



## Highly Efficient, Fast, Room Temperature Synthesis of Tetrahydrobenzo[*b*]pyrans Catalyzed by Zn[(*L*)-proline]<sub>2</sub> as Green and Reusable Heterogeneous Catalyst Under Dry Grinding

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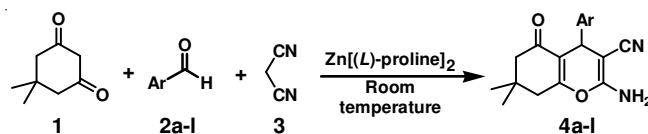
An easy method for the synthesis of tetrahydrobenzo[*b*]pyrans through a one-pot three-component reaction of dimedone, aryl aldehydes and malononitrile under mild reaction conditions using Zn[(*L*)-proline]<sub>2</sub> as catalyst is described. The products were obtained in short reaction times with excellent yields at room temperature under dry grinding. The catalyst could be recycled and reused for several times without noticeably decreasing the catalytic activity. It is believed that this applicability of Zn[(*L*)-proline]<sub>2</sub> with mentioned advantages makes present method superior over all previous reported methods to the synthesis of tetrahydrobenzo[*b*]pyrans.

**Key Words:** Tetrahydrobenzo[*b*]pyrans, Zn[(*L*)-proline]<sub>2</sub>, Heterogeneous catalysis, Dry grinding.

### INTRODUCTION

Multi-component reactions (MCRs) have emerged as efficient and powerful tool in modern synthetic organic chemistry because the synthesis of complex organic molecules from simple and readily available substrates can be achieved in a very fast and efficient manner without the isolation of any intermediate<sup>1-4</sup>. Bigenilli<sup>5</sup>, Ugi<sup>6</sup>, Passerini<sup>7</sup> and Mannich<sup>8</sup> reactions are some examples of multi-component reactions. Nevertheless, great efforts have been and still are being made to find new multi-component reactions and improve the already known multi-component reactions. 4H-pyrans have attracted strong interest to their useful biological and pharmacological properties such as anticoagulant, spasmolytic, diuretic, anticancer and antianaphylactin characteristics<sup>9,10</sup>. These compounds constitute the structural unit of a series of natural products<sup>11</sup>. 4H-benzo[*b*]pyrans are also an important class of compounds which have received considerable attention in recent years due to their wide range of biological activities<sup>12</sup>. Compounds with these ring systems have diverse pharmacological activities such as anticoagulant, anticancer, spasmolytic, diuretic, antianaphylactin, *etc.*<sup>9,13</sup>. A number of 2-amino-tetrahydropyrans are useful as photoactive materials<sup>14</sup>. Tetrahydrobenzo[*b*]pyrans are generally synthesized *via* one-pot three-component reaction of an aryl aldehyde, malononitrile and dimedone in the presence of several catalysts such as Na<sub>2</sub>SeO<sub>4</sub><sup>15</sup>, Caro's acid-SiO<sub>2</sub><sup>16</sup>, trisodium citrate<sup>17</sup>, PPA-SiO<sub>2</sub><sup>18</sup>, KF-basic alumina under ultrasound irradiation<sup>19</sup>, ZnO-β-zeolite<sup>20</sup> and NaBr<sup>21</sup>. However, many of these procedures

are not entirely satisfactory and suffer from long reaction time, expensive reagents, low yields of products or tedious work up. These problems prompted us towards further investigation in search for a new catalyst, which will carry out the synthesis of tetrahydrobenzo[*b*]pyrans under simpler experimental set up and eco-friendly conditions. Recently, Darbre's group have showed that Zn-amino acids complexes such as Zn[(*L*)-proline]<sub>2</sub> are efficient and enantioselective catalysts for the direct aldol reaction<sup>22</sup>. There are also a few reports that show Zn[(*L*)-proline]<sub>2</sub> can act as an efficient recyclable and inexpensive Lewis acid catalyst for the preparation of heterocyclic compounds such as Hantzsch 1,4-dihydropyridine derivatives<sup>23</sup>, 1,5-Benzodiazepines under microwave conditions<sup>24</sup>, 1,2-disubstituted benzimidazoles<sup>25</sup> and quinoxaline derivatives<sup>26</sup>. However, there is still lot of scope to further explore the catalyst for its application in forming various heterocycle rings. In continuation of our efforts to develop novel synthetic routes using reusable catalysts in organic reactions<sup>27-29</sup> and due to our interest in the synthesis of heterocyclic compounds<sup>30-34</sup>, herein we wish to report an efficient and solvent-free synthesis of tetrahydrobenzo[*b*]pyrans by cyclocondensation reaction of dimedone, aryl aldehydes and malononitrile using Zn[(*L*)-proline]<sub>2</sub> as a Lewis acid catalyst (**Scheme-I**).



**Scheme-I:** Synthesis of tetrahydrobenzo[*b*]pyrans catalyzed by Zn[(*L*)-proline]<sub>2</sub>

## EXPERIMENTAL

All chemicals were available commercially and used without additional purification. The catalyst was synthesized according to the literature<sup>22</sup>. Melting points were recorded on an electrothermal type 9100 melting point apparatus. The IR spectra were obtained using a 4300 Shimadzu spectrophotometer as KBr disks. The <sup>1</sup>H NMR (500 MHz) spectra were recorded with a Bruker DRX500 spectrometers.

