Facile Ionic Liquids-Promoted One-Pot Synthesis of Polyhydroquinoline Derivatives under Solvent Free Conditions

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Abstract: An efficient synthesis of polyhydroquinoline derivatives were reported via four-component coupling reactions of aldehydes, dimedone, ethyl acetoacetate and ammonium acetate in the presence of a catalytic amount of ionic liquid under solvent free conditions. In the meantime, the catalytic effect of different ionic liquids on the reaction has also been investigated.

Key words: ionic liquids, catalyze, one-pot synthesis, polyhydroquinoline derivatives

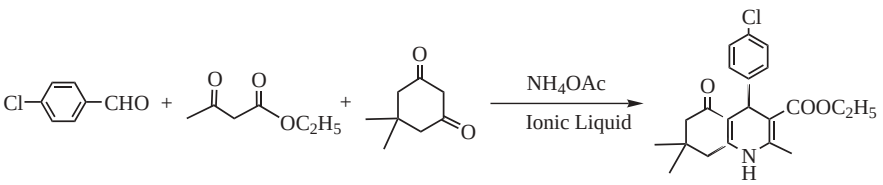
In recent years, much attention has been directed towards the syntheses of 1,4-dihydro pyridyl compounds due to the fact that 1,4-dihydro pyridyl compounds possess a variety of biological activities.[1–6] For example, 1,4-dihydro pyridyl compounds as the chain-cutting agent of factor IV channel[1–4] can cure the disordered heart ratio.[5,6] Relatively speaking, 1,4-dihydro pyridine derivatives combining single ring have been mostly reported.

In view of the importance of polyhydroquinoline derivatives, many classical methods for the synthesis of polyhydroquinoline derivatives were reported[7–12] by conventional heating and refluxing approaches in the presence of organic solvent. These methods, however, involve long reaction time, harsh reaction conditions, the use of a large quantity of organic solvent and unsatisfactory yields. Therefore, improvements in such syntheses have been sought continuously. More recently, Tu et al. reported the preparation of polyhydroquinoline derivatives under microwave irradiation.[13,14]

Owing to the great potential of ionic liquids as an environmentally friendly media for catalytic processes, much attention currently has been focused on organic reactions catalyzed by ionic liquids, and several reactions catalyzed by ionic liquids have been reported with good results,[15–20] which offered some new clues that using ionic liquids as catalysts for those traditionally reactions may not only be possible but also practical and even highly efficient. To our knowledge, so far there is no report on this reaction catalyzed by ionic liquids under solvent free conditions.

In past reports, our group described asymmetric Mannich-type reactions[21] and the syntheses of bis(indolyl)methanes[22] utilizing ionic liquids as a new reaction media, and good results have been achieved. In continuation of our work to apply ionic liquids to organic reactions in the context of green and economical chemistry, herein, we would like to report a facile synthesis of polyhydroquinoline derivatives in the presence of a catalytic amount of ionic liquid under solvent free conditions, as shown in Scheme 1.

In our initial research, 4-chlorobenzaldehyde was selected as a representative aldehyde in order to optimize the reaction conditions. As can be seen from Table 1, it was found that the reaction in the presence of a catalytic amount of ionic liquid needs shorter reaction time than that without any catalyst at room temperature (Table 1, entries 1 and 2). But when the reaction was investigated at 90 °C, the reaction catalyzed by ionic liquid [hmim]BF_4 was completed with higher yield and in shorter reaction time (Table 1, entries 3 and 4). Obviously, the temperature and the catalyst have important effect on the reaction. So the best condition was that the reaction was catalyzed by ionic liquid [hmim]BF_4 at 90 °C.



