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Ionic liquid is an efficient catalyst for Knoevenagel condensation under grinding method

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ABSTRACT

A simple, green and environmentally benign route has been developed for the Knoevenagel condensation of 4-oxo-(4H)-1-benzopyran-3-carbaldehydes and 2-chloroquinoline-3-carbaldehyde with various active methylene compounds viz. malononitrile, ethylcyanoacetate, cyanoacetic acid, cyanoacetamide and Meldrum's acid were carried out in the presence of catalytic amount of basic ionic liquid 1-benzyl-3-methylimidazolium hydroxide ([bnmim]OH) by grinding method. The remarkable advantages of the present method are mild reaction conditions, short reaction time, excellent yields and green aspects by avoiding toxic catalyst and hazardous solvent. Additionally, the ionic liquid was successfully reused for four cycles without significant loss of activity.

Keywords: Knoevenagel reaction, ([bnmim]OH), hetero aryl aldehyde, active methylene compound, grinding

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INTRODUCTION

Knoevenagel condensations are one of the most useful and widely employed reactions for carbon-carbon bond formation in organic synthesis [1]. It is widely used in the synthesis of important intermediates or end products for perfumes [2]. pharmaceuticals [3] and polymers [4]. Bases, acids, or catalysts containing both acid-base sites [5] catalyze the reactions. Several homogeneous and heterogeneous catalysts such as Al_2O_3 [6], anionic resins [7], clays [8], $MgBr_2.OEt_2$ [9], CaO [10], ionic liquids [11], nanocrystalline ZnO [12], PEG-600 [13] and ammonium formate [14] have been documented in the literature for Knoevenagel condensation.

Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) is an active methylene compound with rigid cyclic structure and high acidity (pKa = 4.9) and undergo hydrolysis very easily [15]. It is well known that Meldrum's acid can undergo Knoevenagel condensation [16]. They are useful intermediates for the synthesis of heterocyclic compounds with potential pharmacological activities [17]. However, in most of the above-mentioned methods require prolonged reaction time and exotic reaction condition. Thus, the development of a new method for the Knoevenagel condensations reaction would be highly desirable.

The grinding method has gained increasing use in organic synthesis. Compared with traditional methods, many organic reactions occur more efficiently in the solid-state than in solution and in many cases even more selectively, because molecules in the crystals are arranged tightly and regularly [18].

Compounds having chromone moiety are synthetically versatile molecules with a reactive carbonyl group. They have considerable significance for their biological activities [19] and for their reactivity towards nucleophiles, which allow the synthesis of a wide variety of heterocycles. The substrate, 3-formylchromone [4-oxo-(4H)-1-benzopyran-3-carbaldehyde] has three active sites such as α, β-unsaturated carbonyl group, a carbon–carbon double bond and a formyl group. Of these, the formyl group has the highest reactivity towards active methylene compound. The condensation reactions of 3-formylchromone with active methylene compounds are well known [20].

Ionic liquid as environmentally benign media for catalytic processes, much attention has currently been focused on organic reaction catalyzed by ionic liquids have been reported with high performance [21]. In particular, imidazolium ionic liquids has been successfully used in many organic transformations includes Diels–Alder [22a], Wittig [22b], Suzuki cross-coupling [22c], Hantzsch condensation [22d], etc. In additionally, the basic ionic liquid [bmim]OH used in organic transformation [23]. Also, we have reported the synthesis of 1,2-benzisoxazole catalyzed basic ionic liquid by 1-butyl-3-methylimidazolium hydroxide ([bmim]OH) [24].

MATERIALS AND METHODS

Experimental section:

All chemicals were purchased from Merck, Aldrich and Rankem chemical companies and used without further purification. The uncorrected melting points of compounds were taken in an open capillary in a paraffin bath. The progress of the reaction was monitored by TLC (Thin Layer Chromatography). IR spectra were recorded on Perkin-Elmer FTIR spectrophotometer in KBr disc. ^{1}H NMR spectra were recorded on an 300 MHz FT-NMR spectrometer in $CDCl_3$ as a solvent and chemical shift values are recorded in units δ (ppm) relative to tetramethylsilane (Me_4Si) as an internal standard.

