The First I₂-Promoted Efficient Aminoacetylation of Activated Aziridines in Ionic Liquid

Vijai K. Rai,¹,a,b Nihar Sharma,¹ b Anil Kumar¹

¹ Department of Applied Chemistry, Institute of Technology, Guru Ghasidas Vishwavidyalaya, Bilaspur, Chhattisgarh 495 009, India
b School of Biology and Chemistry, Shri Mata Vaishno Devi University, Katra, Jammu & Kashmir 182 320, India

Fax +91(7752)260148; E-mail: vijai@krai@hotmail.com

Received: 27.10.2012; Accepted after revision: 29.10.2012

Abstract: A novel and efficient aminoacetylation of aziridines is reported. Herein, 2-phenyl-1,3-oxazolan-5-one with tosylaziridines affords 3-(N-substituted)aminopyrrolidin-2-ones via regioselective terminal aziridine opening—aminoacetylative cyclization cascades. The reaction is performed using [bmim]OH/molecular iodine as a new catalyst system where ionic liquid [bmim]OH also works as reaction media and proceeds via an isolable intermediate. After isolation of the product, the ionic liquid, [bmim]OH can be easily recycled for further use without any loss of efficiency. No byproduct formation and operational simplicity, ambient temperature, high yield, and excellent diastereoselectivity are salient features of the present synthetic protocol.

Key words: pyrrolidine-2-ones, ionic liquid, aziridines, diastereoselectivity, molecular iodine

Aziridines are an elite class of compounds present in various natural products and have been useful intermediates as well as building blocks in organic synthesis.¹ In terms of synthetic transformations, the utility of aziridines derives from their selective ring-opening reactions with various nucleophiles, which often form the basis for more complex target syntheses, especially N-containing compounds.²³γ-Butyrolactams (pyrrolidin-2-ones) are a class of versatile core structures present in various natural products such as isocynamatrine⁴b and clausenamide⁵c–f and are also important intermediates in the synthesis of a variety of nitrogenated heterocycles with interesting biological activities (Figure 1).⁴–⁸

Due to their versatile applications in organic and medicinal chemistry, the development of new synthetic routes for the preparation of pyrrolidin-2-ones is an important endeavor and has been well documented in the literature.¹⁰–²¹ However, most of the reactions suffer from one or more disadvantages, such as expensive reagents, long reaction times, low yields, tedious workup, and, most importantly, none of these methods cater a direct process for the synthesis of 3-(N-substituted)aminopyrrolidin-2-ones and tend to be lengthy and cumbersome if the lactam contains any sort of substitution. Recently, Ghorai et al. have reported the synthesis of pyrrolidin-2-one via a nucleophilic ring opening with a methylene group,²² in addition to other literature reports on the synthesis of 4-(N-substituted)aminopyrrolidin-2-ones.²²b,c Very recently, we have reported the synthesis of 3-mercapto-pyrrolidin-2-one starting via ring opening of aziridines with masked mercaptoacid.²²d To date, there is no report on the direct synthesis of 3-aminopyrrolidin-2-ones.

Figure 1 Pyrrolidin-2-one ring-containing natural products and pharmaceutical molecules

Ionic liquids (IL) have attracted much attention as environmentally friendly reaction media,²³–²⁵ catalysts,²⁶–²⁸ and reagents²⁹,³⁰ and are also easy to recycle.²⁹,³⁰ Moreover, the synthesis of amides is important in many areas of chemistry, including peptide, polymer, and complex molecule synthesis.³¹ Inspired by these valid points and keeping the synthetic and pharmacological importance of the amide group in mind we turned our attention to utilize masked amino acids as substrates viz. 2-phenyl-1,3-oxazolan-5-one, which can introduce an amide group at the α position into γ-lactam, which is the target molecule in the present investigation.

In this Letter, we report a new molecular-iode-catalyzed one-pot atom efficient method for the preparation of 3-(N-substituted)aminopyrrolidin-2-ones 3 in a single step using [bmim]OH as a green reaction promoter. This one-pot synthetic protocol is highly atom efficient as there is no byproduct formation and involves novel utilization of the masked amino acid 2-phenyl-1,3-oxazolan-5-one (1) with terminal aziridines 2 affording 3-(N-substituted)aminopyrrolidin-2-ones 3 in high yield and excellent diastereoselectivity, in favor of the cis isomer (Scheme 1). Furthermore, the present synthesis of 3-(N-substituted)amino functionalized γ-lactam 3 is an outcome of our
quest for developing new synthetic routes employing green chemistry protocols.\textsuperscript{32}

