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Introduction

Ionic liquids have attracted a great deal of attention scientists over the last decade due to their particular properties [1] and applications in organic synthesis [2]. Recent trends in MAOS using ILs as solvent, co-solvent and/or catalyst are reported by several researchers across the globe [3] since their use is believed to be a green approach in synthesis [4]. Their ionic nature allows a very effective coupling under microwave energy [5].

Microwave-assisted organic synthesis becomes a significant tool for accelerating drug discovery and development processes [6]. This process produces a sufficient amount of internal heat, which results in the overall heating of the reaction mixture [7]. It has the ability to couple directly with the reacting molecules which are responsible for the rapid rise in the temperature [8]. The rapid growth of microwave-assisted organic synthesis was started in 1986 by Gedye [9]. Many reviews are available on MAOS [10]. Thus, the microwave irradiation technique offers a simple, clean, fast, and efficient synthesis method [11].

Tetrahydrobenzo[b]pyrans have recently attracted attention as an important class of heterocyclic scaffold in the field of pharmaceutical drugs [12]. These compounds found to be active against various microorganisms and reported as anti-coagulant, spasmolytic, anticancer, anti-anaphylactic and diuretics agents [13]. They can also use as cognitive enhancers in the treatment of neurodegenerative Alzheimer's disease, in amyotrophic lateral sclerosis, in Parkinson's disease, in AIDS associated dementia and Down's syndrome as well as for the treatment of schizophrenia and myoclonus, and Huntington's disease [14]. Tetrahydrobenzo[b]pyran nucleus is known to be a structural scaffold of several natural products [15]. They can be converted into pharmacologically important calcium antagonist dihydropyridine systems [16]. In addition to their biological importance, some 2-amino-4H-pyrans have been widely used as photoactive materials [17].

Due to the wide applications in various fields, the synthesis of heterocyclic tetrahydrobenzo[b]pyran derivatives received great importance in medicinal chemistry and organic synthesis. Several strategies for the synthesis of these compounds have been reported, varied from one-pot to multi-step approaches [18]. The simplest method of synthesis involved one-pot, three-component condensation of malononitrile, aldehyde and dimedone at different conditions using various catalysts such as Na$_2$SeO$_4$ [19], hexadecyl dimethyl benzyl ammonium bromide [20], NaBr [21], tetra-methyl ammonium hydroxide [22], TBAB [23], starch [24], KF-alumina [25], imidazole [26], and p-dodecylbenzene sulfonic acid [27a] etc., all these reported methods have certain advantages and disadvantages. Owing to the synthetic utility of ionic liquids [27b, 27c, 27d], in present work, we explore the catalytic activity of [EMIM][OH] ionic liquid for the synthesis of tetrahydrobenzo[b]pyran derivatives under microwave irradiation.
Experimental

Materials and methods

All the chemicals were purchased from spectrochem and SD fine chemicals, and used without further purification. Progress of the reaction was monitored by thin layer chromatography (TLC). The melting point of products was recorded in capillaries open at one end and was uncorrected. $^1$H NMR spectra were recorded on 400 MHz FT-NMR spectrometer in DMSO-$d_6$ as a solvent and chemical shift values are recorded in units $\delta$ (ppm) relative to tetramethylsilane (Me$_4$Si) as an internal standard. IR spectra were scanned on PerkinElmer FT-IR spectrophotometer 65 using KBr discs. The microwave irradiation was carried out in a scientific microwave oven (CATA-4R model No. QW-99, 2450 MHz frequency, at the power 140-700 watt).

General procedure for the synthesis of tetrahydrobenzo[b]pyrans

A mixture of aromatic aldehyde (1 mmol), dimedone (1 mmol), malononitrile (1 mmol), [EMIM][OH] (1 mL) and ethanol (1 mL) was mixed properly with a glass rod and the content was irradiated in a scientific microwave oven (CATA-4R model No. QW-99, India makes) at 210 watt periodically after 10 sec each. The progress of the reaction was monitored by TLC in ethyl acetate: hexane (1:4). After completion of the reaction, the mixture was cooled to room temperature and poured on 5 mL ice cold water. The separated solid was filtered and washed with water several times. The residue was dried and recrystallized from ethanol to afford corresponding tetrahydrobenzo[b]pyrans. The products were confirmed by comparisons with authentic samples, IR, $^1$H NMR, melting points.

2-amino-3-cyano-5,6,7,8-tetrahydro-7,7-dimethyl-4-(4-hydroxy-3-methoxyphenyl)-5-oxo-4H-benzopyran

(Entry 3, Table 1), mp 225–227 °C, IR (KBr) ($\nu_{\text{max}}$/ cm$^{-1}$): 3390 (NH$_2$), 3306, 3214, 2193 (CN) and 1679 (C=O). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.74 (s, 1H, OH), 6.51-6.54 (m, 3H, ArH), 6.65 (s, 2H, NH$_2$), 4.09 (s, 1H, CH), 3.73 (s, 3H, OCH$_3$), 2.43 (s, 2H, CH$_2$), 2.13–2.22 (m, 2H, CH$_2$), 1.05 (s, 3H, CH$_3$), 1.07 (s, 3H, CH$_3$).

