Magnesium–Cadmium Chloride, a Bimetallic Catalyst System for the Allylation of Aldehydes with Allyl Bromide: An Efficient Protocol for the Synthesis of Homoallylic Alcohols

A. Venkat Narsaiah,*a A. Ramesh Reddy,a Y. Gopala Rao,a E. Vijay Kumar,b R. S. Prakasham,b Basi V. Subba Reddy,a Jhillu S. Yadav

a Organic Chemistry Division, Indian Institute of Chemical Technology, Hyderabad 500 007, India
Fax +91(40)27160387; E-mail: vnakkirala2001@yahoo.com
b Bioengineering and Environmental Centre, Indian Institute of Chemical Technology, Hyderabad 500 007, India

Received 23 June 2008; revised 2 July 2008

SYNTHESIS 2008, No. 21, pp 3461–3464
Advanced online publication: 16.10.2008
DOI: 10.1055/s-0028-1093170; Art ID: Z14508SS
© Georg Thieme Verlag Stuttgart · New York

Abstract: A simple and efficient procedure for the allylation of aldehydes has been developed using the magnesium–cadmium chloride reagent system. This bimetallic catalytic system works well in a tetrahydrofuran–water solvent medium. A variety of aldehydes undergo smooth nucleophilic addition with allyl bromide to afford the corresponding homoallylic alcohols in excellent yields. All the reactions were performed at room temperature.

Key words: aldehydes, homoallylic alcohols, bimetallic catalyst, allyl bromide

The development of new methods for the preparation of homoallylic alcohols is an important area in organic synthesis for carbon–carbon bond formation. The allylation is generally carried out by treating the carbonyl compounds with a variety of allylating agents like allyl halides, allylstannanes, allyltrimethylsilane, allyl alcohols, and allylic phosphates. Among these allylating agents, allyl bromide is frequently used due to its commercial availability at low cost. Since homoallylic alcohols are extremely important as crucial intermediates for the synthesis of various biologically active compounds, like nonpeptide neurokinin NK1 receptor antagonists L-733,060 and CP-99,990 (cytotoxicity against KB and P-388 cancer cell lines) and also antifungal leucascandrolide A (Figure 1). Hence, the synthesis of homoallylic alcohols has become more important and, as a consequence, several methods have been developed for allylation using allylorganometallic reagents derived from a number of metallic elements under anhydrous conditions, owing to rapid protonolysis. However, many of these catalysts are expensive, moisture sensitive, difficult to handle, and involve the use of strongly acidic conditions, which limit their use in the synthesis of complex molecules containing acid sensitive functionalities. One of the most straightforward synthetic procedures involves the nucleophilic addition of allyl bromide to a carbonyl moiety in the presence of a bimetallic system under aqueous conditions. In recent years, there has been increasing demand for organic reactions that can be performed in aqueous media.

Thus, there is scope for further improvements towards milder reaction conditions and better yields. Lewis acids, especially metals or transition metal complexes, have been extensively utilized to catalyze or promote allylations in the recent years. Water tolerant Lewis acids have been developed as catalysts for the allylation of aldehydes, but they are rather expensive. As part of our ongoing program to develop novel synthetic methodologies, herein we report, a new reagent system, magnesium–cadmium chloride, for the allylation of aldehydes in aqueous medium; there are no previous reports on this catalytic system for this reaction.

Accordingly, an equimolar amount of benzaldehyde (1a) and allyl bromide (2) were treated with the reagent system containing magnesium metal–cadmium chloride (1.5:1.0

Figure 1

(+)-L-733,060
(+)-CP-99,994

Leucascandrolide A
equiv) to give 1-phenylbut-3-en-1-ol (3a) in 93% yield (Table 1, entry 1). The reaction proceeds efficiently at room temperature in the tetrahydrofuran–water (4:1) solvent system. In a similar manner, 4-methoxybenzaldehyde (1b) was treated with allyl bromide in the presence of the same reagent system; the reaction went to completion giving 3b within 3.5 hours (Table 1, entry 2). In the case of 2-furfuraldehyde (1c), the allylation to give 3c took 3.0 hours (Table 1, entry 3). Encouraged by these results, we turned our attention to various aldehydes, such as as aliphatic and aromatic systems containing both electron-donating groups as well as electron-withdrawing groups, \( \alpha, \beta \)-unsaturated, heterocyclic, and alicyclic systems. Acid sensitive aldehydes such as 2-furfuraldehyde (1c), 2-phenylacetaldehyde (1g), and thiophene-2-carboxaldehyde (1n) (Table 1, entries 3, 7, 13) were efficiently converted into the corresponding homoallylic alcohols 3c, g, n in excellent yields. In the case of \( \alpha, \beta \)-unsaturated aldehyde 1d (Table 1, entry 4), the allylation reaction proceeded smoothly to give 3d without the formation of the 1,4-addition product.

In a similar manner, 3,4,5-trimethoxybenzaldehydes (1k) was reacted efficiently to give the corresponding homoallylic alcohol 3k in excellent yield (Table 1, entry 11); no bis-allylated products were observed. The aliphatic systems such as octanal (1f), butanal (1i), and cyclohexanecarboxaldehyde (1l) were treated with allyl bromide in presence of magnesium–cadmium chloride to afford the corresponding homoallylic alcohols 3f, i, l in very good yields (Table 1, entries 6, 9, 12). The reactions were very clean and no side products were observed. All the reactions were carried out at room temperature in tetrahydrofuran–water and completed in three to six hours. Generally, the yields were high ranging from 80–95% (Table 1). The aliphatic aldehydes and electron-deficient aromatic aldehydes such as 4-nitrobenzaldehyde (1e) required a little more time for completion of the reaction. Mechanistically, the reaction proceeds via a bimetallic process in which magnesium reacts with Cd(II) to generate active Cd(0). Thus, in situ formed Cd(0) reacts rapidly with allyl bromide to furnish allylcadmium bromide, which in turn reacts with aldehyde 1 to provide homoallylic alcohol 3 as depicted in Scheme 1.

