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Green, Catalyst-Free Protocol for Synthesis of Dihydropyrano[3,2-C]chromenes in Ionic Liquid [bmim]Br as an Efficient Promoting Medium

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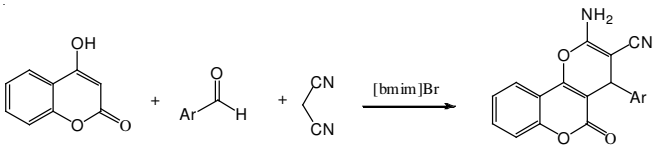
A simple and green procedure for the synthesis of dihydropyrano[3,2-c]chromene derivatives by one-pot three-component reaction of 4-hydroxycoumarin, aromatic aldehydes and malononitrile using [bmim]Br, a neutral ionic liquid, as an efficient medium without any catalysts has been developed. The present methodology offers several advantages, such as simple procedure with an easy work-up, excellent yields, short reaction times, environmentally benign milder reaction conditions.

Key Words: [bmim]Br, Ionic liquids, Catalyst-free, 4-Hydroxycoumarin, Dihydropyrano[3,2-c]chromenes.

INTRODUCTION

Pyrano[3,2-c]chromenes are a class of important heterocycles with a wide range of biological properties[1] such as spasmolytic, diuretic, anticoagulant, anticancer and antianaphylactic activity[2]. Moreover they can be used as cognitive enhancers for the treatment of neurodegenerative diseases, including Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease, Huntington's disease, AIDS associated dementia and Down's syndrome as well as for the treatment of schizophrenia and myoclonus[3]. Despite their importance from pharmacological, industrial and synthetic point of views, comparatively few methods for the preparation of pyrano[3,2-c]chromene derivatives have been reported. 2-Amino-4-aryl-5-oxo-4*H*,5*H*-pyrano[3,2-c]chromene-3-carbonitriles have already been prepared in the presence of organic bases like piperidine or pyridine in an organic solvent *i.e.* ethanol and pyridine[4]. They are also prepared in the presence of diammonium hydrogen phosphate in aqueous ethanol[5], K_2CO_3 under microwave irradiation[6] and $H_6P_2W_{18}O_{62}$ in aqueous ethanol[7]. Some of the reported procedures require long reaction times, multi-step reactions and complex synthetic pathways, afford products with only modest yields and non-reusability of the catalyst[8-10]. Therefore, the development of more effective methods for their preparation is still necessary.

Room-temperature ionic liquids, especially those based on 1-alkyl-3-methylimidazolium cations are the subject of considerable interest as benign reaction media in organic synthesis because of their unique properties, such as nonvolatility, nonflammability, recyclability, high thermal stability and ability to dissolve a wide range of organic and inorganic substrates. During the past decade, a variety of ionic liquids have been demonstrated as efficient and practical alternatives to volatile organic solvents for many important organic reactions[11,12]. Moreover their polar nature makes them useful for use under solvent-free conditions. As part of our current studies on the development of new routes for the synthesis of organic compounds in ionic liquids[13-19], we now report an efficient and clean synthetic route to dihydropyrano[3,2-c]chromene derivatives by one-pot three-component reaction of 4-hydroxycoumarin, aromatic aldehydes and malononitrile in ionic liquid [bmim]Br as a green medium (**Scheme-I**).



1 2a-2i 3 4a-4i

Scheme-I: Synthesis of dihydropyrano[3,2-c]chromenes

EXPERIMENTAL

All compounds were known and their physical and spectroscopic data were compared with those of authentic samples and found to be identical. Melting points were recorded on an electrothermal type 9100 melting point apparatus. The IR spectra were obtained on a 4300 Shimadzu spectrophotometer as KBr

disks. The ^{1}H NMR (500 MHz) spectra were recorded on Bruker DRX500 spectrometer.

General procedure for the prepration of dihydropyrano[3,2-c]chromenes (4a-4i): To a mixture of 4-hydroxycoumarin (**1**) (1 mmol), aryl aldehyde (**2a-2i**) (1 mmol) and malononitrile (**3**) (1.2 mmol), [bmim]Br (1 mL) was added. The reaction mixture was stirred at 100 ºC for appropriate time. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature and then ethanol was added. The precipitate was filtered off and recrystallized from ethanol to give pure dihydropyrano[3,2-c]chromenes (Table-2).

