Oxidative C-C bond cleavage of N-alkoxycarbonylated cyclic amines by sodium nitrite in trifluoroacetic acid

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Abstract— Oxidative carbon-carbon bond cleavage of N-alkoxycarbonylated cyclic amines was accomplished by NaNO2 in TFA to afford α-amino carboxylic acid in high yield. Optically active 3-hydroxypiperidine derivatives and 3-pipEColinate, were converted to enantiomerically pure (R)-4-amino-3-hydroxybutanoic acid (GABOB) and (S)-2-pyrrolidone-4-carboxylate, respectively.

It is well known that trifluoroacetic acid (TFA) acts as an efficient medium for oxidation of hydrocarbons.1 Recently, we found that efficient oxidation of adamantanes to 1-adamantanols was catalyzed by sodium nitrite (NaNO2) under oxygen atmosphere in TFA.2 In addition, 2 equiv of NaNO2 in TFA3 oxidized acyclic and cyclic secondary alcohols to the corresponding ketones and α,ω-dicarboxylic acid, respectively.4 In the latter case, oxidative cleavage of cyclic secondary alcohols occurred between the α-carbon and the β-carbon. We report herein that this oxidizing agent works well as demonstrated by a unique reaction of N-alkoxycarbonylated cyclic amines 1 which reacted with NaNO2 to afford the ring-opened products 25 and its application to preparation of optically active compounds 3e and 4 (Eq. 1).

A typical example for the oxidative carbon-carbon (C-C) bond cleavage is shown in Eq. 2. The oxidation of 1a (1 mmol) was carried out in TFA (5 mL) containing NaNO2 (2 mmol) and H2O (10 mmol) under aerobic condition. The oxidation smoothly proceeded

Key words: carbon-carbon cleavage; cyclic amines; trifluoroacetic acid; sodium nitrite; ω-amino acid

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at 0°C to rt for 3 h to afford an oxidative ring-opened product 2a in 94% yield.6

\[
\begin{align*}
\text{N} & \quad \text{CO}_2\text{Ph} \\
1\text{a} & \quad \text{NaNO}_2 \text{ (2 equiv)} \\
& \quad \text{H}_2\text{O} \text{ (10 equiv)} \\
& \text{in TFA} \\
& 0^\circ\text{C to rt} \quad 3\text{h} \\
& \text{under air} \\
\rightarrow & \quad \text{N} \quad \text{CHO} \\
\text{2a} & \quad \text{CO}_2\text{Ph} \\
& \text{98%}
\end{align*}
\]

The oxidative cleavages of \(N\)-protected pyrrolidines 1b-d and piperidines 1e-i with NaNO\(_2\) in TFA were examined to clarify generality of substrates (Eq. 3). The results are summarized in Table 1.

\[
\begin{align*}
\text{N} & \quad \text{PG} \\
1\text{b-i} & \quad \text{NaNO}_2 \text{ (2 equiv)} \\
& \quad \text{H}_2\text{O} \text{ (10 equiv)} \\
& \text{in TFA} \\
& 0^\circ\text{C to rt} \quad 3\text{h} \\
& \text{under air} \\
\rightarrow & \quad \text{N} \quad \text{CHO} \\
2\text{b-i} & \quad \text{CO}_2\text{H} \\
& \text{PG} \\
\rightarrow + & \quad \text{N} \quad \text{PG} \quad \text{CHO} \\
6\text{b-i} & \quad \text{PG} \\
\rightarrow + & \quad \text{N} \quad \text{PG} \quad \text{NO}_2 \\
7\text{b-i} & \text{PG} \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Yield (%)</th>
<th>2</th>
<th>6</th>
<th>7</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0 CO(_2\text{Me}) 1b</td>
<td>74</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0 CO(_2\text{Ph}) 1c</td>
<td>83</td>
<td>11</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0 CO(_2\text{CH}_2\text{CF}_3) 1d</td>
<td>88</td>
<td>11</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1 CO(_2\text{Me}) 1e</td>
<td>79</td>
<td>0</td>
<td>15</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1 CO(_2\text{CH}_2\text{CF}_3) 1f</td>
<td>99</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>1 CHO 1g</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>&gt;99</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>1 COMe 1h</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>&gt;99</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>1 CO(_2\text{Ph}) 1i</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>&gt;99</td>
<td></td>
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</tbody>
</table>