**General procedure for the synthesis of tetrahydrobenzo[*b*]pyrans 4a-1 using Zn[(*L*)-proline]<sub>2</sub>:** A mixture of dimedone **1** (1 mmol), an aromatic aldehyde **2a-1** (1 mmol), malononitrile **3** (1 mmol) and Zn[(*L*)-proline]<sub>2</sub> (0.059 g, 0.2 mmol) was ground in a mortar with pestle at room temperature for a few min and then chloroform was added. The catalyst was insoluble in chloroform and could therefore be recycled by a simple filtration. The filtrate was heated *in vacuo* to evaporate the solvent. The solid residue was collected and recrystallized from ethanol to give compounds **4a-1** in 94 -> 99 % yields.

**Recycling and reusing of the catalyst:** The recyclability and reusability of the catalyst in the model reaction was checked. The catalyst is insoluble in chloroform and could therefore be recycled as the filtrate. The separated catalyst was washed with chloroform, dried at 60 °C under vacuum for 1 h and reused in another reaction without appreciable reduction in the catalytic activity.

## RESULTS AND DISCUSSION

Solvent-free conditions are especially important for providing an eco-friendly system. One advantage of solvent-free reactions, in comparison to the reaction in molecular solvents, is that the compounds formed are often sufficiently pure to circumvent extensive purification using chromatography. Hence solvent-free heterogeneous catalysis has received much attention among the researchers and has forced them to seek solvent-free heterogeneous reactions. Due to the increasing demand in modern organic processes for avoiding expensive purification, we decided to investigate the efficiency of Zn[(*L*)-proline]<sub>2</sub> as a heterogeneous catalyst in the synthesis of tetrahydrobenzo[*b*]pyrans under solvent-free conditions. The catalyst, Zn[(*L*)-proline]<sub>2</sub>, was prepared according to the literature procedure<sup>22</sup>. At first, the synthesis of compound **4a** was selected as a model reaction to optimize the reaction conditions. The reaction was carried out by magnetically stirring an equimolar mixture of dimedone (1 mmol), benzaldehyde

(1 mmol) and malononitrile (1 mmol) in the presence of Zn[(*L*)-proline]<sub>2</sub> under solvent-free conditions (Table-1). Only a trace product was obtained in the absence of the catalyst even at 100 °C (entry 1), but it is noted that the synthesis of compound **4a** was efficiently catalyzed by Zn[(*L*)-proline]<sub>2</sub> at room temperature leading to 85-93 % yields of the product in 10-15 min (entries 2-5). The best catalytic activity of Zn[(*L*)-proline]<sub>2</sub> was optimized to be 20 mol % (entry 3) and any excess of the catalyst, beyond this proportion, did not show any further increase in the conversion and yield (entries 4-5). For comparison, the reaction was also carried out in different solvents including EtOH, CH<sub>2</sub>Cl<sub>2</sub> and CHCl<sub>3</sub> in the presence of 20 mol % of the catalyst at reflux temperature. As shown in Table-1, in comparison with neat conditions, the reaction times were longer and the yields were lower (entries 6-8). We then tried to prepare compound **4a** in better conditions in terms of yields and reaction times. Interestingly, dry grinding a mixture of dimedone (1 mmol), benzaldehyde (1 mmol) and malononitrile (1 mmol) in the presence of Zn[(*L*)-proline]<sub>2</sub> (0.2 mmol) and at room temperature furnished exclusively the product **4a** with more than 99 % yield during 3 min (entry 10). Therefore, all subsequent reactions were carried out with grinding at room temperature in the presence of 20 mol % of Zn[(*L*)-proline]<sub>2</sub> under solvent-free conditions to obtain higher yields of the products in shorter times.

In order to evaluate the general character of this model reaction, we included a range of other aromatic aldehydes in the reaction of dimedone and malononitrile under the optimized reaction conditions. In all cases, the expected products were obtained with 94 -> 99 % yields in very short reaction times. The results are given in Table-2. As shown, aromatic aldehydes with substituents carrying either electron-donating or electron withdrawing groups reacted successfully and gave the products in high yields. The results also revealed that electron-donating or -withdrawing groups on the aromatic ring did not seem to affect the reaction significantly either in the yield of the product or the rate of the reaction.

Compared to other methodologies reported so far for the synthesis of tetrahydrobenzo[*b*]pyrans, the present methodology offers suitable conditions with respect to reaction times and yields. Some of the results are summarized in Table-3.

