AN EXPLORATION OF OXETANES: SYNTHESIS AND RELEVANCE

KIMBERLY HILBY
GROUP MEETING 7/21/2020
OVERVIEW OF PRESENTATION

- Physical Chemical Properties of Oxetanes
- Relevance in Medicinal Chemistry
- Strategies for Synthesis/Installation of Oxetanes
  - Displacement by an alcohol
  - Formal $[2+2]$ type cycloaddition
  - Oxetane fragments as building blocks
- Overview of Oxetanes as synthetic blocks
- Future Directions/ Conclusions
NAMING PRIMER FOR OXETANES

Common 4 membered rings:

- Cyclobutane
- Oxetane
- Azetidine
- Thietane

Functionalized Oxetanes:

- $\beta$-Lactone (2-Oxetanones)
- 3-Oxetanones
- Oxetene

Naming convention of Spirocompounds:

- 2,6-diX
- spiro[3.3]
- heptane
- 2,6-diXspiro[3.3]heptane
Reboul (1878): Isolated parent compound
- Much of the work done for the next hundred years looked at the physical organic properties

Comparisons of Strain Energy’s

- Ethylene oxide: Ring Strain 27.5 kcal/mol
- Oxetane: Ring Strain 24.7 kcal/mol
- Tetrahydrofuran: Ring Strain 5.4 kcal/mol
- Tetrahydropyran: Ring Strain 0.5 kcal/mol
- Oxetane: Ring Strain 24.7 kcal/mol
- Cyclobutane: Ring Strain 26.5 kcal/mol
- Azetidine: Ring Strain 25.2 kcal/mol
- Thietane: Ring Strain 16.6 kcal/mol

Oxetanes are highly strained rings and undergo ring openings in presence of Lewis Acids.
Exhibited through electron diffraction (ED) that cyclobutane was not planar but “puckered”

Gwinn (1961): Exhibited through ED that oxetane was essentially a planar molecule but had a “puckering” vibration

Planar structure minimizes ring strain and heteroatom leads to less gauche effects
### NMR Properties of Oxetanes

**1H NMR of Oxetanes: Effects on substitution on chemical shift**

<table>
<thead>
<tr>
<th>Substituent</th>
<th>$H_A$</th>
<th>$H_B$</th>
<th>$H_C$</th>
<th>$H_D$</th>
<th>$H_E$</th>
<th>$H_F$</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>4.73</td>
<td>4.73</td>
<td>2.72</td>
<td>2.72</td>
<td>4.73</td>
<td>4.73</td>
</tr>
<tr>
<td>2-Me</td>
<td>1.35 (Me)</td>
<td>4.85</td>
<td>2.24</td>
<td>2.63</td>
<td>4.37</td>
<td>4.49</td>
</tr>
<tr>
<td>2,2-Me$_2$</td>
<td>1.36 (Me)</td>
<td>1.36 (Me)</td>
<td>2.34</td>
<td>2.34</td>
<td>4.32</td>
<td>4.32</td>
</tr>
<tr>
<td>3,3-Me$_2$</td>
<td>4.23</td>
<td>4.23</td>
<td>1.27 (Me)</td>
<td>1.27</td>
<td>4.23</td>
<td>4.23</td>
</tr>
<tr>
<td>trans-2,4-Me$_2$</td>
<td>1.36 (Me)</td>
<td>4.72</td>
<td>2.28</td>
<td>2.28</td>
<td>4.72</td>
<td>1.36 (Me)</td>
</tr>
<tr>
<td>cis-2,3-Me$_2$</td>
<td>1.22 (Me)</td>
<td>4.92</td>
<td>1.13 (Me)</td>
<td>2.94</td>
<td>3.98</td>
<td>4.64</td>
</tr>
<tr>
<td>trans-2,3-Me$_2$</td>
<td>1.37 (Me)</td>
<td>4.52</td>
<td>2.62</td>
<td>1.18</td>
<td>4.59</td>
<td>4.21</td>
</tr>
<tr>
<td>4-Me-2-one</td>
<td>1.53 (Me)</td>
<td>4.57</td>
<td>2.98</td>
<td>3.50</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**13C NMR of Oxetanes: Effects on substitution on chemical shift**