![Scheme 1](image)

**Scheme 1** One-pot aminoacetylation of aziridines 2 in ionic liquid [bmim]OH

In a preliminary experimentation, a controlled reaction was carried out using 2-phenyl-1,3-oxazolan-5-one (1) and aziridine 2a (Ar = Ph) in [bmim]OH but the reaction did not afford the desired \(\gamma\)-lactam 3a (Table 1, entry 1) even after 48 hours, rather conversion of tosylaziridines 2a into the corresponding amine 4a was observed (Scheme 2). Then, we turned our attention to use molecular iodine as catalyst in conjunction with different room-temperature ionic liquid (RTIL). For this purpose, 2-phenyl-1,3-oxazolan-5-one (1) and aziridine 2a (R = Ph) were chosen as model substrates for the synthesis of representative compound 3a (Table 1) wherein molecular iodine evidenced its catalytic efficacy in conjunction with RTIL, affording 3a in excellent yield (Table 1, entry 1). A variety of RTIL were screened for the present reaction and amongst [bmim]BF\(_4\), [bmim]OH, [bmim]PF\(_6\), and [bmim]Br, [bmim]OH was found to be the most effective RTIL for the conversion of the tosyl aziridine 2a to the corresponding \(\gamma\)-lactam 3a (Table 1, entries 2–4).

In order to elucidate the role of other solvents in lieu of RTIL as reaction medium, various solvents were used under the present reaction conditions. The results validate our premise that the reaction would not only be faster but also result in higher yield using RTIL as compared to other conventional solvents (Table 1, entries 2, 5–9). Interestingly, yield of the target compound 3a is poor using polar aprotic solvents (Table 1, entries 8 and 9). Thus, RTIL [bmim]OH stands out as the choice, with its fast conversion and quantitative yield in conjunction with molecular iodine, as an inexpensive and versatile catalyst in the present envisaged synthetic protocol. The optimum catalyst loading for molecular iodine was found to be 10 mol\%. When the amount of catalyst decreased from 10 mol\% to 5 mol\% relative to the substrates, the yield of product 3a was reduced (Table 2, entries 2 and 10). However, the use of 15 mol\% of the catalyst showed the same yield, and the same time was required (Table 1, entries 2 and 11). It was noted that a higher reaction temperature (up to 60 °C) instead of room temperature had no appreciable effect on the yield.

Next, in order to investigate the substrate scope for the general validity of the present investigation, a variety of tosyl aziridines 2 were used under the optimized reaction conditions, and different 3-(N-substituted)aminopyrroolidin-2-ones 3 were synthesized. The yields were consistently good (Table 2), and the highest yield was 96\% (Table 2, entry 3). Thus, the present optimized synthesis is accomplished by stirring a mixture of 2-phenyl-1,3-oxazolan-5-one (1), aziridine 2, and molecular iodine in [bmim]OH at room temperature for 5–6 hours.\textsuperscript{33}

![Scheme 2](image)

**Scheme 2** Reaction of masked amino acid 1 and aziridines 2 in [bmim]OH

<table>
<thead>
<tr>
<th>Entry</th>
<th>RTIL/solvent</th>
<th>I(_2) (mol%)</th>
<th>Time (h(^b))</th>
<th>Yield (%)(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[bmim]OH</td>
<td>–</td>
<td>48</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>[bmim]OH</td>
<td>10</td>
<td>5</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td>[bmim]OH</td>
<td>10</td>
<td>10</td>
<td>86</td>
</tr>
<tr>
<td>4</td>
<td>[bmim]Br</td>
<td>10</td>
<td>10</td>
<td>88</td>
</tr>
<tr>
<td>5</td>
<td>1,4-dioxane</td>
<td>10</td>
<td>17</td>
<td>74</td>
</tr>
<tr>
<td>6</td>
<td>MeCN</td>
<td>10</td>
<td>15</td>
<td>78</td>
</tr>
<tr>
<td>7</td>
<td>CH(_2)Cl(_2)</td>
<td>10</td>
<td>18</td>
<td>75</td>
</tr>
<tr>
<td>8</td>
<td>DMF</td>
<td>10</td>
<td>16</td>
<td>41</td>
</tr>
<tr>
<td>9</td>
<td>DMSO</td>
<td>10</td>
<td>16</td>
<td>46</td>
</tr>
<tr>
<td>10</td>
<td>[bmim]OH</td>
<td>5</td>
<td>5</td>
<td>88</td>
</tr>
<tr>
<td>11</td>
<td>[bmim]OH</td>
<td>15</td>
<td>5</td>
<td>94</td>
</tr>
</tbody>
</table>

\(^a\) Reaction conditions: 1 (2 mmol), 2a (2 mmol), I\(_2\) (0.2 mmol), [bmim]OH (5 mL).

