Ytterbium(III) Chloride: A Superior Reagent for the Synthesis of 4-Chloro-5, 6-Dihydro-2H-Pyran Derivatives via Cyclization of Epoxides and Homopropargyl Alcohols

TIRUKOVELA MANJULA\textsuperscript{1,2} and JEYANTHI ARASAN\textsuperscript{*}

\textsuperscript{1}Department of Chemistry, Satavahana University, Karimnagar-505002, (Telangana) India.
\textsuperscript{2}Department of Chemistry, Government Degree College, Luxettipet-504231, (Telangana) India.
\textsuperscript{*}Corresponding author E-mail: jeyanthi.arasan@gmail.com

http://dx.doi.org/10.13005/ojc/390433

(Received: June 09, 2023; Accepted: July 15, 2023)

ABSTRACT

Prins type cyclization reaction of epoxides and homopropargyl alcohols in the presence of Ytterbium trichloride results in high yields of the corresponding dihydropyran derivatives under mild conditions.

Keywords: Ytterbium trichloride, Dihydropyran, Homopropargyl alcohol and Epoxide.

INTRODUCTION

Dihydropyrans are six-membered oxygenated ring heterocycles that are important intermediates for the synthesis of various natural products and pharmaceutical agents.\textsuperscript{1,2} Among them, (+)-cacospiongonolide B, a marine natural product has been shown to have potent anti-inflammatory activity in diseases such as asthma, psoriasis and rheumatoid arthritis (Fig. 1).\textsuperscript{3} In addition, dihydropyrans are important intermediates for the synthesis of tetrahydropyrans and glycals, which in turn are important intermediates for the synthesis of carbohydrate compounds.\textsuperscript{4-12} Since dihydropyrans contain olefin functionality, they are also suitable for further functionalization such as epoxidation, dihydroxylation, and halogenation leading to the formation of multi-substituted ring systems.\textsuperscript{13-16} Prins cyclization between aldehydes and homopropargyl alcohols is a common method for the synthesis of dihydropyrans. However, the dihydropyrans can also be synthesized by the cyclization reaction between epoxides and homopropargyl alcohols and are the emerging method for dihydropyran synthesis.\textsuperscript{17-21} Since there are few methods for the cyclization of epoxides and homopropargyl alcohols in the literature, there is an opportunity to develop a better method with improved yield and reduced reaction time for dihydropyran synthesis. In particular, epoxides are more favorable starting...
materials compared to aldehydes because aldehydes undergo aerobic oxidation to form carboxylic acids.\textsuperscript{22} In recent years, Ytterbium trichloride has been shown to be a good Lewis acid for many organic reactions.\textsuperscript{23-25} In this study, we describe the improvement in terms of yield and reaction time reduction for the synthesis of dihydropyran derivatives from the cyclization reaction of epoxides and homopropargyl alcohol with ytterbium trichloride.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{image.png}
\caption{(+)-cacospiongonilolide B}
\end{figure}

MATERIALS AND METHODS

The chemicals used for these reactions were purchased from Sigma-Aldrich and used as received. All epoxides were prepared from the relevant olefins according to the methods described in the literature. For TLC, silica gel 60 F\textsubscript{254} coated on aluminium sheets was used and purchased from Merck. Silica gel with 60-120 meshes was used for column chromatography. \textsuperscript{1}HNMR and \textsuperscript{13}CNMR spectra were recorded on a Bruker 300-MHz NMR spectrometer using trimethylsilane as an internal standard on a $\delta$-scale of parts per million. Mass spectra were recorded using a Waters G2-XS QT of mass spectrometer. IR Spectra were recorded using the Nexus 670 Thermo Nicolet Fourier transform infrared spectrometer.

RESULTS AND DISCUSSION

The reaction was studied by treating a mixture of styrene oxide and 3-butyn-1-ol with ytterbium trichloride in anhydrous dichloromethane at room temperature under a nitrogen atmosphere. The mixture is stirred at room temperature for 30 min and the complete transformation of the products is found. After post-treatment, the crude product was separated by silica gel column chromatography, which separated the major product in 80% yield. The major product was determined as 3a from the spectral data and compared with the literature data.\textsuperscript{11} (Scheme 1).

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{image.png}
\caption{Scheme 1}
\end{figure}

The above result was encouraged us to explore the method on different combination of epoxides and homopropargyl alcohols. The reaction with all combinations gave corresponding 4-chloro dihydropyran derivatives in good yield in shorter reaction time. This demonstrates the wide applicability of this method for the synthesis of a variety of 4-chloro dihydropyrans using epoxides as starting materials (Table 1). However, slight variation in reaction time is observed with different combinations. It is observed that, reaction of homopropargyllic alcohols with 1,2-dihydronaphthalene oxide, stilbene oxide and methylenecyclohexane oxide took longer reaction time with low yield compared to styrene oxide. The variation in reaction time may possibly depending on steric effects and stability of carbonium ion after epoxide ring opening.

The expected reaction mechanism for this cyclization may possibly Ytterbium trichloride mediated ring opening of epoxide to form alkoxy carbonoum ion, which is after rearrangement nucleophilic addition with alcohol produces dihydropyran carbonium species. The dihydropyran carbonium species is further undergoes nucleophilic addition with chloride nucleophile originated from Ytterbium trichloride to give 4-Chloro-dihydropyran derivative (Scheme 2).
Table 1: YbCl₃ mediated Prins-types reaction between epoxides and homopropargylic alcohols

<table>
<thead>
<tr>
<th>Entry</th>
<th>Epoxide</th>
<th>Alcohol</th>
<th>Productsa</th>
<th>Yield(%)b</th>
<th>Time(min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Epoxide 1a" /></td>
<td><img src="image" alt="Alcohol 2a" /></td>
<td><img src="image" alt="Product 3a" /></td>
<td>80</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Epoxide 1b" /></td>
<td><img src="image" alt="Alcohol 2a" /></td>
<td><img src="image" alt="Product 3b" /></td>
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<td>40</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Epoxide 1c" /></td>
<td><img src="image" alt="Alcohol 2a" /></td>
<td><img src="image" alt="Product 3c" /></td>
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<td>45</td>
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<tr>
<td>4</td>
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<td><img src="image" alt="Alcohol 2a" /></td>
<td><img src="image" alt="Product 3d" /></td>
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<td><img src="image" alt="Product 3f" /></td>
<td>62</td>
<td>60</td>
</tr>
</tbody>
</table>

a: All the products were characterized by NMR, IR and mass spectroscopy.
b: Yields are after isolation by column chromatography.

CONCLUSION

In conclusion, we investigated a simple method for the synthesis of dihydropyran derivatives using Ytterbium trichloride. The method has the characteristics of short reaction time, clean reaction and high yield, and is a good alternative to the existing dihydropyran synthesis method.

REFERENCES


