ADDITION REACTION OF INDOLIZINE DERIVATIVES WITH DIMETHYL ACETYLENEDICARBOXYLATE

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Abstract — Indolizine derivatives reacted with dimethyl acetylenedicarboxylate to give 1:1 adducts 2-6. In some cases 1:2 adducts 7 were obtained from which cycl[4.3.2]azine derivatives 11 were synthesized by dehydrogenation. The addition reaction was dependent on the substituents and solvents employed.

The reaction of indolizines with electron deficient acetylenes provides a useful method for synthesis of cycl[3.2.2]azines and (8+2)n cycloadducts have been postulated as intermediates to give the cyclazines.1 The details, however, remain ambiguous because the addition reaction has been carried out under dehydrogenating conditions. We report here the addition reaction of indolizine derivatives with dimethyl acetylenedicarboxylate (DMAD) in the absence of dehydrogenating catalyst. When a dry acetone solution of indolizines 1a-4 and DMAD (1.0 : 1.3 equiv) was stirred under N₂ at room temperature for 15 h, several 1:1 adducts 2-6 and 1:2 adducts 7 were obtained in the yields shown in Table 1. These products could be separated by flash column chromatography on silica gel. The structural assignments of these products were based on their spectroscopic data along with chemical evidence. The ¹H NMR spectrum of 2a, for example, is as follows.3 2a: δ ppm (200 MHz, C₆D₆) 3.58 (s, Me), 3.86 (s, Me), 5.25 (brd, H-1, J=5.0 Hz), 5.32 (d, H-2, J=5.0 Hz), 6.53 (br δ, H-7, J=7.0 Hz), 6.70 (dd, H-6, J=9.0, 7.0 Hz), 7.15 (ddd, H-5, J=9.0, 1.0, 1.0 Hz), 7.28 (s, H-4), 7.26 (m, 1H, Ph), 7.40 (m, 2H, Ph), 7.64 (m, 2H, Ph). The fact that the olefinic proton signal assigned to H-7 is observed as broad doublet and the absorptions of two methine proton couple with each other (J=5.0 Hz) strongly supports this structure. The structures of 1:1 adducts 3 were also deduced from the ¹H NMR spectra. The spectrum of 3, for example, exhibits the methyl signal...
Table 1 Yields and melting points of the adducts in the reaction in acetone

<table>
<thead>
<tr>
<th>Compd number</th>
<th>Yield, % (m.p., °C)</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>4</td>
<td>8</td>
<td>13</td>
<td>4</td>
<td>-a)</td>
<td>(107-108)</td>
<td>(138-139)</td>
</tr>
<tr>
<td>b</td>
<td>4</td>
<td>6</td>
<td>1</td>
<td>11</td>
<td>5</td>
<td>(117-119)</td>
<td>(129-131)</td>
</tr>
<tr>
<td>c</td>
<td>5</td>
<td>4</td>
<td>16</td>
<td>-a)</td>
<td>8</td>
<td>(oil)</td>
<td>(186-187)</td>
</tr>
<tr>
<td>d</td>
<td>27</td>
<td>5</td>
<td>8</td>
<td>20</td>
<td>-a)</td>
<td>(113-116)</td>
<td>(117-120)</td>
</tr>
</tbody>
</table>

Table 2 Yields (%) of the adducts in the reaction of the indolizines 1b with DMAD in several solvents at room temperature

<table>
<thead>
<tr>
<th>Compd</th>
<th>C6H6</th>
<th>CH2Cl2</th>
<th>CH3COCH3</th>
<th>CH2CN</th>
<th>CH3CH2OH</th>
<th>CH3SOCH3</th>
<th>HCON(CH3)2</th>
</tr>
</thead>
<tbody>
<tr>
<td>2b</td>
<td>15</td>
<td>9</td>
<td>4</td>
<td>12</td>
<td>-a)</td>
<td>-a)</td>
<td>2</td>
</tr>
<tr>
<td>3b</td>
<td>10</td>
<td>10</td>
<td>6</td>
<td>-a)</td>
<td>-a)</td>
<td>-a)</td>
<td>3</td>
</tr>
<tr>
<td>4b</td>
<td>5</td>
<td>7</td>
<td>2</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>5b</td>
<td>1</td>
<td>1</td>
<td>11</td>
<td>1</td>
<td>30</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>6b</td>
<td>-a)</td>
<td>-a)</td>
<td>5</td>
<td>-a)</td>
<td>11</td>
<td>-a)</td>
<td>5</td>
</tr>
<tr>
<td>7b</td>
<td>1</td>
<td>3</td>
<td>13</td>
<td>15</td>
<td>4</td>
<td>18</td>
<td>9</td>
</tr>
</tbody>
</table>

a) These products could not be isolated.

