

RESEARCH LETTER

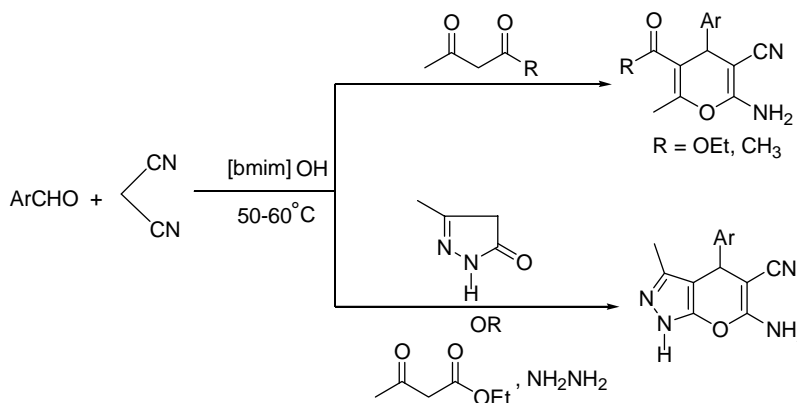
Efficient and green synthesis of 4*H*-pyrans and 4*H*-pyrano[2,3-*c*] pyrazoles catalyzed by task-specific ionic liquid [bmim]OH under solvent-free conditions

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A facile and convenient procedure for the synthesis of 4*H*-pyrans from aldehydes, malononitrile, and ethyl acetoacetate/acetylacetone and also synthesis of 4*H*-pyrano[2,3-*c*]pyrazoles from three-component condensation of aldehydes, malononitrile, and pyrazolone or four-component condensation of aldehydes, malononitrile, ethyl acetoacetate, and hydrazine monohydrate using [bmim]OH as task-specific ionic liquid has been described. The protocol proves to be efficient and environmentally benign in terms of high yields, low reaction times, ease of recovery, and reusability of reaction medium.



Keywords: green chemistry; multi-component reaction; solvent-free conditions; Task-specific ionic liquid

Introduction

Multicomponent processes have recently gained considerable economic and ecological impetus as they address fundamental principles of synthetic efficiency and reaction design. Multicomponent reactions (MCRs) have been proven to be very elegant and rapid way to access complex structures in a single synthetic operation from simple building blocks and show high atom economy and high selectivity (1–6). The diversity, efficiency, and rapid access to small and highly functionalized organic molecules make this approach of central interest in the construction of combinatorial libraries and optimization of drug-discovery processes (7–10).

2-Amino-4*H*-pyran derivatives are important as they are often used in cosmetics and pigments, and as potentially biodegradable agrochemicals (11–13). Poly-functionalized 4*H*-pyran structural motifs occur in a variety of natural products (14,15) and also constitute biologically interesting compounds (11–13, 16, 17, 18–22). Pyranopyrazoles prevalently hold a position of prominence attributing to their biological activities which include insecticidal (23) anti-inflammatory (24), molluscicidal (25,26), besides being identified as a screening kit for Chk1 kinase inhibitor (27).

Different methods have been reported (27–41) for the synthesis of these derivatives. Recently, pyrano[2,3-*c*]pyrazoles have been synthesized using

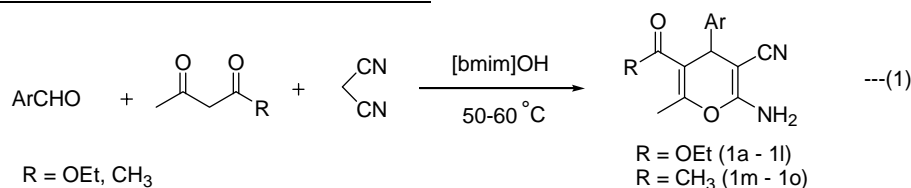
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catalysts like triethylamine (28), Mg/Al hydrotalcite (29), glycine (30), and *L*-proline in [bmim]BF₄ (31) whereas the synthesis of 2-amino-4*H*-pyrans has been reported using catalysts like Cu(II)oxymetasilicate (34), ZnO/MgO solid sample containing ZnO nanoparticles (35), silica nanoparticles (36), piperidine (37), magnesium oxide (38), or 1,1,3,3-tetramethylguanidine (TMG) (39) and also under microwaves exposure (40) in one pot reactions. Though there are many reports on the synthesis of 4*H*-pyrans and 4*H*-pyrano[2,3-*c*]pyrazoles. There is no report on the solvent-free synthesis of these derivatives using the same catalytic system.