\(^b\) Stirring time at r.t.

\(^c\) Yield of isolated and purified product 3a.

Isolation and purification by recrystallization afforded the target compound 3 in 85–96% yield with 96–98% diastereoselectivity (Table 2) in favor of the cis isomer. Product 3 was extracted with EtOAc leaving the [bmim]OH behind, which can be recycled easily for further use without loss of efficiency (Table 3). The diastereomeric ratios in the crude isolates were checked by \(^1\)H NMR spectroscopy to note any alteration of these ratios during subsequent purification. The crude isolates of 3 were found to be a diastereomeric mixture containing 96–98% of the cis isomer. On the basis of \(^1\)H NMR spectroscopy and the literature precedent,\textsuperscript{34} the cis stereochemistry was conclusively assigned to 3, as their coupling constants (\(J_{\text{cis}}\) = 7.0–7.6 Hz, \(J_{\text{cis}}\) = 6.3–6.7 Hz) was lower than that for the minor trans isomer (\(J_{\text{cis}}\) = 10.5–10.8 Hz, \(J_{\text{cis}}\) = 11.5–11.9 Hz). Furthermore, the assigned cis stereochemistry of lac-
Efficient Aminoacetylation of Activated Aziridines

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.
The efficacy of the reaction lies in its high yield, no by-product formation, ambient temperature, and recyclability of the ionic liquid [bmim]OH. Thus, this simple methodology would be a practical alternative to the existing procedures for the production of this kind of fine chemicals to cater to the need of academia as well as of industry.

Acknowledgment

We sincerely thank the CSIR, New Delhi (01(2441)/10/EMR-II) and UGC, New Delhi [F. No. 39-764/2010 (SR)] for financial support. We are also thankful to IJIM Jammu and SAIF, Punjab University, Chandigarh, for providing microanalyses and spectra.

References and Notes

with EtOAc (10 mL). The combined organic layer was washed with brine (10 mL), dried over anhyd Na$_2$SO$_4$, filtered, and evaporated under reduced pressure to afford an analytically pure sample of a single diastereomer 3 (Table 2). After isolation of the products, the remaining aqueous layer containing the ionic liquid was washed with hexane and dried in vacuum resulting in recycled ionic liquid, [bmim]OH (Table 3). The structure of the product 3 was confirmed by their elemental and spectral analyses.

**Characterization Data of Representative Compounds 3**

**Compound 3a:** colorless solid, mp 103–104 °C. IR (KBr): $\nu_{max} = 3348, 3031, 2938, 1746, 1701, 1605, 1583, 1451$ cm$^{-1}$. $^1$H NMR (400 MHz, $\mathrm{CDCl}_3$): $\delta = 2.28$ (s, 3 H), 2.82 (ddd, $J = 10.8, 7.1, 4.3$ Hz, 1 H), 2.90 (ddd, $J = 10.8, 8.9, 6.5$ Hz, 1 H), 4.61 (ddd, $J = 8.9, 7.5, 4.3$ Hz, 1 H), 4.89 (ddd, $J = 7.1, 6.5$ Hz, 1 H), 7.21–7.49 (m, 10 H), 7.85–7.98 (m, 4 H), 8.12 (br, exch, 1 H). $^{13}$C NMR (100 MHz, $\mathrm{CDCl}_3$): $\delta = 25.1, 33.7, 43.3, 53.5, 127.1, 127.9, 128.6, 129.3, 130.0, 130.7, 132.5, 133.2, 133.8, 134.7, 139.2, 141.0, 171.0, 178.3. MS (EI): $m/z = 434$ [M$^+$$]$.

Anal. Calc. for C$_{24}$H$_{21}$N$_2$O$_4$S: C, 66.34; H, 5.10; N, 127.1, 127.9, 128.6, 129.3, 130.0, 131.1, 131.8, 132.5, 134.0, 134.8, 140.1, 171.0, 178.8. MS (EI): $m/z = 452$ [M$^+$$]$.

