

[BMIm]BF₄-LiCl: An effective catalytic system for the synthesis of pyrano[3,2-*c*]chromene and pyrano[4,3-*b*]pyrone derivatives

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ABSTRACT

An efficient and green method for the synthesis of pyrano[3,2-*c*]chromene or pyrano[4,3-*b*]pyrone derivatives is described by using a three-component condensation process of malononitrile, aldehyde, and 4-hydroxycoumarin or 4-hydroxypyron in [BMIm]BF₄-LiCl as an ionic liquid.

Keywords: Ionic liquid, Multicomponent reaction, Homogeneous catalyst, Green chemistry.

1. Introduction

During recent years, ionic liquids (ILs) have attracted increasing interest in the area of organic synthesis particularly by producing an alternative green reaction medium [1]. Recently, the ionic liquids have been found to possess a significant role as catalyst [2]. They can be also used as solvents due to their unique physical and chemical properties such as non-volatility, non-flammability, thermal stability and controlled miscibility [3-5]. Therefore, ionic liquids have been the subject of considerable interest because they are much more advantageous in terms of catalytic efficiency and recycling of the ionic liquid compared to the inorganic salts when used as catalysts. Room temperature ionic liquids have shown great promise as green reaction media in the realm of synthetic organic chemistry [6]. In addition, the synthesis of task-specific ionic liquids, which have a functional group in their framework, may expand the application of ionic liquids in organic chemistry [7-15].

Pyrans and fused pyran derivatives are an important class of structural motif of many natural and synthetic compounds which possess a high activity profile due to their wide range of biological activities such as anticancer [16,17], anti-tuberculosis [18], anti-HIV

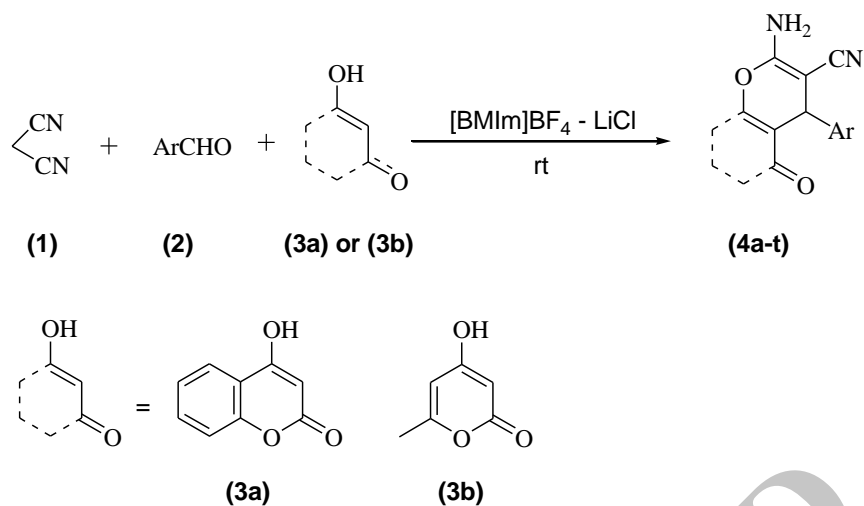
[19], calcium channel antagonist activity [20], antifungal [21], antimicrobial [22], antiproliferative [23], antidiabetic [24], anti-inflammatory, and antiviral [25]. On the other hand, they are also known for their biological properties including antioxidant and cytotoxic activities [26]. Therefore, the synthesis of pyrans and fused pyran derivatives are of great importance in organic synthesis. Recently, some synthetic approaches have been developed for the synthesis of pyrano[4,3-*b*]pyran and pyrano[3,2-*c*]chromene. They have been synthesized in the presence of a variety of catalysts such as TMGT [27], TBAB [28], Trisodium citrate [29], Na₂SeO₄ [30], SDS [31], H₆[P₂W₁₈O₆₂]. 18H₂O [32]. However, many of these methods are associated with several disadvantages such as long reaction time, drastic reaction conditions, difficult catalyst recovery, very expensive reagents, low yields and tedious workup. Therefore, introduction of clean procedures and utilizing ecofriendly green catalyst can be simply recycled at the end of reaction have attracted more attention.

