

## Ammonium-type Basic Ionic Liquid; 2-(2-Hydroxyethoxy)ethaneammonium Formate: Promote Green and Efficient Multicomponent Tandem Synthesis of 4*H*-pyrans and 4*H*-chromenes

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A facile, convenient, green and environmentally benign one-pot three-component synthesis of poly-functionalized 4*H*-pyrans and 4*H*-chromenes is described. A basic ionic liquid 2-(2-hydroxyethoxy)ethaneammonium formate was found to be an efficient catalyst or catalytically active solvent for the synthesis of those important classes of heterocyclic compounds.

**Keyword:** 4*H*-pyran, 4*H*-chromene, Basic ionic liquid, 2-(2-Hydroxyethoxy)ethaneammonium formate, One-pot three-component synthesis

### INTRODUCTION

Ionic liquids (ILs), previously known as molten salts are composed of bulk organic quaternary cations and inorganic small anions with melting points below 100 °C or near room temperature. By the chemical modification of both cations and anions in the structure of the resulting ILs, the liquid properties such as density, polarity, viscosity, melting point and hydrophobicity are tunable. Ionic liquids have certain advantages, such as extremely low vapor pressure, high thermal stability, good ion conductivity, easy recovery, reusability and capability to dissolve many organic and inorganic substrates [1-9].

ILs has recently attracted increased interest in green organic and bio-organic reactions as solvent or catalysts in both homogeneous and heterogeneous conditions [10-17]. Basic ionic liquids (BILs) offer a new opportunity for growing environmentally friendly basic catalysts, show off excellent capacity for the alternative of inorganic or conventional bases and were effectively employed as solvents, catalyst and green reaction media for a variety of

reactions [18-36]. The BILs divide into two categories:

Lewis BILs and Bronsted BILs. Simple literature survey showed that most important and well-known BILs are consisting of ammonium [18-21], imidazolium [22-30], DBU [31,32], guanidinium [33], pyrrolidinium [28, 31, 34], DABCO [35,36]-type cations and generally used anions (X<sup>-</sup>) including OH<sup>-</sup>, and weak acid anions: lactate, formate and acetate.

Multi-component reactions are one of the most important approaches for the one-pot synthesis of heterocyclic compounds due to their valuable features such as good atomic efficiency and high selectivity [37-46]. 4*H*-pyrans and 4*H*-chromene are the most important classes of heterocyclic compounds and are also important building blocks of various biologically active and natural products. They are used as antibacterial, antiviral, antitumor drugs [47-49]. 4*H*-pyrans are also used in the treatment of neurodegenerative diseases such as Alzheimer's and Parkinson's disease [50]. A variety of reactions have been evolved along with two-step as well as the one-pot three-component synthesis of these elegant compounds. One of those is the multicomponent cyclocondensation of an aldehyde with different active methylene compounds.

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Various types of homogeneous or heterogeneous catalysts in acidic or basic conditions have been applied to these transformations [51-61]. Although these procedures are suitable for the synthesis of 4*H*-chromenes and 4*H*-pyrans, the improvement of an efficient and appropriate approach still remains an attractive goal for researchers. This article reports a facile, convenient and environmentally benign one-pot three-component synthesis of poly-functionalized 4*H*-pyrans and 4*H*-chromenes using basic ionic liquid 2-(2-hydroxyethoxy)ethaneammonium formate as a reaction promoter. To our knowledge, no other studies have been reported on the applications of this BIL in organic synthesis.

## EXPERIMENTAL

All reagents were purchased from Merck and Floka and used without further purification. All yields refer to isolated products after purification. Products were recognized by evaluation in their physical and spectra records (IR, Mass, <sup>1</sup>H and <sup>13</sup>C NMR) with those reported in the literature. TLC was performed on silica-gel 60 GF254. Melting points have been corrected and determined on Barnstead/Electrothermal 9100 apparatus. FT-IR spectra were recorded on Bruker FT-IR, Vector-22 spectrophotometer in KBr pellets. Mass spectra were recorded on an Agilent-5975C inert XL MSD (70 eV, EI). The NMR spectra were recorded on a Bruker NMR (<sup>1</sup>H NMR: 400.22 MHz, <sup>13</sup>C NMR: 100.64 MHz). The spectra were measured in DMSO-d<sub>6</sub> relative to TMS (0.00 ppm). Basic ionic liquid 2-(2-hydroxyethoxy)ethaneammonium formate 3 was synthesized according to the formerly reported method [62]. Selected characterization data are available in "Supplementary Materials".