\(N\)-Alkoxycarbonylated pyrrolidines 1b-d were transformed into the corresponding ring-opened products 2b-d in good to high yields along with a small amount of pyrrolidine-2-ones 6b-d (Entries 1-3). The oxidation of \(N\)-methoxycarbonylpiperidine 1e afforded \(\omega\)-amino acid in good yield and 3-nitroenamine 7e as a by-product (Entry 4), while electron-withdrawing groups\(^7\) such as phenoxy and trifluoroethoxyl groups were more efficient than methoxycarbonyl group (Eq. 2 and Entry 5). Interestingly, \(N\)-formylated and acylated piperedines 1g-i were not oxidized at all under the reaction conditions (Entries 6-8). This may be due to the formation of protonated species for 1g-i in TFA,\(^8\) which are hardly oxidizable.
Next, the oxidative cleavages of substituted pyrrolidines 1j-m were examined (Eq. 4). The results are summarized in Table 2.

![Chemical structure of 1j-m and 2j-m](image)

\[
\text{Table 2. Oxidative cleavage of } \alpha\text{-substituted pyrrolidines 1j-m with NaNO}_2 \text{ in TFA}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>PG</th>
<th>R</th>
<th>Oxidation potential (v)</th>
<th>Yield (%)</th>
<th>2</th>
<th>1</th>
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<tbody>
<tr>
<td>1</td>
<td>CO$_2$Me</td>
<td>CH$_2$OAc</td>
<td>2.24</td>
<td>96</td>
<td>0</td>
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</tr>
<tr>
<td>2</td>
<td>CO$_2$CH$_2$CF$_3$</td>
<td>CH$_2$OAc</td>
<td>2.50</td>
<td>41</td>
<td>59</td>
<td></td>
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<tr>
<td>3</td>
<td>CO$_2$Me</td>
<td>CO$_2$Me</td>
<td>2.39</td>
<td>52</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>CO$_2$CH$_2$CF$_3$</td>
<td>CO$_2$Me</td>
<td>2.82</td>
<td>&lt;1</td>
<td>&gt;99</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ vs Ag/AgNO$_3$,

The yields of the cleaved products 2j-m may have interrelation with the oxidation potentials of 1j-m. That is, easily oxidizable prolinol derivative 1j was converted into the corresponding cleaved product 2j in excellent yield (Entry 1), while compounds 1k,l, which have relatively high oxidation potential, afforded 2k,l in moderate yields (Entries 2 and 3). However, proline derivative 1m with high oxidation potential was not oxidized at all (Entry 4).

We then subjected 2, or 3, or 4-methylated piperidines 1n-s to same reaction conditions (Eq. 5). The results are summarized in Table 3.

![Chemical structures of 1n-s, 2n-s, 7n-s, and 8n-s](image)

\[
\text{Table 3. Oxidative cleavage of } \alpha\text{-substituted piperidines 1n-s with NaNO}_2 \text{ in TFA}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>PG</th>
<th>R</th>
<th>Oxidation potential (v)</th>
<th>Yield (%)</th>
<th>2n-s</th>
<th>7n-s</th>
<th>8n-s</th>
</tr>
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<td></td>
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</tbody>
</table>

$^a$ vs Ag/AgNO$_3$,
Table 3. Oxidative cleavage of N-protected piperidines 1n-s with NaNO2 in TFA

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PG</td>
<td>R¹ R² R³</td>
</tr>
<tr>
<td>1</td>
<td>CO₂Me</td>
<td>Me H H H</td>
</tr>
<tr>
<td>2</td>
<td>CO₂CH₂CF₃</td>
<td>Me H H H</td>
</tr>
<tr>
<td>3</td>
<td>CO₂Me</td>
<td>H Me H H</td>
</tr>
<tr>
<td>4</td>
<td>CO₂CH₂CF₃</td>
<td>H Me H H</td>
</tr>
<tr>
<td>5</td>
<td>CO₂Me</td>
<td>H H Me H</td>
</tr>
<tr>
<td>6</td>
<td>CO₂CH₂CF₃</td>
<td>H H Me H</td>
</tr>
</tbody>
</table>

Trifluoroethoxycarbonyl served as a better protecting group than methoxycarbonyl in all cases (Entries 1-6). In the cases where 2-methylpiperidines 1n and 1o were oxidized, C-C bond cleavage occurred exclusively between the 5th and 6th position to afford 2n and 2o (Entries 1 and 2), while for 3-methylpiperidines 1p and 1q, cleavage occurred between the 5th and 6th position to afford 2p and 2q or at the 2nd and 3rd position to afford 8p and 8q, respectively (Entries 3 and 4).

