Ruthenium-Catalyzed Azide-Alkyne Cycloaddation: Scope and Mechanism


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Wipf Group Current Literature
Tingting Mo
June, 28, 2008
Huisgen 1,3-Dipolar Cycloaddation to Make 1,2,3-triazoles

Long reaction times
High temperatures
Formation of regioisomeric mixtures

\[
\begin{align*}
\text{N}_3 \quad \text{OH} \\
\text{N} \quad \text{N} \\
\text{OH}
\end{align*}
\]

\[
\text{Toluene, 32 h, reflux} \quad \text{52%}
\]


\[
\begin{align*}
\text{R'} \quad \text{C} = \text{O} \quad \text{R''} \\
\text{N}_3 \quad \text{rt, H}_2\text{O, 6-12 h}
\end{align*}
\]

\[
\begin{align*}
\text{R'} \quad \text{C} = \text{O} \quad \text{R''} + \text{R'} \quad \text{O} \quad \text{C} \quad \text{R''}
\end{align*}
\]

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<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkyne</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtO(\text{-}\text{C} = \text{O\text{-}Et})</td>
<td>EtO(\text{-}\text{C} = \text{C} - \text{Et})</td>
<td>81</td>
</tr>
<tr>
<td>2</td>
<td>H(\text{-}\text{C} = \text{O\text{-}Et})</td>
<td>EtO(\text{-}\text{C} = \text{C} - \text{Et})</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td>H(\text{-}\text{C} = \text{O\text{-}Me})</td>
<td>MeO(\text{-}\text{C} = \text{C} - \text{Et})</td>
<td>82</td>
</tr>
</tbody>
</table>

Li, Z.; Seo, T. S.; Ju, J. *Tetrahedron Let.* 2004, 45, 3143
Cu(I) Catalyzed 1,3-Dipolar Cycloaddation to Make 1,4 substituted 1,2,3-triazoles

Aqueous systems
Broad temperature range 0-160°C
Insensitive to pH (range from 4 to 12)
Functional group tolerance
Proceeds well in human plasma


Affording Peptidotriazoles of N-Substituted Histidine Analogs

Mechanism of Copper(I)-Catalyzed cycloaddtion of 1,4-Substituted 1,2,3-Triazoles

Proposed according to DFT calculation
Formation of copper(I) acetylide 2
Azide replacement to coordinate
Formation of copper(III) metallacycle 4
Reductive elimination
Proteolysis

Applications of Copper(I)-Catalyzed cycloaddition of 1,4-Substituted 1,2,3-Triazoles

Bioconjugation


Organic synthesis


Click Chemistry on Drug Discovery

Ru-catalyzed Cycloaddition to make 1,5-substituted triazoles

![Chemical structure](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>product</th>
<th>reaction time, h</th>
<th>yield, %</th>
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<tbody>
<tr>
<td>8</td>
<td>8a</td>
<td>2</td>
<td>89&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>9</td>
<td>9a</td>
<td>2</td>
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<td>10a</td>
<td>6</td>
<td>80&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td>11</td>
<td>11a</td>
<td>12</td>
<td>94&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

[Cp*RuCl] most effective catalyst

Aprotic Solvents: THF, PhH, Toluene

Temp range from ambient to 110°C

Not very sensitive to water and oxygen

Primary, secondary and aryl azides

Terminal and Internal alkynes

Good functional group tolerance


Mechanism of the Ru-Catalyzed Azide-Alkyne Cycloaddition

Product release

Displacement of spectator ligands

Reductive elimination

Regioselective oxidative coupling

L = bystander ligands or reactants

Michanistic Consideration

Participation of both terminal and internal alkynes in catalysis: ruthenium acetylides not involved

\[
R \equiv \text{RuL}_n
\]

\( \text{Cp}^* \text{RuCl}(\text{PPh}_3)_2, \ \text{Cp}^* \text{RuCl}(\text{COD}), \ \text{Cp}^* \text{RuCl}(\text{NBD}) \) and \( [\text{Cp}^* \text{RuCl}]_4 \) are competent catalysts, neutral \( [\text{Cp}^* \text{RuCl}] \) is the catalytically active species

\( [\text{Cp}^* \text{RuBr}] \) and \( [\text{Cp}^* \text{RuI}] \) complexes are significantly less active
the removal of the chloride with \( \text{Ag}^+ \) are devoid of the catalytic activity
chelating diphosphines deactivate the catalyst

The higher activity of \( \text{Cp}^* \) complex than \( \text{Cp} \) complex can be attributed to the lability of the spectator ligans in such system (facilitates ligand replacement to form 27), the more sterically demanding nature of the \( \text{Cp}^* \) ligand (facilitates the reductive elimination)

Regioselectivity of Addition with Internal Alknye: Directing Effect

Formation of a strong H-bond between the alcohol or amine and the chloride ligand on the ruthenium.


Hydroxy group, amino group and ether influence the regioselectivity through coordination to Ruthenium.


Tingting Mo @ Wipf Group
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7/3/2008
Regioselectivity of Addition with Internal Alkynes: Electronic Effect

<table>
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<th>procedure</th>
<th>yield, %</th>
<th>m.p., °C</th>
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<td><img src="image3" alt="image" /></td>
<td>B</td>
<td>79</td>
<td>155.5-156.5</td>
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The new bond in the intermediate 28 is formed between the more nucleophilic carbon of the alkyne.

Polarization of the ruthenacycle 53 has been postulated as one of the factors which favors the placement of an EWG at the β-carbon of the ruthenacycle.

Combination of these two factors produces the product with excellent control of regioselectivity.


DFT calculation

Much lower activation energy than uncatalyzed reaction
Cp* amplify the steric interaction to improve catalysis
Reductive elimination is the RDS

Azide coordinates via the nitrogen proximal to carbon (PCA vs PCD)
1,5-disubstituted over 1,4 (PCA vs PCB)

Summary

The first general method for generation of 1,5-disubstituted 1,2,3-triazoles through catalyzed 1,3-dipolar cycloaddition between azides and terminal alkynes

This ruthenium catalyzed process engages internal alkynes in catalysis, providing access to fully substituted 1,2,3-triazoles

Exploration of mechanism provides the basis and impetus by which new reactions may be discovered: other dipoles like nitrile oxides with alkynes?

Applications: Protein Prosthesis: 1,5-Disubstituted[1,2,3]triazoles as cis-Peptide Bond Surrogates