Table-1. Effect of different basic ionic liquids for the synthesis of 2-((4-oxo-4*H*-chromen-3-yl)methylene)malononitrile 2a[a]

Entry	Ionic liquid	Time (min)	Yield (%)[b]
1	[hdmim]OH	10	87
2	[hmim] OH	10	89
3	[bmim] OH	5	94
4	[bnmim] OH	5	96

[a] ***1a*** *(1 mmol) treated with malononitrile (1 mmol) in the presence of different basic ionic liquids.*
[b] *Isolated yield*

Table -2. Knoevenagel condensation of hetero aryl aldehydes with various active methylene compounds using [bnmim] OH by grinding

Compound	Substituents	Z	Time (min)	Yield (%)[b]	m.p.(°C)	
					Found	Reported[25]
2a	R_1-H	CN	5	96	210-212	212
2b	R_1-6-Cl	CN	10	95	252-254	252
2c	R_1-7-Me, 8-Cl	CN	10	94	225-227	226
2d	R_1-6-Me	COOH	10	94	195-197	195
2e	R_1-6-Br	COOH	10	95	184-186	186
2f	R_1-7-Me, 8-Cl	COOH	10	92	242-244	242
2g	R_1-6-Me	$CONH_2$	15	93	217-218	218
2h	R_1-6-Cl	$CONH_2$	15	94	260-262	262
2i	R_1-7-Me, 8-Cl	$CONH_2$	10	95	261-263	262
2j	R_2-H	COOEt	10	92	161-163	160-162
2k	R_2-7-OMe	COOEt	10	90	155-157	155-157
2l	R_2-6-Me	COOEt	10	85	148-150	150-152
2m	R_2-7-Me	COOEt	15	92	144-146	146-148
2n	R_2-8-Me	COOEt	15	93	162-164	162-164
2o	R_2-6-Et	COOEt	15	90	170-172	168-170

[a] ***1(a-o)*** *(1 mmol) treated with active methylene compound (1 mmol) in the presence of [bnmim] OH (10 mol%).* [b]*Isolated yield based upon starting hetero aryl aldehydes*

General Procedure for the preparation of 2(a-o) and 3(a-g):

A mixture of hetero aryl aldehyde (1 mmol), active methylene compound (1 mmol) and [bnmim]OH (10 mol%) were ground at room temperature with a mortar and pestle. The completion of the reaction was monitored by TLC. The product was extracted from diethyl ether (2 × 20 mL), leaving behind [bnmim]OH. Organic layer washed by brine solution (2 × 10 mL) and dried over sodium sulfate and removed the solvent on rotary evaporator under reduced pressure. The solid obtained was recrystallized by proper solvent to get pure product. All the products were characterized by IR, ^{1}H NMR and mass spectra and by comparison of their physical characteristics with those of the authentic compounds

Table -3. Knoevenagel condensation of 4-oxo-4*H*-benzospyran-3-carbaldehyde with Meldrum's acid using [bnmim] OH by grinding

Compound[b]	R_1	R_2	R_3	Time (min)	Yield (%)[c]	m.p. (°C)[d]
3a	H	H	H	5	90	182-185
3b	H	H	Cl	5	92	198-200
3c	H	CH_3	H	5	87	186-188
3d	Cl	H	Cl	5	90	180-182
3e	CH_3	H	Cl	10	96	200-202
3f	H	Cl	Cl	10	92	242-241
3g	H	H	Br	5	93	205-206

*[a] **1(a-g)** (1 mmol) treated with Meldrum's acid (1 mmol) in the presence of [bnmim] OH (10 mol%). [b] All the compounds were characterized by IR, ^{1}H NMR and mass spectral data; [c]Isolated yield based upon starting hetero aryl aldehydes, [d]Reported melting points in Ref. [25a].*

Table-4. Recycling of [bnmim]OH for the synthesis of 2-((4-oxo-4*H*-chromen-3-yl)methylene)malononitrile 2a[a]

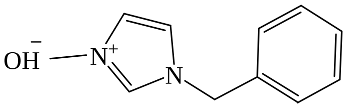
Entry	Cycle[b]	Yield (%)[c]
1	Fresh	96
2	1st	93
3	2nd	91
4	3rd	90
5	4th	88

*[a] **1a** (1 mmol) treated with malononitrile (1 mmol) in the presence of [bnmim] OH (10 mol%). [b]Reaction time-5 min. [c] Isolated yield*

RESULTS AND DISCUSSION

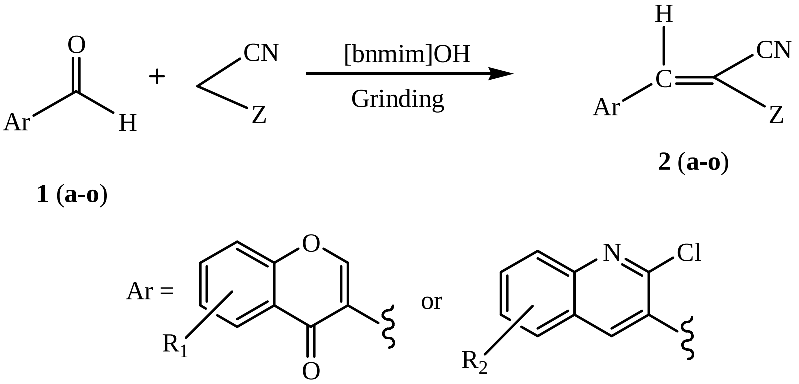
In continuation of our research work on Knoevenagel condensation [25] and development of novel synthetic methodologies [26], herein, we would like to report a facile, efficient and green methodology for the Knoevenagel condensation reaction of hetero aryl aldehydes with various active methylene compounds in the presence of catalytic amount of ([bnmim]OH) (Figure **1**) by grinding method.