Reusability of a catalyst is a very important parameter before recommending any catalyst for industrial-scale use. Therefore, in this work, the reusability of Zn[(*L*)-proline]<sub>2</sub> in model reaction was also investigated. After the completion of

TABLE-1  
OPTIMIZING THE REACTION CONDITIONS<sup>a</sup>

Entry	Zn[( <i>L</i> )-proline] <sub>2</sub> (mol %)	Solvent	T (°C)	Time (min)	Yield (%) <sup>b</sup>
1	None	Solvent-free	100	60	Trace
2	10	Solvent-free	Room temperature (stirring)	20	85
3	20	Solvent-free	Room temperature (stirring)	10	93
4	25	Solvent-free	Room temperature (stirring)	10	93
5	30	Solvent-free	Room temperature (stirring)	10	92
6	20	EtOH	Reflux	15	88
7	20	CH <sub>2</sub> Cl <sub>2</sub>	Reflux	20	68
8	20	CHCl <sub>3</sub>	Reflux	20	75
9	10	Solvent-free	Room temperature (grinding)	5	91
10	20	Solvent-free	Room temperature (grinding)	3	> 99
11	25	Solvent-free	Room temperature (grinding)	3	> 99

<sup>a</sup>Dimedone (1 mmol), benzaldehyde (1 mmol) and malononitrile (1 mmol); <sup>b</sup>Isolated yields.

TABLE-2  
SYNTHESIS OF TETRAHYDROBENZO[b]PYRANS **4a-l** USING Zn[(L)-proline]<sub>2</sub> (0.059 g, 0.2 mmol) AS CATALYST<sup>a</sup>

Entry	Ar	Product <sup>b</sup>	Time (min)	Yield (%) <sup>c</sup>	m.p. (°C)	Lit. m.p. (°C) [ref.]
1	C <sub>6</sub> H <sub>5</sub>	<b>4a</b>	3	> 99	228-230	230-232 [16]
2	4-MeC <sub>6</sub> H <sub>4</sub>	<b>4b</b>	3	> 99	217-218	218-220 [16]
3	3-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	<b>4c</b>	4	95	207-209	205-208 [17]
4	4-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	<b>4d</b>	4	94	179-180	182-184 [18]
5	4-ClC <sub>6</sub> H <sub>4</sub>	<b>4e</b>	4	94	214-216	215-217 [21]
6	2-ClC <sub>6</sub> H <sub>4</sub>	<b>4f</b>	4	97	202-204	205-207 [17]
7	4-MeOC <sub>6</sub> H <sub>4</sub>	<b>4g</b>	3	98	196-198	199-201 [21]
8	4-FC <sub>6</sub> H <sub>4</sub>	<b>4h</b>	2	> 99	199-200	200 [16]
9	4-BrC <sub>6</sub> H <sub>4</sub>	<b>4i</b>	3	98	201-202	200-203 [16]
10	4-HOC <sub>6</sub> H <sub>4</sub>	<b>4j</b>	4	96	207-208	209-211 [18]
11	4-Me <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	<b>4k</b>	4	95	213-215	212-214 [17]
12	3-ClC <sub>6</sub> H <sub>4</sub>	<b>4l</b>	3	97	223-224	223-225 [16]

<sup>a</sup>Dimedone (1 mmol), aryl aldehyde (1 mmol), malononitrile (1 mmol), and Zn[(L)-proline]<sub>2</sub> (0.2 mmol) under dry grinding at room temperature.

<sup>b</sup>All the products were characterized by IR and <sup>1</sup>H NMR spectral data and comparison of their melting points with those of authentic samples.

<sup>c</sup>Isolated yields

TABLE-3  
COMPARISON OF EFFICIENCY OF VARIOUS CATALYSTS IN SYNTHESIS OF TETRAHYDROBENZO[b]PYRANS

Catalyst	Conditions	Time	Yield (%)	Ref.
NaBr	MW; 70-80 °C	10-15 min	85-95	21
PPA-SiO <sub>2</sub>	H <sub>2</sub> O; reflux	8-15 min	77-93	18
Na <sub>2</sub> SeO <sub>4</sub>	EtOH-H <sub>2</sub> O; reflux	0.5-3.0 h	85-98	15
Caro's acid-SiO <sub>2</sub>	EtOH-H <sub>2</sub> O; reflux	15-20 min	92-95	16
ZnO-β-Zeolite	EtOH; reflux	35-52 min	86-95	20
Trisodium citrate	EtOH-H <sub>2</sub> O; reflux	5-120 min	80-96	17
Zn[(L)-proline] <sub>2</sub>	Dry grinding; room temperature	2-4 min	94->99	Present work

the reaction, the catalyst was recovered according to the procedure mentioned in experimental section and reused for a similar reaction. The catalyst could be used at least three times with only slight reduction in the catalytic activity (> 99 for 1st use; 97 % for 2nd use; 96 % for 3rd use).

## Conclusion

In conclusion, we have developed a fast and high-yielding method for the synthesis of tetrahydrobenzo[b]pyrans via a one-pot three-component reaction of dimedone, aryl aldehydes and malononitrile using Zn[(L)-proline]<sub>2</sub> as catalyst under dry grinding at room temperature. Very excellent yields, very short reaction times, simple operation and easy work-up and absence of any volatile and hazardous organic solvents are some advantages of this procedure. Furthermore, the catalyst can be recycled after a simple work-up and reused without substantial reduction in the catalytic activity.

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