Ionic liquids have emerged as a set of green solvents with unique properties such as tunable polarity, high thermal stability, and immiscibility with a number of organic solvents, negligible vapor pressure, and recyclability (42,43). Task-specific ionic liquids further enhance the versatility of ionic liquids, by performing the dual role of solvent as well as catalysts in organic reactions (44–47). In continuation to our endeavor (48–50) aimed at developing green synthetic protocol, we decided to develop a general rapid, high yielding, environmentally benign protocol for the synthesis of 4*H*-pyrans and 4*H*-pyrano[2,3-*c*]pyrazoles using the task-specific basic ionic liquid (TSIL), [bmim]OH.

Results and discussion

We herein present an efficient and facile protocol for the synthesis of 4*H*-pyrans from aldehydes, malononitrile, and ethyl acetoacetate/acetylacetone and also synthesis of 4*H*-pyrano[2,3-*c*]pyrazoles from three-component condensation of aldehydes, malono-



nitrile, and pyrazolone or four-component condensation of aldehydes, malononitrile, ethyl acetoacetate, and hydrazine monohydrate using [bmim]OH as task-specific ionic liquid at 50–60°C.

The reaction of 4-chlorobenzaldehyde (1.0 mmol), malononitrile (1.0 mmol), and ethyl acetoacetate (1.0 mmol) was optimized by varying molar ratios of the TSIL [bmim]OH and temperature. It was observed that 20 mol% of [bmim]OH was most effective for the desired condensation reaction at 50–60°C yielding

Table 1. Optimization of reaction conditions for the condensation of 4-chloro benzaldehyde, malononitrile, and ethyl acetoacetate.

Entry	Ionic liquid	Mol%	Time (h)	Yield (%)
1	[bmim]OH	5	6	56
2	[bmim]OH	10	4	65
3	[bmim]OH	15	4	75
4	[bmim]OH	20	0.5	91
5	[bmim]OH	25	0.5	92
6	[bmim]Br	20	6	Trace
7	[bmim]BF ₄	20	6	Trace

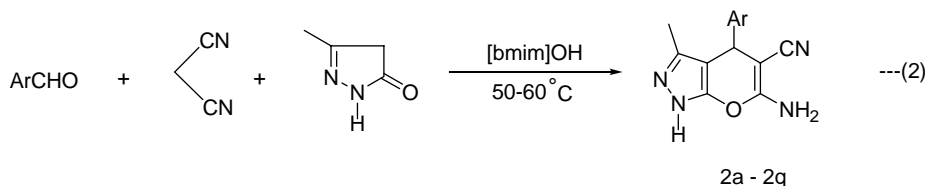
91% of the 5-ethoxycarbonyl-2-amino-4-(4-chlorophenyl)-3-cyano-6-methyl-4*H*-pyran (1a) in 30 min without any catalyst (entries 1–4, Table 1) unlike all previous reports. Higher amount of [bmim]OH did not effect the time or yield of the reaction (entry 5). However [bmim]Br and [bmim]BF₄ were found to be ineffective for this condensation (entries 6–7, Table 1). This confirms the vital role of the hydroxyl counter anion of [bmim]OH functionalized ionic liquid in this transformation. We, thus, chose to use 20 mol% of [bmim]OH to extend the protocol.

