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A green, efficient, and rapid procedure for the synthesis of pyrano[3,2-*c*] quinoline and pyrano[3,2-*c*]pyridone derivatives catalyzed by [BMIm]Cl

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ABSTRACT

A highly practical and efficient preparation of pyrano[3,2-*c*]pyridone and pyrano[3,2-*c*]quinoline derivatives was developed via an ionic liquid mediated and promoted multi-component reaction of malononitrile, aldehyde, and 4-hydroxyquinolin-2(1*H*)-one or 4-hydroxy-6-methylpyridin-2(1*H*)-one. The combinatorial syntheses were achieved for the first time without applying extra activation energy at ambient temperature while making use of [BMIm]Cl as a catalyst solvent.

Keywords*: Aldehydes, Ionic liquid, Catalyst, 1,3-dicarbonyl compounds.*

1. Introduction

The first multi-component reaction (MCR) was reported by Strecker in 1850 for the synthesis of amino acids [1]. In multicomponent reactions (MCRs), three or more reactants come together in a single reaction vessel to form new products that contain structural units of all the components. This type of reaction becomes increasingly important in organic and medicinal chemistry because it allows to obtain highly sophisticated polyfunctional molecules through simple one-pot procedures. Multicomponent reactions have been successfully employed to generate highly diverse combinatorial libraries for high-throughput screening of biological and pharmacological activities. The use of three or more building blocks in a one-pot, high-yield multicomponent reaction leads to a wide structural and functional diversity combined with excellent combinatorial efficiency. Over the past decade, industrial and academic research has made powerful MCR strategies into one of the most efficient and cost-effective tools for combinatorial synthesis [2-4]. However, in case of MCR the prediction of the product is a difficult task due to competitive existence of a variety of intermediates and formation of the byproducts in the reaction. The use of computational tools for calculation of heat of formation makes the task easier. In this view, designing of MCRs without using toxic catalysts in solvent-free conditions as well as in recyclable solvents such as ionic liquids is particularly worthwhile for complementing the significant characters of MCRs, so as to satisfy the green chemistry principles [5]. For nearly two dozens of years ionic liquids (ILs) attract the quickly growing attention due to outstanding properties: negligible vapor pressure, excellent thermal stability, wide interval of hydrophilic–hydrophobic balance, good dissolution properties with many organic and inorganic compounds including polymers or cellulose, and low flammability. Ionic liquids are expected as superior environmentally friendly solvents for homogeneous catalysis, biocatalysis, separation technologies, nanomaterial preparations, templates for production of porous solids, hydraulic fluids, lubricants and chemical synthesis [7].

It is well known that pyrans are important core units in a number of natural products [8] and photochromic materials. Compounds with pyran ring system have

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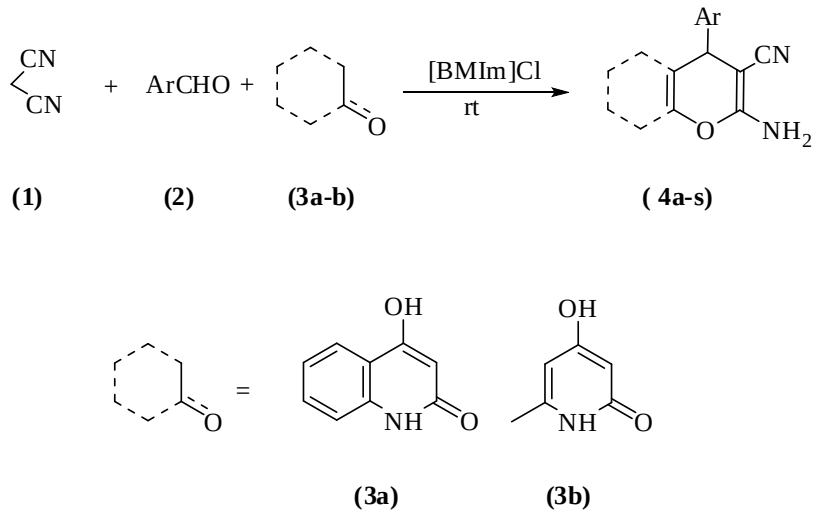