Figure 1

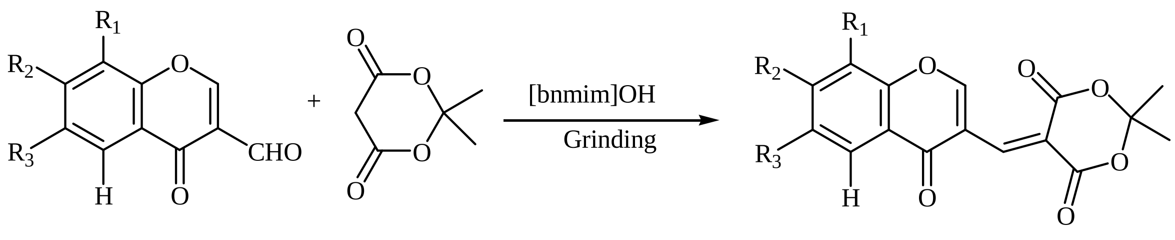


1-benzyl-3-methylimidazolium hydroxide ([bnmim]OH)

Scheme 1



Scheme 2

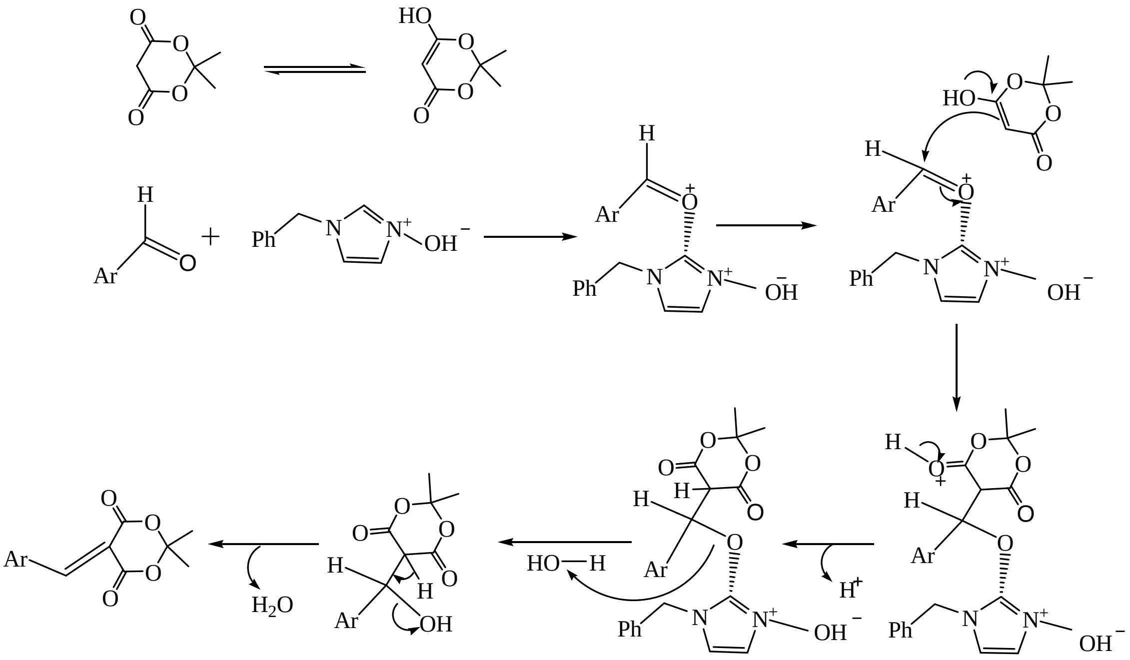


1 (a-g) **2** **3 (a-g)**

In search for the best experimental condition, the reaction of 4-oxo-(4*H*)-1-benzopyran-3-carbaldehyde **1a** with malononitrile in presence of catalytic amount of ionic liquid under grinding has been considered as the standard model reaction. We were screened different basic ionic liquids such as, 1-hexyl-2,3-dimethylimidazolium hydroxide ([hdmim]OH), 1-hexyl-3-methylimidazolium hydroxide ([hmim]OH), 1-butyl-3-methylimidazolium hydroxide ([bmim]OH) and 1-benzyl-3-methylimidazolium hydroxide ([bnmim]OH) for the model reaction. By using, [bmim]OH and [bnmim]OH, the desired product was obtained in satisfactory yields (**Table 1**, entry 3, 4). Considering the reaction time and yield of product, [bnmim]OH was selected as the optimum catalyst to promote the Knoevenagel condensation.

