A CONVENIENT SYNTHESIS OF MONOCYCLIC $\beta$-LACTAMS

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Abstract: The intramolecular N-alkylation of $\beta$-bromopropionamide (1) under phase transfer conditions gave monocyclic $\beta$-lactams (2) in high yields.

Synthesis of 2-azetidinones, the basic structure unit of the $\beta$-lactam antibiotic, is attractive to organic chemists as a synthetic target. Formation of these four-membered rings has been approached from nearly every conceivable way. In continuation of our work on N-alkylation of lactams under phase-transfer conditions, we now report a facile synthesis of $\beta$-lactams by the formation of N-C$_4$ bond, which mimics the proposed biosynthesis by cyclization of $\beta$-bromopropionamides (1), readily available from coupling of $\beta$-bromopropionylchloride with amines, in solid-liquid system.

A typical procedure for the formation of $\beta$-lactams is as follows. To a suspension of pulverized KOH (5.5 mmol) and n-Bu$_4$N$^+$Br$^-$ (1 mmol) in 50 ml of dry CH$_2$Cl$_2$ at room temperature was added a solution containing N-3-bromopropionyl-2-phenylglycine methyl ester (1H) (5 mmol) in 50 ml of dry CH$_2$Cl$_2$ over 6 hr with stirring. After completion of the addition, the reaction mixture was stirred for 30 min. The precipitate was filtered off and then washed with CH$_2$Cl$_2$.

After removal of the combined solvent, the residue was purified by column chromatography on silica gel (CH$_2$Cl$_2$-MeOH (50:1) to give the desired $\beta$-lactam (2H) in 83% yield. The spectral data [ $\nu$ c=o (neat) 1735 and 1725 cm$^{-1}$; $\delta$(CDCl$_3$) 2.83-3.27 (3H, m), 3.67 (1H, t, J=3.5 Hz), 3.38 (3H, s, COO$^-$), 5.67 (1H, s, CHCOO$^-$), 7.45 (5H, s, ArH); m/e 219 (M$^+$)] and elemental analysis (molecular formula C$_{12}$H$_{13}$N$_3$O$_3$) supported this assignment.
Table

<table>
<thead>
<tr>
<th>Compd.</th>
<th>mp (°C)</th>
<th>Yield (%)</th>
<th>IR ν c=o (cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(2A)</td>
<td>79-81</td>
<td>94</td>
<td>1730</td>
</tr>
<tr>
<td>(2B)</td>
<td>104-5</td>
<td>92</td>
<td>1725</td>
</tr>
<tr>
<td>(2C)</td>
<td>137-9</td>
<td>94</td>
<td>1730</td>
</tr>
<tr>
<td>(2D)</td>
<td>162-4</td>
<td>81</td>
<td>1745</td>
</tr>
<tr>
<td>(2E)</td>
<td>52-3</td>
<td>91</td>
<td>1740</td>
</tr>
<tr>
<td>(2F)</td>
<td>oil</td>
<td>86</td>
<td>1740</td>
</tr>
<tr>
<td>(2G)</td>
<td>oil</td>
<td>85</td>
<td>1745</td>
</tr>
<tr>
<td>(2H)</td>
<td>oil</td>
<td>83</td>
<td>1735</td>
</tr>
<tr>
<td>(2I)</td>
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</tr>
<tr>
<td>(2J)</td>
<td>oil</td>
<td>63 (74)</td>
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</tr>
<tr>
<td>(2K)</td>
<td>oil</td>
<td>67 (94)</td>
<td>1745</td>
</tr>
</tbody>
</table>

a) All new compounds gave satisfactory elemental analyses.

b) The oil compounds were purified by chromatography, because the distillation resulted in partial decomposition of β-lactams.

c) (2A-E) (nujol), (2F-K) (neat).

d) The solvent (CH₂Cl₂: CH₃CN) (19:1) was used.

e) The acrylamides of by-products were obtained in 14% and 6% yields.

f) The THF was used as a solvent.

The results are summarized in Table. The cyclization of amides (1) to the β-lactams (2) was dependent on the concentration of the solution, the addition rate of amides to the base and the solvent. Both the high concentration over 0.05 M and the rapid addition of the amides resulted in low yields of β-lactams, along with the formation of substantial amounts of N-alkyl acrylamides. With regard to the solvent employed, the β-lactams (2A-1) could be prepared in good yields by using CH₂Cl₂, however, the use of THF for their cyclization caused complication. On the other hand, the use of THF was favoured over that of CH₂Cl₂ for cyclization of (1J) and (1K). In particular, this reaction proceed at room temperature, the procedure is simple, straightforward, and easy to work up, the formation of by-products was scarcely caused, and the desired products were obtained in high yields. In conclusion, this procedure under phase transfer conditions is more convenient for N-alkyl monomeric β-lactams syntheses.¹,⁶,⁷,⁸

In addition, the β-lactams thus readily obtained have high reactivities (Fries rearrangement,⁹
C-C bond formation at C_3-position,\(^\text{10}\) azidation at C_3-position,\(^\text{11}\) oxidation at C_4-position,\(^\text{12}\) and so on.\(^\text{13}\) Therefore, they would be served as potential synthetic intermediates as well as those of natural products containing the 8-lactam ring.\(^\text{11}\)

References and Notes

4. Compounds (1) were obtained in satisfactory yields (70-90\%). The details of preparation will be described in full papers.

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