as doublet, indicating the presence of a hydrogen at the C5-position. 3d: 8ppm (60 MHz, CDC13) 1.48 (d, Me, J=7.5 Hz), 3.60 (s, Me), 3.78 (s, Me), 3.7-3.8 (m, H-5), 5.01 (d, H-7a, J=4.0 Hz), 6.39 (br s, H-4), 6.41 (dd, H-7, J=9.5, 4.0 Hz), 6.99 (dd, H-6, J=9.5, 2.0 Hz), 7.1-7.6 (m, 5H, Ph). Upon heating a chloroform solution of 3 at 60 °C, 3 isomerized to 2, whereas 2 were stable even in refluxing toluene. When the addition reaction was carried out in refluxing toluene, only 2 were isolated in 25-30 % yields. Treating the adducts 2a-d with 10 % Pd-C in refluxing toluene gave
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cyclazines 4a-d in 80-90 % yields, while the reaction of 3b with Pd-C gave 4b in
64 % yield. These results support the structures of 1:1 cycloadducts 2 and 3. The
Michael type adducts 5 are geometrical isomers of 64,5 because both of them gave the
same compounds 8 by reduction with NaBH₄ in tetrahydrofuran.
their structures could be determined on the basis of the ¹H
NMR spectra. Thus, the singlet signals of the vinyl protons
Ha appear at lower field in 5 than in 6. (5a: 67.02, 5b: 7.10
6a: 6.06, 6b: 6.05). These values of chemical shifts are in good agreement with
the values reported for the dimethyl (E)- and (Z)-butenedioate derivatives.6 The
structures of 1:2 cycloadducts 7 were suggested by their elemental and mass
spectra.7 Table 1 indicates that the 1:2 adducts 7 were isolated only in the
reaction of indolizines bearing a methyl group at the C₆ or C₇ position. The yields
of 7 increased when more amounts of DMAD were used. Thus, when indolizines 1b,c
and DMAD (1.0 : 3.0 equiv) were reacted in acetone at room temperature, 7b,c were
obtained in 50 and 38 % yields, respectively. In contrast, no 1:2 adduct was
isolated in the reaction of indolizines 1a,d even if the excess of DMAD was used.
The addition reaction was also sensitive to the solvent effects. The reaction of
indolizine 1b with DMAD was examined in several solvents as shown in Table 2. In
nonpolar solvents, the formation of the Michael type adducts 5 and 6 is depressed,
while their formation is favored in ethanol. The better yields of the 1:2 adducts
7 are accomplished in aprotic polar solvents.
Considering these findings, the following reaction mechanism can be assumed.
Indolizines 1 react with DMAD to give dipole intermediate 9 and/or 9', protonation
of which leads to the Michael type adducts 5 and 6, respectively. The fact that
the anti-addition is preferred is in agreement with the reported results for
nucleophilic additions to acetylenes.8 The 1:1 adducts 3 can be formed by a 1,5-
hydrogen shift from (8+2)π cycloadducts 10 which are formed by a stepwise mechanism via 9' or a concerted cycloaddition. The formation of indolizines 2 can be explained by tautomerization of 3 in which aromatization is considered to drive the reaction. The 1:2 adducts 7 can be formed by attack of another DMAD to 9'. The better yields of 7 obtained in polar solvents such as acetonitrile or acetone can be attributed to the fact that the dipolar intermediate 9' is stabilized in these solvents. The methyl substituents (R^1 or R^2) may also stabilize 9'.

Dehydrogenation of the adducts 7a and 7b with DDQ or chloranil in refluxing benzene afforded cycl[4.3.2]azine derivatives 11b (mp 186-189 °C) and 11c (mp 162-164 °C), respectively, in 60-80% yields. They are stable red crystals and the longer absorption maxima were observed at 320 nm (log ε=4.46) in 11b and 310 nm (log ε=4.50) in 11c. Thus, the reaction of indolizines with DMAD provides a convenient method to synthesize cycl[4.3.2]azines besides cycl[3.2.2]azines.

REFERENCES AND NOTES


2. All new compounds obtained here showed satisfactory elemental analyses and spectral data. The stereochemistry of the adducts 2, 3, and 7 has not been unambiguously determined.

3. We thank Professor Toshio Mukai at Tohoku University for providing the measurements of the 200 MHz NMR spectra.

4. The formation of one Michael type adduct has been reported, but the stereochemistry was ambiguous.


7. Recently the formation of this type of 1:2 adducts has been reported in the reaction of 3-cyanoindolizines with DMAD although Pd-C is needed as catalyst in this case. T. Uchida and K. Matsumoto, Chem. Lett., 1980, 149.


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