We have developed a newer route for the Knoevenagel condensation of different hetero aryl aldehydes with active methylene compounds in an basic ionic liquid, [bnmim]OH carried out under grinding method (**Table 2** and **3**). The reaction does not require any additional catalyst because ionic liquid acts as a catalyst as well as solvent. The liberated water during the reaction was adsorbed by the ionic liquid and hence the reactions proceed well. In this methodology, condensation reactions were completed in a shorter reaction time (5-15 min) and with excellent yields (85-96%). The results are summarized in **Table 2** and **3**. Thus, this is an excellent method for the Knoevenagel condensation reaction. The possible mechanism of this reaction is shown in Scheme 3.

Scheme 3



The reusability of the catalyst is an important factor from economical point of views and has attracted much attention in recent years. Therefore, the reusability of [bnmim]OH was examined in the model reaction under optimized reaction condition and it was observed that the [bnmim]OH was successfully reused for four cycles without significant loss of activity (**Table 4**).

CONCLUSION

We have described a facile and efficient synthetic methodology for the Knoevenagel condensation of hetero aryl aldehydes with active methylene compounds *viz.* malononitrile, ethylcyanoacetate, cyanoacetic acid, cyanoacetamide and Meldrum's acid in the presence of catalytic amount of [bnmim] OH by grinding method. The salient features offered by this method are mild reaction conditions, shorter reaction time, high selectivity, easy for product isolation and excellent yield of product. In addition, the [bnmim] OH was successfully reused for four cycles without significant loss of activity, which makes the present protocol is more economic and environmentally benign.

Selected data for compounds

2a: IR (KBr, cm^{-1}): 3050–2900 (C–H of Ar–H), 2232 (CN), 1590 (CNC), 1659 (CNO of chromone), 1461 (g-pyrone), 1090 and 1050 (C–O–C). ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 8.70 (s, 1H), 7.3 (m, 4H), 6.7 (s, 1H). MS: m/z (%) 222 [M$^+$].

2d: IR (KBr, cm^{-1}): 3300–2500 (OH of CO$_2$H), 2228.86 (CN), 1709 (CNO of CO$_2$H), 1588 (CNC), 1660 (CNO of chromone), 1460 (g-pyrone), 1088 and 1050 (C–O–C). ^{1}H NMR (300 MHz, CDCl$_3$): δ (ppm) 8.65 (s, 1H), 8.12 (m, 1H), 7.62 (dd, 1H), 7.49 (d, 1H), 6.67 (s, 1H), 2.00 (s, 3H), 10.48 (br s, 1H). MS: m/z (%) 241 [M$^+$].

2g: IR (KBr, cm^{-1}): 3350 (N–H asymmetric stretch), 3170 (N–H symmetric stretch) 3010–2980 (C–H of Ar–H), 2238.21 (CN), 1649 (CNO of amide), 1592 (CNC), 1659 (CNO group of chromone), 1460 (g-pyrone), 1089 and 1060 (C–O–C), 700–600 (broad NH out of plane bend). ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 8.66 (s, 1H), 8.13 (m, 1H), 7.62 (dd, 1H), 7.47 (d, 1H), 6.67 (s, 1H), 6.51 (br s, 2H), 2.01 (s, 3H). MS: m/z (%) 240 [M$^+$].

3a: IR (KBr, cm^{-1}): 3062, 2996, 1732, 1670 1396, 1251. ^{1}H NMR (300 MHz, CDCL$_3$) δ (ppm): 1.8 (6H, s, 2×CH$_3$), 7.2-8.1 (4H, m, aromatic), 8.7 (1H, s, olefinic), 9.6 (1H, s, C$_2$-H of chromone moiety). MS: m/z (%) 300 [M$^+$].
3d: IR (KBr, cm^{-1}): 3065, 2989, 1729, 1674, 1392, 1293, 791. ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm): 1.9 (6H, s, 2×CH$_3$), 7.2-8.2 (3H, m, aromatic), 8.6 (1H, s, olefinic), 9.5 (1H, s, C$_2$-H of chromone moiety). MS: m/z (%) 369 [M$^+$].

3g: IR (KBr, cm^{-1}): 3063, 2993, 1735, 1664, 1395, 1280, 805. ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm): 1.8 (6H, s, 2×CH$_3$), 7.2-8.2 (3H, m, aromatic), 8.6 (1H, s, olefinic), 9.6 (1H, s, C$_2$-H of chromone moiety). MS: m/z (%) 379 [M$^+$].

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