A Modular Approach to Polyketide Building Blocks: Cycloadditions of Nitrile Oxides and Homoallylic Alcohols

*Organic Letters, 2005, ASAP*

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\[ \text{Nitrile Oxide} + \text{Alcohol} \rightarrow \text{Polyketide Building Block} \]

1. t-BuOCl, -78°C
2. EtMgBr
   - i-PrOH
   - CH₂Cl₂ or toluene
   - 0°C - rt

Anthony Cuzzupe
April 30, 2005
Polyketides: Natural compounds containing alternating carbonyl and methylene groups ("β-polyketones"), biogenetically derived from repeated condensations of acetyl coenzyme A.


-Usually possess potent biological activity and are structurally (stereochemically) complex.
-Some examples:
Some Common Methods for Polyketide Synthesis:

Aldol:

\[
\text{O} \quad \text{O} \\
\text{N} \quad \text{O} \\
\text{Ph} \quad \text{Ph}
\]

\[
\text{O} \quad \text{O} \\
\text{N} \quad \text{O} \\
\text{Ph} \quad \text{Ph}
\]

\[
\begin{align*}
\text{Ph} & \xrightarrow{\text{Ph-CHO}} \text{Ph} \\
\text{CHO} & \xrightarrow{n-\text{Bu}_2\text{BOTf, NET}_3} \text{CHO}
\end{align*}
\]


(Macbecin 1)

Allylmetallation:

\[
\text{TBSO} \quad \text{CHO} \\
\text{OMe} \quad \text{CHO}
\]

\[
\text{TBSO} \quad \text{CHO} \\
\text{OMe} \quad \text{CHO}
\]

\[
\begin{align*}
\text{1. TiCl}_4, -78^\circ\text{C} & \xrightarrow{\text{TBSO}} \text{CHO} \\
\text{2. \text{SnBu}_3} & \xrightarrow{\text{TBSO}} \text{CHO}
\end{align*}
\]


(Rhizoxins)

Crotolymetallation:

\[
\text{TBDPSO} \quad \text{H} \\
\text{CHO} \quad \text{CHO}
\]

\[
\text{TBDPSO} \quad \text{H} \\
\text{CHO} \quad \text{CHO}
\]

\[
\begin{align*}
toluene, -78^\circ\text{C} & \xrightarrow{\text{TBDPSO}} \text{CHO} \\
98\% & > 99\% \text{ d.e.}
\end{align*}
\]


(Nargenicin A₁)
Some Alternative Methods for Polyketide Synthesis:

Dithiane coupling:

\[
\begin{array}{c}
\text{BnO} \\
\text{79%} \\
\end{array}
\]

\[
\begin{array}{c}
\text{t-BuLi} \\
10\% \text{HMPA/THF} \\
\end{array}
\]


Hydroboration:

\[
\begin{array}{c}
\text{BzO} \\
1. \text{B}_2\text{H}_6, \text{THF}, 0^\circ\text{C} \\
2. \text{aq. NaOH, H}_2\text{O}_2, \text{rt} \\
\end{array}
\]


Cyclopropylcarbinol ring-opening:

\[
\begin{array}{c}
\text{AcO} \\
1. \text{Hg(OCOCF}_3)_2, \text{CH}_2\text{Cl}_2 \\
2. \text{aq. NaCl} \\
3. \text{LAH, THF} \\
\text{40\%} \\
\end{array}
\]

Isoxazolines are Latent Aldol Products

- Reduction of isoxazolines usually result in complete reduction to the amino alcohol:

\[
\begin{align*}
\text{N} & \quad \text{O} \\
\text{R} & \quad \text{R'} \\
\text{H}_2 & \quad \text{Catalyst} \\
\rightarrow & \\
\text{NH} & \quad \text{OH} \\
\text{R} & \quad \text{R'} \\
\text{H}_2 & \\
\rightarrow & \\
\text{NH}_2 & \quad \text{OH} \\
\text{R} & \quad \text{R'}
\end{align*}
\]

Some important discoveries:

- Raney-Ni (cat), H₂, MeOH/H₂O (15:1), B(OCH₃)₃ (2 equiv) rt

\[
\begin{align*}
\text{N} & \quad \text{O} \\
\text{R} & \quad \text{R'} \\
\rightarrow & \\
\text{C} & \quad \text{OH} \\
\text{R} & \quad \text{R'} \\
77 - 92\% & \text{ yield}
\end{align*}
\]