Scheme 1.

many pharmacological properties and play important roles in biochemical process [9]. Moreover, 4*H*-pyrans are useful intermediates for the synthesis of various compounds, such as pyranopyridine derivatives [10], polyazanaphthalenes [11], pyrano[2]pyrimidines [12], and pyridin-2-ones [13]. Therefore, preparation of this heterocyclic nucleus has gained great importance in organic synthesis. To the best of our knowledge, there are little reports in literature on the synthesis of pyran derivatives. Wang et al reported the synthesis of 2- amino-3-cyano -1,4,5,6-tetrahydropyrano [3,2-*c*] quinolin-5-one derivatives in the presence of $KF–Al_2O_3$ [14]. Hu et al has been developed by one-pot condensation of 4-hydroxyquinolin- 2(1*H*)-one, aldehyde, and malononitrile in the presence of ammonium acetate in EtOH [15]. Recently, two methods have been reported for the synthesis of pyrano[3,2-*c*]pyridones in the presence of Et_3N in refluxing ethanol, $[BMIm]BF_4$ ionic liquid [16]. Mekheimer et al and Stoyanov et al have reported two stepwise versions for the synthesis of pyrano[3,2-*c*] pyridones in refluxing methanol in the presence of piperidine [17].

2. Experimental

2.1. General

All chemicals were purchased from Merck or Fluka Chemical Companies. All known compounds were identified by comparison of their melting points and spectral data with those reported in the literature. Progress of the reactions was monitored by thin layer chromatography (TLC) using silica gel SIL G/UV 254 plates. IR spectra were recorded using a Shimadzu IR-470 spectrometer with KBr plates. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance-400 MHz spectrometer.

2.2. General procedure

A mixture of malononitrile **1** (1 mmol), aromatic aldehyde **2** (1 mmol) and 4-hydroxyquinoline or 4-hydroxypyridone **3** (1 mmol) was added to a vial containing a magnetic stirring bar and 1 mL of the ionic liquid ([BMIm]Cl). The reaction mixture was sealed and stirred at room temperature until disappearance of the starting materials (5-10 sec) (see Table 2). At this stage, the product due to poor solubility in the ionic liquid appears as a precipitate. In order to extract the ionic liquid, after completion of the reaction, the residue was washed with 2 × 10 mL of water. Washing the solid residue with ethanol (10 mL, 95.5%) has given remarkably pure powders of product **4**. The ionic liquid was recovered from the aqueous extracts by evaporating under reduced pressure and reused in the next cycles.

The selected spectral data

2-amino-4-(3-bromophenyl)-5-oxo-5,6-dihydro-4H-pyrano[3,2-c]quinoline-3-carbonitrile (4f); IR (KBr, *v* cm^{-1}): 3000, 1723, 1668, 1579, 1511, 1412, 1245; ^{1}HNMR (400.13 MHz, DMSO-d_6): δ 4.60 (s , 1H), 7.11 (s, 2H), 7.30–7.25 (m, 1H), 7.70–7.50 (m, 4H), 8.00–7.95 (s, 3H), 12.06 (s, 1H); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 32.4, 55.1, 102.4, 110.2, 112.5, 116.7, 119.3, 119.9, 121.1, 125.5, 128.8, 129.7, 130.9, 131.6, 136.7, 143.4, 144.9, 154.9, 155.2.

2-amino-4-(3-hydroxyphenyl)-5-oxo-5,6-dihydro-4H-pyrano[3,2-c]quinoline-3-carbonitrile (4j); IR (KBr, *v* cm^{-1}): 3396, 3325, 3201, 3100, 2903, 2196, 1381. ^{1}H NMR (400.13 MHz, DMSO-d_6): δ 4.48 (s, 1H), 6.57-6.59 (m, 2H), 6.63(d, *J*= 8.0 Hz, 1H), 7.27 (t, *J*= 7.6 Hz, 1H), 7.30 (t, *J*= 7.6 Hz, 1H), 7.32 (s, 2H), 7.40

(d, *J*= 8.0 Hz, 1H), 7.62 (t, *J*= 7.2 Hz, 1H), 7.83 (d, *J*= 8.0Hz, 1H), 9.20 (s, 1H) 12.01 (s, 1H); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 34.7, 36.4, 110.2, 112.1, 112.4, 114.6, 115.5, 120.3, 122.3, 122.8, 127.0, 128.0, 131.3, 133.4, 138.2, 154.5, 158.6, 161.4, 166.4.

