr>
<tr>
<td>(2d)</td>
<td>3-CF₃, 4-ClC₆H₄</td>
<td></td>
<td>3</td>
<td>200</td>
<td>56</td>
<td>300</td>
</tr>
<tr>
<td>(2e)</td>
<td>3-CF₃C₆H₄</td>
<td></td>
<td>24</td>
<td>200</td>
<td>59</td>
<td>301</td>
</tr>
<tr>
<td>(2f)</td>
<td>3,5-(CH₃)₂C₆H₃</td>
<td></td>
<td>3</td>
<td>150</td>
<td>48</td>
<td>282–284</td>
</tr>
<tr>
<td>(2g)</td>
<td>4-FC₆H₄</td>
<td></td>
<td>3</td>
<td>150</td>
<td>31</td>
<td>264–265</td>
</tr>
</tbody>
</table>

*Lit. m.p. 263–264 °C.5

(15 MHz; [²H₆]Me₂SO): δ 100.7 (C-3a), 132.1 (C-3), 153.9, 154.7 (C-4, C-7a), 154.9 (C-6), 116.5, 119.0, 124.0, 126.5, 129.6, 140.2 (Ar), 121.0 (CF₃). IR(KBr) 1640 cm⁻¹. Anal. C₁₂H₃F₃N₅: C, H, N.

References

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