2. Experimental

2.1. General

Chemicals were purchased from Merck and Fluka Chemical Companies and used without further purification. The purity determination of the products was accomplished by TLC on silica gel polygram SIL

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Scheme 1.

G/UV 254 plates. All products were confirmed by their m.p., IR, NMR and comparison with data in references [27, 29, 31, 34-36]. Melting points were determined on an electrothermal type 9200 melting point apparatus. IR spectra were recorded using a Shimadzu IR-470 spectrometer with KBr plates. In all the cases the ^1H NMR spectra were recorded with Bruker Avance 400 MHz instrument. Chemical shifts are reported in parts per million in DMSO with tetramethylsilane as an internal standard. ^{13}C NMR data were collected on Bruker Avance 100 MHz instrument.

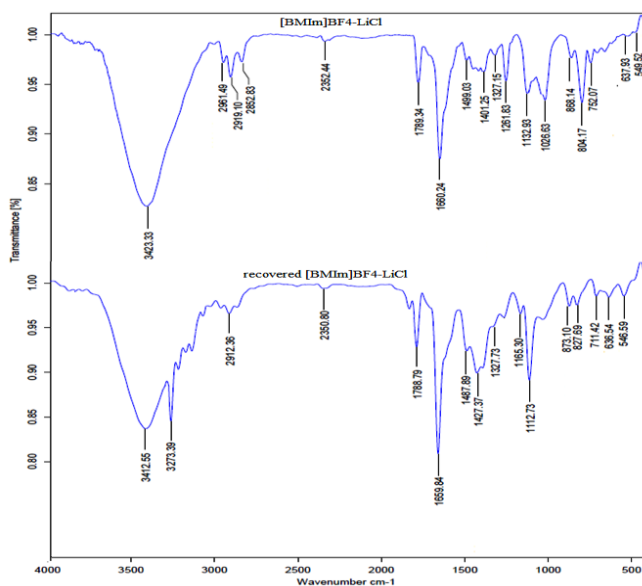
2.2. Catalyst Preparation

Procedure for the preparation of [BMIm]BF₄-LiCl

Ionic liquid [BMIm]BF₄-LiCl was prepared by the reported method [33]. 1-Methylimidazole (5.1 g, 62.1 mmol) was added to 32 mL of 1-chlorobutane. The mixture was heated to reflux for 24 h and then cooled to room temperature, the obtained oily product was separated from reaction mixture by decanting, washed with EtOAc (2 × 20 mL), and the collected solvent of organic phase was removed under reduced pressure to give 1-butyl-3-methylimidazolium chloride ([BMIm]Cl). In the second step, to a solution of [BMIm]Cl (9.3 g, 53 mmol) in anhydrous acetone (40 mL), LiBF₄ (5 g, 53 mmol) was added. The mixture was then stirred for 48 h at room temperature to get a solution and then stored at 4°C over 2 days in refrigerator giving the excess of the dissolved LiCl crystals to precipitate. After separation of the precipitated LiCl crystals (0.87 g, 20.5 mmol) the solvent of the filtered solution was removed under reduced pressure thereby the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate doped with 60 mol % of LiCl ([BMIm]BF₄-LiCl) was obtained as a yellow oil.

2.3. General procedure for the synthesis of pyrano[3,2-c]chromene or pyrano[4,3-b]pyrone derivatives

A mixture of malononitrile **1** (1 mmol), aromatic aldehyde **2** (1 mmol) and 4-hydroxycoumarin or 4-hydroxypyron **3** (1 mmol) was added to a vial containing a magnetic stir bar and the ionic liquid ([BMIm]BF₄-LiCl, 1 mL). The reaction mixture was sealed and stirred at room temperature until disappearance of the starting materials (7 min), as monitored by TLC on silica gel using 2:1 mixture of ethyl acetate/n-hexane. After completion of the reaction, the residue was washed with 2 × 15 mL of cold water to extract the ionic liquids. The solid residues were recrystallized from ethanol (95.5%) to afford pure products **4a-v**. The ionic liquids were recovered from the aqueous extracts by evaporation of water in reduced pressure and reused in the next cycles.