2-amino-3-cyano-5,6,7,8-tetrahydro-7,7-dimethyl-4-(3,4-dimethoxyphenyl)-5-oxo-4H benzopyran

(Entry 4, Table 1), mp 164–166 °C, IR (KBr) ($\nu_{\text{max}}$/ cm$^{-1}$): 3404 (NH$_2$), 2955 (C-H), 2192 (CN), 1679 (C=O), 1656 (C=C) and 1603 (C=C). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 6.86-6.88 (d, 1H, Ar-H), 6.69-6.70
(d, 1H, Ar-H), 6.64-6.67 (dd, 1H, Ar-H), 3.72 (d, 6H, (OCH₃)₂), 6.94 (s, 2H, NH₂), 4.13 (s, 1H), 2.50 (s, 2H), 2.13 (d, 1H, H), 2.09 (d, 1H), 1.06 (s, 3H, CH₃), 0.99 (s, 3H, CH₃).

Table 1. Microwave assisted, ionic liquid mediated synthesis of tetrahydrobenzo[b]pyrans

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehydes</th>
<th>Products</th>
<th>Time (sec)</th>
<th>Yield%</th>
<th>M.p. (°C)</th>
<th>Observed</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="CHO" /></td>
<td><img src="image2" alt="products" /></td>
<td>90</td>
<td>85</td>
<td>227-228</td>
<td>229-231</td>
<td>[28]</td>
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<tr>
<td>2</td>
<td><img src="image3" alt="CHO" /></td>
<td><img src="image4" alt="products" /></td>
<td>30</td>
<td>92</td>
<td>204-205</td>
<td>206-207</td>
<td>[29]</td>
</tr>
<tr>
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<td><img src="image5" alt="CHO" /></td>
<td><img src="image6" alt="products" /></td>
<td>120</td>
<td>88</td>
<td>225-227</td>
<td>228-230</td>
<td>[30]</td>
</tr>
<tr>
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<td><img src="image7" alt="CHO" /></td>
<td><img src="image8" alt="products" /></td>
<td>120</td>
<td>84</td>
<td>164-166</td>
<td>170-172</td>
<td>[31]</td>
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<tr>
<td>5</td>
<td><img src="image9" alt="CHO" /></td>
<td><img src="image10" alt="products" /></td>
<td>45</td>
<td>90</td>
<td>248-249</td>
<td>250-252</td>
<td>[28]</td>
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</tbody>
</table>
6

\[
\begin{align*}
&\text{CHO} & & \text{F} \\
& & & \text{NH}_2 \\
& & & \text{CN} \\
\end{align*}
\]

50 88 236-238 240-242 [32]

7

\[
\begin{align*}
&\text{CHO} & & \text{Cl} \\
& & & \text{NH}_2 \\
& & & \text{CN} \\
\end{align*}
\]

60 92 215-216 217-218 [30]

8

\[
\begin{align*}
&\text{CHO} & & \text{NO}_2 \\
& & & \text{NH}_2 \\
& & & \text{CN} \\
\end{align*}
\]

60 84 181-183 180-182 [20]

9

\[
\begin{align*}
&\text{CHO} & & \text{OH} \\
& & & \text{NH}_2 \\
& & & \text{CN} \\
\end{align*}
\]

90 88 235-237 236-238 [20]

10

\[
\begin{align*}
&\text{CHO} & & \text{OH} \\
& & & \text{NH}_2 \\
& & & \text{CN} \\
\end{align*}
\]

60 90 206-208 205-207 [23]

11

\[
\begin{align*}
&\text{CHO} & & \text{OCH}_3 \\
& & & \text{NH}_2 \\
& & & \text{CN} \\
\end{align*}
\]

90 87 202-204 201-203 [23]
Results and Discussion

Initially, a model reaction was carried out using 4-chlorobenzaldehyde at different reaction conditions (as mentioned in Table 2 and Scheme 1).

It was found that the reaction without catalyst and solvent did not show any progress until 30 min, whereas, in absence of catalyst the reaction on microwave irradiation in the scientific microwave oven (CATA-4R model No. QW-99, India makes) was completed within 8 to 10 min. Ionic liquid when used as catalyst and solvent along with microwave irradiation, surprisingly the reaction was completed just within 30 s.

Table 2. Reaction of 4-chlorobenzaldehyde, dimeredone, and malononitrile at different reaction conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Reaction conditions</th>
<th>Time</th>
<th>Yield (%)</th>
</tr>
</thead>
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<td>RT, stirring</td>
<td>30 min</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>No catalyst</td>
<td>EtOH, MW, 210 watt</td>
<td>8 min</td>
<td>80</td>
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<tr>
<td>3</td>
<td>[EMIM][OH]</td>
<td>EtOH, MW, 140 watt</td>
<td>30 sec</td>
<td>92</td>
</tr>
</tbody>
</table>

Scheme 1. [EMIM][OH] catalyzed synthesis of tetrahydrobenzopyrans

The use of ionic liquid [EMIM][OH] under microwave irradiation was found to be much time faster offering an excellent yield of products. Therefore, we decided to use this green protocol in combination with ionic liquid [EMIM][OH].
Under these optimized conditions, ionic liquid [EMIM][OH] worked very efficiently as a catalyst as well as the solvent system. Benzaldehyde having electron withdrawing substituents gave products in short reaction time as compared to the other aldehydes which do not have an electron withdrawing substituent. The products were obtained in excellent yield in a shorter time (Table 1).

Conclusions

We have efficiently carried out ionic liquid [EMIM][OH] mediated environment benign synthesis of tetrahydrobenzo[b]pyran derivatives utilizing microwave irradiation in excellent yield. This protocol of ionic liquid along with microwave radiations showed salient features such as clean reaction profiles, simple experimental, work-up procedures, high conversions, and short reaction time. Therefore, the proposed protocol was found to be a superior method over many existing synthetic methods.

Acknowledgments

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Disclosure Statement

No potential conflict of interest was reported by the authors.

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