Improved Synthesis of Pyrrolo[1,2-c]pyrimidine and Derivatives

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Abstract. An improved synthesis of pyrrolo[1,2-c]pyrimidine derivatives by cyclocondensation of pyrrole-2-carboxaldehydes with tosylmethyl isocyanide followed by desulfonylation of the resulting 2-tosylpyrrolo[1,2-c]pyrimidines with sodium amalgam is described Copyright © 1996 Elsevier Science Ltd

We became interested in pyrrolo[1,2-c]pyrimidine¹ as a starting material for a straightforward synthesis of new N-bridged azole systems 3 in which one of the coplanar azole rings is positively charged by quaternization of its bridgehead nitrogen. Such systems exist as a tricyclic cation or alternatively, if internal compensation of the positive charge is accomplished,² as a conjugated mesomeric betaine. We hoped that either the cationic or the heterobetaline structures might exhibit interesting electronic properties associated with charge transfer between the azole-azolium moieties.

\[
\begin{align*}
\text{Y} & = \text{O, S, NR} \\
\text{R} & \text{R}_1 \quad \text{R}_2 \\
\text{N} & \quad \text{Y} \\
\text{R}_3
\end{align*}
\]

Scheme 1

The retrosynthetic analysis for the target heterobetaline system is shown in Scheme 1. A 1,3-dipolar cycloaddition reaction between a pyrrolo[1,2-c]pyrimidinium salt 2 and heterocumulenes was considered to be the key step in building up the tricyclic system. Hence, our initial synthetic proposal involved a known preparation of the pyrrolo[1,2-c]pyrimidine 1a (R₁ = H) as precursor to salt 2a. However, the seven steps synthesis of 1a described by Rapoport,³ which is the only reported procedure (Scheme 2) gives an overall yield of less than 1%. This extremely low yield stimulated us to develop an alternative procedure for the synthesis of 1a and some of its derivatives. In this paper, we report on this improved method along with its scope and limitations.
The reported synthesis\(^3\) of the parent pyrrolo[1,2-c]pyrimidine 1a which is outlined in Scheme 2, commences with 4-methylpyrimidine and butyl glyoxalate and contains a final step which furnishes a yield of only 9\%. We initially chose a strategy whereby condensation of pyrrole-2-carboxaldehyde 4a with ethyl isocyanoacetate\(^4\) would lead to the cyclocondensation product 5a which hopefully could be hydrolysed to the corresponding acid 6a, then decarboxylated to give the desired pyrrolo[1,2-c]pyrimidine. Unfortunately 6a proved to be highly resistant to decarboxylation under various conditions, with 1a being obtained at best in 4\% yield in the best case (refluxing in diphenyl ether for 48 h). Attempted decarbonylation of the aldehyde, which was obtained by treating the ester with DIBAL-H (62\%), with Wilkinson’s catalyst also failed. Consequently, we decide to attempt the cyclocondensation of the starting aldehyde with tosylmethyl isocyanide (TOSMIC)\(^4,5\) in the hope that the resulting sulfone 7a would be more easily converted into 1a by reductive displacement of the tosyl group.

The reaction of pyrrole-2-carboxaldehyde with TOSMIC gave the cyclocondensation product 7a in good yield but removal of the tosyl group initially proved troublesome. For example, attempts to desulfonylate 7a with H\(_4\)LiAl-NiCl\(_2\)\(^6\) afforded 1a in only 7\% yield, while treatment with Na\(_2\)S\(_2\)O\(_4\)\(^7\) gave 1a in just 18\% yield. Numerous conditions were studied using amalgam,\(^8\) and the best results were obtained with a 6\% sodium amalgam and Na\(_2\)HPO\(_4\) in THF-MeOH.\(^8c\) Under these conditions 1a was obtained in 51\% yield.
**Table. Pyrrolo[1,2-c]pyrimidine Derivatives 1 Prepared**

<table>
<thead>
<tr>
<th>Compd No.</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>R&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Yield (%)</th>
<th>mp (°C)</th>
<th>Yield (%)</th>
<th>mp (°C)</th>
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<tr>
<td>b</td>
<td>H</td>
<td>Br</td>
<td>H</td>
<td>79</td>
<td>223-224</td>
<td>15&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>Me</td>
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<td>H</td>
<td>n-Bu</td>
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<td>H</td>
<td>H</td>
<td>80</td>
<td>98-99</td>
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<td>147-149</td>
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</table>

<sup>a</sup> All the compounds exhibited spectral and analytical data consistent with their structure. Compounds 1b-e, 1g and 1i were isolated and characterised as hydrobromides. <sup>b</sup>A 45% yield of the debromination product (1a) was obtained. <sup>c</sup>A complex mixture was formed.

