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Mild basic ionic liquid catalyzed four component synthesis of functionalized benzo[a]pyrano[2,3-c]phenazine derivatives

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ABSTRACT

An efficient, mild, and one-pot quantitative procedure for the preparation of functionalized benzo[a]pyrano[2,3-c] phenazine derivatives from four component reaction of 2-hydroxynaphthalene-1,4-dione, *o*-phenylenediamine, aldehydes, and malononitrile in the presence of basic ionic liquids such as 1-butyl-3-methylimidazolium hydroxide, 3-hydroxypropanaminium acetate, pyrrolidinium formate, pyrrolidinium acetate, 1,8-diazabicyclo[5.4.0]-undec-7-en-8-ium acetate, and piperidinium formate as the catalysts has been developed. The ionic liquid was stable during the reaction process and could also be reused several times with consistent activity. This procedure may be a practical alternative to the existing one reported procedure to meet the need of academe as well as industries.

1. Introduction

Ionic liquids (ILs) have received considerable attention as environmentally benign reaction medium as solvent and catalysts for chemical reactions [1–3]. The organic reaction can be carried out in a homogeneous phase and the ionic liquid can be recycled in a green procedure [1–5]. The importance of the ionic liquid has been effectively utilized for the design of novel bioactive compounds [1–6].

Phenazines are present in natural and synthetic products showing a variety of biological functions, including antimalarial [7,8], trypanocidal [9], fungicidal [10,11], antitumor, and antiplatelet8 activities. In addition, chromenes moiety has been exhibited remarkable effects as pharmaceuticals [12,13], including antifungal [14,15] and antimicrobial activities [16]. Molecules with phenazines [17] and chromenes [18] moieties have attracted great attention in drug discovery. Functionalized benzo[a]pyrano[2,3-c]phenazine derivatives have these moieties.

The designs of multi-component reactions (MCRs) for the synthesis of diverse groups of compounds, especially the ones that are biologically active, have commanded great attention in green organic synthesis [19–21]. Thus, in continuation of our research on applications of ionic liquids in multi-component reactions [22–24], herein, we wish to describe the preparation of functionalized benzo[a]pyrano [2,3-c] phenazine derivatives with phenazines and chromenes moieties from four component reaction of 2-hydroxynaphthalene-1,4-dione, *o*-phenylenediamine, aldehydes, and malononitrile in the presence of basic ionic liquids such as 1-butyl-3-methylimidazolium hydroxide [Bmim]OH, 3-hydroxypropanaminium acetate [3-HPAA], pyrrolidinium formate [Pyrr][HCOO], pyrrolidinium acetate [Pyrr][CH_3COO], 1,8-diazabicyclo[5.4.0]-undec-7-en-8-ium acetate [DBU][CH_3COO], and piperidinium formate [Pip][HCOO] as the catalysts under solvent-free conditions (Scheme 1).

Literature survey showed us that a few research was done on the mentioned ionic liquids. Several products were prepared using [Bmim] OH as catalyst such as 3-benzamidocoumarins [25], quinazoline-2,4(1*H*,3*H*)-diones [26], and 2-amino-2-chromenes [27]. [3-HPAA] was used in synthesis of 2-amino-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile derivatives [28]. The volumetric properties of [Pyrr][HCOO] were studied [29]. [Pyrr][CH_3COO] was applied in Knoevenagel condensation [30]. DBU[CH_3COO] was used in aza-conjugate addition of amines to various electron deficient alkenes [31].

2. Experimental

All reagents were purchased from Merck and Aldrich and used without further purification. The weak basic ionic liquids such as 1-butyl-3-methylimidazolium hydroxide [32], 3-hydroxypropanaminium acetate [28], pyrrolidinium formate [33], pyrrolidinium acetate [33], 1,8-diazabicyclo[5.4.0]-undec-7-en-8-ium acetate [31], and piperidinium formate [34] were prepared according to the reported procedure. All yields refer to isolated products after purification. The NMR spectra were recorded on a Bruker Avance DPX 300 MHz instrument. The spectra were measured in DMSO-d_6 relative to TMS (0.00 ppm). IR spectra were recorded on a JASCO FT-IR 460

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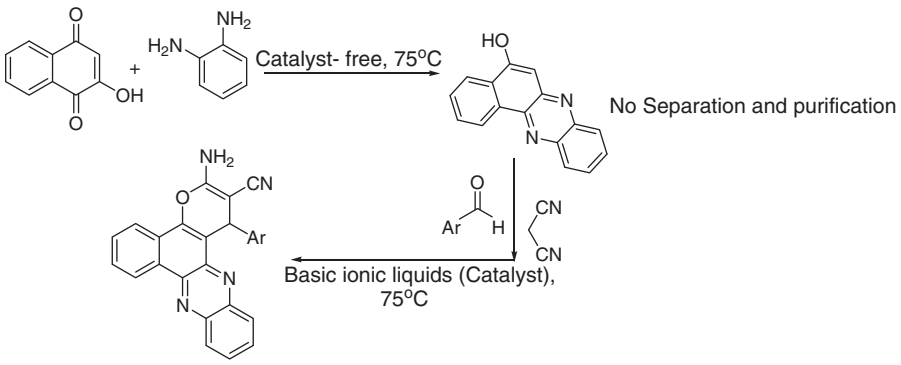

Scheme 1. One-pot synthesis of 3-amino-2-cyano-1-aryl-1*H*-benzo[a]pyrano[2,3-c]phenazines derivatives.

plus spectrophotometer. TLC was performed on silica-gel Poly Gram SIL G/UV 254 plates.

