N-heterocyclic compounds via Radical Cyclization Reactions: Chemistry of The Imidoyl Radical

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Radical Cyclizations: Introduction

- Radical chain reactions:

- Two conditions for successful radical chain reaction
  1. The selectivities of the radicals in chain must differ from one another.
  2. Reactions between radical/non-radicals must be faster than radical/radical reactions
Radical Cyclizations: FMO Analysis

- Both SOMO-HOMO and SOMO-LUMO interactions are stabilizing.
- The nature of the radical is determined by the strongest interaction between the respective Frontier molecular orbitals.
Radical Cyclizations: FMO Analysis

- Radicals with a high-energy SOMO exhibit nucleophilic character
- Radicals with a low-energy SOMO exhibit electrophilic character
Radical Cyclizations: Formation of Heterocycles

- Limited number of ways to construct heterocycles using radical cyclizations.

Case 1: Heteroatom linker in the radical chain

\[
\begin{align*}
\text{Y} & \quad \text{O} \quad \cdot \quad \cdot \\
\text{X} & \quad \equiv \quad \text{O} \quad \cdot \quad \cdot \\
\end{align*}
\]

\[
\begin{align*}
\text{Y} & \quad \text{X} \\
\end{align*}
\]

\[
\begin{align*}
\text{X} & \quad \text{O} \quad \cdot \quad \cdot \\
\text{X} & \quad \equiv \quad \text{O} \quad \cdot \quad \cdot \\
\end{align*}
\]


- Open dot represents a radical acceptor
- Closed dot represents a radical donor
Radical Cyclizations: Formation of Heterocycles

Case 2: Heteroatom as the radical acceptor

\[
\begin{array}{c}
\text{Br} \quad \text{N} \quad \text{Ph} \\
\text{R} \\
\end{array}
\xrightarrow{\text{n-BuSnH, AlBN}}
\begin{array}{c}
\text{N} \\
\text{R} \\
\text{Ph} \\
\end{array}
\]

Radical Cyclizations: Formation of Heterocycles

Case 3: Heteroatom as the radical donor

\[\begin{align*}
\text{R} & \quad \text{H} \quad \text{R}^2 \\
\text{R}^1 & \quad \text{X} \quad \text{R}^2
\end{align*}\]

\[\begin{align*}
\text{R}^1 & \quad \text{X} \quad \text{R}^2 \\
\text{H} \quad \text{H} \quad \text{H} \quad \text{H}
\end{align*}\]

\[\begin{align*}
\text{R} & \quad \text{NCS, PhMe} \\
\text{H} & \quad \text{ii. n-Bu}_3\text{SnH-AIBN, PhMe, Reflux}
\end{align*}\]

\[\begin{align*}
\text{H} & \quad \text{Ph} \\
\text{R}^1 & \quad \text{R} = \text{Me, 63\%} \\
\text{R} & \quad \text{Ph, 43\%}
\end{align*}\]


- Method also highlights a tandem radical cyclization
Radical Cyclizations: Formation of Heterocycles

- Common theme to all three cases is the vicinal relationship between the radical acceptor and radical donor.

Case 1:

Case 2:

Case 3:

- What about geminial radical acceptor/radical donor groupings?
Radical Cyclizations: Formation of Heterocycles

Case 4: Geminal radical acceptor/radical donor synthon

\[
\begin{align*}
\text{TBDPS} & \equiv \text{EtS} \\
\equiv \text{N} & \equiv \text{COOR}^1 \\
\equiv \text{N} & \equiv \text{COOR}^1
\end{align*}
\]

\[
\begin{align*}
\text{TBDPS} & \equiv \text{EtS} \\
\equiv \text{N} & \equiv \text{COOR}^1 \\
\equiv \text{N} & \equiv \text{COOR}^1
\end{align*}
\]

\[
\begin{align*}
\text{EtSH, AIBN} & \quad \text{PhMe, Reflux} \\
\text{R}^1 = \text{t-Bu}, 72\% \\
\text{R}^2 = \text{Et}, 70\%
\end{align*}
\]


- Isonitrile and carbon monoxide variants have both been studied
- Focus of this talk will be on the isonitrile variants
Radical Cyclizations: Imidoyl Radical

