Reaction of Dimethyl N-Aryl- and N-Alkylcarbonimidodithioates with Aminoacetaldehyde Diethyl Acetal: A Direct Synthesis of 1-Aryl- and 1-Alkyl-2-methylthioimidazoles

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The reaction of dimethyl N-aryl- or N-alkylcarbonimidodithioates with aminoacetaldehyde diethyl acetal in refluxing acetic acid affords 1-aryl or 1-alkyl-2-methylthioimidazoles in good yields. Dimethyl N-isopropylcarbonimidodithioate gave 1-isopropylimidazole-2(3H)-thione under similar conditions.

Dimethyl N-aryl- and N-alkylcarbonimidodithioates are known for a long time.1,2 However, their synthetic application has hitherto been relatively limited despite their easy access.
from a large number of aromatic and aliphatic amines. Some of their recent applications include the synthesis of cyclic guanidine derivatives, β-lactams, dihydro-1,3,5-oxadiazines, as well as lithiation reactions leading to 2-arylimino- and 2-alkylimino-1,3-oxathiolanes and x-branched amino acids. We now report the application of these compounds to the synthesis of 1-aryl- and 1-alkyl-2-methylthioimidazoles by reaction with aminocetaldehyde acetals.

The reaction of dimethyl N-phenyliminocarbanildithioate (1a) with aminocetaldehyde diethyl acetal (2) in boiling acetic acid afforded, after work-up, 1-phenyl-2-methylthioimidazole (3a) in 80% yield. The reaction was found to be general for other N-aryliminocarbanildithioates (1b–i), under similar conditions, the corresponding imidazoles 3h–i being obtained in 80–90% overall yields (Table). When the reaction was extended to the synthesis of 1-alkyl-2-methylthioimidazoles, the 1-methyl (3j), 1-ethyl (3k), and 1-benzyl (3l) derivatives could be obtained in good yields. However, the analogous reaction with the N-isopropyl derivative 1m afforded only 1-isopropylimidazole-2(3H)-thione (4). The desired imidazole 3m (R = i-C$_3$H$_7$) which was formed in low yield during the initial period (1h) of the

### Table 1. Aryl- and 1-Alkyl-2-Methylthioimidazoles 3a–l Prepared

<table>
<thead>
<tr>
<th>Product</th>
<th>Reaction time (h)</th>
<th>Yield (%)</th>
<th>m.p. (°C)</th>
<th>Molecular Formula or Lit. m.p. (°C)</th>
<th>MS (70 eV)</th>
<th>IR (KBr pellet)</th>
<th>1H-NMR (CDCl$_3$, TMS) δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>10</td>
<td>80</td>
<td>55</td>
<td>C$_1$H$_7$N$_2$S (204.2)</td>
<td>204 (61)</td>
<td>3160, 3010, 1510, 1440</td>
<td>2.39 (s, 3H, CH$_3$); 2.54 (s, 3H, SCH$<em>3$); 7.00 (s, 1H, H-4); 7.03 (s, 1H, H-5); 7.31 (s, 4H$</em>{arom}$)</td>
</tr>
<tr>
<td>3b</td>
<td>10</td>
<td>89</td>
<td>75</td>
<td>C$_1$H$_7$N$_2$S (204.2)</td>
<td>204 (61)</td>
<td>3160, 3010, 1510, 1440</td>
<td>2.39 (s, 3H, CH$_3$); 2.54 (s, 3H, SCH$<em>3$); 7.00 (s, 1H, H-4); 7.03 (s, 1H, H-5); 7.31 (s, 4H$</em>{arom}$)</td>
</tr>
<tr>
<td>3c</td>
<td>11</td>
<td>85</td>
<td>100</td>
<td>C$_1$H$_7$N$_2$OS (220.2)</td>
<td>220 (60)</td>
<td>3120, 3000, 1510, 1442</td>
<td>2.45 (s, 3H, SCH$_3$); 3.76 (s, 3H, OCH$<em>3$); 6.70–7.29 (m, 6H, H-4, H-5, 4H$</em>{arom}$)</td>
</tr>
<tr>
<td>3d</td>
<td>10</td>
<td>81</td>
<td>110–112</td>
<td>C$_1$H$_7$N$_2$OS (224.6)</td>
<td>222 (100); 226 (96)</td>
<td>3120, 2900, 1440, 1345</td>
<td>2.50 (s, 3H, SCH$<em>3$); 6.89 (s, 1H, H-4); 7.07 (s, 1H, H-5); 7.32 (m, 4H$</em>{arom}$)</td>
</tr>
<tr>
<td>3e</td>
<td>10</td>
<td>90</td>
<td>97</td>
<td>C$_1$H$_7$N$_2$OS (206.1)</td>
<td>268 (35); 270 (10)</td>
<td>3095, 2925, 1481, 1440</td>
<td>3.45 (s, 3H, CH$_3$); 2.54 (s, 3H, SCH$<em>3$); 6.89 (s, 1H, H-4); 7.05 (s, 1H, H-5); 7.00–7.65 (m, 4H$</em>{arom}$)</td>
</tr>
<tr>
<td>3f</td>
<td>15</td>
<td>82</td>
<td>oil</td>
<td>C$_1$H$_7$N$_2$S (204.2)</td>
<td>204 (38)</td>
<td>3102, 3024, 1490, 1458</td>
<td>2.05 (s, 3H, CH$_3$); 2.51 (s, 3H, SCH$<em>3$); 6.81 (s, 1H, H-4); 6.96 (s, 1H, H-5); 7.05–7.40 (m, 4H$</em>{arom}$)</td>
</tr>
<tr>
<td>3g</td>
<td>16</td>
<td>83</td>
<td>oil</td>
<td>C$_1$H$_7$N$_2$S (224.6)</td>
<td>224 (80); 226 (35)</td>
<td>3100, 3051, 1590, 1480</td>
<td>2.50 (s, 3H, SCH$<em>3$); 6.84 (s, 1H, H-4); 6.94 (s, 1H, H-5); 7.0–7.55 (m, 4H$</em>{arom}$)</td>
</tr>
<tr>
<td>3h</td>
<td>10</td>
<td>80</td>
<td>45</td>
<td>C$_1$H$_7$N$_2$OS (224.6)</td>
<td>222 (81); 226 (79)</td>
<td>3108, 3092, 1590, 1482</td>
<td>2.51 (s, 3H, SCH$<em>3$); 6.90 (s, 2H, H-4 and H-5); 7.0–7.35 (m, 4H$</em>{arom}$)</td>
</tr>
<tr>
<td>3i</td>
<td>10</td>
<td>81</td>
<td>120</td>
<td>C$_1$H$_7$N$_2$OS (200.1)</td>
<td>280 (93)</td>
<td>3100, 3095, 1595, 1493</td>
<td>2.51 (s, 3H, SCH$_3$); 3.71 (s, 3H, OCH$_3$); 6.37 (s, 6H, OCH$<em>3$); 6.50 (s, 2H, H-4 and H-5); 6.90 (s, 2H$</em>{arom}$)</td>
</tr>
<tr>
<td>3j</td>
<td>11</td>
<td>80</td>
<td>oil</td>
<td>oil</td>
<td>204 (100)</td>
<td>3100, 3058, 1492, 1450</td>
<td>2.52 (s, 3H, SCH$_3$); 5.00 (s, 2H, C$_3$H$_4$CH$<em>2$); 6.72 (s, 1H, H-4); 6.90 (s, 1H, H-3); 7.30 (m, 5H$</em>{arom}$)</td>
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<tr>
<td>3k</td>
<td>12</td>
<td>81</td>
<td>oil</td>
<td>oil</td>
<td></td>
<td>1245</td>
<td></td>
</tr>
<tr>
<td>3l</td>
<td>15</td>
<td>85</td>
<td>oil</td>
<td>oil</td>
<td></td>
<td>204 (100)</td>
<td>3100, 3058, 1492, 1450</td>
</tr>
</tbody>
</table>

