Notes

Bifunctional organocatalysts for the synthesis of jasminaldehyde and their derivatives

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L-Proline in the presence of benzoic acid is found to be an effective catalytic system for the cross-aldol condensation of benzaldehyde with 1-heptanal under solvent free condition amongst the several amino acids screened for this reaction. Under the optimized reaction conditions, the desired product (e.g. jasminaldehyde) is formed up to 96\% selectivity in one hour using the desired arylaldehyde:1-alkanaldehyde ratio as low as 2:1 under controlled addition of 1-alkanaldehyde.

Keywords: Catalysis, Organocatalysts, Bifunctional organocatalysts, Cross-aldol condensation, Jasminaldehyde, Heptanal

Organocatalysis is a powerful tool to perform highly selective organic transformations including C-C bond forming reactions, e.g. aldol-type reactions\textsuperscript{1-4}. In this direction, the use of naturally occurring compounds particularly amino acids and their derivatives have been the first choice as catalysts for a variety of organic transformations\textsuperscript{5,6}. Among these, proline has shown remarkable activity to catalyze diverse organic transformations like C-C bond forming reactions including aldol condensation\textsuperscript{7-14}. Sodium or potassium hydroxide are generally used as catalysts for aldol condensation reaction\textsuperscript{15,16}. These corrosive hydroxides cause damage to reactors and also pose environment issues during post-reaction work-up. To mitigate these, efforts have been made to use solid bases\textsuperscript{17,18}, solid acid\textsuperscript{19,25} or solid materials having both acidic and basic sites\textsuperscript{26-29}. However, preference towards the use of organocatalyst is gaining importance vis-à-vis inorganic catalysts due to the risk of metal contamination and related toxicity issues in the product\textsuperscript{30-33}. Coming to the specific aldol reaction, cross-aldol condensation of benzaldehyde with 1-heptanal is of immense commercial value as its product has an aroma akin to jasmine flowers.

However, a major challenge in this reaction is to avoid or minimize the self-condensation of 1-heptanal, which contributes to the formation of byproducts such as 2-\textit{n}-pentyl-2-nonenal and related polymers. To some extent the formation of byproducts have been minimized by slow addition of 1-heptanal to the reaction mixture containing catalyst and benzaldehyde\textsuperscript{26,27}. In this backdrop, the development of environmentally benign, metal and solvent-free aldol reaction protocols with high product yield and selectivity is highly desirable. Herein, we wish to report a practical and solvent-free protocol for the synthesis of jasminaldehyde by the cross-aldol condensation of 1-heptanal with benzaldehyde using amino acids as catalyst (Scheme 1). Among the amino acids screened, L-Proline (I) in combination with benzoic acid was found to catalyze this reaction to give jasminaldehyde in >96\% yield with 100\% conversion with respect to 1-heptanal.

Experimental

Benzaldehyde, 1-heptanal and amino acids were procured from Sigma-Aldrich and used as received. All the solvents were purified before use.\textsuperscript{34} Flash chromatography was used with 100-200 mesh silica gel as stationary phase for the product purification. The aldol condensation was carried out by taking freshly distilled benzaldehyde (15.8 mmol) along with 40 mol\% of the amino acid as a catalyst, 40 mol\% of \textit{n}-decane as an internal standard in a three-necked round bottom flask. The reaction was carried out under inert atmosphere at a desired temperature to minimize the oxidation of aldehydes used in the reaction. In order to improve the selectivity for the cross-aldol product and maximize atom efficiency of the reaction, 1-alkanaldehydes (7.9 mmol) were added to the reaction mixture under a controlled condition (1130 µl/h) using a syringe pump. The reaction mixture was cooled down to room temperature after...
completion of the reaction (checked by GC). All the reactions were done in triplicate to ensure the reproducibility of the reaction. Conversion and selectivity were calculated as follows:

%Conv. = \frac{\text{Moles of 1-heptanal reacted}}{\text{Moles of 1-heptanal fed}} \times 100

%Sel. = \frac{\text{Moles of jasminaldehyde}}{\text{Moles of (jasminaldehyde+2-n-pentyl-2-nonenal)}} \times 100

Results and discussion

Initially, we used the conventionally employed reaction conditions for the condensation of benzaldehyde (2 equiv.) with slow addition of 1-heptanal (1 equiv.) over a period of 60 minutes at 125 °C under nitrogen atmosphere in the presence of L-proline (1) (40 mol% wrt 1-heptanal). Under these conditions, it resulted in 83% conversion (with respect to 1-heptanal) with jasminaldehyde selectivity of 66% (Table 1; entry 1). Here we would like to mention the results were consistent while using freshly distilled benzaldehyde. However on using undistilled benzaldehyde, the selectivity of jasminaldehyde was better, but the consistency of the results varied with different batches. Invariably we found that the benzaldehyde stocks had varying degree of benzoic acid formed due to aerobic oxidation under the storage condition. For subsequent aldol condensation reaction, with freshly distilled benzaldehyde or benzaldehyde stored under strict oxygen-free condition and 1-heptanal and benzoic acid as a co-catalyst (40 mol%) along with L-proline (1) (40 mol%) under the above mentioned reaction conditions, significant improvement in both conversion (99%) and jasminaldehyde selectivity (96%) were observed (Table 1; entry 2).