- Reaction pathways available to imidoyl radicals

Radical Cyclization: Pyrrolines and Pyroglutamates

- The pyrroline ring can be broken into two radical synthons

- Bachi and co-workers used this general scheme for the synthesis of several pyrroline and pyroglutamates derivatives
Radical Cyclization: Pyrrolines

- Thioisocynate formation results when $R^5$ is a stable radical
Radical Cyclization: Pyrrolines

![Chemical structures](image)

### Pyrrolines 11 + 12

<table>
<thead>
<tr>
<th>temp, time, °C h</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>R⁴</th>
<th>R⁵</th>
<th>yield</th>
<th>11/12 ratio</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>R⁴</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>110 1.0</td>
<td>k</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>tBu</td>
<td>Ph</td>
<td>74</td>
<td>1:1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>110 1.5</td>
<td>l</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>tBu</td>
<td>Et</td>
<td>83</td>
<td>1:4</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>40   1.5</td>
<td>m</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>Et</td>
<td>Et</td>
<td>85</td>
<td>1:2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>40   1.5</td>
<td>n</td>
<td>H</td>
<td>Me</td>
<td>Me</td>
<td>Me</td>
<td>Et</td>
<td>83</td>
<td>1:4</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>85   2.0</td>
<td>o</td>
<td>H</td>
<td>Me</td>
<td>Me</td>
<td>Et</td>
<td>(CH₂)₂CO₂Me</td>
<td>84</td>
<td>1:1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>40   1.5</td>
<td>p</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>tBu</td>
<td>Ph</td>
<td>traces</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>110  1.5</td>
<td>30</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>40   3.5</td>
<td>q</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>tBu</td>
<td>Et</td>
<td>56</td>
<td>-</td>
<td>d</td>
<td>Me</td>
<td>H</td>
<td>tBu</td>
</tr>
<tr>
<td>110  2.5</td>
<td>50</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>10</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>45   3.0</td>
<td>r</td>
<td>H</td>
<td>Me</td>
<td>Me</td>
<td>Et</td>
<td>CH₂CO₂Me</td>
<td>38</td>
<td>1:1</td>
<td>c</td>
<td>H</td>
<td>Me</td>
<td>Me</td>
</tr>
<tr>
<td>5°   2.0</td>
<td>58</td>
<td>1:1</td>
<td>c</td>
<td></td>
<td>36</td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>-20° 4.5</td>
<td>r</td>
<td>70</td>
<td>1:1</td>
<td>c</td>
<td></td>
<td>28</td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>-60° 8.5</td>
<td>r</td>
<td>78</td>
<td>1:1</td>
<td>c</td>
<td></td>
<td>2</td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Radical Cyclization: Pyroglutamates

- The authors found that pyroglutamates could be obtained in high yield with the use of mercaptoethanol.

\[
\begin{align*}
\text{CO}_2\text{t-Bu} & \quad \text{HS-} \quad \text{OH} \\
\text{AlBN} & \quad \text{PhMe} \\
\rightarrow & \quad 72\% \\
\text{Me} & \quad \text{CH}_2\text{O}_2\text{t-Bu}
\end{align*}
\]

(1:2.5 cis/trans)

- The authors proposed that the pyroglutamates were forming through the following intermediates.
Radical Cyclization: Catalytic Method

- Placement of a cleavable phenylthiyl radical in the substrate allowed for a "catalytic" process to occur.

- Product 24 was obtained after isomerization to give a conjugated pyrroline in 85% yield.
Radical Cyclization: Quinoline Derivatives

- Quinoline structure is present in a variety of natural products including the anti-tumor candidate (S)-camptothecin

![Chemical structure of (S)-Camptothecin](image)

- Researchers have found that substituents at the 7 and 9 position on the quinoline ring favorable modulate the activity of the drug.

- Methods for making the 7,9-substitution pattern are limited.

Curran, D.P.; Du, W. *Synlett* **2003**, 1299
Radical Cyclization: Quinoline Derivative

- The breaking apart camptothecin core reveals possibility for a radical cyclization reaction

![Chemical structure 1]

- Curran and co-workers envisioned a radical cyclization between phenyl isonitrile and a N-propargyl-6-iodo-pyridone derivative

![Chemical structure 2]
Radical Cyclization: Quinoline Derivatives

- In the 7,9 isomer the orientation of $R^A$ has changed from ortho to meta.