**Compound 3b:** colorless solid, mp 151–153 °C. IR (KBr): $\nu_{max} = 3355, 3032, 2925, 1741, 1701, 1596, 1577, 1451$ cm$^{-1}$. $^1$H NMR (400 MHz, $\mathrm{CDCl}_3$): $\delta = 2.28$ (s, 3 H), 2.78 (ddd, $J = 10.7, 7.4, 4.8$ Hz, 1 H), 2.90 (ddd, $J = 10.7, 9.0, 6.6$ Hz, 1 H), 4.63 (ddd, $J = 9.0, 7.5, 4.8$ Hz, 1 H), 4.85 (ddd, $J = 7.4, 6.6$ Hz, 1 H), 7.26–7.53 (m, 9 H), 7.88–7.91 (m, 4 H), 8.15 (br, exch, 1 H). $^{13}$C NMR (100 MHz, $\mathrm{CDCl}_3$): $\delta = 25.5, 33.2, 43.8, 54.0, 127.2, 127.9, 128.7, 129.5, 130.1, 130.8, 131.4, 132.0, 132.7, 133.3, 134.0, 138.9, 171.2, 178.2. MS (EI): $m/z = 468, 470$ [M$^+$$]$, 4$.$

**Compound 3c:** colorless solid, mp 153–155 °C. IR (KBr): $\nu_{max} = 3350, 3029, 2932, 1743, 1702, 1601, 1578, 1445$ cm$^{-1}$. $^1$H NMR (400 MHz, $\mathrm{CDCl}_3$): $\delta = 2.28$ (s, 3 H), 2.82 (ddd, $J = 10.9, 7.1, 4.3$ Hz, 1 H), 2.92 (ddd, $J = 10.9, 8.9, 6.7$ Hz, 1 H), 4.66 (ddd, $J = 8.9, 7.5, 4.3$ Hz, 1 H), 4.86 (ddd, $J = 7.1, 6.7$ Hz, 1 H), 7.19–7.55 (m, 9 H), 7.79–7.92 (m, 4 H), 8.17 (br, exch, 1 H). $^{13}$C NMR (100 MHz, $\mathrm{CDCl}_3$): $\delta = 25.6, 33.1, 43.5, 53.5, 127.7, 128.4, 129.0, 129.6, 130.3, 131.1, 131.8, 132.5, 134.0, 134.8, 140.1, 171.0, 178.8. MS (EI): $m/z = 452$ [M$^+$$]$.

Anal. Calc. for C$_{24}$H$_{21}$N$_2$O$_4$S: C, 63.70; H, 4.68; N, 6.19. Found: C, 63.89; H, 4.91; N, 5.87.


(35) Isolation of 4a (Ar = Ph), 4c (Ar = 4-ClC$_6$H$_4$), and 4i (Ar = 4-FC$_6$H$_4$) and Their Conversion into the Corresponding Pyrrolidin-2-ones 3a, 3e, and 3i.

The procedure followed was the same as described above for the synthesis of 3, except that the reaction time in this case was only 2 h instead of 5–6 h used for 3. To obtain analytically pure samples of 3a, 3e, and 3i and to assign stereochemistry the same procedure was adopted as described for 3a, 3e, and 3i. Finally, these intermediates were stirred at r.t. for the next 3–4 h to give the corresponding cyclized products 3a, 3e, and 3i respectively.

**Characterization Data of Representative Compound 4a**

4a: IR (KBr): $\nu_{max} = 3345, 3030, 2930, 1708, 1605, 1581, 1455$ cm$^{-1}$. $^1$H NMR (400 MHz, $\mathrm{CDCl}_3$): $\delta = 2.23$ (s, 3 H), 2.51–2.53 (m, 2 H), 3.81 (m, 1 H), 4.01 (dd, $J = 7.9$, 3.8 Hz, 1 H), 5.29 (br, exch, 1 H), 7.21–7.59 (m, 12 H), 7.85–7.81 (m, 2 H). $^{13}$C NMR (100 MHz, $\mathrm{CDCl}_3$): $\delta = 25.1, 37.2, 45.5, 64.2, 126.7, 127.8, 128.9, 129.0, 129.7, 130.3, 132.0, 132.6, 133.3, 134.0, 135.2, 138.5, 160.8, 177.2. MS (EI): $m/z = 434$ [M$^+$$]$.

Anal. Calc. for C$_{24}$H$_{21}$N$_2$O$_4$S: C, 66.34; H, 5.10; N, 6.45. Found: C, 66.63; H, 4.88; N, 6.19.