

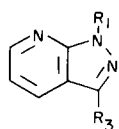
A Novel Synthesis of Pyrazolo[3,4-*b*]pyridine

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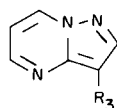
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Sir:

Pyrazolo[3,4-*b*]pyridines have been synthesized from both pyrazole and pyridine intermediates (1,2); the only reported synthesis (3) of the parent compound **1** used the hydrazinolysis of 2-chloro-3-cyanopyridine to the 3-amino derivative **2**, followed by deamination of the corresponding diazonium salt (we have used a similar approach to the 1-methyl derivative **3** (4)). In more recent work in our laboratory (5), far better yields of **3** were obtained by the MDTA (malondialdehyde tetramethylacetal) treatment of 1-methyl-5-aminopyrazole in refluxing ethanolic solution in the presence of zinc chloride (*cf.* Klemm and co-workers (6)), and this approach to **1** was attempted, using 3(5)-aminopyrazole.



- 1 $R_1 = H$ $R_3 = H$
 2 $R_1 = H$ $R_3 = NH_2$
 3 $R_1 = Me$ $R_3 = H$



- 4 $R_3 = H$
 5 $R_3 = CO_2H$
 6 $R_3 = CN$

However, cyclization occurred on to the nitrogen atom, yielding the previously unreported pyrazolo[1,5-*a*]pyrimidine **4**, m.p. 103° (7). Similar cyclization using the commercially available 3(5)-aminopyrazole-4-carboxylic acid and 3(5)-aminopyrazole-4-carbonitrile (8) gave the 3-carboxylic acid derivative **5**, m.p. 285° (7), and the 3-carbonitrile **6**, m.p. 195° (7), in excellent yields (over 80%).

In view of Makisumi's report (9) of the smooth decarboxylations of the 5,7-dimethyl derivative **5** to the corresponding derivative of **4**, we were surprised to find that the pyrazolo[3,4-*b*]pyridine **1** was readily accessible from **5** or from **6**; decarboxylation or decarboxylative acid hydrolysis of **5** and of **6** furnished **1** in excellent yields as the major reaction product, in a two-step sequence from a commercially available starting material. Thus, heating of **5** at 290-300° in a beaker on a Fisher-Johns block with provision for a cold condensing surface (a larger beaker was inverted over the reaction vessel) gave

an 85% yield of decarboxylation products; **1**, m.p. 99° (lit. 98-99° (3)) (7) and **4** were produced in the weight ratio 5:1; the product **4** sublimes readily on to the cool surface, and pure **1** remains in the beaker. The nitrile **5** underwent smooth decarboxylative conversion into **1** in 80% yield on heating under reflux in 85% w/w aqueous sulfuric acid for 8 hours. The pyrazolo[1,5-*a*]pyrimidine **4** is stable under the conditions used for decarboxylation or for decarboxylative hydrolysis.

Investigations of the scope and mechanism of these unprecedented conversions are being pursued; preliminary investigations have established that Makisumi's reported decarboxylations are not accompanied by extensive rearrangement from the pyrazolo[1,5-*a*]pyrimidine system to the pyrazolo[3,4-*b*]pyridine.

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