NOVEL DIMERIZATION PRODUCTS OF N-ACYLINDOLES WITH AlCl₃

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Abstract: The reactivity of N-methoxycarbonylindole 2 in the presence of aluminum chloride was studied and the structures of the products were determined to be dimers 3a-c, 4a-c, 5 and 6.

Although many indole alkaloids containing functional groups on the benzene part of indole nucleus had been appeared, introduction of the functional groups at the specific positions was difficult except a few cases (1). We have developed novel methods (2) introducing various functional groups on the benzene part of stabilized indoles and applied them for total synthesis of Teleocidin B (3) and efficient synthesis of the Mitomycin skeleton (4). In the study of chemical reactivity of N-pivaloylindole, we found novel dimerization of N-pivaloylindole in presence of AlCl₃ to give 1a-c (Fig. 1.) (5). These were completely different from polymerization products (6) of indole itself in acidic conditions. In this publication we report novel dimerization products of N-methoxycarbonylindole 2.

Fig. 1. Dimers of N-pivaloylindole
First of all, we examined polymerization of N-acetyl and N-benzoylindoles in the presence of 5 eq. AlCl₃ and the results were very similar with N-pivaloylindole to give dimers corresponding to 1a-e.

N-Methoxycarbonylindole 2 (7) was treated with AlCl₃ under various conditions, we isolated eight dimers. Two types of dimers of 2 were observed. One of them was produced by condensation between a pyrrole part and a benzene part of each indole moiety (dimers 3a-c and 4a-c) and the other one was between both pyrrole parts (5 and 6) (Scheme 1).

When the reaction was carried out with 1.0 eq. AlCl₃ in CH₂Cl₂ at 25°C for 120 min, major product was 2,3'-dimer 5 in 70% yield (entry 1 in Table). It is considered that the dimer 5 was formed by condensation between coordinated 2 with AlCl₃ at the pyrrole part (electrophile) and AlCl₃-free 2 (nucleophile).

When the reaction was carried out with 5.0 eq. AlCl₃ in CH₂Cl₂ at 25°C (entry 2), 3a-c were obtained as a major component in 24% (a:b:c = 1:1:4), and 4a-c were obtained in 6% (a:b:c = 1:1:8). When the reaction was carried out at -20°C (entry 3), 2,4'-6'-dimers 4a-c were obtained as a major component in 18% (a:b:c = 1:1:9). At low temperature, the selectivity of electrophilic addition at 2-position was increased. Purification of dimer 3-6 was carried out by HPLC using reversed-phase column (solvent : 75% MeOH, 1% AcOH in H₂O) to give a mixture of 4a-c. Further purification of 4a-c by normal phase HPLC (solvent : 7% EtOAc in hexane) gave 4c (8) and 4ab. Since separation of 4ab was difficult, a mixture of 4ab was hydrolyzed with 1N NaOH in MeOH at 25°C for 10 min. 7a and 7b (9, 10) were isolated by reversed-phase HPLC (solvent : 55% MeOH, 1% AcOH in H₂O). In the same way, a mixture of 3a-c and 6 were also hydrolyzed with 1N NaOH in MeOH at 50°C for 15 min and it has succeeded in refining each component by HPLC. Structures of each isolated compounds were determined by ¹H-NMR etc.

Dimerization mechanism for the reaction of 2 to dimer 4c was shown in Scheme 2. Though AlCl₃ coordinated at N-position for N-pivaloylindole, the nucleophilicity of pyrrole part is lost by the coordination of 2 with AlCl₃ (1) at the 3-position and electrophilic 2-position was attacked with a benzene part of the other 1 to give 2,6'-dimer 4c.

Thus obtained 4a-c were novel dimers of simple indole. Reactivity of N-acylindole and application of these reaction is now in progress.
Scheme 1. Dimerization of N-methoxycarbonylindole

<table>
<thead>
<tr>
<th>Entry</th>
<th>Eq.</th>
<th>Temp.</th>
<th>Time</th>
<th>3a-c</th>
<th>4a-c</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0</td>
<td>25°C</td>
<td>120 min</td>
<td>-</td>
<td>-</td>
<td>70%</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>5.0</td>
<td>25°C</td>
<td>2 min</td>
<td>24%</td>
<td>6%</td>
<td>1%</td>
<td>5%</td>
</tr>
<tr>
<td>3</td>
<td>5.0</td>
<td>-20°C</td>
<td>30 min</td>
<td>10%</td>
<td>18%</td>
<td>1%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Fig. 2. Purification of a mixture of dimers 4a-c

Scheme 2. Dimerization mechanism of N-methoxycarbonylindole
References and Notes

8) 4c : m.p. 137-138°C; 1H-NMR δ ppm (500MHz, d6-Aceton): 3.00 (1H, dd, J=3, 16Hz), 3.64 (3H, br.s), 3.82 (1H, dd, J=11, 16Hz), 3.99 (3H, s), 5.65 (1H, dd, J=3, 11Hz), 6.62 (1H, br.d, J=4Hz), 7.01 (1H, brt, J=8Hz), 7.08 (1H, br.d, J=8Hz), 7.19 (1H, d, J=8Hz), 7.25 (1H, t, J=8Hz), 7.51 (1H, d, J=8Hz), 7.61 (1H, d, J=4Hz), 7.88 (1H, br.s), 8.07 (1H, s); EI-MS m/z : 350 (M^+).
9) 7a : amorphous solid; 1H-NMR δ ppm (400MHz, 10% CD3OD in CDCl3) : 3.12 (1H, dd, J=3, 16Hz), 3.38 (3H, br.s), 3.80 (1H, dd, J=10, 16Hz), 5.87 (1H, dd, J=3, 10Hz), 6.37 (1H, br.s), 6.85 (1H, br.d, J=8Hz), 7.01 (1H, t, J=8Hz), 7.05 (1H, t, J=8Hz), 7.13 (1H, d, J=8Hz), 7.21 (1H, br.s), 7.27 (1H, t, J=8Hz), 7.31 (1H, d, J=8Hz), 7.96 (1H, br.s), 9.57 (1H, br.s); EI-MS m/z : 292 (M^+).
10) 7b : amorphous solid; 1H-NMR δ ppm (500MHz, d6-Aceton) : 3.00 (1H, dd, J=3, 16Hz), 3.63 (3H, s), 3.77 (1H, dd, J=10, 16Hz), 5.58 (1H, dd, J=3, 10Hz), 6.38-6.39 (1H, m), 6.95 (1H, d, J=8Hz), 6.99 (1H, t, J=7Hz), 7.18 (1H, d, J=7Hz), 7.23 (1H, t, J=7Hz), 7.27 (1H, t, J=3Hz), 7.32 (1H, d, J=8Hz), 7.38 (1H, s), 7.86 (1H, br.s), 10.15 (1H, br.s); EI-MS m/z : 292 (M^+).

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