Scheme 1

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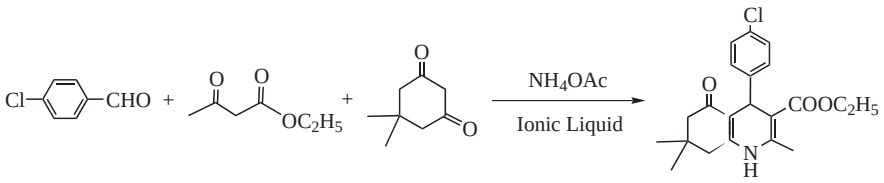
Table 1 The Selection of the Reaction Conditions[a]



Entry	Temperature (°C)	Ionic liquid	Time (min)	Yield (%)[b]
1	25	–	140	76
2	25	$[hmim]BF_4$	90	78
3	90	–	16	81
4	90	$[hmim]BF_4$	8	95

[a] All reactions were run in 4-chlorobenzaldehyde–ethyl acetoacetate–dimedone–ammonium acetate = 1:1:1:1.5 (mmol) at 80–90 °C under solvent free conditions.
[b] Isolated yields

Using the best conditions reported in Table 1(entry 4), we continued to investigate the reaction at the temperature of 90 °C using seven different ionic liquids, i.e. butylmethylimidazolium tetrafluoro borate ($[bmim]BF_4$), hexylmethylimidazolium tetrafluoroborate ($[hmim]BF_4$), octylmethyl imidazolium tetrafluoroborate ($[omim]BF_4$), nonylmethylimidazolium tetrafluoroborate ($[nmim]BF_4$), decylmethylimidazolium tetrafluoroborate ($[dmim]BF_4$), hexylmethylimidazolium hexafluorophosphate ($[hmim]PF_6$), and hexylmethylimidazolium bromide ([hmim]Br), has been investigated. All the results are listed in Table 2. In ionic liquids such as $[hmim]BF_4$, $[dmim]BF_4$, $[hmim]PF_6$, and [hmim]Br, the desired product was obtained in satisfactory yields.

Table 2 Synthesis of 4-(*p*-Chlorobenzyl)-3-ethoxyl Carbonyl-1,4,5,6,7,8-hexahydro-5-oxo-2,7,7-trimethyl Quinoline Catalyzed by Various Ionic Liquids under Solvent-Free Conditions[a]

Entry	Ionic liquid	Time (min)	Yield (%)[b]
1	$[bmim]BF_4$	7	83
2	$[hmim]BF_4$	8	95
3	$[omim]BF_4$	15	91
4	$[nmim]BF_4$	6	86
5	$[dmim]BF_4$	10	96
6	$[hmim]PF_6$	10	95
7	[hmim]Br	12	96

[a] All reactions were run in 4-chlorobenzaldehyde–ethyl acetoacetate–dimedone–ammonium acetate = 1:1:1:1.5 (mmol) at 80–90 °C under solvent free conditions.
[b] Isolated yields

Considering the reaction time and the yield, ionic liquid $[hmim]BF_4$ was selected as the optimum catalyst for this reaction to promote the synthesis of polyhydroquinoline derivatives (Table 2, entry 2). Encouraged by these results, we then continued to study the reaction using various aldehydes in the presence of a catalytic amount of ionic liquid $[hmim]BF_4$. The results were summaized in Table 3 indicating that both aliphatic and aromatic aldehydes underwent smooth reaction with dimedone, ammonium acetate and ethyl acetoacetate to give high yields of products (Table 3).

Clearly, the effect of the nature of the substituents on the aromatic ring showed no obvious effect on this conversion, because they were obtained in excellent yields; aliphatic aldehydes such as heptaldehyde also afforded good yields of product in 18 minutes. In addition, the structure of **2d** was further confirmed by single crystal X-ray crystallography (Figure 1).

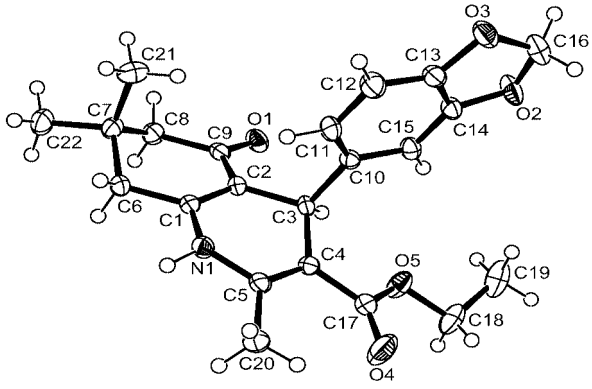


Figure 1 The X-ray crystallography of **2d**.[24]

Table 3 Synthesis of Polyhydroquinoline Derivatives with Various Aldehydes Catalyzed by Ionic Liquid [hmim]BF_4 under Solvent-Free Conditions

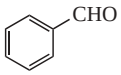
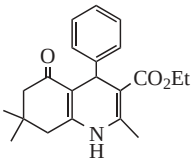
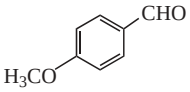
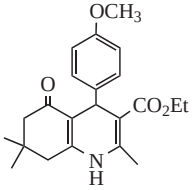
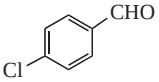
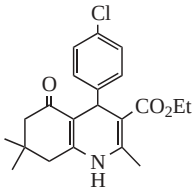
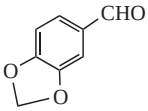
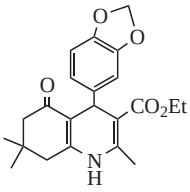
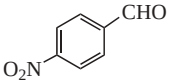
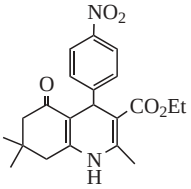
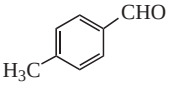
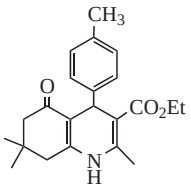
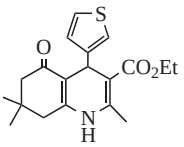
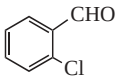
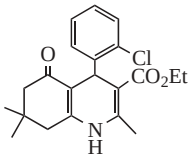
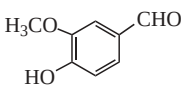
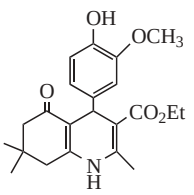
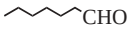
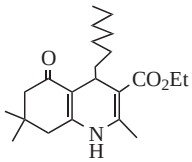
Entry	RCHO	Products[a,25]		Time (min)	Yield (%)[b]	Mp (°C)	
						Obtained	Reported
1			**2a**	10	95	227–229	265–266[23]
2			**2b**	9	96	260–261	263–264[12,23]
3			**2c**	8	95	246–247	245–246[12,23]
4			**2d**	5	94	251–253	197–199[14]
5			**2e**	14	91	242–244	
6			**2f**	12	93	267–268	297–298[12,23]
7			**2g**	15	91	248–250	
8			**2h**	26	92	208–210	
9			**2i**	10	94	235–237	210–212[14]

Table 3 Synthesis of Polyhydroquinoline Derivatives with Various Aldehydes Catalyzed by Ionic Liquid [hmim]BF_4 under Solvent-Free Conditions (continued)

Entry	RCHO	Products[a,25]		Time (min)	Yield (%)[b]	Mp (°C)	
						Obtained	Reported
10			**2j**	18	89	153–154	

[a] All products were characterized by IR, ^{1}H NMR spectroscopy and elemental analysis.
[b] Isolated yields.

In summary, an efficient cyclization reaction of dimedone with various aldehydes, ammonium acetate and ethyl acetoacetate utilizing ionic liquids as catalyst under solvent free conditions was developed with high yields for the first time. The main advantages of this methodology are: (1) relatively simple catalyst system; (2) short reaction times; (3) higher yields; (4) simple manipulation. Ionic liquids [hmim]BF_4, [dmim]BF_4, [hmim]PF_6, and [hmim]Br all exhibited high catalytic activities in this reaction. Efforts to develop more active and available catalytic system are currently in progress.

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(24) Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 226173 for compounds **2d**. Copies of this information may be obtained free of charge from: The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [E-mail: linstead@ccdc.cam.ac.uk or deposit@ ccdc.cam.ac.uk; Fax:+44 (1223)336033]. Structural parameters for **2d**: data collection: Rigaku Mercury CCD area detector; radiation: MoK. wavelength = 0.71070 Å; crystal size: $0.24 \times 0.15 \times 0.70$ mm^3; crystal system: monoclinic; space group: Cc (#9); unit cell: a = 18.607 (6) Å, b = 9.136 (3) Å, c = 12.157 (4) Å, α = 111.623 (5)°.
(25) **Typical Experimental Procedure**: 4-Chlorobenzaldehyde (1 mmol), dimedone (1 mmol), ammonium acetate (1.5 mmol), ethyl acetoacetate (1 mmol) and [hmim]BF_4 (12 mmol%) were successively charged into a 25 mL round-bottomed flask equipped with a magnetic stirrer. Then the reaction proceeded at 90 °C for 8 min and a solid product gradually formed. After the completion of reaction as indicated by TLC, the resulting solid product was crushed,

washed with water, filtered and dried in vacuum to afford the crude product. A pure product was obtained by further recrystallization using absolute alcohol. **2a**: IR (KBr): 3290, 1698, 1612 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.92 (s, 3 H, CH_3), 1.06 (s, 3 H, CH_3), 1.08 (m, 3 H, CH_2CH_3), 2.18 (m, 4 H, 2 × CH_2), 2.41 (s, 3 H, CH_3), 4.08 (q, $J_1 = J_2 = 6.0$ Hz, 2 H, CH_2CH_3), 5.06 (s, 1 H, CH), 5.90 (s, 1 H, NH), 7.03–7.4 (m, 5 H, ArH). Anal. Calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.57; H, 7.51; N, 4.06. **2f**: IR (KBr): 3275, 1702, 1647 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.92 (s, 3 H, CH_3), 1.08 (s, 3 H, CH_3), 1.24 (t, $J_1 = J_2 = 7.2$ Hz, 3 H, CH_2CH_3), 2.16 (s, 3 H, CH_3), 2.26 (m, 4 H, 2 × CH_2), 2.40 (s, 3 H, CH_3), 4.08 (m, 2 H, CH_2CH_3), 5.00 (s, 1 H, CH), 5.80 (s, 1 H, NH), 7.00 (d, J = 8.0 Hz, 2 H, ArH) 6.80 (d, J = 8.0 Hz, 2 H, ArH). Anal. Calcd for $C_{22}H_{27}NO_3$: C, 74.76; H, 7.70; N, 3.96. Found: C, 74.92; H, 7.79; N, 3.90. **2i**: IR (KBr): 3399, 3293, 1698, 1644 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.94 (s, 3 H, CH_3), 1.06 (s, 3 H, CH_3), 1.22 (t, $J_1 = J_2 = 7.2$ Hz, 3 H, CH_2CH_3), 2.20 (s, 3 H, CH_3), 2.38 (m, 4 H, 2 × CH_2), 3.89 (s, 3 H, CH_3), 4.12 (q, $J_1 = J_2 = 7.2$ Hz, 2 H, CH_2CH_3), 5.00 (s, 1 H, CH), 5.40 (s, 1 H, OH), 5.76 (s, 1 H, NH), 6.74 (m, 2 H, ArH) 7.00 (d, 1 H, ArH). Anal. Calcd for $C_{22}H_{27}NO_5$: C, 68.55; H, 7.06; N, 3.63. Found: C, 68.53; H, 7.11; N, 3.51.