<table>
<thead>
<tr>
<th>Substituent</th>
<th>$C_1$</th>
<th>$C_2$</th>
<th>$C_3$</th>
<th>Me</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>72.8</td>
<td>23.1</td>
<td>72.8</td>
<td>-</td>
</tr>
<tr>
<td>2-Me</td>
<td>78.3</td>
<td>29.2</td>
<td>66.6</td>
<td>24.1</td>
</tr>
<tr>
<td>cis-2,3-Me$_2$</td>
<td>79.6</td>
<td>31.8</td>
<td>74.5</td>
<td>16.9, 13.0</td>
</tr>
<tr>
<td>trans-2,3-Me$_2$</td>
<td>85</td>
<td>37.4</td>
<td>73.5</td>
<td>22.8, 17.5</td>
</tr>
</tbody>
</table>

Different substituents can shield or deshield different protons because of proximity effects in the small ring and changes in the puckering of the ring.
Luger (1984): Published an influential paper exhibiting the first crystal structure of an unsubstituted oxetane.

Table I. Crystallographic Data for Oxetane, C₃H₆O, at 90 and 140 K

<table>
<thead>
<tr>
<th>property</th>
<th>90 K data</th>
<th>140 K data</th>
</tr>
</thead>
<tbody>
<tr>
<td>lattice constants, Å</td>
<td>a = 8.620 (4)</td>
<td>a = 8.657 (1)</td>
</tr>
<tr>
<td></td>
<td>b = 6.384 (15)</td>
<td>b = 6.401 (5)</td>
</tr>
<tr>
<td></td>
<td>c = 6.038 (13)</td>
<td>c = 6.010 (5)</td>
</tr>
<tr>
<td>cell volume, Å³</td>
<td>332.3</td>
<td>333.0</td>
</tr>
<tr>
<td>formula units/cell</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>X-ray density, g cm⁻³</td>
<td>1.154</td>
<td>1.151</td>
</tr>
<tr>
<td>space group</td>
<td>orthorhombic Pnam</td>
<td>orthorhombic Pnam</td>
</tr>
<tr>
<td>total no. of refinns (θ ≤ 30°)</td>
<td>527</td>
<td>606</td>
</tr>
<tr>
<td>unobserved (I &lt; 2σ)</td>
<td>91</td>
<td>212</td>
</tr>
<tr>
<td>linear absorption coeff (cm⁻¹, Mo Kα, λ = 0.71068 Å)</td>
<td>0.92</td>
<td>0.92</td>
</tr>
<tr>
<td>$R_{\text{wp}},ab$%</td>
<td>5.1</td>
<td>4.9</td>
</tr>
<tr>
<td>$R_a$</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>$b^a$</td>
<td>5.0</td>
<td>5.0</td>
</tr>
<tr>
<td>$R$ value, %</td>
<td>3.8</td>
<td>4.1</td>
</tr>
</tbody>
</table>

The function minimized was $\sum w(|F_o| - |F_c|)^2$ with $w = xy$; $x = 1$ for sin θ > a, $x = \sin \theta/a$ otherwise; $y = 1$ for $|F_o| < b$, $y = b/|F_o|$

This crystal structure exhibited the slight “puckering” of the ring that had been shown by electron diffraction.
Searles and Tamres (1951): Found that cyclic ethers such as oxetanes are excellent hydrogen bond acceptors (4 > 5 > 6 > 3 membered rings ≈ linear ethers).

