Abstract: The Diels-Alder reactions of furans with α-chloro- and α-acetoxyacrylonitrile very nicely proceeded under the conditions of 15 kbar and 30 °C in dichloromethane. The adducts were proved to be a useful precursor for the synthesis of 7-oxa-bicyclo[2.2.1]heptanone derivatives.

Recent investigations from our laboratory and others have shown that the use of high pressure is a very valuable tool for synthetic organic chemistry. In this communication, we wish to report the successful Diels-Alder reactions of furans with α-chloro- and α-acetoxyacrylonitrile by the application of high pressure techniques.

In connection with our studies toward the total synthesis of cerulenin and muscarine, we envisaged 7-oxa-bicyclo[2.2.1]heptanones as a common key intermediate as designed in the following scheme:

\[
\text{cerulenin} \quad \text{NH}_2 \quad \rightarrow \quad \text{bicycle} \rightarrow \quad \text{muscarine}
\]

Consequently, we set out to develop a general method for the preparation of 7-oxa-bicyclo[2.2.1]heptanones.

The most direct route to this compound would be Diels-Alder reactions between furan and ketene equivalents such as α-chloro- or α-acetoxyacrylonitrile. Although the diene character of furan was well recognized, the reactions with these dienophiles have not been reported. Not unexpectedly, all attempts of the Diels-Alder reactions under conventional conditions (e.g. refluxed in ether...
Table. Diels-Alder reactions of furans with α-chloro- and α-acetoxy-acrylonitrile

![Diels-Alder reaction diagram]

<table>
<thead>
<tr>
<th>Run</th>
<th>$R^1$</th>
<th>$R^2$</th>
<th>Time, hr</th>
<th>Yield, %b)</th>
<th>IR(neat or CHCl$_3$) cm$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>H</td>
<td>8</td>
<td>83</td>
<td>2245, oil</td>
</tr>
<tr>
<td>2</td>
<td>CH$_3$</td>
<td>H</td>
<td>8</td>
<td>85</td>
<td>2245, oil</td>
</tr>
<tr>
<td>3</td>
<td>CH$_3$</td>
<td>CH$_3$</td>
<td>8</td>
<td>85</td>
<td>2245, oil</td>
</tr>
<tr>
<td>4</td>
<td>CH$_2$OAc</td>
<td>H</td>
<td>8</td>
<td>70c)</td>
<td>2245, 1750, oil</td>
</tr>
<tr>
<td>5</td>
<td>CH$_2$OAc</td>
<td>H</td>
<td>8</td>
<td>66c)</td>
<td>2245, oil</td>
</tr>
<tr>
<td>6</td>
<td>H</td>
<td>H</td>
<td>15</td>
<td>70</td>
<td>2240, 1750, oil</td>
</tr>
<tr>
<td>7</td>
<td>CH$_3$</td>
<td>H</td>
<td>15</td>
<td>88</td>
<td>1750, d) mp 84-86 °C</td>
</tr>
<tr>
<td>8</td>
<td>CH$_3$</td>
<td>CH$_3$</td>
<td>15</td>
<td>90</td>
<td>2240, 1755, oil</td>
</tr>
<tr>
<td>9</td>
<td>CH$_2$OAc</td>
<td>H</td>
<td>15</td>
<td>72</td>
<td>1750, d) mp 110-112.5 °C</td>
</tr>
<tr>
<td>10</td>
<td>CH$_2$OAc</td>
<td>H</td>
<td>15</td>
<td>65</td>
<td>1755, d) mp 158 °Ce)</td>
</tr>
</tbody>
</table>

a) All the reactions were performed at a concentration of 3 M of the reactants. The structures of all adducts were confirmed by elemental analysis, NMR, and IR.

b) Crude yields by NMR unless otherwise noted. The values are the average of two or more runs.

c) Isolated yields after short column chromatography on neutral alumina.


e) The ortho adduct was obtained as crystals, whereas the meta one as an oil.

without or with the catalysis of BF$_3$·OEt$_2$) were fruitless. And we have found the reactions in dichloromethane proceeded very nicely at 15 kbar and 30 °C. The results are summarized in Table.
The spectral evidences showed that the reactions proceeded almost regio-
selectively to form ortho adducts with both dienophiles (Runs 2, 4, 7, 9).
Exceptionally in the case of furfural ethyleneacetal, an approximately 1:1 regio-
isomeric mixture was obtained (Runs 5, 10). With respect to the stereochemistry of
the adducts the endo/exo ratios of those with 1a were found to be around 3:1
from the NMR integrals or GLC analysis of hydrogenated compounds. In the case of
1b endo isomers were obtained mostly.

Although furfural, 5-methylfurfural, and 2-acetylfuran were unreactive even
at high pressures, the reactions occurred with the protected furfural in moderate
yields (Runs 5, 10).

With the cycloaddition accomplished, we attempted hydrolysis of masked ketone
function after hydrogenation because of the relative instability of adducts. The
hydrolysis of 3a under a variety of conditions (Na2S-EtOH or KOH-DMSO) was
unsuccessful and gave only a carboxylic acid 4. 3b was smoothly converted to the
对应的酮 5 (2N NaOH-EtOH, IR 1755 cm⁻¹).

Thus we have demonstrated a simple approach to 7-oxa-bicyclo[2.2.1]heptanones
by an application of high-pressure Diels-Alder reactions. We are presently
developing the utility of these adducts to natural product synthesis.

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continuous encouragements.

References and Notes

2. H. Kotsuki, H. Nishizawa, S. Kitagawa, M. Ochi, N. Yamasaki, K. Matsuoka,
   and T. Tokoroyama, Bull. Chem. Soc. Jpn., 52, 544 (1979), and references cited
   therein.
3. For a recent review see, Kagaku Sosetsu, No. 22, Chap. 7 (1979).


7. Attempted reaction between furan and vinyl acetate was failed and gave only recovery of starting materials.

8. A typical isolated yield is 580 mg of adducts from 328 mg of 2-methylfuran and 350 mg of la. For a description of our high-pressure apparatus and general procedure for high pressure reactions, see ref. 2. α-Acetoxyacrylonitrile was prepared according to the literature: R. M. Nowak, J. Org. Chem., 28, 1182(1963).

9. The major isomer of endo adducts was assigned as having a Cl or OAc group in endo orientation based on the 1H NMR data (δ, CDCl3):

\[
\text{endo: } \begin{align*}
\text{CN} & \quad 2.86(1H, dd, J=12, 5 Hz) \\
\text{H} & \quad 1.81(1H, d, J=12 Hz)
\end{align*}
\]

\[
\text{exo: } \begin{align*}
\text{CN} & \quad 2.51(1H, dd, J=12, 4 Hz) \\
\text{H} & \quad 2.33(1H, d, J=12 Hz)
\end{align*}
\]


10. \(2\beta(R^1=R^2=H); 1H\ NMR (CDCl_3): \delta 1.66(1H, d, J=13 Hz), 2.01(3H, s), 2.63(1H, dd, J=13, 5 Hz), 5.02(1H, dd, J=5, 1.5 Hz), 5.49(1H, d, J=1.5 Hz), 6.15(1H, dd, J=6, 1.5 Hz), 6.55(1H, dd, J=6, 1.5 Hz). \)


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