Thereafter, a series of reactions were carried out using diversely substituted aldehydes under identical reaction conditions. All these aldehydes underwent three-component cyclo-condensation reaction with malononitrile and ethyl acetoacetate to produce 4*H*-pyran derivatives in excellent yields (entries 1–12, Table 2) (Equation 1). All the functionalities were compatible under the reaction conditions. Reactions of aromatic aldehydes with electron-withdrawing groups such as chloro, nitro, proceeded at faster rates and gave better yields than those with electron donating groups such as methoxy and methyl.

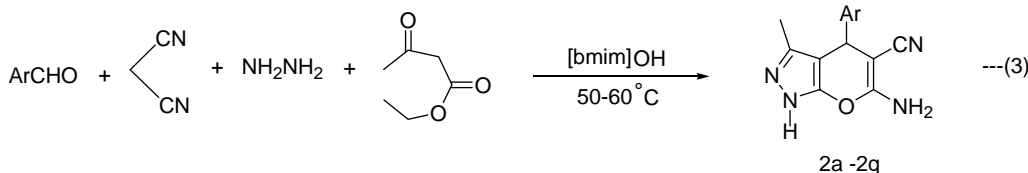
The replacement of ethyl acetoacetate by acetylacetone was also examined. In accord with our expectations, these reactions proceeded smoothly and afforded 5-acetyl-2-amino-4-aryl-3-cyano-6-methyl-4*H*-pyrans (entries 13–15, Table 2) in good yield (Equation 1).

The scope of this protocol was then investigated for one pot cyclo-condensation of aldehydes, malononitrile, and 5-methyl-2,4-dihydropyrazol-3-one to afford 4*H*-pyrano[2,3-*c*]pyrazoles. To our delight, the

reaction proceeded smoothly under above optimized conditions. A wide range of diversely substituted aromatic, and heteroaromatic aldehydes underwent this three-component cyclo-condensation with malononitrile and 5-methyl-2,4-dihydropyrazol-3-one to produce 4*H*-pyrano[2,3-*c*] pyrazoles (2a–2q) using 20 mol% of [bmim]OH as TSIL at 50–60°C (Equation 2). The reactions were completed in 5–10 min giving excellent yield of the products (Method A, Table 3). The substituents in the aromatic ring did not show any significant effect on the rate of the reaction and yield of the products.



Furthermore, synthesis of 4*H*-pyrano[2,3-*c*]pyrazoles (2a–2q) could also be achieved via four-component cyclo-condensation of hydrazine monohydrate, ethyl acetoacetate, aldehydes, and malononitrile (Equation 3) using 20 mol% of TSIL [bmim]OH at 50–60°C (Method B). A comparison of the results (Method A and B) is drawn in Table 3. Though comparative yields were obtained by both methods, the reactions carried out via three-component condensation required shorter duration for completion. It should be noted that ethyl acetoacetate and hydrazine undergo condensation to give 5-methyl-2,4-dihydropyrazol-3-one.



Finally, the recycling of the basic ionic liquid [bmim]OH was investigated during the synthesis of 1a. After completion of the reaction, the solid product was collected by filtration. The filtrate containing the ionic liquid was rinsed with ether and further vacuumed to dryness at 90°C for 2 h to remove any trapped water, to afford [bmim]OH which was reused directly for the next run. It was found that the ionic liquid can be used for the reactions for up to three runs without any appreciable loss of efficiency.

Experimental

All the chemicals used were purchased from Sigma–Aldrich and were used as such. All products are known, and were identified by comparison of spectral and physical data with the literature. Melting points were determined on a melting point apparatus and are uncorrected. IR (KBr) spectra were recorded on Perkin–Elmer FTIR spectrophotometer. The ¹H NMR spectra were recorded on Bruker Spectrospin spectrometer (300 MHz) and Jeol JNM ECX-400P (400 MHz) using TMS as an internal standard.

General procedure for the synthesis of 4*H*-pyran derivatives (1a–1o)

A mixture of aldehyde (1.0 mmol), malononitrile (1.0 mmol), ethyl acetoacetate or acetylacetone (1.0 mmol), and [bmim]OH (20 mol%) were stirred magnetically in an oil-bath maintained at 50–60°C for an appropriate time as mentioned in Table 2. After completion of the reaction as monitored by TLC using petroleum ether:ethyl acetate (60:40) as eluent, the reaction mixture was allowed to cool to room temperature and quenched with water (~ 5 mL).