2-amino-7-methyl-4-(3-bromophenyl)-5-oxo-5,6-dihydro-4H-pyrano[3,2-*c*]pyridine-3-carbonitrile (4r); IR (KBr, *v* cm^{-1}): 3000, 1723, 1668, 1579, 1511,1412, 1245; ^{1}HNMR (400.13 MHz, DMSO-d_6): δ, 2.32 (s, 3H), 4.25 (s , 1H), 6.11 (s, 1H), 6.25 (s, 2H), 7.35–7.23 (m, 2H), 7.85 (s, 1H), 8.01 (d, *J* = 7.7Hz, 1H), 11.99 (s, 1H); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 21.6, 37.4, 55.2, 93.3, 104.1, 119.9, 121.8, 122.5, 129.1, 133.3, 147.5, 148.0, 148.9, 153.2, 159.9, 163.8.

2-amino-4-(3-hydroxyphenyl)-7-methyl-5-oxo-5,6-dihydro-4H-pyrano[3,2-c]pyridine-3-carbonitrile (4s); IR (KBr, *v* cm^{-1}): 3396, 3325, 3201, 3100, 2903, 2196, 1381. ^{1}H NMR (400.13 MHz, DMSO-d_6): δ 4.48 (s, 1H), 6.57-6.59 (m, 2H), 6.63(d, *J*= 8.0 Hz, 1H), 7.27 (t, *J*= 7.6 Hz, 1H), 7.30 (t, *J*= 7.6 Hz, 1H), 7.32 (s, 2H), 7.40 (d, *J*= 8.0 Hz, 1H), 7.62 (t, *J*= 7.2 Hz, 1H), 7.83 (d, *J*= 8.0Hz, 1H), 9.20 (s, 1H) 12.00 (s, 1H); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 34.7, 36.4, 110.2, 112.1, 112.4, 114.6, 115.5, 120.3, 122.3, 122.8, 127.0, 128.0, 131.3, 133.4, 138.2, 154.5, 158.6, 161.4, 166.4.

3. Results and Discussion

With this background in mind and in line with our interest in the synthesis heterocyclic compounds with the aid of ionic liquids [18,19], we report an efficient and environmentally benign protocol for the synthesis of pyran motifs compounds by multi-component condensation of malononitrile **1**, aromatic aldehydes **2**, and 4-hydroxy-6-methylpyridin-2(1*H*)-one or 4-hydroxyquinolin-2(1H)-one **3** catalyzed by ionic liquid ([BMIm]Cl) and without using any solvent or additional catalyst. The products were obtained in high yields by a simple work-up (Scheme 1). In order to optimize the reaction conditions, the condensation of malononitrile **1** (1.0 mmol), benzaldehyde **2a** (1.0 mmol), and 4-hydroxyquinoline **3a** (1.0 mmol) was attempted in different ionic liquids at room temperature. The condensation was performed in different ionic liquids but the efficiency and the yield of the reaction in [BMIm]Cl were higher than those in other ionic liquids thereby making [BMIm]Cl the most suitable reaction medium for successive reactions (Table 1).

After optimization of the reaction conditions, various aromatic aldehydes were subjected to reaction with Malononitrile and pyrano[3,2-*c*]quinoline or pyrano[3,2-*c*]pyridone under the selected conditions. The reactions proceeded with different aldehydes substituted with electron-donating/electron-withdrawing groups giving excellent yields. Interestingly halo-substituted aromatic aldehydes produced high yield of products than their electron-rich counterparts. These results are compiled in Table 2. As showed in Table 2, in all cases the reaction gives the products in good yields and prevents problems associated with solvent use such as cost, handling, safety and pollution.