- Increasing the size of the o-aryl substituents gives rise to the more crowded 7,9-isomer.

<table>
<thead>
<tr>
<th>Entry</th>
<th>$R^A$</th>
<th>$R^B$</th>
<th>Ratio 9/10 or 11/12</th>
<th>Yield$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>i-Pr</td>
<td>H</td>
<td>9b/10b, 3/1</td>
<td>53%</td>
</tr>
<tr>
<td>2</td>
<td>i-Pr</td>
<td>TMS</td>
<td>9c/10c, 7/1</td>
<td>43%</td>
</tr>
<tr>
<td>3</td>
<td>i-Pr</td>
<td>Et</td>
<td>9a/10a, 8/1</td>
<td>53%</td>
</tr>
<tr>
<td>4</td>
<td>i-Pr</td>
<td>i-Bu</td>
<td>9d only</td>
<td>59%</td>
</tr>
<tr>
<td>5</td>
<td>Et</td>
<td>TMS</td>
<td>11c/12c, 3.1/1</td>
<td>66%</td>
</tr>
<tr>
<td>6</td>
<td>Et</td>
<td>TES</td>
<td>11e/12e, 2.7/1</td>
<td>70%</td>
</tr>
<tr>
<td>7</td>
<td>Et</td>
<td>TBS</td>
<td>11f/12f, 0.9/1</td>
<td>79%</td>
</tr>
</tbody>
</table>
Radical Cyclization: Quinoline Derivative

- Proposed Mechanism: 7,12-isomer
Radical Cyclization: Quinoline Derivatives

- Proposed Mechanism 7,9-isomer
Radical Cyclization: Quinoline Derivatives

- 7,9-Isomer favored when $R^1$ is large
- Authors contend this could result from unfavorable steric interaction during 6-endo cyclization
Radical Cyclization: 2,3-Substituted Indoles

- Indole and indoline rings can be found throughout a wide range of alkaloid natural products.

- Few practical methods are available for the construction of 2,3-substituted indoles.

- Fisher indole synthesis is not compatible with acid labile functionalities.
Radical Cyclization: 2,3-Substituted Indoles

General Method:

1. \( \text{Bu}_3\text{Sn}^- \) treatment of \( 1 \) results in the formation of 2.

2. Treatment of 2 with \( \text{Bu}_3\text{SnH} \) leads to 3.


4. Reaction of 4 with \( R'X, \text{Pd}(0) \) leads to 5.

- Allows for both 3-substituted and 2,3-substituted indole rings
- 2-stannylindoles are further reacted through Still conditions to give 2,3-substituted indoles.
Radical Cyclization: 3-substituted indoles

- E/Z double bonds tolerated in most cases.

- Formation of tetra-hydroquinoline (6) could be avoided by use of Z-double bond.
Radical Cyclization: 2,3-substituted indoles

- Decreasing the radical stabilizing ability of the R-group resulted in decreased yields.

- Substrate scope of coupling partner in Stille reaction was high.
Radical Cyclization: (-) Aspidophytine

- Fukuyama showcased his radical cyclization methodology in the synthesis of (-)-Aspidophytine

Radical Cyclizations: (-)-Aspidophytine
Radical Cyclizations: (−)-Aspidophytine

- Synthesis of indole core

\[ \begin{align*}
\text{CHO} & \xrightarrow{(EtO)_{2}P=CO_{2}Et} \text{MeO} \xrightarrow{81\%} \text{MeO} \\
\text{MeO} & \xrightarrow{\text{NO}_{2}} \text{MeO} \xrightarrow{\text{NC}} \text{MeO} \\
81\% & \xrightarrow{63\%} \text{MeO} \\
\end{align*} \]

- 7 manipulations, 37\% overall yield
Radical Cyclization: Concluding Remarks

- The radical cyclization chemistry of the imidoyl radical has been used for the synthesis of a variety of N-heterocyclic compounds in moderate to high yields.
Radical Cyclization: Concluding Remarks

- Applications in total synthesis have led to the successful construction of (-)-aspidophytine as well as derivatives of the camptothecin and mappicine families.
Radical Cyclizations: References

Introduction:

Formation of Heterocycles:

Pyrrrolines:

Quinolines:

Indoles:

(-)-Aspidophytine:

Reviews: