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-adamanntanols 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).

\[
\begin{align*}
\text{N} & \text{CO}_2\text{R} \quad \text{NaNO}_2 \\
& \text{H}_2\text{O in TFA} \\
\alpha & \beta
\end{align*}
\]

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; α-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. 

\[
1a + \text{NaNO}_2 (2 \text{ equiv}) + H_2O (10 \text{ equiv}) \rightarrow 2a, 98\% 
\]

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

\[
\text{Entry} \quad n \quad \text{PG} \quad 1b \quad 1c \quad 1d \quad 1e \quad 1f \quad 1g \quad 1h \quad 1i \\
1 \quad 0 \quad \text{CO}_2\text{Me} \quad 74 \quad 9 \quad 0 \quad 0 \quad 0 \quad 0 \quad 0 \quad 0 \\
2 \quad 0 \quad \text{CO}_2\text{Ph} \quad 83 \quad 11 \quad 0 \quad 0 \quad 0 \quad 0 \quad 0 \quad 0 \\
3 \quad 0 \quad \text{CO}_2\text{CH}_2\text{CF}_3 \quad 88 \quad 11 \quad 0 \quad 0 \quad 0 \quad 0 \quad 0 \quad 0 \\
4 \quad 1 \quad \text{CO}_2\text{Me} \quad 79 \quad 0 \quad 15 \quad 0 \quad 0 \quad 0 \quad 0 \quad 0 \\
5 \quad 1 \quad \text{CO}_2\text{CH}_2\text{CF}_3 \quad 99 \quad 0 \quad 0 \quad 0 \quad 0 \quad 0 \quad 0 \quad 0 \\
6 \quad 1 \quad \text{CHO} \quad 0 \quad 0 \quad 0 \quad 0 \quad >99 \quad >99 \quad >99 \quad >99 \\
7 \quad 1 \quad \text{COMe} \quad 0 \quad 0 \quad 0 \quad 0 \quad >99 \quad >99 \quad >99 \quad >99 \\
8 \quad 1 \quad \text{COPh} \quad 0 \quad 0 \quad 0 \quad 0 \quad >99 \quad >99 \quad >99 \quad >99 \\
\]

\(N\)-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 phenoxyl and trifluoroethoxyl groups were more efficient than methoxycarbonyl group (Eq. 2 and Entry 5). Interestingly, \(N\)-formylated and acylated piperidines 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](image)

**Table 2. Oxidative cleavage of α-substituted pyrrolidines 1j-m with NaNO₂ in TFA**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Oxidation potential (v)ᵃ</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CO₂Me CH₂OAc</td>
<td>2.24</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>CO₂CH₂CF₃ CH₂OAc</td>
<td>2.50</td>
<td>41</td>
</tr>
<tr>
<td>3</td>
<td>CO₂Me CO₂Me</td>
<td>2.39</td>
<td>52</td>
</tr>
<tr>
<td>4</td>
<td>CO₂CH₂CF₃ CO₂Me</td>
<td>2.82</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

ᵃ vs Ag/AgNO₃.

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 Structure](image)
Table 3. Oxidative cleavage of N-protected piperidines $\text{1n-s}$ with NaNO$_2$ in TFA

<table>
<thead>
<tr>
<th>Entry</th>
<th>PG</th>
<th>R$^1$</th>
<th>R$^2$</th>
<th>R$^3$</th>
<th>2</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CO$_2$Me</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>1n</td>
<td>47</td>
<td>52</td>
</tr>
<tr>
<td>2</td>
<td>CO$_2$CH$_2$CF$_3$</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>1o</td>
<td>79</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>CO$_2$Me</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>1p</td>
<td>42</td>
<td>trace</td>
</tr>
<tr>
<td>4</td>
<td>CO$_2$CH$_2$CF$_3$</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>1q</td>
<td>74</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>CO$_2$Me</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>1r</td>
<td>43</td>
<td>45</td>
</tr>
<tr>
<td>6</td>
<td>CO$_2$CH$_2$CF$_3$</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>1s</td>
<td>76</td>
<td>15</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 $\text{1n}$ and $\text{1o}$ were oxidized, C-C bond cleavage occurred exclusively between the 5th and 6th position to afford $\text{2n}$ and $\text{2o}$ (Entries 1 and 2), while for 3-methylpiperidines $\text{1p}$ and $\text{1q}$, cleavage occurred between the 5th and 6th position to afford $\text{2p}$ and $\text{2q}$ or at the 2nd and 3rd position to afford $\text{8p}$ and $\text{8q}$, respectively (Entries 3 and 4).