A plausible mechanism for the formation of the selected product **4** in the presence of [BMIm]Cl ionic liquid as a catalyst solvent is outlined in Scheme 2. The condensation of malononitrile **1**, aldehyde **2** and 1,3 diketone **3** may occur by a mechanism of Knoevenagel condensation, Michael addition, intramolecular cyclization, and isomerization. Initially, intermediate **5** is formed by Knoevenagel condensation of malononitrile **1** and aldehyde **2** by the action of ionic liquid. Then, the proton of 1,3 diketone **3** is abstracted by ionic liquid to form intermediate **5**. Michael addition of intermediate **6** on **5** leads to the formation of **7**, followed by cyclization and isomerization, affords the corresponding products **4** (Scheme 2).

Table 1. Optimization of reaction condition.

Entry	ILs	Condition	Time	Yield[a](%)
1	-----	rt	180 min	Trace
2	[BMIm]BF_4	rt	120 min	85
3	[BMIm]BF_4-LiCl	rt	100 min	65
4	[BMIm]OH	rt	100 min	35
5	[BMIm]Cl	rt	5-10 sec	90
6	[BMIm]HSO_3	rt	240 min	50
7	TMGT	rt	120 min	Trace
8	$TMGT_f$	rt	120 min	Trace
9	Et_4NBr	rt	120 min	Trace
10	[BMPy]Cl	rt	150 min	30

[a]Isolated yields.

Table 2. Synthesis of pyran motifs derivatives **4a-s** in the presence of [BMIm]Cl.[a]

Entry	product	Ar	1,3-Diketone	Yield (%)[b]	m.p (°C)	
					found	reported (Lit)
1	**4a**	C_6H_5	3a	90	>300	>300 [20]
2	**4b**	4-CH_3–C_6H_4	3a	89	>300	>300 [20]
3	**4c**	2-Cl–C_6H_4	3a	95	>300	>300 [20]
4	**4d**	4-Cl–C_6H_4	3a	92	>300	>300 [20]
5	**4e**	2,4-Cl_2–C_6H_3	3a	90	>300	>300 [20]
6	**4f**	3-Br–C_6H_4	3a	93[–]	>300	-
7	**4g**	4-NO_2–C_6H_4	3a	93	>300	>300 [20]
8	**4h**	4-F–C_6H_4	3a	90	>300	>300 [20]
9	**4i**	4-Br–C_6H_4	3a	91	>300	>300 [20]
10	**4j**	3-HO–C_6H_4	3a	91[–]	>300	-
11	**4k**	4-HO–C_6H_4	3a	93	>300	>300 [20]
12	**4l**	C_6H_5	3b	87	277-278	278-279 [16 c]
13	**4m**	4-NO_2–C_6H_4	3b	91	261-262	263-265 [16 c]
14	**4n**	3-NO_2–C_6H_4	3b	90	308-310	310-311 [17b]
15	**4o**	4-Cl–C_6H_4	3b	93	241-242	243-244 [16 c]
16	**4p**	4-F–C_6H_4	3b	89[c]	257-258	258-259 [16 c]
17	**4q**	4-Br–C_6H_4	3b	90	253-254	254-255 [16 c]
18	**4r**	3-Br–C_6H_4	3b	92	243-244	-
19	**4s**	3-HO–C_6H_4	3b	91	235-236	-

[a] Reaction time: 5-10 sec

[b] Isolated Yields.

In the next phase of study the viability of catalysis by the recycled ionic liquid was evaluated. In this regard preparation of **4a** was chosen as the model. After completion of the reaction the ionic liquid was washed using water, evaporated under reduced pressure and then subjected to the next run with the same substrates and the same reaction time. Table 3 displays similar high conversions obtained after consecutive recycling of the ionic liquid (Table 3).

4. Conclusions

In summary, an efficient method for the synthesis of the pyrano[3,2-*c*]quinoline and pyrano[3,2-*c*]pyridone drivatives by using simple and readily available starting materials under catalysis of the ionic liquid, [BMIm]Cl, was introduced here. The ionic liquid acts as a catalyst solvent and can be recovered for reuse several times. Another advantage of the present method may be no requirement for metal catalysts or additional solvent and proceeding with similar rate with respect to the methods that gave the similar structure. We expect this method will find extensive applications in the field of combinatorial chemistry, diversity-oriented synthesis, and drug discovery.