Scheme 2. FTIR spectra of [BMIm]BF₄-LiCl (top) and the recovered ionic liquid (bottom).

2.4. The selected spectral data

2-amino-4-(2,4-dichlorophenyl)-4,5-dihydro-5-oxopyrano[3,2-*c*]chromene-3-carbonitrile (4b); IR (KBr): ν (cm⁻¹); 3465, 3293, 3168, 3078, 2195, 1720, 1678, 1592; ¹HNMR (400.13 MHz, DMSO-*d*₆): δ 4.98 (s, 1H), 7.37 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.49 (d, *J* = 8.3 Hz, 1H), 7.43 (br s, 2H), 7.44 (d, *J* = 8.3 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 1H), 7.54 (d, *J* = 2.1 Hz, 1H), 7.76 (t, *J* = 8.2 Hz, 1H), 7.89 (d, *J* = 8.9 Hz, 1H), ¹³C NMR (100.6 MHz, DMSO-*d*₆): δ 57.10, 103.38, 113.71, 117.47, 119.43, 123.42, 125.57, 128.71, 129.73, 132.95, 133.28, 133.96, 134.28, 140.26, 153.14, 155.05, 159.05, 160.23.

2-amino-5-oxo-4-(3,4,5-trimethoxyphenyl)-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (4l); IR (KBr): ν (cm⁻¹); 3123, 1765, 1623, 1535, 1524, 1410, 1230; ¹HNMR (400.13 MHz, DMSO-*d*₆): δ 3.72 (s, 3H), 3.80 (s, 6H), 4.34 (s, 1H), 6.79 (s, 2H), 7.26 (s, 2H), 7.45–7.39 (m, 1H), 7.65 (d, *J* = 7.6 Hz, 1H), 7.75–7.70 (m, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), ¹³C NMR (100.6 MHz, DMSO-*d*₆): δ 38.3, 55.1, 58.9, 59.9, 105.3, 108.9, 111.1, 112.7, 117.8, 120.1, 121.3, 129.5, 134.8, 136.2, 137.4, 147.6, 150.4, 156.6, 157.8.

2-amino-7-methyl-5-oxo-4-(3,4,5-trimethoxyphenyl)-5,6-dihydro-4*H*-pyrano[3,2-*c*]pyridine-3-carbonitrile

(4v); IR (KBr): ν (cm⁻¹); 3118, 1754, 1621, 1565, 1512, 1410, 1230; ¹HNMR (400.13 MHz, DMSO-*d*₆): δ , 2.34 (s, 3H), 3.82 (s, 3H), 3.91 (s, 6H), 4.20 (s, 1H), 6.12 (s, 1H), 6.82 (s, 2H), 7.10 (s, 2H), ¹³C NMR (100.6 MHz, DMSO-*d*₆): δ 20.6, 37.9, 55.9, 59.9, 61.3, 95.6, 104.2, 108.5, 121.1, 133.4, 140.5, 148.2, 155.3, 158.2, 159.8, 162.2.

3. Results and Discussion

In view of our ongoing efforts to explore newer ionic liquids for synthesis of heterocyclic compounds [33], we decided to investigate the possibility of synthesizing pyrano[3,2-*c*]chromene and pyrano[4,3-*b*]pyrone derivatives by one-pot three-component condensation reaction strategy of malononitrile with aldehydes and cyclic 1,3-dicarbonyl compounds in ionic liquid as a catalyst solvent (Scheme 1). In order to optimize the reaction condition, a variety of ionic liquids were employed for this synthesis. It was found that the best results were obtained with 1 mL of [BMIm]BF₄-LiCl ionic liquid at room temperature. The reaction was completed within 7 minutes and the expected product (Table 1, entry 8) was obtained in 81% yield. These results are listed in Table 1.