Under the optimized experimental conditions (Table 1; entry 2), we explored different amino acids L-phenyl alanine (2), L-cysteine (3), L-alanine (4), L-tyrosine (5), L-histidine (6), and L-glutamic acid (7) (Table 1; entries 3-8) as catalysts. In all the cases we could achieve 96-99% conversion (with respect to 1-heptanal). However L-proline (1) remained the best catalyst to give good selectivity (~96%) for the product jasminaldehyde (Table 1; entry 2). Considering that amino acid contains –COOH as well as –NH₂ functional groups, we were interested to know the role of these groups during the catalytic process. Accordingly, we replaced –COOH group of the catalyst 1 and 2 with –OH group and used L-prolinol (8), (Table 1; entry 9) and L-phenyl alaninol (9), (Table 1; entry 10). With the use of catalysts 8 and 9, the conversion was ~99% but product selectivity was relatively low, i.e., 84% and 76% respectively. On the other hand, blocking of amino group as in the case of L-tosylated phenyl alanine (10) (Table 1; entry 11) and N-methyl-L-Proline (11) (Table 1; entry 12) there was drastic reduction in conversion (17 and 23% respectively) as well as selectivity (18 and 13% respectively). Further, with the use of N-Boc-L-prolinol (12) (Table 1; entry 13), where both –COOH and –NH group are missing, only self-condensed product was obtained (conversion 77%) with no formation of the desired product, jasminaldehyde. Therefore, it can be concluded that both amino and carboxyl groups are essential for the system to work in order to achieve higher jasminaldehyde conversion. Further, among the various amino acids used, L-proline (1) was found to be the best catalyst under the reaction condition used (Table 1, entry 2).

It is well established that in catalytic reactions the selectivity and conversions are greatly influenced by
Table 1—Screening of organocatalysts (1-12) for cross-aldol condensation reaction. [React. cond.: Temp.: 125 °C; heptanal: 7.9 mmol; benzaldehyde: 15.8 mmol; 40 mol% catalyst, 40 mol% benzoic acid as a co-catalyst; time: 60 min]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Conv. (%)</th>
<th>Sel. (%)</th>
<th>Entry</th>
<th>Catalyst</th>
<th>Conv. (%)</th>
<th>Sel. (%)</th>
</tr>
</thead>
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<td>1</td>
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<td>83</td>
<td>66</td>
<td>2</td>
<td>(1)</td>
<td>99</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>(2)</td>
<td>99</td>
<td>81</td>
<td>4</td>
<td>(3)</td>
<td>99</td>
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<td>96</td>
<td>64</td>
<td>6</td>
<td>(5)</td>
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<td>(6)</td>
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<td>99</td>
<td>84</td>
<td>10</td>
<td>(9)</td>
<td>99</td>
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</tr>
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<td>17</td>
<td>18</td>
<td>12</td>
<td>(11)</td>
<td>23</td>
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</tr>
<tr>
<td>13</td>
<td>(12)</td>
<td>77</td>
<td>-</td>
<td></td>
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</table>

Table 2—Effect of solvent on the selectivity to jasminaldehyde. [React. cond.: heptanal: 7.9 mmol; benzaldehyde: 15.8 mmol; 40 mol% L-proline (1), 40 mol% benzoic acid as a co-catalyst; time: 60 min]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvents</th>
<th>Conv. (%)</th>
<th>Jasminaldehyde (%)</th>
<th>2-Pentyl-non-2-enal (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Water</td>
<td>80</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>Ethanol</td>
<td>83</td>
<td>59</td>
<td>41</td>
</tr>
<tr>
<td>3</td>
<td>Dimethyl carbonate</td>
<td>99</td>
<td>87</td>
<td>13</td>
</tr>
<tr>
<td>4</td>
<td>Propylene carbonate</td>
<td>79</td>
<td>85</td>
<td>15</td>
</tr>
<tr>
<td>5</td>
<td>Toluene</td>
<td>99</td>
<td>98</td>
<td>02</td>
</tr>
<tr>
<td>6</td>
<td>Without solvent</td>
<td>99</td>
<td>96</td>
<td>04</td>
</tr>
</tbody>
</table>

Therefore, the reaction was carried out in different polar and non-polar solvents such as water, ethanol, dimethyl carbonate, propylene carbonate and toluene (Table 2) for the condensation of benzaldehyde with 1-heptanal under reflux condition with L-proline (1) as catalyst, keeping other reaction parameters the same as per entry 2 of Table 1. It is evident from the Table 2 that protic solvents (water and ethanol) tend to form more of the 1-heptanal self-condensation products (Table 2; entry 1 and 2). Among the polar aprotic (green) solvents used (Table 2; entries 3 and 4), dimethyl carbonate (Table 2; entry 3) was found to give better jasminaldehyde yield with 87% selectivity, whereas the selectivity was significantly improved when toluene was used as a solvent (Table 2; entry 5). Noticeably, the selectivity of the desired product obtained under the solvent-free condition (96%; Table 2; entry 6) was closer to toluene (Table 2; entry 5). Considering the
environment benign nature, the neat reaction condition was used for further optimization studies.