The proposed mechanism in Scheme 1 shows that the allylmagnesium reagent is formed through the oxidative addition of an allyl bromide to zero-valent cadmium generated in situ by reduction of cadmium (II) chloride with metallic magnesium. Magnesium–cadmium chloride activates the carbonyl carbon so that the reaction takes place rapidly. This action makes the allyl bromide more nucleophilic and at the same time more susceptible to decomposition.

An alternative mechanism is as follows; magnesium initially reacts with allyl bromide to give allylmagnesium bromide. Thus, in situ formed allylmagnesium bromide reacts simultaneously with cadmium chloride to generate an allylcadmium species that in turn reacts with aldehyde 1 to furnish the desired homoallyl alcohol 3 (Scheme 2).

The reaction was studied using various amounts of magnesium and cadmium chloride in the reaction of benzaldehyde (1a) with allyl bromide (2) and the results are presented in the Table 2. The allylation of benzaldehyde (1a) with allyl bromide (2) was studied using various reagent systems and the results are presented in Table 3.

### Table 1  Magnesium–Cadmium Chloride Bimetallic Catalyst System for Allylation of Aldehydes with Allyl Bromide

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>3a</td>
<td>4.0</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>4-MeOC₆H₄</td>
<td>3b</td>
<td>3.5</td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td>2-furyl</td>
<td>3c</td>
<td>3.0</td>
<td>94</td>
</tr>
<tr>
<td>4</td>
<td>(E)-CH=CHPh</td>
<td>3d</td>
<td>4.0</td>
<td>83</td>
</tr>
<tr>
<td>5</td>
<td>4-O₂NC₆H₄</td>
<td>3e</td>
<td>6.0</td>
<td>86</td>
</tr>
<tr>
<td>6</td>
<td>(CH₃)₃Me</td>
<td>3f</td>
<td>5.5</td>
<td>85</td>
</tr>
<tr>
<td>7</td>
<td>CH₃CH₂Ph</td>
<td>3g</td>
<td>6.0</td>
<td>87</td>
</tr>
<tr>
<td>8</td>
<td>2-naphthyl</td>
<td>3h</td>
<td>4.5</td>
<td>90</td>
</tr>
<tr>
<td>9</td>
<td>Pr</td>
<td>3i</td>
<td>5.0</td>
<td>80</td>
</tr>
<tr>
<td>10</td>
<td>4-MeC₆H₄</td>
<td>3j</td>
<td>3.5</td>
<td>92</td>
</tr>
<tr>
<td>11</td>
<td>3,4,5-(MeO)₃C₆H₂</td>
<td>3k</td>
<td>3.0</td>
<td>5</td>
</tr>
<tr>
<td>12</td>
<td>Cy</td>
<td>3l</td>
<td>5.5</td>
<td>86</td>
</tr>
<tr>
<td>13</td>
<td>Bn</td>
<td>3m</td>
<td>4.5</td>
<td>90</td>
</tr>
<tr>
<td>14</td>
<td>2-thienyl</td>
<td>3n</td>
<td>3.5</td>
<td>92</td>
</tr>
</tbody>
</table>

* All the products were characterized by spectroscopy data.
* Yields were isolated and unoptimized.
To a stirred mixture of Mg turnings (1.5 equiv) and CdCl₂ (1.0 equiv) in THF–H₂O (8:2, 10 mL) was added allyl bromide (2.0 equiv) in THF–H₂O (8:2, 10 mL) was added allyl bromide (2.0 equiv) and the mixture was stirred for 20 min. The aldehyde residue obtained was added EtOAc (10 mL) and H₂O (10 mL) and the mixture was stirred well and extracted with EtOAc. The organic layer was washed with brine and dried (Na₂SO₄). The EtOAc was removed under reduced pressure and the obtained crude homoallylic alcohol products were purified by column chromatography (silica gel 60–120 mesh). The pure products were confirmed by their 1H NMR, IR, and MS data.

1-Phenylbut-3-en-1-ol (3a)
Colorless oil.
IR (neat): 3416, 3081, 2965, 2853, 1647, 1508, 1459, 1347, 1261, 1138, 1055, 948, 867, 739 cm⁻¹.
1H NMR (CDCl₃): δ = 2.18 (br s, 1 H), 2.37–2.43 (m, 2 H), 4.63 (t, J = 6.0 Hz, 1 H), 5.05–5.20 (m, 2 H), 5.35–5.70 (m, 1 H), 7.27–7.40 (m, 5 H).
MS (EI): m/z (%) = 148 (M⁺ 12), 130 (10), 115 (15), 107 (100), 91 (20), 79 (54), 63 (25), 51 (33).

1-(2-Furyl)but-3-en-1-ol (3c)
Colorless oil.
1H NMR (CDCl₃): δ = 1.98 (br s, 1 H), 6.58 (d, J = 16.0 Hz, 1 H), 7.18–7.38 (m, 5 H).

References

(c) Yamamoto, Y.; Asao, N. Chem. Rev. 1993, 93, 2207.