- SmI₂, THF, 0°C then B(OH)₃, H₂O

\[
\begin{align*}
\text{R}^1 & \quad \text{N} & \quad \text{O} \\
\text{R}^2 & \quad \text{R}^3 \\
\rightarrow & \\
\text{C} & \quad \text{OH} \\
\text{R}^1 & \quad \text{R}^2 & \quad \text{R}^3 \\
62 - 89\% & \text{ yield}
\end{align*}
\]


---

Products are β-hydroxy ketones (equivalent to Aldol adducts!)

---

Isoxazolines can be used in polyketide synthesis.
Isoxazoline Synthesis by Nitrile Oxide Cycloaddition

Problems:

> Difficult to control regio- and stereochemistry in the typical nitrile oxide cycloaddition reaction

> Use of substituted olefins usually unsuccessful

Kanemasa's work on the first metal coordinated control of 1,3-dipolar cycloadditions:

> Works best with allylic alcohols (terminal, di-substituted and tri-substituted alkenes) with yields up to and above 90%

> High syn selectivity, up to 99:1 syn:anti

> Grignard Reagents work best, but amines, alkyllithiums, alkylaluminum and alkylzincs also work with lower selectivity

> Use of homoallylic alcohols led to diminished regio- and diastereoselectivity and lower yields
Isoxazoline Synthesis by Nitrile Oxide Cycloadditions

Why such high syn selectivity?

\[
\begin{array}{c}
\text{TS-A} \\
\text{Regioselective} \\
\text{Syn-cycloadducts MAJOR}
\end{array}
\]

\[
\begin{array}{c}
\text{TS-B} \\
\text{Anti-cycloadducts}
\end{array}
\]

> Stereochemical outcome governed by TS-A being favoured due to less steric hindrance from allylic strain between \( R_2 \) and \( R_4 \)

**Reaction Scope:**

> Although a number of allylic alcohols were used successfully, this study was limited to the use of benzonitrile oxide

Isoxazoline Synthesis by Nitrile Oxide Cycloadditions

Extension to Kanemasa's work:

> Conditions developed by Carreira and co-workers for the use of functionalised, aliphatic nitrile oxides in the hydroxy-directed nitrile oxide cycloaddition:

\[
\begin{align*}
\text{N=O} & + \text{R}^2\text{OH} & \xrightarrow{1. t-BuOCl, -78^\circ C, 2. 3.3 equiv iPrOH, 3.0 equiv EtMgBr, CH}_2\text{Cl}_2, \text{0}^\circ \text{C - rt}} \text{Syn to hydroxyl moiety}\\
\text{R}^1\text{H} & 1 \text{ equiv} & \text{R}^2\text{R}^3\text{R}^4 & 1 - 1.3 \text{ equiv}
\end{align*}
\]


> Nitrile oxides prepared in situ by preparation of the corresponding hydroximinoyl chloride with \textit{t}-BuOCl and reacted directly with the allylic magnesium alkoxide

> Magnesium alkoxides also generated in situ

> Use of \textit{i}-PrOH as additive improved reaction time and yields

> Procedure is tolerant of a wide range of functionality and olefin substitution

> Desired cycloadducts obtained in good yields and high diastereoselectivities
Isoxazoline Synthesis by Nitrile Oxide Cycloadditions

> Single-step preparation of all possible diastereomers of latent propionates:

> All adducts regio- and stereochemically pure by $^1$H and $^{13}$C NMR

> Structure of a derivative of adduct 6 confirmed by X-ray crystallography

A Modular Approach to Polyketide Building Blocks: Cycloadditions of Nitrile Oxides and Homoallylic Alcohols

Problems anticipated:
> Homoallylic alkoxides less reactive than allylic alkoxides
> In absence of a highly reactive alkene, aliphatic nitrile oxides might undergo dimerization

Aim:
> Develop strategies to provide access to the stereochemical permutations of dipropionate subunits, allowing divergent asymmetric synthesis from a single diastereoselective cycloaddition reaction

**Results:**

> A broad range of nitrile oxides react smoothly with (s)-2-methyl-3-butanol under the conditions previously optimised for allylic alcohols.