- Strained O-C-O bond angles exposes oxygen lone pair electrons.
- Increased P characters in bonds of ring and exocyclic bonds have increased bond angles.
- Increased S character on oxygen does not significantly influence H-bonding till 3 membered rings.
Many natural products with interesting biological activity contain oxetanes in them.

- **Paclitaxel**: Cancer Chemotherapy
- **Mitrephorone A**: Cytotoxic activity
- **Merrilactone A**: Stimulates rat neurons
- **Maoyecrystal I**: Cytotoxic activity
- **Oxetin**: Antibacterial and herbicidal activity
- **Thromboxane A₂**: Prothrombotic properties
- **Oxetanocin A**: Inhibits HIV
- **Dictyoxetane**
Proposed Biosynthesis: Three different pathways have been proposed for installation of the oxetane.

**Pathway I: Neutral-Concerted**

**Pathway II: Acid-Catalyzed Route**

**Pathway III: Dissociative Pathway**

Method of Action: Believe that oxetane is imperative to its activity by rigidifying the structure of Taxol and hydrogen bonding.
Carreira (2006): Published an influential paper exhibiting that oxetanes could be used as an isostere for gem-dimethyl and carbonyl.
Carreira (2009): 3,3-substituted Spirocyclic oxetanes in recent years have gotten interest.

3,3-substituted oxetanes cause larger “puckering” which causes these molecules to favor a synclinal gauche conformation.

Oxetanes have become an isostere for a variety of functional groups.

- Similar molar volume to gem di-methyl
- Much bigger molar volume to carbonyl but now has increased lateral bulk and lipophilicity
- Also less metabolically labile than either group
SYNTHESIS OF OXETANES

Williamson Ether Synthesis

Epoxide Displacement

Electrophilic Halocyclization

Alcohol Displacement

Oxetane Building Blocks

C-O/C-C Formal [2+2]

Addition into Ketone

Cross Coupling

Paterno-Buchi Reaction

Lewis Acid-Promoted Strategy
Nelson (1999): Enantioenriched alcohols can be stereoselectively displaced to form oxetanes.

\[
\begin{align*}
\text{OH} & \quad \text{OH} \\
\text{Ph} & \quad \text{cHex} \\
\text{1. (MeO)}_3\text{CMe} & \quad \text{PPTS} \\
\text{2. AcBr} & \quad \text{Ph} & \quad \text{Br} & \quad \text{OAc} \\
\text{26\% yield over 3 steps} & \quad \text{cHex} \\
\end{align*}
\]


\[
\begin{align*}
\text{KHF} & \quad \text{THF} \\
\text{36\%, 98\%ee} & \quad \text{Ph} & \quad \text{CF}_3
\end{align*}
\]
Williamson ether synthesis is a popular strategy for installation of oxetane in Taxol.


Danishefsky (1996): Step 13 of 49

Wender (1997): Step 40 of 44

Baran (2020): Step 14 of ~20
Servin (1980): Epoxides can be opened with selenium lithium species to ring expand epoxides.

\[
\text{LiSePh} + \text{OCCl}_2 \xrightarrow{1. \text{THF/HMPT}} \text{H}_2\text{OCCl}_2 \xrightarrow{2. \text{Mel, NaI, DMF}} \text{C}_6\text{H}_{13}
\]

Okuma (1983): Sulfur ylides will ring expand epoxides to form oxetanes.

<table>
<thead>
<tr>
<th>R</th>
<th>ee% of Epoxide</th>
<th>%Yield of Oxetane</th>
<th>ee% of Oxetane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>96</td>
<td>74</td>
<td>99</td>
</tr>
<tr>
<td>2-Napthyl</td>
<td>96</td>
<td>62</td>
<td>99</td>
</tr>
<tr>
<td>4-ClPh</td>
<td>94</td>
<td>86</td>
<td>99</td>
</tr>
<tr>
<td>n-octyl</td>
<td>93</td>
<td>88</td>
<td>99</td>
</tr>
</tbody>
</table>