The procedure was then applied to different substituted pyrrole-2-carboxaldehydes, the results of which are shown in the Table. As expected some functionalities were not compatible with the conditions used in the desulfonylation step. Thus, reductive desulfonylation of 7b was accompanied by extensive debromination, and 1b was obtained in only 15% yield. Similarly, only a 12% yield was obtained in the conversion of 7f into 1f with a complex mixture being observed.

The preparation outlined for 1a is representative of the general procedure.<sup>9</sup> To a mixture of 214 mg (1.1 mmol) of TOSMIC and 167 mg (1.1 mmol) of DBU in 2 ml of dry THF under argon, 95 mg (1 mmol) of pyrrole-2-carboxaldehyde in 2 ml of anhydrous THF was added. The mixture was stirred at room temperature for 2 h and then neutralised with acetic acid. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel using Hex-EtOAc (7:3) as eluent. Recrystallization from CH<sub>3</sub>CN gave 223 mg (82%) of 7a. To 6% sodium amalgam (184 mg, 8 mmol Na) under argon, a suspension of 639 mg (4.5 mmol) of Na<sub>2</sub>HPO<sub>4</sub> in 15 ml of anhydrous MeOH was added. Subsequently, 272 mg (1 mmol) of the sulfone 7a in anhydrous THF (10 ml) were added. The mixture was stirred at room temperature for 3 h, then it was hydrolyzed with water, and extracted with Et<sub>2</sub>O (3x10 ml). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, the solvent removed under reduced pressure, and the residue chromatographed on silica gel (CH<sub>2</sub>Cl<sub>2</sub>-acetone, 9.5:0.5) to give the pyrrolo[1,2-c]pyrimidine 1a (60 mg, 51%).
In conclusion, we have developed an efficient method for the synthesis of pyrrolo[1,2-c]pyrimidine and some derivatives by the reaction of pyrrole-2-carboxaldehydes with TOSMIC, followed by desulfonylation of the resulting 2-tosylpyrrolo[1,2-c]pyrimidines. Unlike the previously reported strategy this protocol allows the preparation of this system in synthetically useful yields, though it has some limitations arising from the reductive conditions used for the desulfonylation step. An alternative milder displacement of the tosyl group is currently being investigated.

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References and Notes


9. (7a): IR (KBr) $\nu_{max}$ 1594, 1348, 1301, 1147 cm$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.72 (s, 1H, $H_1$) 8.25 (s, 1H), 7.94 (d, 2H, J = 8.2 Hz), 7.49 (d, 1H, J = 2.9 Hz), 7.31 (d, 2H, J = 8.2 Hz), 7.02 (dd, 1H, J = 4.0 Hz, J = 2.9 Hz), 6.82 (d, 1H, J = 4.1 Hz), 2.41 (s, 3H) ppm. MS (m/z, rel intensity) 272 (M+, 29), 207 (18), 139 (18), 106 (100). Anal. calcd. for C$_{14}$H$_{12}$N$_2$O$_2$S: C, 61.75; H, 4.44; N, 10.29; Found: C, 61.50; H, 4.58; N, 10.58. (1a): $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.78 (s, 1H, $H_1$, $H_1'$), 7.36-7.38 (m, 2H), 7.22 (d, 1H, J = 6.4 Hz), 6.87 (dd, 1H, J = 4.0 Hz J = 2.9 Hz), 6.43 (d, 1H, $H_5$, J = 4.0 Hz) ppm. $^{13}$C NMR (300 MHz, CDCl$_3$) $\delta$ 138.54, 136.09, 130.91, 115.77, 113.12, 110.35, 99.27 ppm. MS (m/z, rel intensity) 118 (M+, 100), 91 (26), 80 (28), 63 (22).

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