Synthesis of 4-Chloro-5-cyano-2-dimethylamino-6H-1,3-oxazin-6-one from the Salts of Alkyl Dicyanoacetates and Some of Its Reactions

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Dedicated in friendship to my dear colleague Hans-Jürgen Bestmann, Erlangen with best wishes on the occasion of his 65th birthday

The salts of alkyl dicyanoacetates and methyl 3-amino-3-chloro-2-cyanoacrylate react in chloroform with N-(dichloromethylene)dimethylammonium chloride to give 4-chloro-5-cyano-2-dimethylamino-6H-1,3-oxazin-6-one. The chloro atom of this compound can be easily substituted by alcohols or amines in good yield.

Recently we reported an investigation of the structures and some reactions of alkyl dicyanoacetates and their salts,\(^2\)\(^-\)\(^7\) which had previously been very seldom used in organic syntheses, although they are readily available by alkoxy- or amino- or carboxylation of malonodinitrile\(^8\)\(^-\)\(^13\) or cyanation of cyanoacetates etc.\(^14\)\(^,\)\(^15\)

We have found that the salts of alkyl dicyanoacetates react in chloroform at room temperature with \(N\)-(dichloromethylene)dimethylammonium chloride to give 4-chloro-5-cyano-2-dimethylamino-6H-1,3-oxazin-6-one in moderate yield (Scheme A), these compounds can also be obtained by refluxing 2 with methyl 3-amino-3-chloro-2-cyanoacrylate (4) in chloroform in 25% yield (Scheme B).

A mechanism to explain the formation of 3 is shown in Scheme A: 3 is obtained by the nucleophilic attack of the oxygen anion of 1 at the imine carbon of 2 and the cyclization of the intermediate \(3\alpha\) to \(3\beta\) followed by elimination of the alkyl chlorides.

\[
\begin{align*}
1a-d & \quad + \quad [\text{Cl} \quad \text{Cl} \quad \text{Cl}^-] \quad \text{CHCl}_3, \text{r.t., } 5-24\text{h} \\
& \quad \text{CHCl}_3, \text{reflux, } 8\text{h} \\
& \quad 42-72\% \\
& \quad \text{CHCl}_3, \text{reflux, } 8\text{h} \\
& \quad 25\% \\
& \quad \text{CHCl}_3, \text{reflux, } 8\text{h} \\
& \quad 25\% \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>Substrate</th>
<th>R</th>
<th>M</th>
<th>Time (h)</th>
<th>Yield of 3 (%)</th>
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<tbody>
<tr>
<td>1a</td>
<td>Me</td>
<td>K</td>
<td>16</td>
<td>52</td>
</tr>
<tr>
<td>1b</td>
<td>Et</td>
<td>K</td>
<td>24</td>
<td>72</td>
</tr>
<tr>
<td>1c</td>
<td>Bu</td>
<td>K</td>
<td>5</td>
<td>42</td>
</tr>
<tr>
<td>1d</td>
<td>Bn</td>
<td>Na</td>
<td>6</td>
<td>50</td>
</tr>
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</table>

Scheme A
Table 1. 4-Substituted Oxazinones 6–8 Prepared

<table>
<thead>
<tr>
<th>Product</th>
<th>Yield* (%)</th>
<th>mp (°C) (solvent)</th>
<th>Purification Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>6a</td>
<td>62</td>
<td>189–191 (MeOH)</td>
<td>recrystallization</td>
</tr>
<tr>
<td>6b</td>
<td>52</td>
<td>162.5–165 (EtOH)</td>
<td>recrystallization</td>
</tr>
<tr>
<td>7a</td>
<td>93</td>
<td>114–115 (CCl₄)</td>
<td>recrystallization</td>
</tr>
<tr>
<td>7b</td>
<td>86</td>
<td>229–230 (CHCl₃)</td>
<td>recrystallization</td>
</tr>
<tr>
<td>7c</td>
<td>76</td>
<td>154–155 (CHCl₃)</td>
<td>column chromatography</td>
</tr>
<tr>
<td>8c</td>
<td>19</td>
<td>85–86 (CHCl₃)</td>
<td>column chromatography</td>
</tr>
</tbody>
</table>

* Yields of pure products.
* Separated with silica gel; CHCl₃ (7c: Rₜ = 0.44; 8c: Rₜ = 0.54).