Table 1. Optimization of reaction condition. ^a

Entry	ILs	Condition	Time	Yield ^b (%)	Ref.
1	TMGT	Solvent-free/ 100 °C	60 min	79	[27]
2	TBAB	Solvent-free/ 100 °C	40 min	88	[28]
3	TBAB	H ₂ O/ reflux	45 min	91	[28]
4	Sodium Dodecyl Sulfate (SDS)	H ₂ O/ 60 °C	120 min	85	[31]
5	H ₆ [P ₂ W ₁₈ O ₆₂].18H ₂ O	EtOH:H ₂ O/ reflux	30 min	89	[32]
6	-----	Rt	200 min	Trace	---
7	[BMIm]BF ₄	Rt	150 min	70	---
8	[BMIm]BF ₄ -LiCl	Rt	7 min	81	---
9	[BMIm]OH	Rt	50 min	50	---
10	[BMIm]Cl	Rt	15 min	75	---
11	[BMIm]HSO ₃	Rt	200 min	60	---
12	TMGT	Rt	100 min	Trace	---
13	TMGT _f	Rt	120 min	Trace	---
14	Et ₄ NBr	Rt	120 min	Trace	---
15	[BMPy]Cl	Rt	120 min	50	---

^a Reaction conditions: malononitrile **1** (1.0 mmol), benzaldehyde **2a** (1.0 mmol), and 4-hydroxychromene-2(1*H*)-one **3a** (1.0 mmol).

^b Isolated yields.

Table 2. Synthesis of pyran motifs derivatives **4a-v** in the presence of [BMIm] BF₄-LiCl. ^a


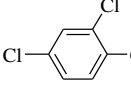
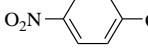
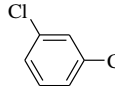







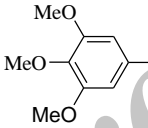

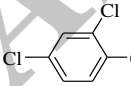
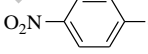
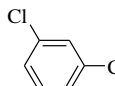

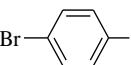
Entry	product	Aldehyde	1,3-Diketone	Yield (%) ^b	Time (min)	mp (°C)		Ref.
						found	reported	
1	4a		3a	81	7	241-243	(243-245)	[29]
2	4b		3a	85	5	256-258	(255-257)	[34]
3	4c		3a	84	6	251-253	(250-252)	[34]
4	4d		3a	92	6	242-244	(243-245)	[27]
5	4e		3a	95	6	261-263	(262-265)	[27]
6	4f		3a	92	7	254-256	(255-257)	[34]
7	4g		3a	90	5	280-282	(281-283)	[34]
8	4h		3a	83	7	271-273	(270-272)	[34]
9	4i		3a	89	6	259-261	(260-262)	[34]
10	4j		3a	88	5	260-262	(261-263)	[27]
11	4k		3a	84	7	253-255	(255-256)	[31]
12	4l		3a	80	7	275-277	-	
13	4m		3b	81	7	234-236	(235-237)	[35]
14	4n		3b	85	6	231-233	(233-235)	[36]
15	4o		3b	83	5	214-216	(215-217)	[35]
16	4p		3b	92	7	253-255	(254-256)	[36]
17	4q		3b	95	4	270-272	(269-271)	[36]
18	4r		3b	92	4	224-226	(223-225)	[36]

Table 2. (Continued).

19	4s		3b	89	5	239-241	(238-240)	[36]
20	4t		3b	85	6	234-236	(235-237)	[35]
21	4u		3b	88	4	231-233	(230-232)	[36]
22	4v		3b	78	7	235-237	-	

