A New Route to 4-Unsubstituted \( \beta \)-Lactams through Ureidomethylation of Ketene Silyl Acetals

Kiyoshi Ikeda, Yoshiyasu Terao, and Minoru Sekiya*

Shizuoka College of Pharmacy, 2-2-1 Oshika, Shizuoka, 422, Japan

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\( \alpha \)-Ureidomethylated carboxylates were obtained by the reaction of ketene silyl acetals with benzyl \( N \)-(chloromethyl)carbamates in the presence of titanium tetrachloride. Successive hydrogenolysis over palladium-on-charcoal followed by treatment with lithium diisopropylamide gave \( \beta \)-lactams.

**Keywords**—\( \beta \)-lactam; titanium tetrachloride; ureidomethylation; hexahydro-1,3,5-triazine; benzylxoycarbonyl chloride

Methods for synthesizing monocyclic \( \beta \)-lactams are of particular interest in connection with the synthesis of analogs of the naturally occurring antibiotics such as nocardicin A.\(^{1)}\)

\[
\begin{align*}
\text{N} & \quad \text{CICOCH}_{3} \text{Ph} & \quad \text{ClCH}_{2} \text{NCOCH}_{2} \text{Ph} \\
\text{R} & \quad \text{R}^{3} & \quad \text{R}^{3} \quad \text{R}^{3}
\end{align*}
\]

\[1a, b\]

\[
\begin{align*}
\text{R}^{1} & \quad \text{OSi} & \quad \text{OMe} \\
\text{R}^{2} & \quad \text{TiCl}_{4}
\end{align*}
\]

\[2a-d\]

\[
\begin{align*}
\text{R}^{3} & \quad \text{NCOCH}_{2} \text{Ph} \\
\text{R}^{3} & \quad \text{OMe}
\end{align*}
\]

\[3a-e\]

\[
\begin{align*}
\text{R}^{1} & \quad \text{R}^{3} \\
\text{R}^{2} & \quad \text{N}^{3}
\end{align*}
\]

\[4a-e\]

Chart 1
In very recent papers the titanium tetrachloride-aided reaction of silyl enol ethers has provided, at α to carbonyl, N-alkylmidoalkylation\(^b\) in the 1,3,5-trialkylhexahydro-1,3,5-triazine–acetyl chloride system and ureidomethylation\(^b\) with N-(chloromethyl)carbamates. As a continuation of this work, we examined the possibility of synthesizing β-lactams by extending the reaction to ketene silyl acetics.

The present paper reports a new route to β-lactam synthesis, as summarized in Chart 1. Ureidomethylation at α to an alkoxycarbonyl group was achieved by the reaction of ketene silyl acetics with benzyl N-(chloromethyl)carbamates in the presence of titanium tetrachloride. Benzyl N-(chloromethyl)carbamates\(^a\) (1a, R\(^3\) = Me; 1b, R\(^3\) = iso-Pr) were prepared by the

### Table I. Syntheses of 4-Unsubstituted β-Lactams

<table>
<thead>
<tr>
<th>R(^1)</th>
<th>R(^2)</th>
<th>Substrate No.</th>
<th>R(^3)</th>
<th>Product No.</th>
<th>Yield (%)(^a)</th>
<th>Product No.</th>
<th>Yield (%)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH(_3)</td>
<td>CH(_3)</td>
<td>2a</td>
<td>CH(_3)</td>
<td>3a</td>
<td>86</td>
<td>4a</td>
<td>61</td>
</tr>
<tr>
<td>CH(_3)</td>
<td>CH(_2)</td>
<td>2b</td>
<td>CH(_3)</td>
<td>3b</td>
<td>90</td>
<td>4b</td>
<td>56</td>
</tr>
<tr>
<td>CH(_3)</td>
<td>H</td>
<td>2c</td>
<td>CH(_3)</td>
<td>3c</td>
<td>85</td>
<td>4c</td>
<td>5</td>
</tr>
<tr>
<td>-(CH(<em>2)</em>(_3))^-</td>
<td>2d</td>
<td>CH(_3)</td>
<td>3d</td>
<td>83</td>
<td>4d</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>C(_6)H(_5)O</td>
<td>CH(_3)</td>
<td>2d</td>
<td>CH(_3)</td>
<td>3e</td>
<td>81</td>
<td>4e</td>
<td>24</td>
</tr>
</tbody>
</table>

\(^a\) Molar proportion of \(2\): TiCl\(_4\) = 1.2:1.2. Solvent: CH\(_2\)Cl\(_2\). Temp.: 0–10\(^\circ\)C.

