SYNTHESIS OF BENZOXAZOLES FROM IMINO ESTERS

I. 2-Alkyl(Aryl)-Substituted Benzoxazoles*


UDC 547.78 + 542.953 + 543.422

It is found that condensation of esters of iminocarboxylic and iminoperfluorocarboxylic acids with o-aminophenol is a convenient general method for preparing 2-alkyl, 2-perfluoroalkyl, and 2-aryl substituted benzoxazoles. Hydrochlorides of esters of iminocarboxylic acids react smoothly with o-aminophenol even at room temperature. Condensation of esters of iminoperfluorocarboxylic acids, whose hydrochlorides are unstable, is suitably carried out in the presence of an equimolecular quantity of the corresponding perfluorocarboxylic acid. 2-Alkyl substituted benzoxazoles can also be obtained by heating o-aminophenol with esters of iminocarboxylic acids in the form of free bases. Esters of iminoperfluorocarboxylic acids also react similarly. Under similar conditions diesters of bisiminoearboxylic and bisiminoperfluorocarboxylic acids and o-aminophenol give α, ω-di(benzoxazolyl-2)alkanes, and α, ω-di(benzoxazolyl-2)perfluoroalkanes respectively.

2-Alkyl substituted benzoxazoles are for the most part obtained by condensing o-aminophenols with acids and their derivatives [2, 4], e.g., acid chlorides, amines, nitriles, and amidines, reaction usually being effected at about 200° and even higher. Such drastic conditions lead to the formation of undesirable by-products, whose removal is often difficult [5, 6]. Hence we turned our attention to indications that [7] 2-methylbenzoxazole can be obtained by the action of ethyl iminoacetate hydrochloride on o-aminophenol in cold methanol or boiling methanol, in yields of 30 and 78% respectively. Even earlier it had been stated that condensing o-aminophenol with methyl iminobenzoate [8] gives 2-phenylbenzoxazole, though the yield was not given. At the start of the present work there was no other information about synthesis of benzoxazoles from imino esters.**

A detailed study of this reaction led us to a general method for preparing 2-substituted benzoxazoles (II) from o-aminophenol and imino ester hydrochlorides, enabling I to be synthesized in dry chloroform in yields up to 82% at room temperature (method A)

\[
\text{H}_2\text{N} - \text{O} + \text{RC} = \text{NH} . \text{HCl} \rightarrow \text{R} . \text{NHCl} \rightarrow \text{H}_2\text{N} = \text{O} + \text{RC} = \text{NH} \]

a R = H; b R = \text{CH}_3; c R = \text{n-C}_3\text{H}_7; d R = \text{CH}_2\text{C}_6\text{H}_5; e R = \text{C}_6\text{H}_5

Benzoxales Ia–e can also be obtained by reacting o-aminophenol with imino esters in the free base form. However it is then necessary to heat for some hours at about 100° in dry dioxane (method B). The yield of 2-substituted benzoxazoles is then somewhat less (see Table 1). The difference in the readiness with which imino esters condense, as hydrochlorides and as free bases, with o-aminophenol is probably due to the reactions proceeding by different mechanisms, as obtains in preparing 1, 3, 4-oxadizoles from imino esters and acid hydrazides [10]. 2-Trifluoromethyl- and 2-(α-perfluoropropyl)benzoxazoles (If, g) which are obtained, respectively, from methyl iminotrifluoroacetate (II) [11] and methyl iminoperfluorobutyrate (III) [12], whose hydrochlorides are unstable, can be synthesized by method B, but then the yields of benzoxazoles If, f do not exceed 35–40%. The best results are obtained by reacting o-aminophenol with the imino esters II and III in the presence of equimolecular amounts of, respectively, trifluoroacetic and perfluorobutyric acids at room temperature (method B).

It was also found that esters of aliphatic bisimino-carboxylic acids react rather smoothly with o-aminophenol by methods A and B, to give α, ω-dif(benzoxazolyl-2)-alkanes (IVa, b). * Esters of bisiminoperfluorocarboxylic acids and o-aminophenol give, by method B, α, ω-dif(benzoxazolyl-2)perfluoroalkanes (IVc, d) (see Table 2).

\[
\begin{align*}
\text{a R} & = -(\text{CH}_2)\text{H} & \text{b R} & = -(\text{CH}_2)\text{K} \\
\text{c R} & = -(\text{CF}_2)\text{H} & \text{d R} & = -(\text{CF}_2)\text{K}
\end{align*}
\]

The structures of the benzoxazoles I and α, ω-dif-benzoxazolylalkanes IV prepared by us are confirmed by studying their IR spectra. The spectra of compounds I and IV have absorption bands in the regions 1615–1630 and 1560–1590 cm⁻¹, characteristic [14] of the benzoxazole ring. The band at about 925 cm⁻¹ is also assigned [14] to benzoxole ring vibrations, and is

*The synthetic part of the work was communicated at the conference on Heterocycles in Organic Synthesis, Kiev, June 1964. For a preliminary communication see [1].