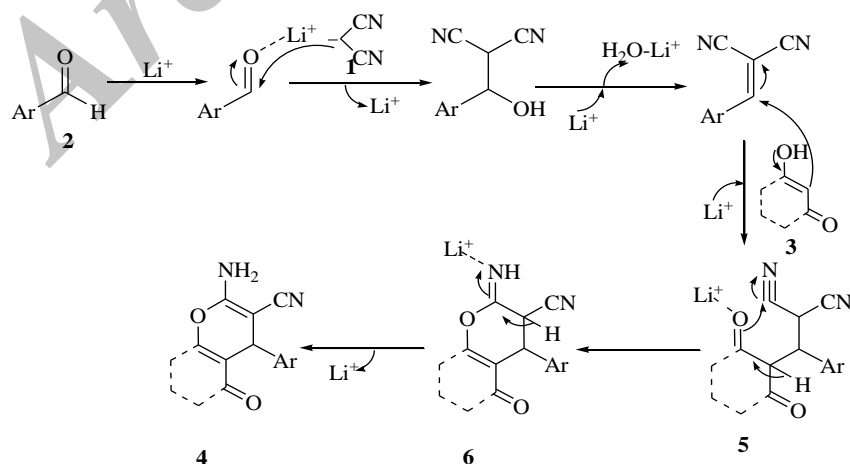
^a Reaction conditions: malononitrile **1** (1.0 mmol), aromatic aldehydes **2** (1.0 mmol), and 4-hydroxychromene-2(1*H*)-one **3a** or 4-hydroxypyrrone **3b** (1.0 mmol).

^b Isolated yields.

To assess the efficiency and scope of the new method, malononitrile was reacted with various aromatic aldehydes and 4-hydroxycoumarin or 4-hydroxypyrrone. The results are displayed in Table 2, which indicates that all reactions proceeded efficiently, and the desired products were produced in high yields and in short reaction times. The effect of electron-withdrawing substituents, electron-releasing substituents and halogens on the aromatic ring of aldehydes on the reaction results was investigated. As seen in Table 2, electron-withdrawing substituents and halogens produced higher yield of products than their electron-rich counterparts. Also, we have found that the reaction of aromatic aldehydes having electron-withdrawing groups was rapid as compared to the reaction of aldehydes having electron donating groups.

The procedure worked well without the formation of any side products with a variety of structurally and electronically divergent aldehydes.

A possible mechanism for the formation of the selected product **4** in the presence of [BMIm]BF₄-LiCl is outlined in Scheme 3. In first step, aldehyde is condensed with malononitrile by Knoevenagel condensation to afford the α -cyanocinnamionitrile derivative. In the second step, the active methylene of 1,3 diketone **3** reacts with electrophilic β carbon of C=C of α -cyanocinnamionitrile giving the Michael adduct intermediate **5**. Then, it is cyclized by nucleophilic attack of the carbonyl group on cyano group giving intermediate **6**. Finally, the expected product **4** is afforded by tautomerization



Scheme 3. Possible mechanism for synthesis of pyran ring systems **4** in the presence of [BMIm]BF₄-LiCl ionic liquid as a catalyst solvent.

Table 3. The effect of [BMIm]BF₄-LiCl recycling on the **4a** yield.^a

Recovery cycle	Yield (%) ^b
1	81
2	79
3	78
4	76

^a Reaction conditions: malononitrile **1** (1.0 mmol), benzaldehyde **2a** (1.0 mmol), and 4-hydroxychromene-2(1*H*)-one **3a** (1.0 mmol); 1 mL of [BMIm]BF₄-LiCl at room temperature.

^b Isolated yields.

A series of catalyst cycles were run to investigate the consistency of the catalytic activity. In this regard preparation of **4a** was chosen as the model. In each cycle, the catalyst was separated and then used for the next experiment directly and the results are listed in Table 3. The data showed that the IL could be reused at least four times with slight decrease in the yield of the product. To compensate the loss of IL during washing, 0.5 ml of IL was added after four runs.

4. Conclusion

In conclusion, an efficient synthesis of pyrano[3,2-*c*]chromene and pyrano[4,3-*b*]pyrone derivatives has been achieved via a one-pot three-component reaction of an aromatic aldehyde, malonitrile, and 4-hydroxycoumarin or 4-hydroxypyron using the reusable and environmentally benign [BMIm]BF₄-LiCl as a solvent catalyst. The key advantages of this method are the very short reaction time, high yields and simple workup. The present method does not involve any hazardous organic solvent. Therefore, this procedure can be classified in green chemistry.

Acknowledgement

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