2.1. General procedure for the synthesis of functionalized benzo[a]pyrano [2,3-c]phenazine derivatives under solvent-free conditions

2-Hydroxynaphthalene-1,4-dione (10 mmol) and *o*-phenylenediamine (10 mmol) were mixed at 75 °C until an orange solid of benzo[a]phenazine was formed (<5 min). Then, aryl aldehydes (10 mmol), malononitrile (10 mmol), and ionic liquids including 1-butyl-3-methylimidazolium hydroxide (15 mol%), 3-hydroxypropanaminium acetate (16 mol%), pyrrolidinium formate (18 mol%), pyrrolidinium acetate (17 mol%), 1,8-diazabicyclo[5.4.0]-undec-7-en-8-ium acetate (19 mol%), and piperidinium formate (16 mol%) as weak basic catalyst were added and stirred under thermal solvent-free conditions at 75 °C for the specific time. After completion of the reaction, 5 mL of water was added to the mixture. The ionic liquid was dissolved in water, and filtered for separation of the crude product. The separated product was

Table 1
Optimization conditions for the preparation of 3-amino-2-cyano-1-(4-chloro-phenyl)-1H-benzo[a]pyrano[2,3-c]phenazine from 2-hydroxynaphthalene-1,4-dione, *o*-phenylenediamine, 4-chlorobenzaldehyde, and malononitrile in the presence of different amounts of ionic liquids A: 1-butyl-3-methylimidazolium hydroxide, B: 3-hydroxypropanaminium acetate, C: pyrrolidinium formate, D: pyrrolidinium acetate, E: 1,8-diazabicyclo[5.4.0]-undec-7-en-8-ium acetate, and F: piperidinium formate, as catalysts under verities temperature.

Entry	Catalyst (mol%)						Temperature (°C)	Time (min)						Yield (%)[a]					
	A	B	C	D	E	F		A	B	C	D	E	F	A	B	C	D	E	F
1	20	18	18	20	22	18	25	34	42	32	34	28	32	40	31	30	30	31	32
2	32	25	26	28	30	26	25	30	34	30	30	26	30	46	40	40	43	40	41
3	15	12	10	14	15	15	50	21	31	22	24	24	24	50	52	50	52	48	50
4	23	17	23	22	20	20	50	20	24	18	20	20	18	60	60	61	60	60	62
5	30	25	32	28	29	28	50	14	19	13	12	15	15	66	63	66	65	67	69
6	10	10	12	12	11	10	75	10	11	10	10	13	11	85	82	84	83	81	82
7	15	16	18	17	19	16	75	6	7	8	7	9	8	94	92	93	92	92	93
8	20	20	23	23	25	21	75	6	7	8	7	9	8	94	92	94	92	93	93

[a] Yields refer to isolated pure product.

Table 2
Four component synthesis of 3-amino-2-cyano-1-aryl-1H-benzo[a]pyrano[2,3-c]phenazine derivatives from the reaction of 2-hydroxynaphthalene-1,4-dione, *o*-phenylenediamine, malononitrile and aldehydes in the presence of A: [Bmim]OH, B: [3-HPAA], C: [Pyrr][HCOO], D: [Pyrr][CH_3COO], E: [DBU][CH_3COO], and F: [Pip][HCOO] as catalysts.

Entry	Aldehydes	Time (min)						Yield (%)[a]						Melting point m.p (°C)/Lit. m.p (°C)[Ref]
		A	B	C	D	E	F	A	B	C	D	E	F	
1	Ph	7	7	9	8	10	8	92	91	91	90	91	91	299–302/(298–300) [35]
2	4-ClC_6H_4	6	7	8	7	9	8	94	92	93	92	92	93	291/(288–291) [35]
3	4-$NO_2C_6H_4$	7	8	8	8	9	9	92	91	92	91	92	92	284–285/(281–283) [35]
4	4-MeC_6H_4	6	7	8	7	9	8	90	90	90	89	88	91	295/(293–294) [35]
5	4-F C_6H_4	6	7	8	8	9	8	91	90	91	91	89	91	275/(274–276) [35]
6	4-BrC_6H_4	6	7	8	8	9	8	91	91	91	91	89	91	284–286/(283–285) [35]
7	3-$NO_2C_6H_4$	7	7	9	9	10	9	92	91	92	91	90	89	279–281/(278–279) [35]
8	2-$CH_3OC_6H_4$	7	6	7	7	9	8	89	89	89	89	88	89	273/(270–272) [35]
9	4-OH-3-$CH_3OC_6H_3$	7	7	8	8	9	8	89	88	89	89	87	88	249/(247–248) [35]
10	4-OH-3-$NO_2C_6H_3$	6	7	7	8	10	9	89	89	90	90	89	89	291–292/(290–291) [35]
11	2,3-di $CH_3OC_6H_3$	7	6	9	9	10	9	90	89	89	89	88	88	295/(292–294) [35]
12	3,4,5-tri $CH_3OC_6H_2$	7	7	9	9	10	9	89	88	88	88	87	87	253–255/(252–254) [35]
13	*n*-Heptanal	24 h	–	–	–	–	–	–	–	–	–	–	–	–

[a] Yields refer to the isolated pure products. The desired known pure products were characterized by the comparison of their physical data (melting points, IR, ^1H and ^{13}C NMR) with those of known compounds.