### Table II. Physical and Spectral Data for the Products

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>bp °C (mmHg)</th>
<th>IR ν(_\text{max}) cm(^{-1}) (C=O)</th>
<th>NMR δ (in CDCl(_3)) ((J=Hz))</th>
<th>Formula</th>
<th>Analysis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>158—159(0.15)</td>
<td>1720</td>
<td>3.49(s) 2.88(s) 3.65(s) C(<em>6)H(</em>{12})N(_4)O(_4)</td>
<td>64.49 7.85 5.01</td>
<td></td>
</tr>
<tr>
<td>3b</td>
<td>157—158(0.10)</td>
<td>1730</td>
<td>3.45(s) 1.22 3.83(s) C(<em>6)H(</em>{12})N(_4)O(_4)</td>
<td>66.42 8.20 4.56</td>
<td></td>
</tr>
<tr>
<td>3c</td>
<td>151—152(0.20)</td>
<td>1740</td>
<td>3.47 2.88(s) 3.59(s) C(<em>6)H(</em>{12})N(_4)O(_4)</td>
<td>63.38 7.22 5.28</td>
<td></td>
</tr>
<tr>
<td>3d</td>
<td>184—185(0.07)</td>
<td>1735</td>
<td>3.38(s) 2.85(s) 3.59(s) C(<em>6)H(</em>{12})N(_4)O(_4)</td>
<td>67.69 7.89 4.39</td>
<td></td>
</tr>
<tr>
<td>3e</td>
<td>220—221(0.40)</td>
<td>1740</td>
<td>3.82(s) 3.10(s) 3.65(s) C(<em>6)H(</em>{12})N(_4)O(_4)</td>
<td>67.21 6.49 3.92</td>
<td></td>
</tr>
<tr>
<td>3f</td>
<td>71—72(20)</td>
<td>1760</td>
<td>3.03(s) 2.79(s) C(<em>6)H(</em>{12})N(_4)O(_4)</td>
<td>63.68 9.80 12.39</td>
<td></td>
</tr>
<tr>
<td>3g</td>
<td>72—73(20)</td>
<td>1750</td>
<td>2.96(s) 1.15 2.79(s) C(<em>6)H(</em>{12})N(_4)O(_4)</td>
<td>68.04 10.71 9.92</td>
<td></td>
</tr>
<tr>
<td>3h</td>
<td>74—76(90)</td>
<td>1760</td>
<td>3.2—3.8(m) 2.79(s) C(<em>6)H(</em>{12})N(_4)O(_4)</td>
<td>60.58 9.15 14.13</td>
<td></td>
</tr>
<tr>
<td>3i</td>
<td>65—66(12)</td>
<td>1775</td>
<td>3.02(s) 2.79(s) C(<em>6)H(</em>{12})N(_4)O(_4)</td>
<td>70.55 9.87 9.14</td>
<td></td>
</tr>
<tr>
<td>3j</td>
<td>126—127(5)</td>
<td>1770</td>
<td>3.31 3.53 2.84(s) C(<em>6)H(</em>{12})N(_4)O(_4)</td>
<td>(69.46 7.06 7.21)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) The 1R spectra of 4a–e were measured in CDCl\(_3\).

\(^b\) s = singlet, d = doublet, m = multiplet.

\(^c\) E. Tosta, L. Fontanella, and V. Arei, Amn., 67B, 60 (1964).

reaction of 1,3,5-trialkylhexahydropyrazine-1,3,5-triazines with benzylxycarbonyl chloride.