Danishfesky (2002): Used an epoxide displacement in racemic synthesis of Merrilactone A.
Fleet (1990): Showed that sugars could be used as enantiomERICally starting to diastereoselectively form oxetanes.
Fleet (1990): Showed that sugar functionalization could be applied in the synthesis of Oxetanocin A

1. NaOH, MeOH
2. H2 atm, Pd(OH)2
Cyclohexane

1. Cl2, CHCl3
2. Benzoyl Adenine
K2CO3
23% over 2 steps

Mixture of epimers (1:1.6 trans:cis C2/C3)

Rousseau (1999): Similar reaction was shown but with Bromonium.

\[
\text{R=Me, 63% yield, \text{>98:\<2}} \\
\text{R=Et, 90% yield, 82:18} \\
\text{R=i-Pr, 77% yield, 81:19}
\]

SYNTHESIS OF OXETANES

Pros:
- Allows for good control over diastereoselectivity and regioselectivity.
- Reaction conditions are scalable, and this reaction is commonly used on industrial scale.
- Method works well to make a variety of substituted oxetanes

Cons:
- Synthesis of substrates can be long
- Certain substitution patterns are limited
Paterno-Buchi Reaction

Paterno (1909): First example of reaction described.

\[
\begin{align*}
\text{Ph}^\text{O} + \text{C=C} &\xrightarrow{\text{hv}} \text{Photoadduct Products} \\
\text{Ph}^\text{O} + \text{C=C} &\neq \text{Ph}^\text{O} \\
\text{Ph}^\text{O} + \text{C=C} &\neq \text{Ph}^\text{O}
\end{align*}
\]

Could not differentiate constitutional isomers or stereoisomers

Buchi (1954): A rediscovered reaction found that 2 cycloadducts were formed.

General Mechanism for Paterno-Buchi Reaction

\[
\begin{align*}
\text{R}^\text{O} + \text{R} &\xrightarrow{n\to\pi^*} \text{R}^\text{O} \\
\text{R}^\text{O} + \text{R} &\neq \text{R}^\text{O} \\
\text{R}^\text{O} + \text{R} &\neq \text{R}^\text{O}
\end{align*}
\]

\[
\begin{align*}
\text{R}^\text{O} + \text{R} &\xrightarrow{\text{intersystem crossing}} \text{R}^\text{O} \\
\text{R}^\text{O} + \text{R} &\neq \text{R}^\text{O} \\
\text{R}^\text{O} + \text{R} &\neq \text{R}^\text{O}
\end{align*}
\]

\[
\begin{align*}
\text{R}^\text{O} + \text{R} &\xrightarrow{\text{n,}\pi^* \text{ singlet}} \text{R}^\text{O} \\
\text{R}^\text{O} + \text{R} &\neq \text{R}^\text{O} \\
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\end{align*}
\]

\[
\begin{align*}
\text{R}^\text{O} + \text{R} &\xrightarrow{\text{n,}\pi^* \text{ triplet}} \text{R}^\text{O} \\
\text{R}^\text{O} + \text{R} &\neq \text{R}^\text{O} \\
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\end{align*}
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\[
\begin{align*}
\text{R}^\text{O} + \text{R} &\xrightarrow{\text{R}^1 \text{R}^1} \text{R}^\text{O} \\
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\text{R}^\text{O} + \text{R} &\neq \text{R}^\text{O}
\end{align*}
\]
Multiple Mechanisms come into play depending on both the nature of the partners and solvent.

Eciplex mechanism occurs with electron poor alkenes.

