Synthesis of \( \text{tert-Butyl 1,3-Diaryl-3-oxopropylcarbamates by a Regiocontrolled Reduction of Ketoaziridines} \)

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Abstract: A new, convenient approach for the reductive ring opening of \( \text{N-H ketoaziridines} \) is described. Treatment of \( \text{N-H ketoaziridines} \) with di-\( \text{tert-butyl dicarbonate} \) \([\text{(Boc)}_2\text{O}]\) in the presence of sodium iodide and nickel(II) chloride results in the corresponding \( \text{tert-butyl 1,3-diaryl-3-oxopropylcarbamates} \) 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 \( \beta \)-amino ketones,\(^1\)\(^2\) which are important for the synthesis of biologically active compounds.\(^3\)\(^4\)

Several methods are known for the synthesis of \( \beta \)-amino ketones from the ring opening of aziridines. A literature survey shows the few reducing agents, including Raney nickel in ethanol,\(^5\) Pearlman's catalyst \([\text{Pd(OH)}_2/\text{C}]\),\(^6\) Adam's catalyst \([\text{PtO}_2/\text{HCO}_2\text{H}]\),\(^7\) sodium borohydride,\(^8\) tributyltin hydride,\(^9\) poly(methylhydroxiloxane) (PMHS),\(^10\) silyllithium reagents,\(^11\) magnesium\(^12\) and lithium\(^13\) metal reagents, titantium tetraiodide,\(^14\) samarium(II) iodide\(^15\) and visible-light photoredox ruthenium catalysts,\(^16\) for the reductive ring opening of aziridines. None of these methods, however, result in a direct reduction reaction of \( \text{N-H aziridines} \) to give derivatives of \( \beta \)-carbamato ketones.

Our recent interest in the ring opening and ring expansion of ketoaziridines motivated us to synthesize \( \text{tert-butyl 1,3-diaryl-3-oxopropylcarbamates} \).\(^20\)\(^21\)

Previous reports have shown that replacement of the hydrogen of the \( \text{N-H moiety} \) with an electron-withdrawing substituent increases the susceptibility of \( \text{N-H aziridines} \) to ring-opening or ring-enlargement reactions.\(^22\)\(^30\) So, our first aim was to synthesize \( \text{N-Boc-substituted ketoaziridines} \) as a precursor for preparation of the corresponding nitrogen-containing compounds via ring opening or ring enlargement. At first, we investigated the reaction of \( \text{di-\( \text{tert-butyl dicarbonate} \)} ([\text{(Boc)}_2\text{O}] \) and \( \text{2-(4-chlorobenzoyl)-3-(4-chlorophenyl)aziridine} \) \( \text{(1a)} \) in chloroform, acetonitrile, ethanol or acetone in the presence of triethylamine. The mixture was stirred for 10 hours under refluxing conditions, but \( \text{1a} \) was recovered unchanged (Table 1, entries 1–4); none of the desired product was detected.

Based on the well-documented transformation of \( \text{N-acyl-} \) or \( \text{N-Boc-substituted aziridines} \) into oxazolines in the literature,\(^31\)\(^34\) and our success\(^30\)\(^31\) with the ring-expansion reaction of \( \text{N-acyl-substituted aziridines} \) with sodium iodide, we envisioned that ring expansion of \( \text{1a} \) with \( \text{(Boc)}_2\text{O} \) in the presence of sodium iodide might be similarly achieved to give oxazolidin-2-one \( \text{6a} \) in a one-pot reaction. Thus, we examined the reaction of aziridine \( \text{1a} \) with \( \text{(Boc)}_2\text{O} \) 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 \( \text{2-(4-chlorobenzoyl)-3-(4-chlorophenyl)aziridine} \) \( \text{(1a)} \) with \( \text{(Boc)}_2\text{O} \) in the presence of sodium iodide and some Lewis acids \((\text{ZnCl}_2, \text{CuCl}_2)\) in refluxing acetone; with zinc chloride and copper(II) chloride, a new product \( \text{4a} \) was obtained in low yields (Table 1, entries 6 and 7).

In another attempt, we examined the reaction of \( \text{1a} \) with \( \text{(Boc)}_2\text{O} \) 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)$_2$O 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)$_2$O 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 $^1$H NMR, $^{13}$C 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. We have now found that the action of nickel(II) chloride with sodium iodide on 2-aryl-3-arylaziridines is

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**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>0</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>0</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>0</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>0</td>
</tr>
<tr>
<td>5$^a$</td>
<td>NaI</td>
<td>acetone</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>NaI, ZnCl$_2$</td>
<td>acetone</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>7</td>
<td>NaI, CuCl$_2$</td>
<td>acetone</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>23</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>0</td>
</tr>
<tr>
<td>10$^a$</td>
<td>CuCl$_2$</td>
<td>acetone</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>NiCl$_2$</td>
<td>acetone</td>
<td>10</td>
<td>44</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

$^a$ 1a/(Boc)$_2$O/reagent = 1:1:1.

$^b$ Isolated yields.

$^c$ The starting material was recovered.
Stereocontrolled ring-expansion reaction, while N-Boc-substituted ketoaziridines produce tert-butyl 1,3-diaryl-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)$_2$O 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 $^1$H NMR spectra, TLC, melting and boiling points). NMR spectra were recorded in CDCl$_3$ on a Bruker AMX-400 spectrometer ($^1$H NMR at 400 MHz and $^{13}$C NMR at 100 MHz) with chemical shift values ($\delta$) in ppm downfield from TMS. IR spectra were recorded on a JASCO FTIR-6300 spectrometer. All solvents used were dried and distilled according to standard procedures.