The structure of 3 was determined by ¹³C-NMR and ¹H-NMR; both give two signals for the methyl groups in 3, and suggest strongly the zwitterionic structure of 3.

The chloro atom in 3 can easily be substituted by nucleophilic reagents, such as alcohols and amines. Thus, the substituted compounds 6–8 were obtained in high yields. In the reaction of 3 with butylamine the ring opening product 8c was observed together with the 4-butyramino substituted oxazinone 7c.

Table 2. Compounds 6–8 Prepared

| Product  | Molecular Formula* | UV (MeCN) /max/nm (log ε) | IR (KBr) ν/cm⁻¹ | ¹H-NMRb δ | ¹³C-NMRb δ | MS (80eV) m/z (%<)
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>6a</td>
<td>C₆H₄N₂O₃ (195.2)</td>
<td>210 (4.307), 295 (4.325)</td>
<td>2220 (s), 1640 (s)</td>
<td>3.24 (s, 3H, =N(CH₃)₂), 3.33 (s, 3H, =N(CH₃)₂), 4.04 (s, 3H, OCH₃)</td>
<td>36.96 (q, =N(CH₃)₂), 38.07 (q, =N(CH₃)₂), 56.08 (q, OCH₃), 63.31 (s, C-5), 114.47 (s, CN), 158.89 (s, C-2), 160.19 (s, C-6), 175.38 (s, C-4)</td>
<td>195 (M⁺, 69), 151 (100)</td>
</tr>
<tr>
<td>6b</td>
<td>C₆H₁₀N₄O₃ (209.2)</td>
<td>210 (4.449), 292 (4.350)</td>
<td>2220 (s), 1640 (s)</td>
<td>1.38 (t, 3H, CH₂CH₃), 3.23 (s, 3H, =N(CH₃)₂), 4.52 (q, 2H, CH₂CH₃)</td>
<td>14.66 (q, CH₃CH₂), 36.94 (q, =N(CH₃)₂), 38.03 (q, =N(CH₃)₂), 63.48 (s, C-5), 65.70 (q, CH₃CH₂), 114.55 (s, CN), 159.03 (s, C-2), 160.18 (s, C-6), 174.93 (s, C-4)</td>
<td>209 (M⁺, 73), 72 (100)</td>
</tr>
<tr>
<td>7a</td>
<td>C₁₁H₁₆N₄O₂ (236.3)</td>
<td>235 (4.496), 285 (4.218)</td>
<td>2210 (s), 1630 (s)</td>
<td>1.27 (t, 6H, CH₂CH₃), 3.14 (s, 3H, =N(CH₃)₂), 3.19 (s, 3H, =N(CH₃)₂), 3.76 (q, 4H, CH₂CH₃)</td>
<td>14.07 (q, CH₃CH₂), 36.30 (q, =N(CH₃)₂), 37.54 (q, =N(CH₃)₂), 45.20 (t, CH₂CH₃), 58.44 (s, C-5), 118.54 (s, CN), 157.28 (s, C-2), 160.90 (s, C-6), 162.47 (s, C-4)</td>
<td>236 (M⁺, 28), 72 (100)</td>
</tr>
<tr>
<td>7b</td>
<td>C₁₂H₁₄N₂O₂ (256.3)</td>
<td>210 (4.368), 288 (4.368)</td>
<td>3280 (w), 1620 (s)</td>
<td>3.16 (s, 3H, =N(CH₃)₂), 3.19 (s, 3H, =N(CH₃)₂), 7.19–7.47 (m, 6H arom, NH)</td>
<td>36.64 (−, −, =N(CH₃)₂), 37.76 (−, −, −, =N(CH₃)₂), 60.37 (+, 115.63 (+, CN), 123.12, 125.90, 128.96 (−, Phenyl), 136.49 (+, Phenyl), 157.90 (−, C-2), 158.81 (−, C-6), 163.41, 164.84 (+, C-4)</td>
<td>256 (M⁺, 94), 72 (100)</td>
</tr>
<tr>
<td>7c</td>
<td>C₁₁H₁₆N₂O₂ (236.3)</td>
<td>230 (4.572), 282 (4.207)</td>
<td>3340 (m), 1620 (s)</td>
<td>0.95 (t, 3H, CH₂CH₃), 1.37 (sext, 2H, CH₂CH₃), 1.59 (quint, 2H, CH₂CH₂CH₃), 3.17 (s, 3H, =N(CH₃)₂), 3.20 (s, 3H, =N(CH₃)₂), 3.48 (q, 2H, NHCH₂CH₂), 5.90 (br s, 1H, NH)</td>
<td>13.88 (−, −, CH₂CH₃), 19.90 (+, CH₂CH₃), 31.59 (+, CH₂CH₂CH₃), 36.52 (−, =N(CH₃)₂), 37.56 (−, =N(CH₃)₂), 41.46 (+, NHCH₂CH₃), 58.73 (+, C-5), 116.20 (+, CN), 158.25 (+, C-2), 158.70 (−, C-6), 164.84 (+, C-4)</td>
<td>236 (M⁺, 33), 72 (100)</td>
</tr>
<tr>
<td>8c</td>
<td>C₁₅H₁₈N₃O₂ (309.4)</td>
<td>210 (4.264), 280 (4.419)</td>
<td>3360 (m), 1680 (s)</td>
<td>0.93, 0.95 (t, 6H, CH₂CH₃), 1.29–1.70 (m, 8H, CH₂CH₂CH₃), 3.17 (s, 6H, CH₂CH₂CH₃), 3.27, 3.65 (q, 4H, NHCH₂CH₃), 5.97 (br t, 1H, NH), 10.02 (br t, 1H, NH), 13.43 (br s, 1H, NH)</td>
<td>13.88 (q, CH₃CH₂), 13.79 (CH₃CH₂), 19.82 (t, CH₂CH₃), 20.06 (t, CH₂CH₂CH₃), 31.59 (t, CH₂CH₂CH₃), 31.76 (t, CH₂CH₂CH₃), 36.23 (q, N(CH₃)₂), 39.42 (t, NCH₂CH₃), 43.83 (t, NCH₂CH₃), 56.73 (s, C-2), 122.24 (s, CN), 156.19 (s, NCON&lt;), 160.34 (s, C-3), 169.48 (s, C-1)</td>
<td>309 (M⁺, 11), 72 (100)</td>
</tr>
</tbody>
</table>

