Novel and Efficient Method for the Synthesis of 4-Chloro-5, 6-dihydro Pyran Derivatives using Lewis Acidic Chloroaluminate Ionic Liquids

N. MARUTHI RAJU, K. RAJASEKHAR*, J. MOSES BABU and B. VENKATESWARA RAO

1Ragas Pharmaceuticals Private Limited (OPC), IDA Cherlapally, Hyderabad, 500051, India.
2Custom Pharmaceutical Services, Dr Reddy’s Laboratories Limited, Bollaram Road, Miyapur, Hyderabad, 500049, India.
3Department of Organic Chemistry, Foods, Drugs and Water, Andhra University, Visakhapatnam, 530003, India.
*Corresponding author E-mail: koorella.rajasekhar@gmail.com

http://dx.doi.org/10.13005/ojc/320459
(Received: May 30, 2016; Accepted: August 07, 2016)

ABSTRACT

The reaction of aldehydes/ketones with homopropargylic alcohols in the presence of 1-n-Butyl-3-methylimidazolium chloroaluminate [bmim]Cl·AlCl3 (N = 0.56-0.67) ionic liquid generates the 4-chloro-5,6-dihydro-2H-pyran derivatives in excellent yield and in short reaction times.

Keywords: 1-n-Butyl-3-methylimidazolium chloroaluminate, Aldehydes, Ketones, Homopropargylic alcohols, 4-chloro-5,6-dihydro-2H-pyran derivatives.

INTRODUCTION

Substituted dihydropyranos are the key intermediates for the synthesis of many natural products. Many natural products like Swinholides, Lauimalides, Ambruticins and Jerangolids contains dihydropyran skeleton. Moreover, the olefin function is having synthetic value for further functionalization in obtaining polysubstituted tetrahydropyrans. The coupling of alkynes to aldehydes is an important transformation in organic synthesis. The direct synthesis of dihydropyranos by the coupling of alkynes to aldehydes provides a useful synthetic method for the synthesis of dihydropyranos. Although other methods were reported, Consequent methods that successfully minimize the use of toxic and volatile organic solvents are the focus of much attention. In this respect, ionic liquids are attracting growing interest as alternative reaction media for various chemical and biotransformations. In particular, chloroaluminate ionic liquids are having Lewis acidity, which can be varied over a wide range, and their intrinsic ability to solvate a variety of substances. These ionic liquids are easily prepared from AlCl3 and 1-butyl-3-methylimidazolium chloride. These chloroaluminate ionic liquids have...
the advantage of being liquid at room temperature over a considerable composition range of apparent mol fraction of AlCl₃ (N = 0.30-0.67) and also have negligible vapour pressures, making them useful alternatives to conventional molecular organic solvents for various synthetically useful transformations. Furthermore, chloroaluminate ionic liquids play dual roles both as Lewis acid catalyst and as solvent.

RESULTS AND DISCUSSION

In view of the emerging importance of the use of ionic liquids as cost-effective and environmentally benign catalysts, we herein describe a simple and efficient protocol for the cyclization reactions of aldehydes and homopropargylic alcohols to produce dihydropyran using 1-n-Butyl-3-methylimidazolium chloroaluminate [bmim]Cl·AlCl₃ (N = 0.56-0.67) ionic liquid under mild reaction conditions (Scheme I).

For instance treatment of benzaldehyde with 3-butyln-1-ol in [bmim]Cl·AlCl₃ ionic liquid afforded dihydropyran in 70% yield. The reaction is very clean and complete within 30 sec. at room temperature. In a similar manner, various aldehydes and ketones underwent smooth cyclization reaction with homopropargylic alcohols to give the corresponding dihydropyran derivatives in high yields. In all cases, the reactions proceeded readily at room temperature with high efficiency. The reaction worked well both with aromatic, aliphatic aldehydes and ketones. When symmetrical ketones like cyclohexanone and 3-pentanone reacted with 2c and 2d the formation of single product was observed. But when applied to aldehydes the formation of a mixture of the isomers were observed by TLC and 1H NMR spectrum. This is due to the formation of the diastereomers in the later case (Scheme II).

