2-SUBSTITUTED IMIDAZOLES.
3.* METALLATION OF 1-METHYL-2-PHENYL- AND 1-METHYL-2-(FURYL-2)IMIDAZOLES

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1-Methyl-2-phenylimidazole reacts with butyllithium to give 5-lithium substituted products. On the other hand, 1-methyl-2-(furyl-2)imidazole is metallated under the same conditions exclusively on the furan ring and primarily in the 3 position. The introduction of triethylamine into the reaction mixture, or replacement of butyllithium by lithium 2,2,6,6-tetramethylpiperidide leads to the formation of a lithium derivative substituted at the 5-position of the furan ring exclusively.

Metallation of imidazoles [2-4] and furans [5] is an important synthetic procedure in the chemistry of these heterocycles. Generally, 1-R-imidazoles are metallated at position 2 but when this is occupied the reaction leads to the formation of the 5-lithio-derivative. Metallation at the α-position is characteristic for furan although in recent years a series of derivatives of furan metallated mainly in the β-position have been isolated. This is peculiar to furans with substituents which, on account of specific coordination, facilitate a change in the direction of the reaction [6, 7].

In this connection it was of interest to examine the metallation of 1-methyl-2-(furyl-2)imidazole [8] in parallel with the metallation of 1-methyl-2-phenylimidazole (I).

Compound I, like 1-ethoxymethyl-2-phenylimidazole [9], is metallated by butyllithium in dry ether at --70°C. Treatment of the anion with DMF, dry ice, benzaldehyde, and benzonitrile gives the corresponding 1-methyl-5-R-phenylimidazoles (II) in 27-53% yield and reaction with anhydrous copper chloride gives the 5,5'-biimidazole III in 20% yield.

\[
\text{BuLi} \rightarrow \begin{array}{c}
\text{Ph} \\
\text{Me}
\end{array} \rightarrow \begin{array}{c}
\text{Ph} \\
\text{Me}
\end{array} \rightarrow \begin{array}{c}
\text{Ph} \\
\text{Me}
\end{array}
\]

\[ \text{CuCl}_2 \rightarrow \begin{array}{c}
\text{Ph} \\
\text{Me}
\end{array} \rightarrow \begin{array}{c}
\text{Ph} \\
\text{Me}
\end{array} \rightarrow \begin{array}{c}
\text{Ph} \\
\text{Me}
\end{array} \rightarrow \begin{array}{c}
\text{Ph} \\
\text{Me}
\end{array} \rightarrow \begin{array}{c}
\text{Ph} \\
\text{Me}
\end{array}
\]

On the other hand, 1-methyl-2-(furyl-2)imidazole (IV) is metallated exclusively on the furan ring. Thus the action of butyllithium on compound IV in 9:1 ether—hexane at --70°C followed by treatment with DMF results in the formation of a mixture of 1-methyl-2-(3-formylfuryl-2)imidazole (V) and 1-methyl-2-(3-formylfuranyl-2)imidazole (VI) in 3:1 ratio with an overall yield of 48% (the experimental conditions have not been optimized). Isomers V and VI were separated by column chromatography on acidic alumina and their structure established from their PMR spectra. The PMR spectrum of the aldehyde V showed, in the aromatic region, doublets of the two protons of the furan ring (7.1 and 8.07 ppm) with J\text{4,5} = 1.75 Hz which is characteristic for a 2,3-substituted furan [10], together with a scarcely separated doublet (J\text{4,5} = 0.94 Hz) from the imidazole protons at 7.3 and 7.62 ppm (Table I). The aldehyde VI was identical to a sample which we prepared earlier by the formylation of compound IV by the Vilsmeier complex [8].

*For Communication 2, see [1].


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TABLE 1. PMR Spectra of Compounds V-VII and IX-XI (DMSO-D₆)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Chemical shift, δ ppm</th>
<th>J, Hz</th>
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<tbody>
<tr>
<td></td>
<td>imidazole (benzimidazole) ring</td>
<td>furan ring</td>
</tr>
<tr>
<td></td>
<td>N-CH₃</td>
<td>4-H, d</td>
</tr>
<tr>
<td>V</td>
<td>4.07</td>
<td>7.62</td>
</tr>
<tr>
<td>VI</td>
<td>4.05</td>
<td>7.47</td>
</tr>
<tr>
<td>VII</td>
<td>3.8</td>
<td>7.15</td>
</tr>
<tr>
<td>IX</td>
<td>4.3</td>
<td>(7.95 m)</td>
</tr>
<tr>
<td>X</td>
<td>4.27</td>
<td>(7.9 m)</td>
</tr>
<tr>
<td>XI</td>
<td>3.8</td>
<td>(7.57 m)</td>
</tr>
</tbody>
</table>

*J₄,₅ could not be measured on account of inadequate resolution of the instrument.

The direction of the metallation of compound IV is strongly influenced by the nature of the solvent. Thus, in toluene the aldehydes V and VI are formed in approximately equal quantities whereas in tetrahydrofuran compound V is formed with only traces of VI. The high regioselectivity of the metallation reaction in THF was confirmed by the preparation of 1-methyl-2-[3-(α-hydroxybenzhydryl)furyl-2]imidazole (VII), in which none of the isomeric 1-methyl-2-[5-(α-hydroxybenzhydryl)furyl-2]imidazole was detected.

Metallation of 1-methyl-2-(furyl-2)benzimidazole (VIII) by butyllithium in ether with subsequent treatment with DMF yielded, as in the case of compound IV, 1-methyl-2-(3-formylfuryl-2)benzimidazole (IX) and the previously reported [11] 1-methyl-2-(5-formylfuryl-2)benzimidazole (X) in 3:1 ratio (from PMR results).

However, when DMF was replaced by benzophenone, unexpectedly only the 5-substituted furylbenzimidazole XI was isolated. Evidently, the reaction in this case is controlled largely by thermodynamic factors, i.e., in the course of the slower addition of benzophenone to the molecule of organometallic compound, the latter has time to rearrange to the 5-lithioderivative. This suggestion is confirmed by experiment. If the 3-lithioderivative which is formed at −70°C is warmed to 0°C and then treated with DMF, only the aldehyde X is formed.