PET mechanism happens with electron rich alkenes.
Site Selectivity for Paterno-Buchi Reaction:

Carbonyl Electronics:

\[
\text{RCHO} + \text{Rf} \xrightarrow{\text{hv}} \text{RCHO} + \text{Rf} \xrightarrow{\text{toluene, 52 °C}} \text{A} \quad \text{R} = \text{H, 45:55}
\]

\[
\text{RCHO} + \text{Rf} \xrightarrow{\text{hv}} \text{RCHO} + \text{Rf} \xrightarrow{\text{toluene, 52 °C}} \text{B} \quad \text{R} = \text{Ph}
\]

If triplet energy of carbonyl is lower can be more selective

Regioselectivity:

\[
\text{AcO} \quad \text{OAc} \quad \text{OTMS} \xrightarrow{\text{hv, benzene}} 56\%
\]

Changing the electronics/sterics of alkene can also make reaction more selective

Depends on which produces most stable diradical
Diastereoselectivity: In certain mechanism regimes can predict selectivity.

\[
\text{PhCO}_2\text{Et} + \text{Ph} = \text{EtO}_2\text{C-Ph} \quad \text{hv} \quad 70\% \quad \text{PhCO}_2\text{Et}
\]

Depends on the stability of the molecule's triplet state and spin-orbit coupling.

Endo vs. Exo Selectivity: Geometry of the diradical triplet

\[
\text{PhCO} = \text{R} \quad \text{hv} \quad \text{toluene} \quad 52 \degree C \quad \text{Ph} \quad \text{R}
\]

\[
\text{R=H, 212:1} \quad \text{R=Me, >49:1} \quad \text{R=CN, 3.7:1}
\]
Reaction in Flow: Reaction applied to flow chemistry can improve scalability.

<table>
<thead>
<tr>
<th>Method</th>
<th>Irr. Time (sec)</th>
<th>Conversion</th>
<th>Yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Batch</td>
<td>140</td>
<td>34</td>
<td>21</td>
</tr>
<tr>
<td>Flow</td>
<td>20</td>
<td>80</td>
<td>51</td>
</tr>
</tbody>
</table>

Applied to total Synthesis of racemic Oxetanocin A

1. O₃, CH₂Cl₂, -78 °C
2. Me₂S (10 equiv), -78 °C to 23 °C, 18 h
3. NaBH₄/Al₂O₃
4. Ac₂O, Py, DMAP

Oxetanocin A Inhibits HIV
Mikami (2011): Enantioselective Lewis Acid catalyzed addition to form oxetanes.

\[
\begin{align*}
\text{RO} & \overset{\text{Cat (10 mol%)}}{\text{Et}_2\text{O}} \rightarrow \text{CF}_3 & \text{CO}_2\text{Et} \\
\text{F}_3\text{C} & \text{CO}_2\text{Et} & \text{RO} & \text{R}^1 \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>R</th>
<th>R(^1)</th>
<th>Catalyst</th>
<th>D.R.</th>
<th>E.R.</th>
<th>Yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMS</td>
<td>H</td>
<td>A</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>TBS</td>
<td>H</td>
<td>A</td>
<td>82:18</td>
<td>96:4</td>
<td>38</td>
</tr>
<tr>
<td>TIPS</td>
<td>H</td>
<td>A</td>
<td>97:3</td>
<td>97:3</td>
<td>95</td>
</tr>
<tr>
<td>TIPS</td>
<td>Me</td>
<td>A</td>
<td>89:11</td>
<td>93:7 (Cis)</td>
<td>92</td>
</tr>
<tr>
<td>Ac</td>
<td>H</td>
<td>B</td>
<td>92:8</td>
<td>94:6</td>
<td>86</td>
</tr>
</tbody>
</table>

SYNTHESIS OF OXETANES

Pros:
- Allows for synthesis of oxetanes that would otherwise be hard to form by other methods
- Economical reactions

Cons:
- Lack of selectivity in site/regio and diastereoselectivity for certain substrates.
- Troublesome to scale up because of the light dependence
Cheap Oxetane Building Blocks