The solid product obtained was filtered, washed with water and dried. The crude product was washed well with hot ethanol to yield pure 4*H*-pyran derivatives.

General procedure for the synthesis of 4*H*-pyrano [2,3-*c*]pyrazoles (2a–2q)

Method A

A mixture of 5-methyl-2,4-dihydro-pyrazol-3-one (1 mmol), aldehyde (1 mmol), malononitrile (1 mmol),

Table 2. [bmim]OH catalyzed three-component synthesis of 5-acyl/alkoxycarbonyl-2-amino-4-aryl-3-cyano-6-methyl-4*H*-pyrans.

Entry	Ar	Product	Time (min)	Yield (%)	Melting point (°C) (Observation)	Melting point (°C) (Literature)
1	4-ClC ₆ H ₄	1a	30	91	171–173	172–174 (38)
2	3-ClC ₆ H ₄	1b	50	91	153–155	153–156 (38)
3	C ₆ H ₅	1c	45	90	195–197	195–196 (38)
4	4-CH ₃ C ₆ H ₄	1d	60	87	177–179	177–179 (38)
5	2,4-Cl ₂ C ₆ H ₃	1e	45	91	166–168	– ^a
6	4-O ₂ NC ₆ H ₄	1f	30	90	179–181	180–183(38)
7	4-CH ₃ OC ₆ H ₄	1g	55	88	140–142	142–144(38)
8	3-O ₂ NC ₆ H ₄	1h	35	90	182–184	182–183(38)
9	4-HOC ₆ H ₄	1i	40	87	175–177	– ^a
10	3-HOC ₆ H ₄	1j	35	88	165–167	164–165 (38)
11	Piperonyl	1k	45	87	136–138	– ^a
12	2-ClC ₆ H ₄	1l	35	92	167–169	– ^a
13	4-CH ₃ OC ₆ H ₄	1m	40	89	158–160	157–159 (41)
14	4-CH ₃ C ₆ H ₄	1n	35	88	138–140	135–137 (41)
15	C ₆ H ₅	1o	35	90	158–160	158–160 (41)

^aCompounds are known but their melting points are reported for the first time.

Table 3. Synthesis of 4*H*-pyrano[2,3-*c*]pyrazoles catalyzed by [bmim]OH via Methods A & B.

Entry	Ar	Product	Method A		Method B		Melting point (°C)	
			Time (min)	Yield (%)	Time (min)	Yield (%)	Observation	Literature
1	C ₆ H ₅	2a	5	90	10	88	244–245	245–246 (32)
2	4-ClC ₆ H ₄	2b	5	94	10	90	233–234	234–235 (32)
3	4-CH ₃ C ₆ H ₄	2c	5	96	10	89	196–198	197–198 (33)
4	4-CH ₃ OC ₆ H ₄	2d	5	94	10	90	211–213	212–213 (32)
5	4-O ₂ NC ₆ H ₄	2e	5	94	10	91	251–252	251–252 (32)
6	3-BrC ₆ H ₄	2f	5	90	10	87	222–223	223–224 (32)
7	3,4,5-(CH ₃ O) ₃ C ₆ H ₂	2g	5	84	15	82	226–228	228 (33)
8	4-FC ₆ H ₄	2h	5	86	10	83	245–246	247–248 (33)
9	4-HOC ₆ H ₄	2i	5	87	15	82	224–226	223–224 (32)
10	3-O ₂ NC ₆ H ₄	2j	5	85	10	81	232–234	232–233 (33)
11	4-(CH ₃) ₂ N C ₆ H ₄	2k	10	95	10	86	218–220	219–220 (33)
12	2-CH ₃ OC ₆ H ₄	2l	5	92	15	88	251–252	252–253 (33)
13	4-BrC ₆ H ₄	2m	5	91	10	90	248–251	249–250 (33)
14	2-ClC ₆ H ₄	2n	5	89	10	88	246–247	245–246 (32)
15	2-O ₂ NC ₆ H ₄	2o	5	87	10	86	241–244	242–243 (33)
16	2-Furanyl	2p	5	93	10	90	232–234	233–234 (33)
17	1-Naphthyl	2q	5	86	10	82	226–228	226–228 (31)