### General Procedure for the Catalytic Synthesis of 4*H*-pyrans

A mixture of an aromatic aldehyde (1 mmol), malononitrile (1 mmol) and ethyl acetoacetate or acetylacetone (1 mmol) was added to the mixture of basic ionic liquid and ethanol (1:5) (1.5 ml), as a catalytically active solvent. The resulting reaction mixture was stirred at room temperature and the progress of the reaction was monitored by TLC plate in a *n*-hexane:ethyl acetate 9:1 mixture. After completion of the reaction, 20 ml of cool water was added

to the mixture for completion of the precipitation and removal of basic ionic liquid. Then, the crude product was collected by filtration, air-dried and recrystallized from EtOH to obtain pure products with good to excellent yields (Table 2).

### General Procedure for the Catalytic Synthesis of 4*H*-chromenes

One drop of basic ionic liquid (0.06 mmol) was added to the mixture of aromatic aldehyde (1 mmol), malononitrile (1 mmol) and 2-naphthol or 1-naphthol (1 mmol). Then, the mixture was fixed in an oil bath at 100 °C under a solvent-free condition for an appropriate time. The progress of the reaction was monitored by TLC plate in a *n*-hexane:ethyl acetate 9:1 mixture. After completion of the reaction, the crude solid product was washed with cold ethanol (15 ml). The product was dissolved in a smallest quantity of DMF and gently recrystallized after addition of 5 ml H<sub>2</sub>O to afford good yields of pure product (Table 4).

## RESULTS AND DISCUSSION

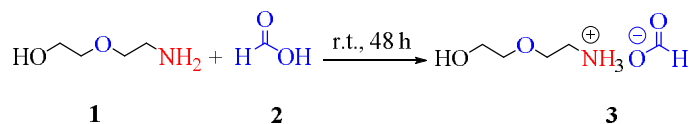
### Synthesis 2-(2-Hydroxyethoxy)ethaneammonium formate

Basic ionic liquid 2-(2-hydroxyethoxy)ethaneammonium formate 3 was synthesized according to the formerly reported method (Scheme 1) [62]. The as-synthesized BIL was characterized by comparison with authentic samples and by physical and spectroscopy data (IR, <sup>1</sup>H and <sup>13</sup>C NMR).

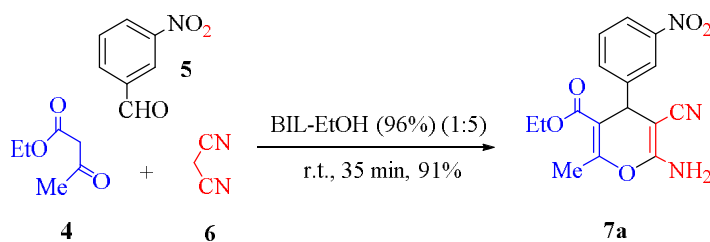
### Synthesis of 4*H*-pyrans

Initially, to optimize the experimental conditions for the synthesis of 4*H*-pyrans, we focused on the reaction between 3-nitrobenzaldehyde 4, malononitrile 5 and ethyl acetoacetate 6 as the model reaction (Scheme 2). As shown in Table 1, the reaction was carried out in various solvent systems and distinct quantities of basic ionic liquid. The best result for the model reaction was obtained with catalytically active solvent basic ionic liquid/ethanol (96%) (1:5) (Table 1, entry 7).