**Recently the preparation, in 37% yield, of 2-nitromethylbenzoxazole from ethyl iminonitroacetic acid hydrochloride has been described [9].

*It is interesting that condensation of o-aminophenol and its ring-substitution products with dimethyl bisiminoxalate free base gives 3-amino-2-iminobenzazines. Condensing o-aminophenol with the dihydrochloride of this bisimino ester gave the 2, 2'-dibenzo-xazolyl [13].
Table 1

2-Alkyl(aryl) Substituted Benoxazoles (Ia–g)

<table>
<thead>
<tr>
<th>Compound no.</th>
<th>Starting material</th>
<th>Method</th>
<th>Bp (pressure, mm) or mp, °C</th>
<th>$n_d^20$</th>
<th>d,20</th>
<th>Formula</th>
<th>Found, %</th>
<th>Calculated, %</th>
<th>Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>$\text{HC}(=\text{NH} \cdot \text{HCl})OC_2H_5$</td>
<td>A</td>
<td>44.5–46.5 (5)$^9$</td>
<td>1.5548$^{10}$</td>
<td></td>
<td>$\text{C}_7\text{H}_5\text{NO}$</td>
<td>70.43</td>
<td>70.58</td>
<td>35</td>
</tr>
<tr>
<td>Ib</td>
<td>$\text{C}_2\text{H}_3(=\text{NH} \cdot \text{HCl})OC_2H_5$</td>
<td>A</td>
<td>80–80.5 (12)</td>
<td>1.5490</td>
<td>1.1294</td>
<td>$\text{C}_9\text{H}_7\text{NO}$</td>
<td>72.47</td>
<td>72.17</td>
<td>76</td>
</tr>
<tr>
<td>Ic</td>
<td>$\text{n-C}_3\text{H}_2\text{C}(=\text{NH} \cdot \text{HCl})OC_2H_5$</td>
<td>A</td>
<td>97 (8)</td>
<td>1.5335</td>
<td>1.0592</td>
<td>$\text{C}_{10}\text{H}_7\text{NO}$</td>
<td>74.61</td>
<td>74.51</td>
<td>69</td>
</tr>
<tr>
<td>Id</td>
<td>$\text{C}_2\text{H}_4\text{CH}_2\text{C}(=\text{NH} \cdot \text{HCl})OC_2H_5$</td>
<td>A</td>
<td>185–185.5 (13)</td>
<td>1.5990</td>
<td></td>
<td>$\text{C}_{11}\text{H}_9\text{NO}$</td>
<td>7.18</td>
<td>7.18</td>
<td>70</td>
</tr>
<tr>
<td>Ie</td>
<td>$\text{C}_2\text{H}_4\text{C}(=\text{NH} \cdot \text{HCl})OCH_3$</td>
<td>A</td>
<td>101–102$^5$</td>
<td></td>
<td></td>
<td>$\text{C}_{12}\text{H}_9\text{NO}$</td>
<td>7.18</td>
<td>7.18</td>
<td>68</td>
</tr>
<tr>
<td>If</td>
<td>$\text{CF}_3\text{C}(=\text{NH})OCH_3$</td>
<td>C</td>
<td>62.5–63 (19)</td>
<td>1.4609</td>
<td>1.3571</td>
<td>$\text{C}<em>{14}\text{H}</em>{13}\text{NO}$</td>
<td>51.21</td>
<td>51.06</td>
<td>75</td>
</tr>
<tr>
<td>Ig</td>
<td>$\text{n-C}_3\text{F}_2\text{C}(=\text{NH})OCH_3$</td>
<td>C</td>
<td>85 (22)</td>
<td>1.4198</td>
<td>1.5028</td>
<td>$\text{C}<em>{16}\text{H}</em>{15}\text{NO}$</td>
<td>41.60</td>
<td>41.60</td>
<td>57$^*$</td>
</tr>
</tbody>
</table>

$^1$ Unpurified.
$^2$ The literature gives [19] 45° (4 mm), $n_d^20$ 1.5580.
$^3$ at 25°.
$^5$ Ex aqueous EtOH; the literature gives 102.5–103.5°.
$^6$ Found: f 30.31%; MRD 37.34. Calculated: f 30.32%; MRD 37.56.
$^7$ By method (b) the yield was 39%. When prepared by method (c) but in the presence of an equimolecular quantity of CF$_3$COOH instead of C$_4$F$_7$COOH, the yield dropped to 35%.