and [bmim]OH (20 mol%) was stirred and heated in an oil-bath maintained at 50–60°C for 5–10 min. Progress of the reaction was monitored by TLC using ethyl acetate:petroleum ether (60:40) as eluent. Upon completion of the reaction, water (~5 mL) was added and the contents were stirred. The solid product obtained was filtered, washed with water and dried to afford the crude product, which was recrystallized from ethanol to yield pure 4*H*-pyrano[2,3-*c*]pyrazoles.

General procedure for the synthesis of 4*H*-pyrano[2,3-*c*]pyrazoles (2a–2q)

Method B

A mixture of hydrazine hydrate (96%) (1 mmol), ethyl acetoacetate (1 mmol), aldehyde (1 mmol), malononitrile (1 mmol), and [bmim]OH (20 mol%) was stirred at 50–60°C in an oil-bath for 10–15 min until completion of the reaction as monitored by TLC. The reaction was worked up as in Method A to yield pure products (2a–2q).

Representative analytical data

5-Ethoxycarbonyl-2-amino-4-(4-chlorophenyl)-3-cyano-6-methyl-4H-pyran (1a). White solid, ^1H NMR(400 MHz, CDCl_3): δ_{H} 7.27 (d, $J = 8.20$ Hz, 2H, ArH), 7.15 (d, $J = 8.24$ Hz, 2H, ArH), 4.53 (s, br, 2H, NH_2), 4.42 (s, 1H, CH), 4.05 (q, $J^{1,3} = 6.88$ Hz, $J^{1,2} = 3.44$ Hz, 2H, OCH_2), 2.37 (s, 3H, CH_3), 1.13 (t, $J = 7.12$ Hz, 3H, CH_3); IR (KBr) (ν_{max} , cm^{-1}): 3410, 3333, 2193, 1693, 1595.

5-Acetyl-2-amino-3-cyano-6-methyl-4-(4-methoxyphenyl)-4H-pyran (1m). White solid, ^1H NMR(400 MHz, CDCl_3): δ_{H} 7.12 (d, $J = 8.8$ Hz, 2H, ArH), 6.86 (d, $J = 8.8$ Hz, 2H, ArH), 4.48 (s, br, 2H, NH_2), 4.39 (s, 1H, CH), 3.78 (s, 3H, OCH_3), 2.28 (s, 3H, CH_3), 2.05 (s, 3H, CH_3); IR (KBr) (ν_{max} , cm^{-1}): 3460, 3300, 3170, 2180, 1695, 1660, 1600, 1510.

6-Amino-3-methyl-4-(4-nitrophenyl)-1,4-dihydro-pyran[2,3-c]pyrazole-5-carbonitrile (2e). White solid, ^1H NMR (300 MHz, DMSO-d_6): δ_{H} 12.14 (s, 1H, NH), 8.19 (d, $J = 8.7$ Hz, 2H, ArH), 7.45 (d, $J = 8.4$ Hz, 2H, ArH), 6.96 (s, br, 2H, NH_2), 4.80 (s, 1H, CH), 1.78 (s, 3H, CH_3); IR (KBr) (ν_{max} , cm^{-1}): 3477, 3229, 3119, 2196, 1651, 1595, 1516, 1401.

Conclusion

In conclusion, we have demonstrated a novel, convenient, expeditious, and common protocol for the synthesis of 4H-pyrans and 4H-pyrano[2,3-c]-pyrazoles in excellent yields, using the task-specific basic ionic liquid, [bmim]OH which can be recycled.

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