Subsequently, for the synthesis of 4*H*-pyran derivatives, a range of various aryl aldehydes with electron-withdrawing



Scheme 1. Preparation of basic ionic liquid, 2-(2-hydroxyethoxy)ethaneammonium formate

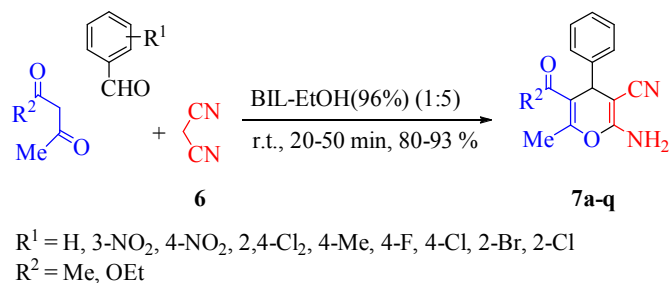
Scheme 2. Model reaction for the synthesis of 4*H*-pyrans**Table 1.** Optimization of the Reaction Conditions for the Synthesis of 7a

Entry	IL/solvent <sup>a</sup>	Time (min)	Yield (%) <sup>b</sup>
1	Ethanol 96% <sup>c</sup>	120	0
2	BIL (0.18 mmol) <sup>d</sup> -ethanol 96%	120	62
3	BIL (1 ml)	30	90
4	BIL-EtOH 96% (1:1)	20	88
5	BIL-EtOH 96% (1:2)	20	88
6	BIL-EtOH 96% (1:3)	30	86
7	BIL-EtOH 96% (1:5)	35	91
8	BIL-EtOH 96% (1:7)	60	79
9	BIL-CTAB (3 CMC) (1:2)	60	45
10	BIL-SDS (3 CMC) (1:2)	40	70
11	BIL-water (1:1)	50	60

<sup>a</sup>Catalyst-solvent = 1.5 ml. <sup>b</sup>Isolated yield. <sup>c</sup>Cheap solvent that is available commercially. <sup>d</sup>One drop with Pasteur pipette.

and releasing group were reacted with malononitrile and acetylacetone or ethyl acetoacetate to yield a corresponding

product (Scheme 3). As can be seen in Table 2, aryl aldehyde with an electron-withdrawing group, such as

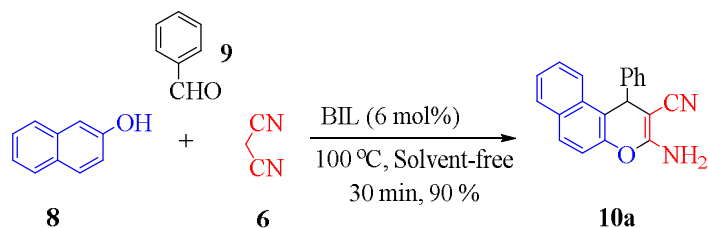


Scheme 3. Synthesis of 4H-pyran derivatives

**Table 2.** Synthesis of 4H-pyran Derivatives under the Above-mentioned Conditions

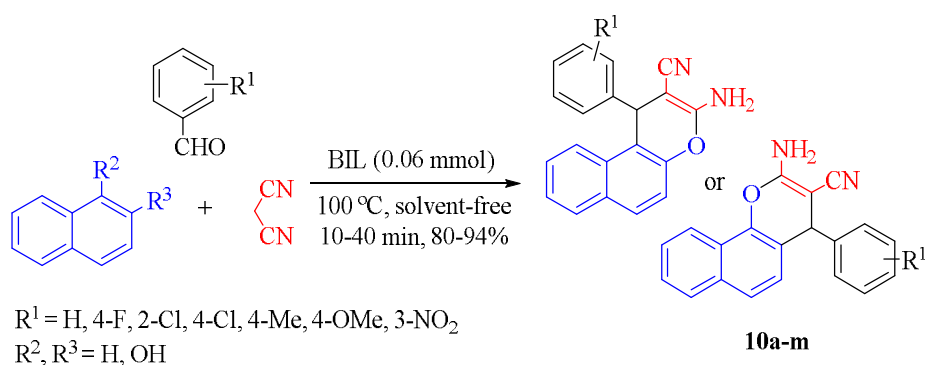
Entry	R <sup>1</sup>	R <sup>2</sup>	Product	Time (min)	Yield (%) <sup>a</sup>	M. P. (°C)
1	3-NO <sub>2</sub>	OEt	7a	35	91	181-183
2	H	OEt	7b	35	85	184-186
3	2,4-Cl <sub>2</sub>	OEt	7c	30	90	144-145
4	4-NO <sub>2</sub>	OEt	7d	20	93	173-175
5	4-OMe	OEt	7e	300	- <sup>b</sup>	-
6	4-Cl	OEt	7f	25	92	171-174
7	4-Me	OEt	7g	50	82	174-177
8	4-F	OEt	7h	25	88	169-171
9	2-Br	OEt	7i	20	88	178-182
10	2-Cl	OEt	7j	32	87	189-191
11	3-NO <sub>2</sub>	Me	7k	20	88	218-220
12	H	Me	7l	35	82	153-155
13	4-Cl	Me	7m	25	82	159-160
14	4-F	Me	7n	30	85	162-165
15	2-Br	Me	7o	25	86	123-126
16	4-Me	Me	7p	50	80	130-131
17	2-Cl	Me	7q	30	82	122-125