Compound 4a: m.p. 257-259 °C [lit[6]: 256-258]; IR (KBr, ν_{max}, cm^{-1}): 3380, 3286, 3180, 2198, 1709, 1675, 1607; ^{1}H NMR (DMSO-d_6) δ ppm: 4.45 (s, 1H), 7.20-7.28 (m, 3H), 7.31 (t, 2H, *J* = 7.5 Hz), 7.38 (br s, 2H), 7.46 (d, 1H, *J* = 8 Hz), 7.49 (t, 1H, *J* = 7.8 Hz), 7.71 (t, 1H, *J* = 7.5 Hz), 7.91 (d, 1H, *J* = 7.8 Hz).

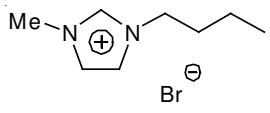
Compound 4c: m.p. 259-261 °C [lit[6]: 263-265]; IR (KBr, ν_{max}, cm^{-1}): 3381, 3291, 3189, 2193, 1714, 1677, 1611; ^{1}H NMR (DMSO-d_6) δ ppm: 4.50 (s, 1H), 7.31 (d, 2H, *J* = 8 Hz), 7.35 (br s, 2H), 7.36-7.40 (m, 2H), 7.45 (d, 1H, *J* = 8 Hz), 7.49 (t, 1H, *J* = 7.8 Hz), 7.72 (t, 1H, *J* = 7.8 Hz), 7.91 (d, 1H, *J* = 7.8 Hz).

Compound 4h: m.p. 261-263 °C [lit[7]: 258-260]; IR (KBr, ν_{max}, cm^{-1}): 3405, 3324, 3194, 2203, 1703, 1672, 1608; ^{1}H NMR (DMSO-d_6) δ ppm: 4.74 (s, 1H), 7.44 (d, 1H, *J* = 6.7 Hz), 7.51 (t, 1H, *J* = 7.6 Hz), 7.56 (br s, 2H), 7.64 (t, 1H, *J* = 7.6 Hz), 7.73 (dt, 1H, *J* = 7.5, 1.3 Hz), 7.82 (d, 1H, *J* = 6.8 Hz), 7.92 (dd, 1H, *J* = 6.8, 1.2 Hz), 8.12 (dd, 1H, *J* = 8.4, 1.4 Hz), 8.14 (s, 1H).

Recycling and reusing of the ionic liquid: [bmim]Br is soluble in ethanol and therefore could be recycled of the filtrate. The ionic liquid could be recovered by evaporation of the ethanol, washed with diethyl ether and dried at 50 ºC under vacuum for 1 h and reused in another reaction without appreciable reduction in its activity.

RESULTS AND DISCUSSION

For present investigations, ionic liquid [bmim]Br (Fig. 1) was prepared according to the literature procedure[20].



[bmim][Br]

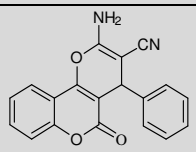
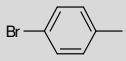
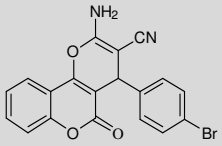
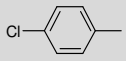
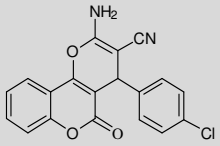
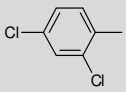
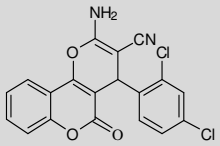
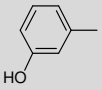
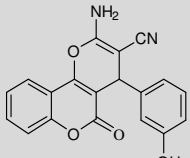
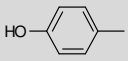
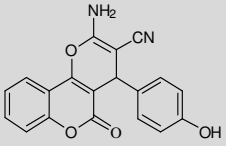
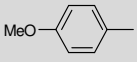
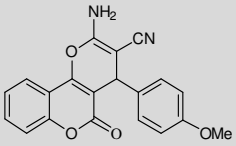
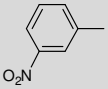
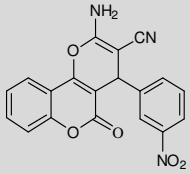
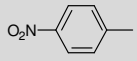
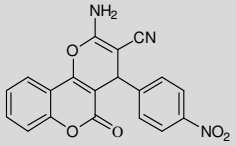
Fig. 1. Structure of ionic liquid