Table 3. The effect of [BMIm]Cl recycling on the **4a** yield[a].

Entry	Cycle	Yield (%) [b]
1	fresh	90
2	first recycle	89
3	second recycle	87
4	third recycle	85

[a]Reaction conditions: malononitrile **1** (1.0 mmol), benzaldehyde **2a** (1.0 mmol), and 4-hydroxyquinolin-2(1H)-one **3a** (1.0 mmol); 1 mL of [BMIm]Cl at room temperature.
[b]Isolated yields.

Acknowledgements

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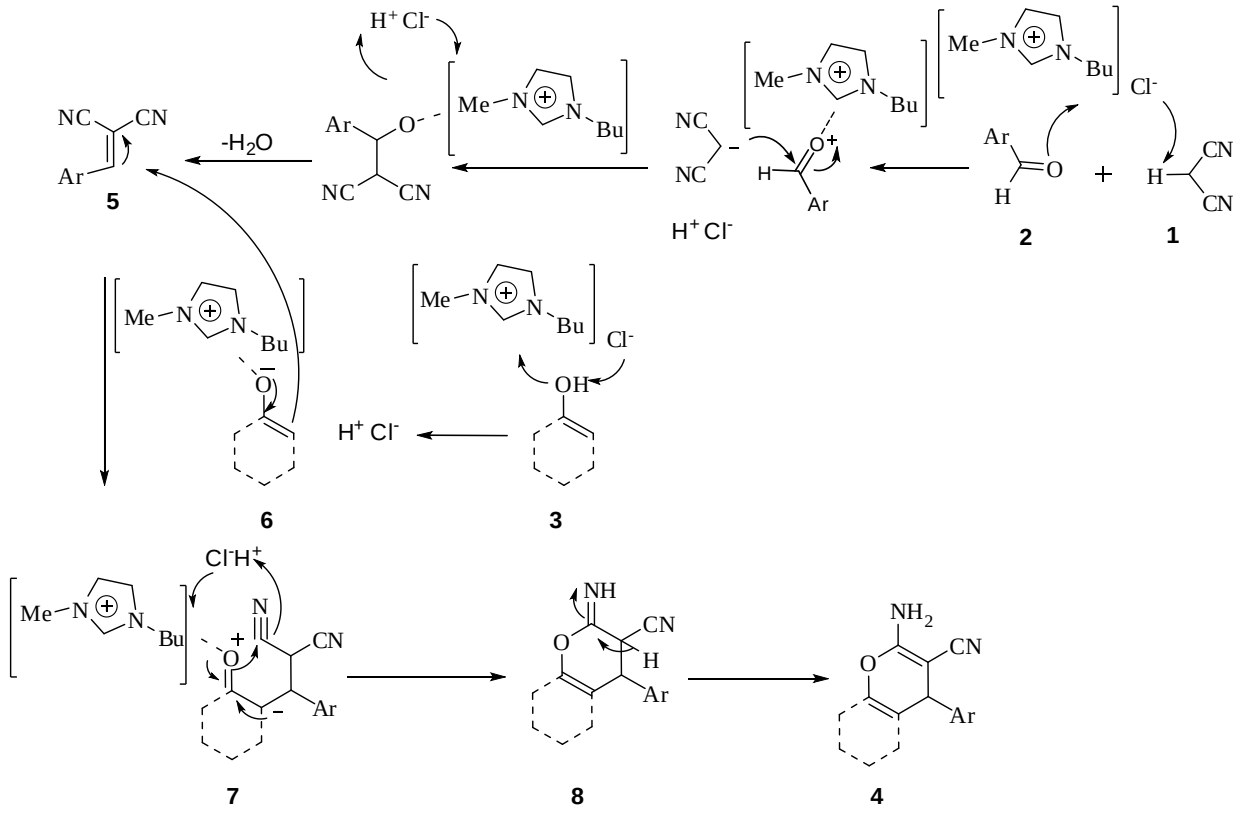

Scheme 2. Plausible mechanism for synthesis of pyran ring systems **4** in the presence of [BMIm]Cl ionic liquid as a catalyst

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