The mechanism for the formation of dihydropyran can be explained by the attack of homopropargylic alcohol and cyclised to the dihydropyran carbenium ion which is further attacked by the chloride nucleophile to form the 4-Chloro dihydropran derivative (Scheme III).
Table I - Lewis Acidic Chloroaluminate Ionic Liquid promoted synthesis of 4-chloro-5,6-dihydro pyran derivatives

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde/Ketone</th>
<th>Alcohol</th>
<th>Products [a]</th>
<th>Yield (%)[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{PhCHO}) 1a</td>
<td>(\text{PhOH}) 2a</td>
<td>(\text{3a} )</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>(\text{FCHO}) 1b</td>
<td>(\text{PhOH}) 2a</td>
<td>(\text{3b} )</td>
<td>73</td>
</tr>
<tr>
<td>3</td>
<td>(\text{CHO}) 1c</td>
<td>(\text{PhOH}) 2b</td>
<td>(\text{3c} )</td>
<td>68</td>
</tr>
<tr>
<td>4</td>
<td>(\text{CHO}) 1d</td>
<td>(\text{PhOH}) 2a</td>
<td>(\text{3d} )</td>
<td>75</td>
</tr>
<tr>
<td>5</td>
<td>(\text{CHO}) 1d</td>
<td>(\text{PhOH}) 2a</td>
<td>(\text{3e} )</td>
<td>66</td>
</tr>
<tr>
<td>6</td>
<td>(\text{CHO}) 1e</td>
<td>(\text{PhOH}) 2a</td>
<td>(\text{3f} )</td>
<td>70</td>
</tr>
<tr>
<td>7</td>
<td>(\text{CHO}) 1f</td>
<td>(\text{PhOH}) 2c</td>
<td>(\text{3g} )</td>
<td>68</td>
</tr>
<tr>
<td>8</td>
<td>(\text{CHO}) 1g</td>
<td>(\text{PhOH}) 2d</td>
<td>(\text{3h} )</td>
<td>72</td>
</tr>
<tr>
<td>9</td>
<td>(\text{CHO}) 1h</td>
<td>(\text{PhOH}) 2d</td>
<td>(\text{3i} )</td>
<td>68</td>
</tr>
</tbody>
</table>

\[a\]All the products were characterized by \(^1\text{H} \text{NMR} \) and mass spectroscopy and compared with previously reported data.

\[b\]Yields are isolated after column chromatography.

\[\text{CONCLUSION}\]

In summary, we have described a green protocol for the preparation of dihydropyran derivatives through cyclization reaction of aldehydes/ketones with homopropargylic alcohols using 1-n-Butyl-3-methylimidazolium chloroaluminate ionic liquid system. The attractive features of this process are the mild reaction conditions, eco-friendly reagent, short reaction times and cleaner reactions with good yields, which makes it a useful process for the synthesis of dihydropyran core structure.
Experimental Section

Chloro Aluminate Ionic liquids were prepared as described previously8.

General Procedure

To a mixture of benzaldehyde (500 mg, 4.71 mmol) and 3-butyn-1-ol (330 mg, 4.71 mmol) was added 1-n-Butyl-3-methylimidazolium chloroaluminate (2 mL) at room temperature. The mixture was stirred for 30 sec. and the reaction mass was quenched with icecold water and extracted with diethyl ether (10-15 mL). The combined organic layers were dried over anhydrous Na₂SO₄, concentrated in vacuo and purified by column chromatography on silica gel (Merck, 60-120 mesh, ethyl acetate/hexane, 2.0-8.0) to afford dihydropyran 3a. The products were characterized by IR, NMR and mass spectroscopy. All the products 3b-i were prepared by the same procedure.

ACKNOWLEDGEMENTS

NMR thanks Dr Reddy’s Laboratories for permitting the research work.

REFERENCES