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Ultrasound-assisted an Efficient Knoevenagel Reaction Catalyzed by Ionic Liquid

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ABSTRACT

A convenient 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 1-benzyl-3-methylimidazolium dihydrogen phosphate ([bnmim]H_2PO_4) acidic ionic liquid under ultrasound at room temperature. This method affords the present method are mild reaction conditions, short reaction time, simple work-up procedure, excellent yield. Additionally, the ionic liquid was successfully reused for four cycles without significant loss of activity.

Keywords: Knoevenagel reaction, Ionic liquid, Hetero aryl aldehyde, Active methylene compound, Ultrsound.

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], , P4VP/Al_2O_3-SiO_2 [12], aminated poly (vinyl chloride) [13] and polycarbosilane supported titanium (IV) [14] have been documented in the literature for Knoevenagel condensation.

In recent years, applications of ionic liquids in organic synthesis have attracted considerable attention due to their special properties such as good solvating capability, wide liquid range, negligible vapor pressure, easy of recycling, high thermal stability and rate enhancers [15]. They have been referred as ''designer solvents'' as their physical and chemical properties could be adjusted by a careful choice of cation and anion. Also, 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 [16]. In particular, imidazolium ionic liquids has been successfully used in many organic transformations includes Diels–Alder [17a], Wittig [17b], Suzuki cross-coupling [17c], Hantzsch condensation [17d] etc. In additionally, ionic liquids with acidic counterions like 1-hexyl-3-methylimidazolium dihydrogen phosphate ([hmim]H_2PO_4) [18a] and 1-butyl-3-methylimidazolium chloroaluminate ([bmim]$Cl._2AlCl_3$) [18b] can be used as good acid catalysts. Also, our laboratory has been reported the one-pot synthesis of 3,4 dihydropyrimidin-2-(1H)-ones catalyzed by 1-benzyl-3-methylimidazolium dihydrogen phosphate ([bnmim]H_2PO_4) acidic ionic liquid under ultasonication [19].
Ultrasound accelerated chemical reactions are well known and proceed *via* the formation and adiabatic collapse of transient cavitation bubbles. Ultrasound irradiation has been demonstrated as an alternative energy source for organic reactions ordinarily accomplished by heating. Many homogeneous and heterogeneous reactions can be conducted smoothly by sonication to provide improved yields and increased selectivities [20], therefore ultrasound irradiation has been established as an important technique in organic synthesis.

MATERIALS AND METHODS

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. Ultrasonication was performed in a KQ-250E ultrasound cleaner with frequency of 40 kHz and an output power of 250W.
General Procedure for the Knoevenagel Condensation Reaction: A mixture of hetero aryl aldehyde (1 mmol), active methylene compound (1 mmol) and [bnmim]H_2PO_4 (10 mol%) were taken in a single neck round bottom flask and the flask with the reaction mixture was immersed into the water bath of an ultrasonic cleaner at room temperature for the prescribed time (Table **2** and **3)**. The completion of the reaction was monitored by TLC. The product was extracted from diethyl ether (2 × 20 mL), leaving behind [bnmim]H_2PO_4. 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 recrystalized 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.
Selected data for compounds
Compound 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^+].

Compound 2d: IR (KBr, cm^{-1}): 3300–2500 (OH of CO_2H), 2228.86 (CN), 1709 (CNO of CO_2H), 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^+].

Compound 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^+].

Compound 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^+].

Compound 3d: IR (KBr, cm^{-1}): 3065, 2989, 1729, 1674, 1392, 1293, 791. ^1H 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^+].

Compound 3e: IR (KBr, cm^{-1}): 3060, 2996, 1718, 1649, 1396, 1283, 796. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 2.5 (3H, s, Ar–CH_3), 1.9 (6H, s, 2-CH_3), 7.2-7.5 (2H, s, aromatic), 8.6 (1H, s, olefinic), 9.5 (1H, s, C_2-H of chromone moiety). MS: m/z (%) 348 [M^+].

Compound 3f: IR (KBr, cm^{-1}): 3084, 3018, 1714, 1662, 1392, 1280, 798. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.8 (6H, s, 2×CH_3), 7.2-8.3 (2H, s, aromatic), 8.6 (1H, s, olefinic), 9.5 (1H, s, C_2-H of chromone moiety). MS: m/z (%) 369 [M^+].

Compound 3g: IR (KBr, cm^{-1}): 3063, 2993, 1735, 1664, 1395, 1280, 805. ^1H 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^+].