As summarized in Table I, various ketene silyl acetals were allowed to react with 1a and 1b in dichloromethane in the presence of titanium tetrachloride to give the corresponding β-amino acid derivatives (3a–e) in good yields. They exhibit satisfactory nuclear magnetic resonance (NMR) and infrared (IR) spectra (see Table II). To remove the benzylxycarbonyl group, the products 3a–e were catalytically reduced over palladium-on-charcoal at room temperature; subsequent treatment of the reaction mixture with 1.2 molar equivalents of lithium disopropylamide (LDA) gave the corresponding β-lactams (4a–e), in the yields listed in Table I. The products, 4a–e, gave absorption bands (1750–1775 cm⁻¹) characteristic of β-lactam carbonyl in their IR spectra and satisfactory NMR spectra. As can be seen in the run with 3c, the yield was appreciably lowered when R=H.

The above process starting from 1,3,5-trialkylhexahydropyrazine-1,3,5-triazine should be useful for synthesizing 4-unsubstituted β-lactams, which are not accessible by the usual synthetic methods starting from Schiff bases.

Experimental

All boiling points are uncorrected. IR spectra were taken on a Hitachi EPI-G2 spectrophotometer and NMR spectra were recorded on a Hitachi R-24 spectrometer.

Benzyl N-(chloromethyl)carbamates (1a, b) and ketene silyl acetals (2a–d) were prepared according to the methods described in the literature, and their boiling points are as follows: 1a, bp 125–126° (0.4 mmHg) [lit., 6] bp 121–122° (0.35 mmHg); 1b, bp 129–130° (0.1 mmHg), IR ν_{max} cm⁻¹ 1720 (C=O), NMR δ (in CDCl₃), 1.32 [6H, d, J=6.6 Hz, CH(CH₃)₂], 5.22 (2H, s, ClCH₂), 5.35 (2H, s, OCH₂), 7.36 (5H, s, C₆H₅); 2a, bp 76–77° (65 mmHg) [lit., 9] bp 35° (15 mmHg); 2b, bp 65–66° (65 mmHg) [lit., 9] bp 70° (3 mmHg); 2c, bp 105–106° (20 mmHg) [lit., 9] bp 80° (2.5 mmHg); 2d, bp 90–91° (1.0 mmHg), IR ν_{max} cm⁻¹ 1722 (C=O), NMR δ (in CDCl₃), 0.13 [6H, s, Si(CH₃)₂], 3.59 (3H, s, OCH₃), 6.75–7.45 (5H, m, C₆H₅).

Syntheses of β-Amino Acid Derivatives (3a–e) General Procedure: A stirred solution of 0.06 mol of benzyl N-(chloromethyl)carbamate (1a, b) in 200 ml of dry CH₂Cl₂ was treated dropwise with 0.05 mol of ketene silyl acetal (2a–d) under cooling, then 0.06 mol of titanium tetrachloride was added at 0–10°. After 1 hr of stirring the reaction mixture was washed with aqueous K₂CO₃. The separated organic layer was dried over MgSO₄. Removal of the solvent gave an oily residue, which was fractionally distilled under reduced pressure to give the product. Yields and physical and spectral data for the products are listed in Tables I and II, respectively.

Syntheses of β-Lactams (4a–e) General Procedure: A suspension of 0.05 mol of 3a–e and 1 g of 10% palladium-on-charcoal in 50 ml of THF was stirred under hydrogen at normal pressure and room temperature. After uptake of hydrogen had ceased, the catalyst was removed by filtration and the filtrate was added dropwise to a solution of LDA in dry THF (freshly prepared from 0.06 mol of n-butyllithium and 0.06 mol of disopropyl amine) at 0° with stirring. After 1 hr of stirring at 0°, the reaction was quenched by adding a few drops of water and bubbling carbon dioxide through the mixture. The solvent was evaporated off under reduced pressure. The residue was extracted with ether and the ethereal layer was dried over anhydrous MgSO₄. Removal of the ether gave an oily residue, which was fractionally distilled under reduced pressure to give the product. Yields and physical and spectral data are recorded in Tables I and II, respectively.

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References and Notes