<sup>a</sup>Isolated Yield. <sup>b</sup>After 5 h, a mixture of products was obtained.

Scheme 4. Model reaction for the synthesis of 4*H*-chromene derivative**Table 3.** Optimization of the Reaction Conditions for the Synthesis of 10a

Entry	IL/solvent	Temperature (°C)	Time (min)	Yield (%) <sup>a</sup>
1	None	r.t.	120	0
2	BIL (0.18 mmol) <sup>b</sup>	r.t.	120	0
3	BIL (0.18 mmol)	80	60	62
4	BIL (0.18 mmol)	100	25	90
5	BIL (0.12 mmol) <sup>c</sup>	100	30	90
6	BIL (0.06 mmol) <sup>d</sup>	100	30	90
7	BIL-EtOH 96% (1:5)	r.t.	120	0
8	BIL-EtOH 96% (1:5)	Reflux	60	0
9	BIL (0.18 mmol)-acetonitrile (1 ml)	Reflux	90	35
10	BIL (0.18 mmol)-water (1 ml)	Reflux	50	81

<sup>a</sup>Isolated yield. <sup>b</sup>One drop with Pasteur pipette. <sup>c</sup>Two drops with a microsyringe. <sup>d</sup>One drop with a microsyringe.

Scheme 5. Synthesis of 4*H*-chromenes

**Table 4.** Synthesis of 4*H*-pyran Derivatives under the Optimum Conditions

Entry	R <sup>1</sup>	Naphthol	Product	Time (min)	Yield (%) <sup>a</sup>	M. P. (°C)
1	H	2-Naphthol	10a	30	90	287-288
2	4-F	2-Naphthol	10b	20	92	226-227
3	2-Cl <sub>2</sub>	2-Naphthol	10c	13	91	269-270
4	4-Cl	2-Naphthol	10d	10	94	215-216
5	4-Me	2-Naphthol	10e	40	84	266-267
6	3-NO <sub>2</sub>	2-Naphthol	10f	12	92	238-239
7	4-OMe	2-Naphthol	10g	50	78	195-197
8	H	1-Naphthol	10h	30	87	213-216
9	2-Cl	1-Naphthol	10i	12	91	242-244
10	4-Cl	1-Naphthol	10j	10	93	234-237
11	4-F	1-Naphthol	10k	15	90	227-229
12	3-NO <sub>2</sub>	1-Naphthol	10l	12	90	213-215
13	4-Me	1-Naphthol	10m	30	85	201-203

<sup>a</sup>Isolated yield.

bromo and nitro, react faster and have better yields than those with an electron-releasing group such as methyl and methoxy. The methoxy group on *para* position of aryl aldehyde resulted in a mixture of product after 5 h (Table 2, entry 5).