![Reactions Diagram](image_url)

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>solvent</th>
<th>d.r. (^a)</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TBSO</td>
<td>$\text{CH}_2\text{Cl}_2$</td>
<td>8:1 (^b)</td>
<td>67%</td>
</tr>
<tr>
<td>2</td>
<td>TBSO</td>
<td>$\text{CH}_2\text{Cl}_2$</td>
<td>7:1</td>
<td>83%</td>
</tr>
<tr>
<td>3</td>
<td>TBSO</td>
<td>$\text{CH}_2\text{Cl}_2$</td>
<td>9:1</td>
<td>85%</td>
</tr>
<tr>
<td>4</td>
<td>TBSO</td>
<td>toluene</td>
<td>4:1 (^b)</td>
<td>89%</td>
</tr>
<tr>
<td>5</td>
<td>TBSO</td>
<td>toluene</td>
<td>6:1 (^e)</td>
<td>82%</td>
</tr>
<tr>
<td>6</td>
<td>TBSO</td>
<td>toluene</td>
<td>5:1 (^e)</td>
<td>83%</td>
</tr>
<tr>
<td>7</td>
<td>TBDPSO</td>
<td>toluene</td>
<td>10:1 (^e)</td>
<td>87%</td>
</tr>
<tr>
<td>8</td>
<td>TBDPSO</td>
<td>toluene</td>
<td>5:1 (^b)</td>
<td>66%(^d,e)</td>
</tr>
<tr>
<td>9</td>
<td>(EtO)_2P=NOH</td>
<td>$\text{CH}_2\text{Cl}_2$</td>
<td>11:1 (^f)</td>
<td>36%</td>
</tr>
<tr>
<td>10</td>
<td>(EtO)_2P=NOCl</td>
<td>$\text{CH}_2\text{Cl}_2$</td>
<td>13:1 (^f)</td>
<td>71%(^g)</td>
</tr>
<tr>
<td>11</td>
<td>TBDPSO</td>
<td>$\text{CH}_2\text{Cl}_2$</td>
<td>7:1</td>
<td>87%(^e,h)</td>
</tr>
</tbody>
</table>

*Carreira, Org. Lett. 2005, ASAP*
> Diastereomeric ratios generally determined by NMR spectroscopy

> Relative stereochemistry determined by conversion of cycloadduct 1 into known isoxazoline 4


.... and further confirmed by derivatisation of two additional adducts and subsequent NOE experiments

Scope of cycloaddition extended to include monoprotected homoallylic diols:

<table>
<thead>
<tr>
<th>entry</th>
<th>monoprotected homoallylic diol</th>
<th>d.r.</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Diagram" /></td>
<td>19:1²</td>
<td>82%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Diagram" /></td>
<td>21:1²</td>
<td>85%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Diagram" /></td>
<td>14:1²</td>
<td>73%</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="Diagram" /></td>
<td>10:1²</td>
<td>78%</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="Diagram" /></td>
<td>6:1²</td>
<td>53%</td>
</tr>
</tbody>
</table>

> Yield and diastereoselectivity increases as steric demand of protecting group increases

> Immediate cycloadducts are *anti*, but the corresponding *syn* derivatives can be accessed by a simple orthogonal protection-deprotection protocol

> Therefore access to both *syn* and *anti* diastereoisomers is possible using same set of starting materials

Carreia, Org. Lett. 2005, ASAP
Example of use in Total Synthesis: Directed Nitrile Oxide Cycloaddition for the Synthesis of Epothilone A

Carreira, J. Am. Chem. Soc. 2001, 123, 3611
Conclusions

> The Mg-mediated, hydroxyl-directed nitrile oxide cycloaddition is highly stereoselective

> Procedure is operationally simple and versatile and is tolerable of a wide range of functionality and olefin substitution

> The methodology considerably expands the range of protected polyketide subunits that can be accessed

> Using isoxazolines as masked aldol adducts:
  - Enables convergent syntheses with the use of complex olefin and nitrile oxide coupling partners
  - Avoids the need for subsequent protection steps

> The cycloaddition with and allylic alcohol has been used successfully in total synthesis

> Use of the extended methodology involving homoallylic alcohols in total synthesis is pending