Synthesis of tert-Butyl 1,3-Diaryl-3-oxopropylcarbamates by a Regiocontrolled Reduction of Ketoaziridines

Heshmat A. Samimi*a
Bohari M. Yaminb
Fatemeh Saberib

a Faculty of Science, Department of Chemistry, Shahrekord University, PO Box 115, Shahrekord, Iran
samimi-h@sci.sku.ac.ir
b School of Chemical Sciences and Food Technology, University Kebangsaan Malaysia, UKM 43500 Bangi Selangor, Malaysia

Received: 03.07.2014
Accepted after revision: 06.08.2014
Published online: 17.09.2014

Abstract A new, convenient approach for the reductive ring opening of N-H ketoaziridines is described. Treatment of N-H ketoaziridines with di-tert-butyl dicarbonate [(Boc)₂O] in the presence of sodium iodide and nickel(II) chloride results in the corresponding tert-butyl-1,3-diaryl-3-oxopropylcarbamates by a regiocontrolled reaction. The structure of the regioisomeric product was confirmed by X-ray crystal structure analysis.

Key words aziridines, regioselectivity, ring opening, reduction, nickel(II) chloride

The reductive ring opening of aziridines is a synthetically useful transformation for the preparation of amino compounds, especially in the synthesis of β-amino ketones,1–2 which are important for the synthesis of biologically active compounds.3–7 Several methods are known for the synthesis of β-amino ketones from the ring opening of aziridines. A literature survey shows the few reducing agents, including Raney nickel in ethanol,8 Pearlman’s catalyst [Pd(OH)₂/C],9 Adam’s catalyst (PtO₂/HCO₂H),10 sodium borohydride,11 tributyltin hydride,12 poly(methylhydrosiloxane) (PMHS),13 silyllithium reagents,14 magnesium15 and lithium16 metal reagents, titanium tetraiodide,17 samarium(II) iodide18 and visible-light photoredox ruthenium catalysts,19 for the reductive ring opening of aziridines. None of these methods, however, result in a direct reduction reaction of N-H aziridines to give derivatives of β-carbamato ketones.

Our recent interest in the ring opening and ring expansion of ketoaziridines motivated us to synthesize tert-butyl 1,3-diaryl-3-oxopropylcarbamates.20–27

Previously reported research has shown that replacement of the hydrogen of the N–H moiety with an electron-withdrawing substituent increases the susceptibility of N-H aziridines to ring-opening or ring-enlargement reactions.28–30 So, our first aim was to synthesize N-Boc-substituted ketoaziridines as a precursor for preparation of the corresponding nitrogen-containing compounds via ring opening or ring enlargement. At first, we investigated the reaction of di-tert-butyl dicarbonate [(Boc)₂O] and 2-(4-chlorobenzoyl)-3-(4-chlorophenyl)aziridine (1a) in chloroform, acetonitrile, ethanol or acetone in the presence of sodium iodide. The mixture was stirred for 10 hours under refluxing conditions, but 1a was recovered unchanged (Table 1, entries 1–4); none of the desired product was detected.

Based on the well-documented transformation of N-acetyl- or N-Boc-substituted aziridines into oxazolines in the literature31–34 and our success20,21 with the ring-expansion reaction of N-acetyl-substituted aziridines with sodium iodide, we envisioned that ring expansion of 1a with (Boc)₂O in the presence of sodium iodide might be similarly achieved to give oxazolidin-2-one 6a in a one-pot reaction. Thus, we examined the reaction of aziridine 1a with (Boc)₂O in the presence of sodium iodide in acetone for achieving this aim; however, no reaction occurred, even under refluxing conditions (Table 1, entry 5).

In order to evaluate the effect of a Lewis acid in this reaction, we tried the reaction of 2-(4-chlorobenzoyl)-3-(4-chlorophenyl)aziridine (1a) with (Boc)₂O in the presence of sodium iodide and some Lewis acids (ZnCl₂, CuCl₂) in refluxing acetone; with zinc chloride and copper(II) chloride, a new product 4a was obtained in low yields (Table 1, entries 6 and 7).

In another attempt, we examined the reaction of 1a with (Boc)₂O in the presence of nickel(II) chloride and sodium iodide (1 mmol) (Table 1, entry 8). At this stage, thin-layer chromatography confirmed the formation of a new...
compound, along with the corresponding chalcone 3a. The crude product was purified by column chromatography, surprisingly to provide tert-butyl 1,3-bis(4-chlorophenyl)-3-oxopropylcarbamate (4a) or tert-butyl 2,3-bis(4-chlorophenyl)-3-oxopropylcarbamate (5a). Since the spectroscopic data were not conclusive for 4a or 5a, X-ray crystallographic analysis was conducted to verify the product structure as 4a (Figure 1).

It is striking to note that X-ray crystal structure analysis of the representative product 4a (Figure 1) confirms the regiocontrolling nature of this reaction. The reaction proceeded with selective ring opening at the C–N bond α to the benzoyl moiety, whereas the C–N bond of the benzyl group was not cleaved. The same stereochemistry has been generalized for all other products formed from this reaction.

A further examination of the reaction of 1a and (Boc)_2O with zinc chloride, copper(II) chloride or nickel(II) chloride in the absence of sodium iodide failed to give any product 4a (Table 1, entries 9–11).

To expand the scope of this novel method, several substituted ketoaziridines 1 were reacted with (Boc)_2O in the presence of nickel(II) chloride and sodium iodide, resulting in production of the tert-butyl 1,3-diaryl-3-oxopropylcarbamates 4 in moderate to good yields (Table 2). All the products were characterized by 1H NMR, 13C NMR and IR spectroscopy.

We have previously reported the mechanism of the iodide ion catalyzed isomerization of N-acyl-substituted aziridines by attack of the nucleophile at C-2 of the aziridine and subsequent cyclization to the corresponding oxazolines.20 We have now found that the action of nickel(II) chloride with sodium iodide on 2-aryloxy-3-aryloxaziridines is

---

**Table 1** Optimization of the Conditions for the Reaction of Aziridine 1a with (Boc)\(_2\)O\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Yield(^b) (%)</th>
<th>3a</th>
<th>4a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^a)</td>
<td>Et(_3)N</td>
<td>CHCl(_3)</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2(^a)</td>
<td>Et(_3)N</td>
<td>MeCN</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>3(^a)</td>
<td>Et(_3)N</td>
<td>EtOH</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>4(^a)</td>
<td>Et(_3)N</td>
<td>acetone</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>5(^a)</td>
<td>NaI</td>
<td>acetone</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>NaI, ZnCl(_2)</td>
<td>acetone</td>
<td>8</td>
<td>0</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>NaI, CuCl(_2)</td>
<td>acetone</td>
<td>8</td>
<td>0</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>NaI, NiCl(_2)</td>
<td>acetone</td>
<td>8</td>
<td>19</td>
<td>71</td>
<td></td>
</tr>
<tr>
<td>9(^a)</td>
<td>ZnCl(_2)</td>
<td>acetone</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>10(^a)</td>
<td>CuCl(_2)</td>
<td>acetone</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>NiCl(_2)</td>
<td>acetone</td>
<td>10</td>
<td>44</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

\(^{a}\) 1a/(Boc)\(_2\)O/reagent = 1:1:1.  
\(^{b}\) Isolated yields.  
\(^{c}\) The starting material was recovered.
the same as that of iodide, also involving a regio- and stereocontrolled ring-expansion process. To test the scope of this novel method, substituted ketoaziridines 1 were reacted with benzoyl chloride in the presence of nickel(II) chloride and sodium iodide, which resulted in the production of oxazolines 7 in moderate to good yields (Table 3); no trace of another regioisomer was detected. All the products were characterized by 1H NMR, 13C NMR and IR spectroscopy.

A striking feature of this process is that N-acyl-substituted ketoaziridines, in the presence of nickel(II) chloride and sodium iodide, result in oxazolines 7 via a regio- and stereocontrolled ring-expansion reaction, while N-Boc-substituted ketoaziridines produce tert-butyl 1,3-diaaryl-3-oxopropylcarbamates 4 through a reductive ring-opening reaction. This shows the influence of the N-substituent on the ring expansion or reductive ring opening of ketoaziridines.

The exact mechanism of the novel reductive ring-opening reaction is not clear. Research in this respect is under way.

In conclusion, we have disclosed the highly efficient, reductive ring opening of N-H ketoaziridines under refluxing conditions via a regioselective reaction promoted with (Boc)2O in the presence of nickel(II) chloride and sodium iodide as an inexpensive reagent system.

All yields refer to isolated products after purification by column chromatography or by distillation under reduced pressure. Products were characterized by comparison with authentic samples (IR and 1H NMR spectra, TLC, melting and boiling points). NMR spectra were recorded in CDCl3 on a Bruker AMX-400 spectrometer (1H NMR at 400 MHz and 13C NMR at 100 MHz) with chemical shift values (δ) in ppm downfield from TMS. IR spectra were recorded on a JASCO FT/IR-6300 spectrometer. All solvents used were dried and distilled according to standard procedures.

tert-Butyl 1,3-Diaaryl-3-oxopropylcarbamates 4a–h (Table 2); General Procedure

NiCl₂ (1.0 mmol) and NaI (1.0 mmol) were added to a solution of the ketoaziridine 1 (1.0 mmol) and (Boc)₂O (1.0 mmol) in acetone at 15 mL. The mixture was refluxed for 8–12 h. The crude product was purified by column chromatography (silica gel; EtOAc–hexane, 2:5) to provide the desired corresponding tert-butyl 3-oxopropylcarbamate 4; yield: 56–78%.

tert-Butyl 1,3-Bis(4-chlorophenyl)-3-oxopropylcarbamate (4a)

Yield: 279 mg (71%); white solid; mp 140–142 °C.
IR (KBr): 3280, 1685, 1596, 1452, 1321, 1228 cm⁻¹.

$$\text{Ar}_1\text{N}^-\text{Ar}_2\text{O} + \text{Boc}_2\text{O} \rightarrow \text{Ar}_1\text{N}^-\text{Ar}_2\text{O}$$

Table 2 Substrate Scope for the Reductive Ring Opening of N-H Ketoaziridines 1 to the Corresponding tert-Butyl 1,3-Diaaryl-3-oxopropylcarbamates 4

<table>
<thead>
<tr>
<th>Product</th>
<th>Ar¹</th>
<th>Ar²</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>4-ClC₆H₄</td>
<td>4-ClC₆H₄</td>
<td>8</td>
<td>71</td>
</tr>
<tr>
<td>4b</td>
<td>3-O₂NC₆H₃</td>
<td>Ph</td>
<td>10</td>
<td>68</td>
</tr>
<tr>
<td>4c</td>
<td>4-ClC₆H₄</td>
<td>Ph</td>
<td>8</td>
<td>73</td>
</tr>
<tr>
<td>4d</td>
<td>Ph</td>
<td>Ph</td>
<td>12</td>
<td>78</td>
</tr>
<tr>
<td>4e</td>
<td>2,4-Cl₂C₆H₃</td>
<td>4-ClC₆H₄</td>
<td>10</td>
<td>76</td>
</tr>
<tr>
<td>4f</td>
<td>3-O₂NC₆H₃</td>
<td>4-ClC₆H₄</td>
<td>12</td>
<td>62</td>
</tr>
<tr>
<td>4g</td>
<td>2,4-Cl₂C₆H₃</td>
<td>Ph</td>
<td>8</td>
<td>73</td>
</tr>
<tr>
<td>4h</td>
<td>4-BrC₆H₄</td>
<td>Ph</td>
<td>10</td>
<td>56</td>
</tr>
</tbody>
</table>

* Refluxing conditions with 1/(Boc)₂O/NiCl₂/NaI = 1:1:1:1.
* Isolated yields.
**tert-Butyl 1-(3-Nitrophenyl)-3-oxo-3-phenylpropylcarbamate (4b)**

Yield: 253 mg (78%); white solid; mp 135–137 °C.