RESULTS AND DISCUSSION

In continuation of our research work on Knoevenagel condensation [21] and development of novel synthetic methodologies [22], 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]H_2PO_4 (Figure **1**) under ultrasound at room temperature.

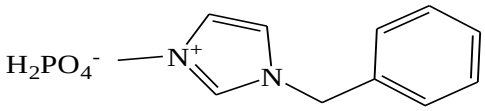


Figure 1: 1-benzyl-3-methylimidazolium dihydrogen phosphate ([bnmim]H_2PO_4)

In search for the best experimental condition, the reaction of 4-oxo-(4H)-1-benzopyran-3-carbaldehyde **1a** with malononitrile in presence of catalytic amount of ionic liquid under ultrasound at room temperature has been considered as the standard model reaction. We were screened different acidic ionic liquids such as,1-hexyl-2,3-dimethylimidazolium dazolium dihydrogen phosphate ([bnmim]H_2PO_4) for the model reaction. By using, [bmim]H_2PO_4 and [bdihydrogen phosphate([hdmim]H_2PO_4), 1-hexyl-3-methyl imidazol ium dihydrogen phosphate ([hmim]H_2PO_4), 1-butyl-3-methylimidazolium dihydrogen phosphate ([bmim]H_2PO_4) and 1-benzyl-3-methyliminmim]H_2PO_4, the desired product was obtained in satisfactory yields (Table **1**, entry 3, 4). Considering the reaction time and yield of product, [bnmim]H_2PO_4 was selected as the optimum catalyst to promote the Knoevenagel condensation.

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

Entry	Ionic liquid	Time (min)	Yield (%)[b]
1	[hdmim]H_2PO_4	15	85
2	[hmim] H_2PO_4	15	86
3	[bmim] H_2PO_4	10	90
4	[bnmim] H_2PO_4	10	94

[a] **1a** (1 mmol) treated with malononitrile (1 mmol) in the presence of different acidic ionic liquids under ultrasound at room temperature.[b] Isolated yield

The standard model reaction proceeded smoothly and was completed within 10 min of reaction time and 94 % yield. We were encouraged by the results obtained with model reaction. In a similar fashion, we have taken the different hetero aryl aldehydes containing electron-withdrawing or electron-donating groups with various active methylene compounds. They all gave the expected results with excellent yields in shorter reaction times.

We have developed a newer route for the Knoevenagel condensation of different hetero aryl aldehydes with active methylene compounds in an acidic ionic liquid, [bnmim]H_2PO_4, carried out at room temperature with constant stirring (Table **2** and **3**). The substrate 4-oxo-(4H)-1-benzopyran-3-arbaldehyde has three active sites: α, β-unsaturated carbonyl group, a carbon-carbon double bond and a formyl group. Of these, formyl has higher reactivity towards the active methylene compounds and we got exclusively single product. The condensation reaction has been successfully carried out in the [bnmim]H_2PO_4. The reaction does not require any additional catalyst because ionic liquid acts as a catalyst as well as solvent [24a,24b]. The liberated water during the reaction was absorbed by the ionic liquid and hence the reactions proceed well. All the reactions were carried out under ultrasound at room temperature i.e. using mild reaction conditions. In this methodology, condensation reactions were completed in a shorter reaction time (10-30 min) and with excellent yields (87-94%). The results are summarized in table **2** and **3**. Thus, this is an excellent method for the Knoevenagel condensation reaction.

Table 2. Knoevenagel condensation of hetero aryl aldehydes with various active methylene compounds using [bnmim]H_2PO_4 under ultrasound at room temperature[a]

Compound	Substituents	Z	Time (min)	Yield (%)[b]	m.p.(°C)	
					Found	Reported
2a	R_1=H	CN	10	94	210-212	212 [21a]
2b	R_1=6-Cl	CN	10	95	252-254	252 [21a]
2c	R_1=7-Me, 8-Cl	CN	15	94	225-227	226 [21a]
2d	R_1=6-Me	COOH	20	94	195-197	195 [21a]
2e	R_1=6-Br	COOH	25	95	184-186	186 [21a]
2f	R_1=7-Me, 8-Cl	COOH	20	92	242-244	242 [21a]
2g	R_1=6-Me	$CONH_2$	25	91	217-218	218 [21a]
2h	R_1=6-Cl	$CONH_2$	20	94	260-262	262 [21a]
2i	R_2=H	COOEt	15	92	161-163	160-162 [21a]
2j	R_2=7-OMe	COOEt	15	90	155-157	155-157 [21a]
2k	R_2=6-Me	COOEt	20	89	148-150	150-152 [21a]
2l	R_2=6-Et	COOEt	25	90	170-172	168-170 [21a]