To obtain insight into the mechanism for our reaction, the kinetic isotope effect was measured using 2,2-dideuteriopiperidines $\text{1t}$, $\text{1u}$ (Eq. 6). The $k_H/k_D$ values for the oxidation of $\text{1t}$, $\text{1u}$ was found to be almost similar with those of electrochemical oxidation.$^9$ These results strongly suggest that our oxidation proceed via single electron transfer.

$$
\begin{align*}
\text{1t} & : \text{PG} = \text{CO}_2\text{CH}_2\text{CF}_3 \\
\text{1u} & : \text{PG} = \text{CO}_2\text{Me} \\
\text{NaNO}_2\text{ (2 equiv)} & \quad \text{H}_2\text{O} \text{ (10 equiv)} \\
\text{0°C to rt} & \quad \text{3 h under air} \\
\text{Et}_4\text{NBF}_4 \text{(0.1M)} & \quad \text{in MeOH} \\
\text{4 F/mol, 50 mA, at 0°C} & \\
\end{align*}
$$

Plausible reaction mechanism is shown in Scheme 1. NO$^+$ generated from NaNO$_2$ and TFA plays an important role as an oxidant for $\text{1}$ and intermediate $\text{A}$ 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.

\[
\text{RO}_{i_1}\text{NPG} \xrightarrow{\text{NaNO}_2 (2 \text{ equiv}) \text{H}_2\text{O (10 equiv)} \text{in TFA} \text{0}\degree\text{C 12h under air}} \text{CO}_2\text{NaNPG}
\]
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>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CO(_2)Ph Ac</td>
<td>10a</td>
</tr>
<tr>
<td>2</td>
<td>CO(_2)Ph Bz</td>
<td>10b</td>
</tr>
<tr>
<td>3</td>
<td>CO(_2)Me Ac</td>
<td>10c</td>
</tr>
<tr>
<td>4</td>
<td>CO(_2)Me Bz</td>
<td>10d</td>
</tr>
<tr>
<td>5</td>
<td>Cbz Ac</td>
<td>10e</td>
</tr>
<tr>
<td>6</td>
<td>Cbz Bz</td>
<td>10f</td>
</tr>
<tr>
<td>7</td>
<td>Cbz CO(_2)Me</td>
<td>10g</td>
</tr>
<tr>
<td>8</td>
<td>Cbz Piv</td>
<td>10h</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 benzyloxycarbonyl 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).

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.

\[
\begin{align*}
1a,e,f & \xrightarrow{\text{NaNO}_2 (2 \text{ equiv})} 5a, e, f \\
& \xrightarrow{(\text{CF}_3\text{CO}_2)\text{O} (7 \text{ equiv}) \text{ in TFA}} 5a \text{: 85% yield} \\
& \text{0°C to rt 3h under air} \\
& \text{5e: 63% yield} \\
& \text{5f: 87% yield}
\end{align*}
\]

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

8. Enantiomerically pure

(R)-3-acetoxy-4-[(N-benzyloxycarbonyl-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), 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); 1H-NMR (300MHz, DMSO-d₆) δ 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), 5.00 (m, 1H), 5.30 (m, 2H), 7.34 – 7.45 (m, 5H), 9.13 (s, 1H); 13C-NMR (75MHz, CDCl₃) δ 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; [α]²⁰ D = +9.3 (c 1.0, CHCl₃); MS [HR-EI]: m/z calcd for C₁₅H₁₇NO₇ [M]+ 323.1005: found 323.0993; Optical purity was determined by HPLC analysis employing a Daicel Chiralcel OJ-H column (4.6 mm x 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/AgNO₃): 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; 1H-NMR (300MHz, CDCl₃) δ 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); 1H-NMR (300MHz, DMSO-d₆) δ 1.00 (s, 9H), 2.64 (d, J = 9.5 Hz, 2H), 3.66 (d, J = 10.6Hz, 1H), 3.92 (m, 1H), 5.29 (m, 3H), 7.36 - 7.43 (m, 5H), 9.12 (s, 1H), 12.39 (br s, 1H); 13C-NMR (100MHz, CDCl₃) δ 26.9, 36.8, 38.6, 38.6, 42.9, 67.3, 69.3, 128.5, 128.8, 128.9, 134.4, 153.6, 162.6, 175.2, 177.7; [α]²⁰ D = +3.0 (c 1.0, CHCl₃); MS [HR-EI]: m/z calcd for C₁₈H₂₃NO₇ [M]+ 365.1474: found 365.1474; Optical purity was determined by HPLC analysis employing a Daicel Chiralcel OJ-H column (4.6 mm x 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/AgNO₃): 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; 1H-NMR (300MHz, CDCl₃) δ 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); 13C-NMR (100MHz, CDCl₃) δ 14.1, 34.9, 35.7, 44.3, 61.9, 159.8, 171.6, 174.2; [α]²⁰ D = +23.6 (c 1.0, CHCl₃); MS [HR-EI]: m/z calcd for C₈H₁₁NO₄ [M]+ 185.0688: found 185.0667; Optical purity was determined by HPLC analysis employing a Daicel Chiralcel OD-H column (4.6 mm x 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).