
LACTAM AND ACID AMIDE ACETALS

68.* 1-CYANOMETHYL-2-PYRROLIDONE DIETHYLACETAL IN THE SYNTHESIS OF 7,8-TRIMETHYLENEPURINE DERIVATIVES

E. N. Dozorova, A. V. Kadushkin, G. A. Bogdanova, N. P. Solov'eva, and V. G. Granik

1-Cyanomethyl-2-cyaniminopyrrolidine was synthesized by the reaction of 1-cyanomethyl-2-pyrrolidone diethylacetal with cyanamide. The product undergoes Thorpe–Ziegler cyclization under the influence of sodium ethoxide to give 2-amino-3-cyano-5,6-dihydro-7H-pyrrolo[1,2-a]imidazole, from which 4-amino derivatives of pyrrolo[2,1-f]purine were synthesized.

This research continues studies of the intramolecular Thorpe–Ziegler cyclization of various synthones obtained from 1-cyanomethyl-2-pyrrolidone diethylacetal (I). It has been previously shown that acetal I reacts smoothly with various CH acids such as cyanoacetic esters and malononitrile to give enamino nitriles II, which are capable, under the influence of bases, of undergoing cyclization to 5-cyano-6-aminopyrrolizine derivatives [2]. The latter were used for the synthesis of the first representatives of two new heterocyclic systems — pyrimido[5,4-e] and pyrimido[4,5-f]pyrrolizine derivatives [3, 4].

The present paper is devoted to the study of a similar scheme but with N-cyano amidines III, rather than enamino nitriles of the II type, as the starting compounds.

Amidines III are readily synthesized by the reaction of acetal I with cyanamide — the reaction proceeds smoothly and gives the products in virtually quantitative yields. Since the N-alkylation of cyano amidines that contain

*See [1] for Communication 67.

TABLE 1. Physicochemical Constants of the Synthesized Compounds

<table>
<thead>
<tr>
<th>Compound</th>
<th>mp, °C</th>
<th>Empirical formula</th>
<th>Yield, %</th>
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<th>Empirical formula</th>
<th>Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>III</td>
<td>98–100</td>
<td>C7H8N4</td>
<td>98</td>
<td>IXc</td>
<td>168–170</td>
<td>C16H12N5</td>
<td>85</td>
</tr>
<tr>
<td>V</td>
<td>253–256</td>
<td>C7H8N4</td>
<td>89</td>
<td>IXd</td>
<td>180–184</td>
<td>C16H12N5O2</td>
<td>88</td>
</tr>
<tr>
<td>VI</td>
<td>280</td>
<td>C12H8N4</td>
<td>97</td>
<td>Xa</td>
<td>235–238</td>
<td>C16H12N5</td>
<td>7</td>
</tr>
<tr>
<td>VIII</td>
<td>135–138</td>
<td>C12H14N4</td>
<td>91</td>
<td>XC</td>
<td>214–217</td>
<td>C16H17N5</td>
<td>98</td>
</tr>
<tr>
<td>IXa</td>
<td>165–168</td>
<td>C12H14N4</td>
<td>88</td>
<td>XD</td>
<td>204–210</td>
<td>C16H21N5O2</td>
<td>92</td>
</tr>
<tr>
<td>IXb</td>
<td>173–177</td>
<td>C17H16N6</td>
<td>57</td>
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</tr>
</tbody>
</table>

*The compounds were crystallized: III from ethanol, V, VI, and Xd from water, VIII, IXb-d, and Xa, c from ethyl acetate, and IXa from isopropyl alcohol.

a secondary NH group is known [5], we attempted, under similar conditions (DMF, K2CO3, 60°C), to carry out the cyanomethylation of amidine IV, which was obtained by the reaction of O-methylbutyrolactim with cyanamide [6]. However, the reaction in this case proceeds ambiguously, and we were unable to isolate III. Nevertheless, the alkylation can be carried out by using another method for obtaining the sodium salt of amidine IV (treatment with sodium metal in toluene) with subsequent reaction with chloroacetanitride. This method seems preparatively more convenient to us, since it does not require obtaining acetal I, which calls for the use of triethylxonium tetrafluoroborate as the alkyating agent [7].

Brief heating (70°C, 5 min) of the resulting N-cyano amidine III in an alcohol solution of sodium ethoxide is accompanied by Thorpe–Ziegler cyclization to give bicyclic amino derivative V.

Thus the combination of the high reactivities of lactim ethers and lactam acetals with respect to cyanamide and the Thorpe–Ziegler reaction, which provides the simple possibility of cyclization of the N-cyano group at the active methylene link, ensures a convenient preparative approach to functionally substituted imidazoles of the V type. This, in turn, makes it possible to accomplish a new synthesis of 7,8-trimethylenepurines. Only a few studies devoted to 7,8-trimethylenepurines — pyrrolo[2,1-f]purines — are known [8-10]. However, these syntheses of derivatives of the indicated system are either quite complex or provide an approach only to N-substituted (in the pyrimidine ring) compounds. The new synthesis of this system, which is based on amino cyano derivative V, is also more universal and more preparative. An amino derivative (VI) of pyrrolo[2,1-f]purine was obtained in 97% yield in the reaction of V with formamide. The condensation of V with DMF acetal (VII) leads to amidine VIII (in 92% yield), which in transamination reactions with various amines should be converted to N-substituted pyrrolo[2,1-f]iminopurines IXa-d (see Table 1).

However, it follows from the structure of IX that they are typical objects of the Dimroth rearrangement, and taking into account the fact that the transamination and cyclization reactions were carried out in the presence of strong amines, the occurrence of the A → B recyclization seemed completely likely.