[a] **1(a-l)** (1 mmol) treated with active methylene compound (1 mmol) in the presence of [bnmim]H_2PO_4 (10 mol%) under ultrasound at room temperature. [b]Isolated yield based upon starting hetero aryl aldehydes

Table 3. Knoevenagel condensation of 4-oxo-4H-benzospyran-3-carbaldehyde with Meldrum's acid using [bnmim]H_2PO_4 under ultrasound at room temperature[a]

Compound[b]	R_1	R_2	R_3	Time (min)	Yield (%)[c]	m.p. (^oC)[d]
3a	H	H	H	15	90	182-184
3b	H	H	Cl	10	92	198-200
3c	H	CH_3	H	20	87	186-188
3d	Cl	H	Cl	15	90	180-182
3e	CH_3	H	Cl	20	96	200-202
3f	H	Cl	Cl	15	92	242-241
3g	H	H	Br	10	93	204-206

[a] **1(a-g)** (1 mmol) treated with Meldrum's acid (1 mmol) in the presence of [bnmim]H_2PO_4 (10 mol%) at room temperature; [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. [21(d)].

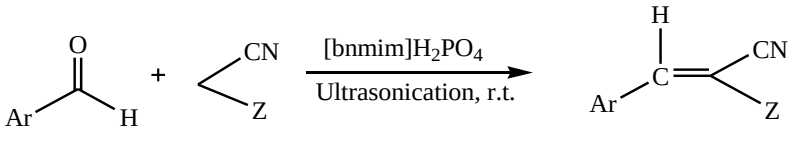
The reusability of the catalyst is an important factor from economical and environmental point of views and has attracted much attention in recent years. Therefore, the reusability of [bnmim]H_2PO_4 was examined in the model reaction under optimized reaction condition and it was observed that the [bnmim]H_2PO_4 was successfully reused for four cycles without significant loss of activity (Table **4**).

Table 4. Recycling of [bnmim]H_2PO_4 for the synthesis of 2-((4-oxo-4H-chromen-3-yl) methylene)malononitrile **2a**[a].

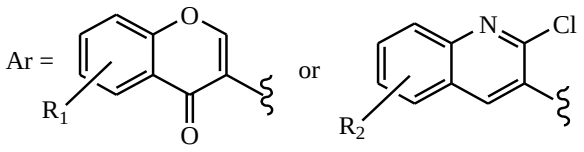
Entry	Cycle[b]	Yield (%)[c]
1	Fresh	94
2	1st	92
3	2nd	90
4	3rd	89
5	4th	87

[a] **1a** (1 mmol) treated with malononitrile (1 mmol) in the presence of [bnmim]H_2PO_4 (10 mol%) under ultrasound at room temperature. [b]Reaction time-10 min. [c] Isolated yield

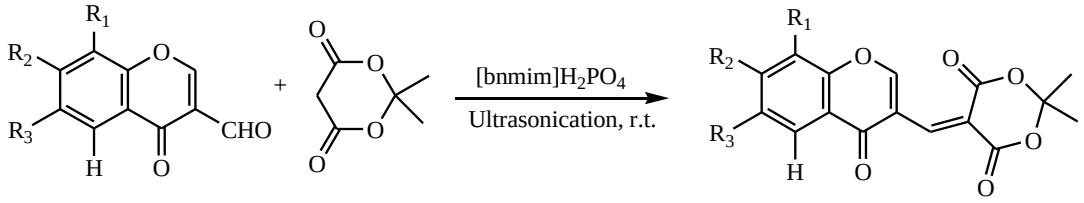
The reaction schemes 1and 2 were given below



1 (a-l) **2 (a-l)**



Scheme 1



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

Scheme 2

CONCLUSIONS

We have described a facile and efficient synthetic methodology for the Knoevenagel condensation of substituted hetero aryl aldehydes with active methylene compounds in the presence of catalytic amount of [bnmim]H_2PO_4 under ultrasound at room temperature. The salient features offered by this method are mild reaction conditions, shorter reaction time, simple work-up procedures and excellent yield of product. In addition, the [bnmim]H_2PO_4 was successfully reused for four cycles without significant loss of activity, which makes the present protocol is more economic and environmentally benign.

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