To obtain insight into the mechanism for our reaction, the kinetic isotope effect was measured using 2,2-dideuteriopiperidines 1t, 1u (Eq. 6). The $k_H/k_D$ values for the oxidation of 1t, 1u was found to be almost similar with those of electrochemical oxidation. These results strongly suggest that our oxidation proceed via single electron transfer.

Plausible reaction mechanism is shown in Scheme 1. NO⁺ generated from NaNO₂ and TFA plays an important role as an oxidant for 1 and intermediate A as well as a
nitrosation agent for enamine C. NO might be oxidized to NO\(^+\) by molecular O\(_2\),\(^{10}\) while nitroso compound E is changed into oxime F, whose hydrated form G smoothly afford ring opened intermediate I. Finally, hydrolysis of I gives \(\omega\)-N-formylamino carboxylic acid 2.

\[
\text{NaNO}_2 + 2\text{CF}_3\text{CO}_2\text{H} \xrightarrow{-\text{H}_2\text{O}} \text{NO}^+ \text{CF}_3\text{CO}_2^- + \text{CF}_3\text{CO}_2\text{Na}^- \\
\]

Scheme 1. Plausible reaction mechanism.

Enantiomerically pure 3e as a precursor for GABOB is of essence. Therefore, we examined the suitability of different protecting groups for both N and O towards exclusive oxidative cleavage between the 5th and 6th position of 3-hydroxypiperidine derivatives 10 (Eq. 7). The results are summarized in Table 4.

\[
\text{RO}_{11} \xrightarrow{\text{NaNO}_2 (2 \text{ equiv}) \ \text{H}_2\text{O (10 equiv)}} \xrightarrow{\text{in TFA} \ 0^\circ\text{C} 12\text{h} \ \text{under air}} \text{RO}_{11}\text{CO}_2\text{H} \\
\]

(7)
Table 4. Oxidative cleavage of \(N,O\)-protected 3-hydroxypiperidines 10

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Yield (%) of 3</th>
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<tr>
<td>1</td>
<td>CO(_2)Ph Ac 10a</td>
<td>trace</td>
</tr>
<tr>
<td>2</td>
<td>CO(_2)Ph Bz 10b</td>
<td>trace</td>
</tr>
<tr>
<td>3</td>
<td>CO(_2)Me Ac 10c</td>
<td>68</td>
</tr>
<tr>
<td>4</td>
<td>CO(_2)Me Bz 10d</td>
<td>59</td>
</tr>
<tr>
<td>5</td>
<td>Cbz Ac 10e</td>
<td>66</td>
</tr>
<tr>
<td>6</td>
<td>Cbz Bz 10f</td>
<td>11</td>
</tr>
<tr>
<td>7</td>
<td>Cbz COEt 10g</td>
<td>63</td>
</tr>
<tr>
<td>8</td>
<td>Cbz Piv 10h</td>
<td>&gt;99</td>
</tr>
</tbody>
</table>

Use of phenoxycarbonyl as \(N\)-protecting group led to only trace amount of the desired cleaved product \(3a,b\) (Entries 1 and 2). Change of the protecting group to methoxycarbonyl led to improvement in yields to 68\% for \(3c\) and 59\% for \(3d\) (Entries 3 and 4). The ease of deprotection made us decide to try benzoxycarbonyl as \(N\)-protecting group, which gave comparable result to methoxycarbonyl (Entries 3 and 5). To further improve the yield, we tried various \(O\)-protecting groups (Entries 5-8), and enantiomerically pure \(3e^{5d,11}\) was obtained from \(10e\) in good yield (Entry 5). Pivaloyl\(^{12}\) emerged as the best protecting group to afford \(3h^{13}\) in quantitative yield.