**tert-Butyl 1-(4-Chlorophenyl)-3-oxo-3-phenylpropylcarbamate (4c)**

Yield: 287 mg (73%); white solid; mp 131–133 °C.

**tert-Butyl 1-(4-Chlorophenyl)-3-oxo-3-phenylpropylcarbamate (4d)**

Yield: 226 mg (56%); white solid; mp 137–139 °C.

**tert-Butyl 1-(4-Bromophenyl)-3-oxo-3-phenylpropylcarbamate (4h)**

Yield: 287 mg (73%); white solid; mp 131–133 °C.
Acetone (15 mL), NaI (1 mmol) and NiCl₂ (1 mmol) were added to the crude product and the mixture was stirred at 50 °C for 6 h. Then, the mixture was rinsed with H₂O (2 × 10 mL), and the organic layer was separated and dried with anhydrous Na₂SO₄. Evaporation of the solvent under reduced pressure and subsequent purification of the residue by column chromatography (silica gel; EtOAc–hexane, 1:4) provided the corresponding oxazoline 7.

\[\text{trans-5-Benzoyl-4-(2,4-dichlorophenyl)-2-phenyl-2-oxazoline (7a)}\]

Yield: 292 mg (74%); white solid; mp 135–137 °C.

\[\text{1H NMR (400 MHz, CDCl₃):} \delta = 6.50 (d, J = 6.5 Hz, 1 H), 7.50 (m, 2 H), 7.53 (dd, J = 7.6, 1.8 Hz, 1 H), 7.60 (m, 2 H), 7.73 (m, 2 H), 7.76 (d, J = 15.5 Hz, 1 H), 8.20 (dd, J = 7.5, 2.2 Hz, 2 H).
\]

\[\text{13C NMR (100 MHz, CDCl₃):} \delta = 122.2, 128.4, 128.5, 129.3, 129.4, 132.2, 133.9, 136.8, 139.1, 144.1, 189.8.
\]

Anal. Calcd for C₂₂H₁₅Cl₂NO₂: C, 66.68; H, 3.82; N, 3.53. Found: C, 66.21; H, 3.79; N, 3.47.

\[\text{trans-5-(4-Chlorobenzoyl)-4-(4-chlorophenyl)-2-phenyl-2-oxazoline (7b)}\]

Yield: 304 mg (77%); white solid; mp 128–130 °C.

\[\text{1H NMR (400 MHz, CDCl₃):} \delta = 6.38 (d, J = 6.5 Hz, 1 H), 7.30–7.70 (m, 9 H), 7.90 (d, J = 7.3 Hz, 2 H).
\]

\[\text{13C NMR (100 MHz, CDCl₃):} \delta = 74.3, 87.4, 127.4, 127.5, 128.3, 128.6, 128.8, 129.2, 129.3, 129.4, 132.3, 134.4, 134.6, 141.1, 164.3, 194.9.
\]

Anal. Calcd for C₁₅H₁₀Cl₂O: C, 65.01; H, 3.64. Found: C, 65.08; H, 3.69.

Acknowledgment

We are thankful to the Research Council of Shahrekord University for supporting this work, and to the Universiti Kebangsaan Malaysia Instrumentation Center (UKM-DIP 2012-11) for the X-ray analysis.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379029.

References

(23) Samimi, H. A.; Mohammadzadeh, S. Synlett 2013, 24, 223.
(26) Samimi, H. A.; Yamin, B. M.; Hiedari, Z.; Narimani, L. J. Heterocycl. Chem. accepted for publication.