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

NiCl$_2$ (1.0 mmol) and NaI (1.0 mmol) were added to a solution of the ketoaziridine 1 (1.0 mmol) and (Boc)$_2$O (1.0 mmol) in acetonitrile (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$^{-1}$.
**tetr-Butyl 1-(3-Nitrophenyl)-3-oxo-3-phenylpropylcarbamate (4b)**

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

IR (KBr): 3299, 1683, 1584, 1451, 1329, 1222 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 1.32 (s, 9 H), 3.36 (dd, J = 16.6, 6.1 Hz, 1 H), 3.57 (br d, 1 H), 5.17 (br d, 1 H), 5.52 (br t, 1 H), 7.16 (J = 6.9 Hz, 1 H), 7.22 (m, 4 H), 7.34 (J = 7.8 Hz, 2 H), 7.46 (t, J = 7.1 Hz, 1 H), 7.80 (J = 7.1 Hz, 2 H).

13C NMR (100 MHz, CDCl₃): δ = 28.3, 43.9, 50.7, 79.8, 127.7, 127.8, 128.7, 128.9, 132.5, 136.5, 140.5, 151.1, 197.8.

Anal. Calcd for C₂₂H₂₃NO₃: C, 73.82; H, 7.12; N, 3.40. Found: C, 73.70; H, 7.15; N, 4.41.

**tetr-Butyl 3-Oxo-1,3-diphenylpropylcarbamate (4d)**

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

IR (KBr): 3289, 1681, 1591, 1449, 1318, 1221 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 1.34 (s, 9 H), 3.36 (dd, J = 16.6, 6.1 Hz, 1 H), 3.57 (br d, 1 H), 5.17 (br d, 1 H), 5.52 (br t, 1 H), 7.16 (J = 6.9 Hz, 1 H), 7.22 (m, 4 H), 7.34 (J = 7.8 Hz, 2 H), 7.46 (t, J = 7.1 Hz, 1 H), 7.80 (J = 7.1 Hz, 2 H).

13C NMR (100 MHz, CDCl₃): δ = 28.3, 42.4, 51.4, 79.6, 126.3, 127.3, 128.1, 128.6, 128.7, 133.3, 141.6, 155.2, 190.2.

Anal. Calcd for C₂₀H₂₁NO₃: C, 73.82; H, 7.12; N, 3.40. Found: C, 73.70; H, 7.15; N, 4.41.

**tetr-Butyl 3-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-3-oxopro pylcarbamate (4f)**

Yield: 250 mg (62%); red oil.

IR (KBr): 2924, 2872, 1594, 1451, 1329, 1222 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 1.34 (s, 9 H), 3.36 (dd, J = 16.7, 5.7 Hz, 1 H), 3.61 (br d, 1 H), 5.27 (br d, 1 H), 5.67 (br t, 1 H), 7.35 (J = 8.7 Hz, 2 H), 7.41–7.45 (d, J = 8.0 Hz, 1 H), 7.63 (d, J = 7.2 Hz, 1 H), 7.78 (d, J = 8.7 Hz, 2 H), 8.02 (d, J = 8.0, 1.2 Hz, 1 H), 8.40 (s, 1 H).

13C NMR (100 MHz, CDCl₃): δ = 28.3, 43.4, 50.5, 80.3, 121.2, 122.4, 122.9, 129.1, 129.4, 132.8, 134.5, 140.3, 148.4, 151.5, 193.8.

Anal. Calcd for C₂₀H₁₆Cl₃NO₃: C, 56.03; H, 4.70; N, 3.59. Found: C, 56.02; H, 4.75; N, 3.59.

**tetr-Butyl 1-(3-Nitrophenyl)-3-oxo-3-phenylpropylcarbamate (4g)**

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

IR (KBr): 3299, 1683, 1584, 1451, 1329, 1222 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 1.32 (s, 9 H), 3.36 (dd, J = 16.8, 6.13 Hz, 1 H), 3.65 (br d, 1 H), 5.13 (br d, 1 H), 5.54 (br t, 1 H), 7.19 (m, 3 H), 7.34 (t, J = 7.67 Hz, 2 H), 7.49 (t, J = 7.2 Hz, 1 H), 7.71 (d, J = 7.48 Hz, 2 H).

13C NMR (100 MHz, CDCl₃): δ = 28.3, 43.9, 50.7, 79.8, 127.7, 128.0, 128.7, 128.9, 132.5, 136.5, 140.3, 151.1, 197.8.

Anal. Calcd for C₂₀H₂₁NO₃: C, 56.03; H, 4.70; N, 3.27. Found: C, 56.02; H, 4.75; N, 3.27.
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 x 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.

**trans-5-Benzoyl-4-(2,4-dichlorophenyl)-2-phenyl-2-oxazoline (7a)**

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

IR (KBr): 3041, 1655, 1597, 883, 774, 699, 682 cm⁻¹.

Yellow crystals; mp 156–158 °C.

**trans-5-(4-Chlorobenzoyl)-4-(4-chlorophenyl)-2-phenyl-2-oxazoline (7b)**

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

IR (KBr): 3058, 2921, 1684, 1650, 1594, 1483, 1266, 761, 709, 696 cm⁻¹.

Yellow crystals; mp 135–137 °C.

**References**


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