Also, oxidative carbon-carbon cleavage of 3-pipecolinate \(11^{14}\) proceeded smoothly to afford \(12\), which was transformed into enantiomerically pure \(4^{15,16}\) (Eq. 8).

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{NaNO}_2 \text{ (2 equiv)} \quad \text{EtO}_2\text{C} \quad \text{H}_2\text{O (10 equiv)} \\
\text{Cbz} & \quad \text{in TFA} \quad \text{N}^+ \quad \text{CHO} \\
\text{11} & \quad 0^\circ\text{C} \quad 12h \\
& \quad \text{under air} \\
& \quad 1) \text{H}_2 \text{ (1 atm)} \\
& \quad \text{cat.}10\% \text{Pd-C in MeOH} \\
& \quad 2) \rho\text{-TsOH (0.4 equiv)} \\
& \quad \text{in toluene, 1,4-dioxane} \\
& \quad \text{at 110\,c} \\
& \quad 53\% \text{ yield} \\
& \quad 4 \quad \text{(8)}
\end{align*}
\]

In summary, oxidative C-C bond cleavage of \(N\)-alkoxycarbonylated cyclic amines was accomplished by NaNO\(_2\) in TFA to afford \(\omega\)-amino carboxylic acid in high yield. Optically active 3-hydroxypiperidine derivative and 3-pipecolinate were converted to enantiomerically pure precursor for \((R)\)-4-amino-3-hydroxybutanoic acid (GABOB) and \((S)\)-2-pyrrolidone-4-carboxylate, respectively. The mechanistic study and further synthetic application are underway.

References and notes


6. Under anhydrous condition, oxidation of 1a,e,f smoothly proceeded to give *ω*-amino nitriles 5a,e,f in good to high yields. The reaction of *ω*-amino nitriles 5a,e,f with NaNO₂ (2 equiv) and H₂O (10 equiv) in TFA did not proceed at all.

\[
\begin{align*}
1a,e,f & \xrightarrow{\text{NaNNO}_2 (2 \text{ equiv})} \text{in TFA} \quad 0^\circ \text{C to rt} \quad \text{3h} \quad \text{under air} \\
& \xrightarrow{(\text{CF}_3\text{CO}_2\text{O})_2\text{O} (7 \text{ equiv})} 5a \quad 85\% \text{ yield} \\
& \quad 5e \quad 83\% \text{ yield} \\
& \quad 5f \quad 87\% \text{ yield}
\end{align*}
\]

7. Oxidation potentials (vs Ag/AgNO₃): 2.16 V for 1a, 2.10 V for 1e, 2.33V for 1f.

8. 


10. The oxidation of 1a under nitrogen atmosphere gave 2a in 25% yield along with recovered 1a in 69% yield.

11. **Enantiomerically pure** *(R)-3-acetoxy-4-[(N-benzoxycarbonyl-N-formyl)amino]butanoic acid (3e):*

    Colorless oil; IR(neat) 3567 (br), 2963, 1730, 1698, 1333, 1237 cm⁻¹; ¹H-NMR (300MHz, CDCl₃) δ 1.92 (s, 3H), 2.64 (d, *J* = 6.9 Hz, 2H), 3.89 (dd, *J* = 3.6, 14.4 Hz, 1H).
Hz, 1H), 4.02 (dd, $J = 6.6, 11.4$ Hz, 1H), 5.32 (s, 2H), 5.45 (m, 1H), 7.40 (m, 5H), 9.24 (s, 1H); $^1$H-NMR (300MHz, DMSO-d$_6$) $\delta$ 1.80 (s, 3H), 2.60 (d, $J = 8.8$ Hz, 2H), 3.71 (dd, $J = 10.6$ Hz, 1H), 3.86 (dd, $J = 5.7, 10.8$ Hz, 1H), 5.45 (m, 1H), 5.50 (m, 2H), 7.34 – 7.45 (m, 5H), 9.13 (s, 1H); $^1$C-NMR (75MHz, CDCl$_3$) $\delta$ 20.3, 36.2, 42.4, 67.7, 69.0, 128.2, 128.4, 128.6, 134.1, 153.4, 163.0, 170.7, 173.2; $[\alpha]_{D}^{20} = +9.3$ (c 1.0, CHCl$_3$); MS [HR-EI]: $m/z$ calcd for C$_{15}$H$_{17}$NO$_7$ [M$^+$] 323.1005: found 323.0993; Optical purity was determined by HPLC analysis employing a Daicel Chiralcel OJ-H column (4.6 mm$\phi$, 250 mm). $n$-Hexane : Ethanol = 5 : 1, 0.1% TFA, wavelength: 220 nm, flow rate: 1.0 mL/min, retention time: 27.3 min ($R$), 30.9 min ($S$).