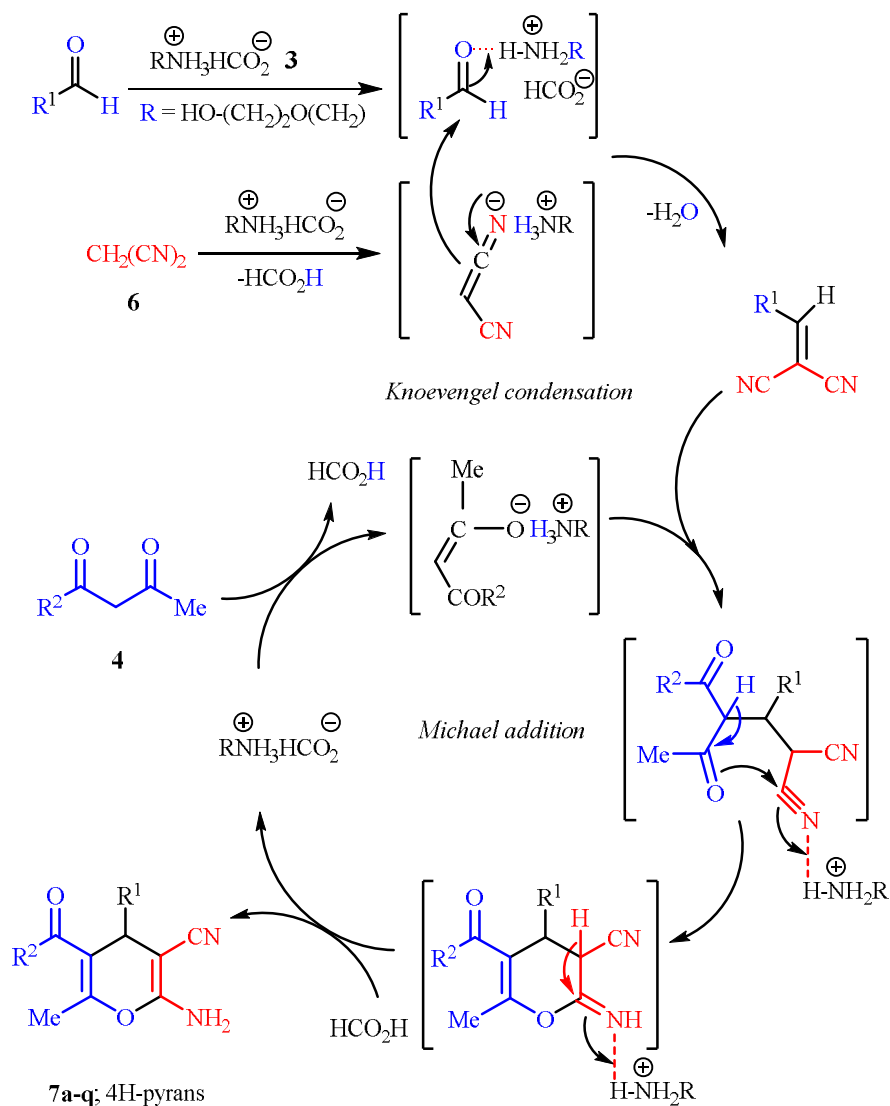
### Catalytic Synthesis of 4*H*-chromenes

At first, the reaction between benzaldehyde 8, malononitrile 5 and 2-naphthol 9 was considered as a test reaction for the synthesis of 2-amino-4*H*-chromene 10a (Scheme 4). As can be seen in Table 3, the reaction was carried out in various solvent systems, different amounts of basic ionic liquid and distinct temperatures. The best result was obtained with a catalytic amount of basic ionic liquid in 100 °C (Table 3, entry 6). To demonstrate the performance of this methodology for the synthesis of 2-amino-4*H*-chromene derivatives, a variety of different aryl aldehydes

were reacted with malononitrile and 2-naphthol or 1-naphthol to yield the corresponding 4*H*-chromene product (Scheme 5). As shown in Table 4, aryl aldehyde with an electron withdrawing group reacted faster than those with an electron releasing group.

### Plausible Mechanism

As expected from the literature data, the mechanism of the reaction initially proceeded *via* Knoevenagel condensation in which catalytic amount of basic ionic liquid promotes the reaction by abstracting a proton from the malononitrile. Bezylididenemalononitrile intermediate may form with the aldehyde that consequently reacts through Michael addition. Finally, cyclization and tautomerization afford the corresponding 4*H*-pyran (Scheme 6). The mechanism for treatment of naphthol with aldehyde for the synthesis of 4*H*-chromenes by a few differences is generally



Scheme 6. Plausible mechanisms of 4H-pyrans synthesis

similar to the mentioned process.

## CONCLUSIONS

In Conclusions, we have reported a facile, convenient and environmentally benign one-pot three-component synthesis of poly-functionalized 4H-pyrans and 4H-chromenes using basic ionic liquid 2-(2-hydroxyethoxy) ethan ammonium formate as a reaction promoter. In this research, we have efficaciously advanced the methodologies

that offer several advantages such as excessive yields, easy and mild experimental procedures, low reaction times, use of cheap and available starting materials and very simple work up.

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