Carreira Synthesis of 3-Oxetanones:

\[
\begin{align*}
\text{HC(OMe)}_3 + \text{TsOH} & \rightarrow \text{MeO} \rightarrow \text{MeO} \\
1) \text{BuLi, TsCl} & \rightarrow \text{MeO} \rightarrow \text{MeO} \\
2) \text{NaH, 33% 3 steps} & \rightarrow \text{O} \\
\text{Montmorillonite K10} & \rightarrow \text{K10} \\
\text{62% yield} & \rightarrow \text{O}
\end{align*}
\]

Addition into Carbonyl:

- S-NH
  - t-Bu
  - Ph, 98%
- (ArBO)₃
  - [RhCl(cod)]₂ (2 mol%)
  - dppbenz (4 mol%)
  - NaOEt (1.2 equiv)
  - dioxane/EtOH (4:1), rt

- Ti(OEt)₄
  - THF, 60 °C

- RLi
  - DCM, -78 °C
  - MsCl, Et₃N
  - CH₃Cl, 55 °C
  - Et₃SiH, TFA
  - DCM, 0 °C to rt
MICHAEL ACCEPTOR VIA KETONE

3-Oxetanones can be made into a variety of Michael Acceptor by doing an olefination on the ketone.

Further Transformation: A lot of transformations can be done on these olefins.
Different nucleophiles have been shown to undergo displacement reactions.

Cross Coupling: Nickel has been shown to be effective at cross coupling oxetanes.
AstraZeneca: G-Protein coupled receptor (GPCR) parent carbamate suffered from non ideal aqueous solubility (24 μM)

Zhang (2015): Inhibitor of wild-type and Mutant ALK Kinase
SYNTHESIS OF OXETANES

Pros:
- Easy to install on molecules and allows for rapid installation on molecules.
- Relatively cheap building blocks.

Cons:
- Can be sensitive to certain conditions.
- Does not allow for stereochemistry on the oxetane.
Lewis Acid can activate oxetanes towards opening by nucleophiles.

<table>
<thead>
<tr>
<th>R</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>Lewis Acid</th>
<th>Yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>C₆H₁₁</td>
<td>H</td>
<td>H</td>
<td>Yb(OTf)₂</td>
<td>60</td>
</tr>
<tr>
<td>C₆H₁₁</td>
<td>Me</td>
<td>H</td>
<td>Me</td>
<td>Yb(OTf)₂</td>
<td>40</td>
</tr>
<tr>
<td>C₆H₁₁</td>
<td>Me</td>
<td>Me</td>
<td>H</td>
<td>TMSOTf</td>
<td>45</td>
</tr>
</tbody>
</table>

Organometallic reagents can also be used to ring open oxetanes.

<table>
<thead>
<tr>
<th>R</th>
<th>Yield(%)</th>
<th>R</th>
<th>Yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhMgBr</td>
<td>84</td>
<td>1-naphthyl-MgBr</td>
<td>80</td>
</tr>
<tr>
<td>CyMgBr</td>
<td>28</td>
<td>PhLi</td>
<td>85</td>
</tr>
<tr>
<td>i-PrMgCl</td>
<td>28</td>
<td>n-BuLi</td>
<td>28</td>
</tr>
</tbody>
</table>
Danishfesky (2002): Used Lewis acid ring opening of an oxetane as a key step.

Jacobsen (2020): This year published a paper using Lewis acid activation/nucleophile delivery.
• Oxetanes are an important moiety and have found uses in both medicinal chemistry and as a synthetic building block.

• Currently there are still few drugs on the market that contain an oxetane in them.

• Much work still needs to be done on the synthesis of these important moieties.

• Not a lot of enantioselective methods have been developed to synthesize oxetanes.
REVIEWS AND FURTHER READING


Spirocycles in Med Chem.-Chem Rev 2014, 114, 8257-8322


Paterno-Buchi Reaction-

Website: https://spirochem.com/catalog/oxetanes.html?limit=5&mode=list&p=5
(This is not me formally endorsing this website and I have not paid to do so.)