12. Oxidation potential (vs Ag/AgNO$_3$): 2.17 V for 10h.

13. Enantiomerically pure (R)-3-pivaloyloxy-4-[(N-benzyloxycarbonyl-N-formyl)amino]butanoic acid (3h): Colorless oil; IR(neat) 3200 (br), 2975, 1732, 1701, 1339, 1152, 1042 cm$^{-1}$; $^1$H-NMR (300MHz, CDCl$_3$) $\delta$ 1.11 (s, 9H), 2.65 (d, $J = 6.9$ Hz, 2H), 3.79 (dd, $J = 3.6, 14.4$ Hz, 1H), 4.07 (dd, $J = 7.8, 14.1$ Hz, 1H), 5.32 (s, 2H), 5.44 (m, 1H), 7.39 (m, 5H), 9.21 (s, 1H); $^1$H-NMR (300MHz, DMSO-d$_6$) $\delta$ 1.00 (s, 9H), 2.64 (d, $J = 9.5$ Hz, 2H), 3.66 (d, $J = 10.6$Hz, 1H), 3.92 (m, 3H), 7.36 - 7.43 (m, 5H), 9.12 (s, 1H), 12.39 (br s, 1H); $^1$C-NMR (100MHz, CDCl$_3$) $\delta$ 26.9, 36.8, 38.6, 42.9, 67.3, 69.3, 128.5, 128.8, 128.9, 134.4, 153.6, 162.6, 175.2, 177.7; $[\alpha]_{D}^{20} = +3.0$ (c 1.0, CHCl$_3$); MS [HR-EI]: $m/z$ calcd for C$_{18}$H$_{23}$NO$_7$ [M$^+$] 365.1474: found 365.1474; Optical purity was determined by HPLC analysis employing a Daicel Chiralcel OJ-H column (4.6 mm$\phi$, 250 mm), $n$-Hexane : Ethanol = 5 : 1, 0.1% TFA, wavelength: 220 nm, flow rate: 1.0 mL/ min, retention time: 10.1 min ($R$), 10.9 min ($S$).

14. Oxidation potential (vs Ag/AgNO$_3$): 2.21 V for 11.

15. Enantiomerically pure ethyl (S)-N-formyl-2-pyrrolidinone-4-carboxylate (4): Colorless oil; IR(neat) 1887, 1767, 1717, 1476, 1399 cm$^{-1}$; $^1$H-NMR (300MHz, CDCl$_3$) $\delta$ 1.30 (t, $J = 7.2$ Hz, 3H), 2.84 (dd, $J = 9.6, 18.6$ Hz, 1H), 2.97 (dd, $J = 7.2, 18.3$ Hz, 1H), 3.30 (m, 1H), 3.94 (m, 2H), 4.23 (q, $J = 7.2$ Hz, 2H), 9.09 (s, 1H); $^1$C-NMR (100MHz, CDCl$_3$) $\delta$ 14.1, 34.9, 35.7, 44.3, 61.9, 159.8, 171.6, 174.2; $[\alpha]_{D}^{20} = +23.6$ (c 1.0, CHCl$_3$); MS [HR-EI]: $m/z$ calcd for C$_8$H$_{11}$NO$_4$ [M$^+$] 185.0688: found 185.0667; Optical purity was determined by HPLC analysis employing a Daicel Chiralcel OD-H column (4.6 mm$\phi$, 250 mm), $n$-Hexane : Ethanol = 15 : 1, wavelength: 220 nm, flow rate: 1.0 mL/ min, retention time: 27.4 min ($S$), 29.3 min ($R$).