* Yield of pure isolated product.
* Uncorrected, measured with a Thomas Pillow Capillary melting-point apparatus.
* Satisfactory microanalyses obtained: C ± 0.29, H ± 0.33, N ± 0.35.
* Recorded on Jeol JMS-D 300 spectrometer.
* Recorded on a Perkin-Elmer 297 Infrared spectrophotometer.

*† Recorded on Varian EM-390 NMR spectrometer.
*‡ The products 3a, 3j, and 3k were characterized by comparison of their IR and 1H-NMR spectral data with reported values as well as by mass spectra and microanalyses.

*§ δ = 4.5 is not clearly resolved.
reaction was found to undergo rapid demethylation to the thione 4 (as monitored by TLC), probably due to steric hindrance. This was further confirmed by refluxing 3m (prepared by a known procedure) in acetic acid for 1 h, the thione 4 being obtained in nearly quantitative yield (95%).

In summary, dimethyl N-aryl- and N-alkylcarbimidodithioates (I) are useful precursors of 1-aryl-, 1-methyl-, 1-ethyl-, and 1-aralkyl-2-methylthioimidazoles which were earlier obtained by a two-step procedure involving synthesis of the corresponding imidazole-2(3H)thiones and their methylation. The starting materials 1a–I were prepared according to the reported procedure.

1-Aryl- and alkyl-2-methylthioimidazoles (3a–I): General Procedure:
A solution of the dimethyl N-aryl- or N-alkylcarbimidothioate 1 (10 mmol) and aminoacetaldehyde diethyl acetal (2, 2.0 g, 15 mmol) in AcOH (10 mL) is heated to boiling for 10–15 h. Then, AcOH is removed under vacuum and the residue is dissolved in CHCl₃ (50 mL). This solution is washed with H₂O (3 × 30 mL), dried (Na₂SO₄), and evaporated to give the crude product 3 which is purified by column chromatography on silica gel using EtOAc/hexane (1:4) as eluent, and crystallized from CH₂Cl₂.

1-Isopropylimidazole-2(3H)-thione (4):
From 1m: A solution of dimethyl 1-isopropylcarbimidothioate (1m; 1.50 g, 10 mmol) and aminoacetaldehyde diethyl acetal (2; 2.0 g, 15 mmol) in AcOH (10 mL) is heated to boiling for 20 h until compound 1m has been consumed completely (TLC, EtOAc/benzene 1:4). Work-up as in the General Procedure gives the thione 4 as pale-colored crystals (from CH₂Cl₂); yield: 1.00 g (75%); m.p. 169–70°C (Lit. m.p. 168–9°C, superimposable IR and NMR spectra).

From 3m: A solution of 1-isopropyl-2-methylthioimidazole (3m; AcOH (10 mL) is refluxed for 1 h. Work-up of the (mixture as described gives 4; yield: 0.43 g (95%) mixture m.p., superimposable IR and NMR spectra).

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