TABLE-1
SYNTHESIS OF COMPOUND **4a** IN DIFFERENT SOLVENTS WITHOUT ANY CATALYSTS

Entry	Solvent	Temp. (ºC)	Time/min	Yield (%)[a]
1	Solvent-free	120	150	None
2	EtOH	78	150	Trace
3	CH_3CN	81	180	Trace
4	$CHCl_3$	61	80	20
5	[bmim][Br]	100	20	94

[a]Isolated yields

TABLE-2
SYNTHESIS OF DIHYDROPYRANO[3,2-C]-CHROMENES USING [bmim]Br

Entry	Ar	Product[a]	Time (min)	Yield (%)[b]
1		 **4a**	20	94
2		 **4b**	17	95
3		 **4c**	17	96
4		 **4d**	15	97
5		 **4e**	20	91
6		 **4f**	20	95
7		 **4g**	30	88
8		 **4h**	15	97
9		 **4i**	14	98

[a]All products were characterized by ^{1}H NMR and IR spectral data and comparision of their physical data with literature reports.
[b]Isolated yields

To find the optimal conditions, the synthesis of 2-amino-5-oxo-4-phenyl-4*H*,5*H*-pyrano[3,2-c]chromene-3-carbonitrile (**4a**) was used as a model reaction. A mixture of 4-hydroxycoumarin (1 mmol), benzaldehyde (1 mmol) and malononitrile (1.2 mmol) was stirred under various reaction conditions. At first, we examined the synthesis of compound **4a** without catalyst and solvent at 100 ºC for 3 h, but under these conditions no product could be detected (entry 1). Increasing the reaction time or temperature did not improve the yield. The reaction was also carried out in various solvents (entries 2-5). As shown, in comparison to conventional solvents, the yield of the reaction in [bmim]Br is higher and the reaction time is shorter. Therefore, it can be suggested that the ionic liquid plays a role as promotor besides the role of the media. The best result was obtained when [bmim]Br was used at 100 ºC for 20 min (Table-1).

Using these optimized reaction conditions, the scope and efficiency of this approach was explored for the synthesis of a wide variety of substituted dihydropyrano[3,2-c]chromene and the obtained results are summarized in Table-2. All the aforementioned reactions delivered excellent product yields and accommodated a wide range of aromatic aldehydes bearing both electron-donating and electron-withdrawing substituents. In all cases, the obtained product was isolated by a simple work-up.

Reusability of [bmim]Br was also investigated. After filtration of the product, [bmim][Br] was recovered from the filtrate according to the procedure mentioned in experimental section and reused for next reactions. The obtained results are summarized in Table-3. As it is shown in this table, [bmim]Br could be reused at least three times without appreciable reduction in its activity as promoting medium.

TABLE-3
COMPARISON OF EFFICIENCY OF [bmim][Br] IN THE SYNTHESIS OF DIHYDROPYRANO[3,2-c]-CHROMENES AFTER THREE TIMES

Entry	Ar	Yield (%)[a]/run		
		First	Second	Third
4a	C_6H_5	94	93	91
4c	4-ClC_6H_4	96	94	93
4i	4-$O_2NC_6H_4$	98	95	94

[a]Isolated yields

Conclusion

A simple and efficient method is developed for the high-yielding synthesis of dihydropyrano[3,2-c]chromenes by one-pot three-component condensations of 4-hydroxycoumarin, aromatic aldehydes and malononitrile in presence of [bmim]Br, a neutral ionic liquid, as an efficient promoting medium. The product was easily separated with high yield. The ionic liquid was readily recycled and reused to produce almost identical results. No organic solvent and catalyst were used, resulting in eco-friendly process.

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