* Satisfactory microanalysis obtained: C ± 0.25, H ± 0.24, N ± 0.21.
* Measured in: CDCl₃/TMS for 7b, c, 8c; acetone-d₆ for 6a, b, 7a. ¹³C-NMR: spin-echo for 7b, 7c.
Scheme C

Melting points were determined on a Reichert hot stage microscope and are uncorrected. Microanalyses were performed on a Heraeus automatical analyser. UV spectra were recorded on a Carl Zeiss DMR 4 spectrophotometer and IR spectra on a Perkin-Elmer 325 spectrophotometer. NMR spectra were recorded on a Bruker WMS-250 Spectrometer (for 1H-NMR at 250.13 MHz, for 13C-NMR at 62.89 MHz). Mass spectra were obtained on a Varian MAT 311 A instrument.

4-Chloro-5-cyano-2-dimethylamino-6H-1,3-oxazin-6-one (3);
Typical Procedure:
A suspension of potassium methyl dicynoacetate (1a; 0.81 g, 5 mmol) and N-(dichloromethylene)dihemiammonium chloride (2; 0.82 g, 5 mmol) in abs. CHCl₃ (30 mL) is stirred at r.t. for 16 h, and then filtered. The solvent is removed under reduced pressure; recrystallization of the solid residue with EtOAc gives colorless crystals; yield: 0.92 g (52%); mp 167–168°C.

C₇H₈ClN₂O₂ calc. C 42.12 H 3.03 Cl 17.76 N 21.06 (199.6) found 42.29 2.99 17.87 21.00

IR (KBr): ν = 2220, 1775, 1630, 1530, 1470 cm⁻¹.

UV (MeCN): λmax (log ε) = 215 (3.827), 322 (4.299).

1H-NMR (CDCl₃/TMS): δ = 3.27 (s, 3 H, =N(CH₃)₂), 3.33 (s, 3 H, =N(CH₃)₂).

13C-NMR (Spinc-Echo)(CDCl₃/TMS): δ = 37.18 (−, =N(CH₃)₂), 38.41 (−, =N(CH₃)₂), 81.61 (+, C-5), 112.88 (+, C-N), 154.99, 157.69, 168.84 (+, C-2, C-4, C-6).

Received: 26 April 1990; revised: 20 June 1990.

(7) Neidlein, R.; Sui, Z. Chem. Ber. in press.