The effect of catalyst loading on the selectivity of jasminaldehyde was studied in the range of 5-50 mol% (Table 3; entries 1-6). The conversion and selectivity of jasminaldehyde was lower in 5 mol% catalyst loading (Table 3, entry 1) and gradually increased up to 40 mol% catalyst loading (Table 3, entry 5). Beyond 40% catalyst loading, (50 mol%; Table 3; entry 6) the results were more or less unchanged, hence 40 mol% catalyst loading was taken as optimum amount.

According to the available literature, temperature has a great influence on the selectivity as well as the conversion for jasminaldehyde. So, the effect of reaction temperature on selectivity of jasminaldehyde was studied in the temperature range of 60–140 °C at 1-heptanal:benzaldehyde molar ratio 1:2 and 40 mol% of L-Proline (1) as catalyst, with benzoic acid (40 mol%) as co-catalyst. It is clear from the Table 3 (Table 3; entries 7-9), that by increasing the temperature, the conversion as well as the selectivity of the jasminaldehyde increased. On further increase of the temperature above the 125 °C (Table 3; entry 10), a decrease in the selectivity was observed without effecting the conversion. So, 125 °C (Table 3; entries 5), was the optimum temperature for the reaction both in terms of selectivity as well as the conversion of the jasminaldehyde.

As mentioned earlier that benzoic acid as co-catalyst has shown remarkable effect in the improvement of conversion as well as jasminaldehyde selectivity, it was prudent to explore different co-catalysts for this reaction (Table 4). For this we took a few organic acids and bases as co-catalysts along with L-proline (1) as catalyst under the reaction conditions given in entry 2 Table 1. When acids like acetic acid and trifluoroacetic acid were used as co-catalysts (Table 4; entries 3 and 4) the conversion and selectivity were not greatly affected. However, with a base like triethylamine (Table 4; entry 5), both conversion and selectivity dropped significantly. Here it is also important to note that co-catalyst alone (without L-proline (1)) was not able to catalyze this reaction (Table 4; entry 6).

After achieving optimum reaction condition (as per Table 4, entry 2) for this reaction, we looked for efficacy of the organocatalyst L-proline (1) for various 1-alkanaldehydes (Table 5). The catalytic efficacy of the organocatalyst was increased with increasing chain length of the 1-alkanaldehydes (Table 5, entries 1-4) and maximum selectivity (98%) of the cross-aldol product was observed with 1-octanal (Table 5, entry 2). We have also tested the efficacy of L-proline (1) for the representative aryl aldehyde bearing electron donating/withdrawing group with 1-heptanal to synthesize substituted jasminaldehydes (Table 6). In each case the cross-aldol product selectivity was excellent irrespective of the nature of the substituents (Table 6, entries 1-3).
It has been reported earlier that a controlled addition of 1-heptanal into the reaction mixture containing benzaldehyde is key to minimize the self-condensation of 1-heptanal. Accordingly, we meticulously monitored the reaction on GC with controlled addition of 1-heptanal (113 µl in 6 min intervals) (Table 7). We found that in 36 min at which time 4.74 mmol (676 µl) of 1-heptanal has gone into the reaction mixture, the selectivity for the jasminaldehyde remained 99% (Table 7, entries 1-6). Further addition of 1-heptanal till 6.32 mmol (902 µl), the selectivity for jasminaldehyde was 98% (Table 7; entries 7 and 8). There was a further drop of 1% in jasminaldehyde selectivity on subsequent addition of 1-heptanal (entries 9 and 10). In conclusion, if addition of 1-heptanal is done in a controlled manner and careful monitoring of the reaction is carried out, the reaction can be stopped at a desired level of jasminaldehyde selectivity to make the entire process economically viable.

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Base on the earlier reports and our experimental observations, a plausible mechanism operating in our catalytic protocol for the production of jasminaldehyde is proposed in Scheme 2. According to Scheme 2, the co-catalyst benzoic acid activates the carbonyl group of benzaldehyde, which in turn condenses with the –NH of proline to form the iminium ion intermediate (I). 1-Heptanal, which is in equilibrium with its enol form, will attack the iminium carbon of intermediate (I), to
generate the intermediate (II). Finally, intramolecular proton transfers in the intermediate (II) leads to the formation of the desired product, jasminaldehyde, and regenerates the catalyst for next cycle.

In conclusion, we have reported a highly selective synthesis of cross-aldol product (up to 96% in the case of jasminaldehyde) using L-proline (I) as an organocatalyst in the presence of benzoic acid as co-catalyst under solvent free reaction condition. The study suggests that the aldol condensation proceeds via iminium ion formed in situ by the condensation of benzaldehyde with L-proline (I). Based on this, a probable mechanism of the aldol reaction is proposed. A controlled addition of 1-heptanal to benzaldehyde is a key factor to high jasminaldehyde selectivity by minimizing self-condensation products of 1-heptanal.

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References