NUCLEOPHILIC SUBSTITUTION REACTIONS IN 4-HALONITRO-
PYRAZOLECARBOXYLIC ACIDS

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The reaction of 4-bromo-1-methyl-3-nitropyrazole-5- and 4-bromo-1-methyl-5-nitro-
pyrazole-3-carboxylic acids with arylamines in aqueous solution in the presence
of monovalent copper salts leads to the formation of 4-arylamino- and 4-hydroxy
substituted nitropyrazolecarboxylic acids.

Nucleophilic substitution reactions in the 4-halopyrazole series has not been adequately
studied. It is known that as a consequence of the high nucleophilicity of the 4 position of
the heterocycle, 4-halopyrazoles are extremely inert in reactions of this sort [1]. Nucleo-
philic substitution of the halogen in these compounds is possible only if nitro groups are
present in neighboring positions of the pyrazole ring [2, 3] or if copper compounds are used
as a catalyst [4, 5].

The activating effect of a carboxyl group on the mobility of a halogen atom in 4-halo-
pyrazolecarboxylic acids in the presence of a copper catalyst was noted in [6] but a syste-
matic study of such reactions was not carried out.

We have established [7] that the reaction of 4-halo-1-methyl-pyrazole-3- and 5-carboxylic
acids with aromatic amines in the presence of a copper catalyst leads to the formation of
4-arylamino substituted pyrazoles and is accompanied by reductive dehalogenation. In this
paper, we consider nucleophilic substitution reactions in the 4-halo-1-methylnitropyrazole-
carboxylic acid series.

The introduction of a nitro group in the 3 or 5 position of a molecule of 4-halo-1-methyl-
pyrazole-3- or -5-carboxylic acid significantly increases the rate of substitution of the
halogen atom in reactions of these compounds with aromatic amines. The reaction of 4-bromo-
1-methyl-5-nitropyrazole-3-carboxylic acid (I) and of 4-bromo-1-methyl-3-nitropyrazole-5-
carboxylic acid (II) with aniline takes place even at 60-70°C while the substitution of the
halogen atom in 4-bromopyrazolecarboxylic acids which do not contain nitro groups requires
prolonged heating at 100°C [7]. As in the case of 4-halopyrazolecarboxylic acids, nucleo-
philic substitution in compounds I and II occurs only in the presence of monovalent copper
salts, but no reductive dehalogenation is observed in this case. Divalent copper salts do
not possess any catalytic activity in this reaction.

In the reaction of compounds I and II with arylamines in aqueous solution, the replace-
ment of the halogen with a hydroxyl group was observed along with the formation of the 4-
arylamino substituted compound. This was not noted in the case of 4-halopyrazolecarboxylic
acids [7].

![Chemical Structure](image)

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TABLE 1. Substituted 1-Methylpyrazolecarboxylic Acids

<table>
<thead>
<tr>
<th>Compound</th>
<th>T_{mp}, °C</th>
<th>PMR spectrum, δ, ppm</th>
<th>Found, %</th>
<th>Empirical formula</th>
<th>Calculated, %</th>
<th>Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>lIa</td>
<td>190–191</td>
<td>4.25 7.90 (5H, m, arom.)</td>
<td>49.8 4.2 20.9</td>
<td>C_{11}H_{10}N_{4}O_{4}</td>
<td>50.4 3.8 21.4</td>
<td>71</td>
</tr>
<tr>
<td>lIb</td>
<td>227–228</td>
<td>4.20 3.76 (4H, CH_{2})</td>
<td>49.1 3.5 19.0</td>
<td>C_{11}H_{10}N_{4}O_{4}</td>
<td>49.3 4.1 19.2</td>
<td>80</td>
</tr>
<tr>
<td>lIc</td>
<td>184–186</td>
<td>4.23 6.93 (2H, d, 2'-H and 6'-H), 7.95 (2H, d, 3'-H and 5'-H)</td>
<td>42.8 2.6 20.0</td>
<td>C_{11}H_{10}N_{4}O_{4}</td>
<td>43.0 2.9 19.8</td>
<td>56</td>
</tr>
<tr>
<td>lV</td>
<td>135–137</td>
<td>4.06 —</td>
<td>31.9 2.7 22.3</td>
<td>C_{11}H_{10}N_{4}O_{4}</td>
<td>32.0 2.7 22.5</td>
<td>69</td>
</tr>
<tr>
<td>lV</td>
<td>143–145</td>
<td>4.14 7.12 (5H, m, arom.)</td>
<td>30.5 4.1 21.2</td>
<td>C_{11}H_{10}N_{4}O_{4}</td>
<td>50.4 3.8 21.4</td>
<td>65</td>
</tr>
<tr>
<td>IX</td>
<td>215–216</td>
<td>4.18 —</td>
<td>32.2 2.7 22.1</td>
<td>C_{11}H_{10}N_{4}O_{4}</td>
<td>32.0 2.7 22.5</td>
<td>50</td>
</tr>
<tr>
<td>X</td>
<td>156–158</td>
<td>4.91 3.17 (4H, m, CH_{2})</td>
<td>41.6 4.6 22.2</td>
<td>C_{11}H_{10}N_{4}O_{4}</td>
<td>42.0 5.0 21.8</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td>(in CDCl_{3})</td>
<td>3.80 (4H, m, CH_{2})</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Compound lIb was crystallized from methanol, compound X from water.

The amount of 4-hydroxy derivative, lV, obtained is determined by the ratio of the rates of the two parallel reactions taking place and depends primarily on the basicity of the aromatic amine in the reaction (in the reaction of compound l with o-anisidine, the yield of compound lV was 8%, and with p-nitroaniline, 24%); in the absence of an arylamine, the reaction proceeds solely to the formation of the 4-hydroxy derivative.

The nonequivalency of the C(4)-C(5) and C(4)-C(3) bonds in the pyrazole ring [8] causes the activation effect of the nitro group to differ in the 3-nitro- and 5-nitro-4-halopyrazolecarboxylic acids in nucleophilic substitution reactions. This is most clearly shown in the different reactivities of 1-methyl-5-nitro-4-chloropyrazole-3-carboxylic acid (lVII) and 1-methyl-3-nitro-4-chloropyrazole-5-carboxylic acid (lVIII). Thus, compound lVII on boiling with o-anisidine for 18 h gives 4-arylaminopyrazole lIib in 67% yield while acid lVIII under similar conditions does not react.

In distinction to the reactions of 4-halopyrazolecarboxylic acids with ammonia and aliphatic amines, which lead to unsatisfactory results because of the high sensitivity of the 4-amino derivatives being formed to atmospheric oxygen, when compound l reacts with ammonia or morpholine, the corresponding 4-aminonitrosubstituted IX and X are obtained in yields of 84% and 77%, respectively.

EXPERIMENTAL

The PMR spectra were measured on a Tesla BS-497 instrument (100 MHz, HMDS internal standard) in DMSO-D_{6}. The mass spectra of compounds lV and lVI were obtained on an MX-1309 instrument with an ionization potential of 70 eV and an ionization chamber temperature of 150°C.

The 4-halonitropyrazolecarboxylic acids l, II, VII, and VIII were obtained according to [9].

The characteristics of compounds lIa-c, lV-VI, IX and X are given in Table 1.

4-Arylamino-1-methyl-5-nitropyrazole-3-carboxylic Acids (lIa-c). A mixture of 2.5 g (0.01 mole) of acid l, 0.011 mole of the corresponding aniline, and 0.4 g CuBr are heated in...