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$[(EtO)_3Si(CH_2)_3N^+H_3][CH_3COO^-]$ as Basic Ionic Liquid Catalyst Promoted Green Synthesis of Benzo[*a*]pyrano[*2,3-c*]phenazine Derivatives in Homogenous Solution

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Abstract

An efficient, one-pot quantitative procedure for the preparation of benzo[*a*]pyrano[2,3-c]phenazine derivatives from four-component condensation reaction of 2-hydroxynaphthalene-1,4-dione, benzene-1,2-diamine, aromatic aldehydes, and malononitrile in the presence of $[(EtO)_3Si(CH_2)_3N^+H_3][CH_3COO^-]$ as basic ionic liquid as catalyst in homogenous solution under solvent-free conditions at 90 °C is described. Simple procedure, high yields, short reaction times, and an environmentally benign method are advantages of this protocol. The $[(EtO)_3Si(CH_2)_3N^+H_3][CH_3COO^-]$ can be recovered and reused several times without loss of its activity.

Keywords Green conditions · Recyclable catalyst · $[(EtO)_3Si(CH_2)_3N^+H_3][CH_3COO^-]$ · Ionic liquid · Solvent-free · Benzo[*a*]pyrano[*2,3-c*]phenazine

1 Introduction

The main feature of the catalysis science in this century is protection of environment and human health by omission of hazardous materials and use safe non-volatile ionic liquids [1]. Ionic liquids are interesting due to high polarity [2], negligible volatility [3], high thermal stability [4], and tunable structures which have been extensively developed to promote of various organic reactions [5]. The properties of ionic liquids differ by change in their cation/anion parts and despite the influence of the anion constituent on the properties of ionic liquids, their cationic parts are mainly based on guanidine [6], amines [7], and heterocyclic salts of pyridinium [8], thiazolium [9], imidazolium [10], or triazolium rings (Fig. 1) [11]. Bronsted acid and protic Ionic liquids (PILs) are among the best green alternatives for corrosive acid catalysts/solvents in chemical transformations [12].

In order to make possible economic savings and pollution prevention, multi-component domino reactions (MDRs), have considerable potential for the synthesis of complex heterocyclic molecules and for drug design and drug discovery, arising from minimization of

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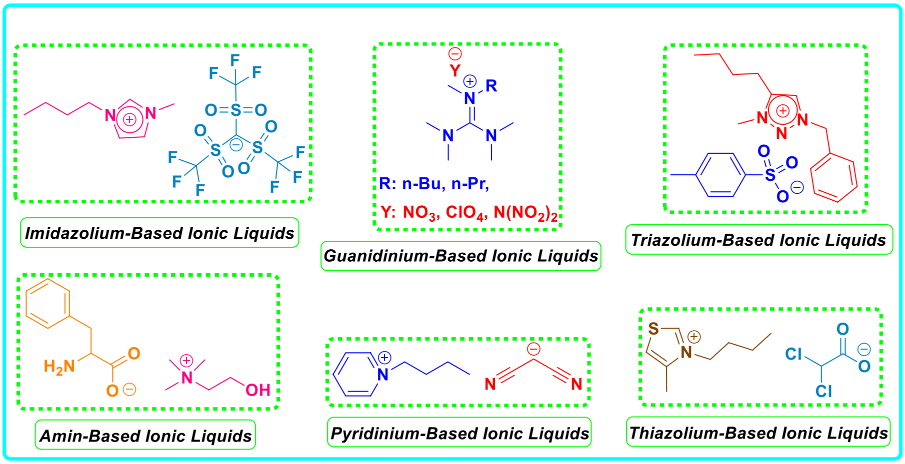


Fig. 1 Samples of various ionic liquids

time, waste, energy, and cost [13]. Phenazine based compounds are nitrogen-containing heterocycles that are present in natural products and synthetic materials showing a variety of biological functions [14], including antibiotic [15], antimicrobial [16], antimalarial [17] and antiparasitic activities [18]. By virtue of their DNA intercalating ability, they exhibit anticancer activity in leukemia and solid tumors [19]. For example, pyridophenazinediones [20] and pyridazinophenazinedione [21] derivatives are known for their antitumor activities (Fig. 2).

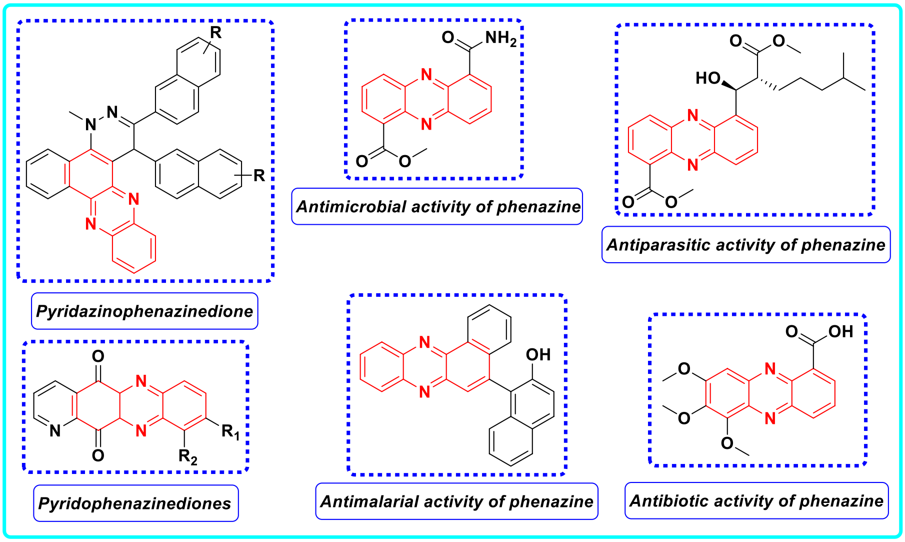
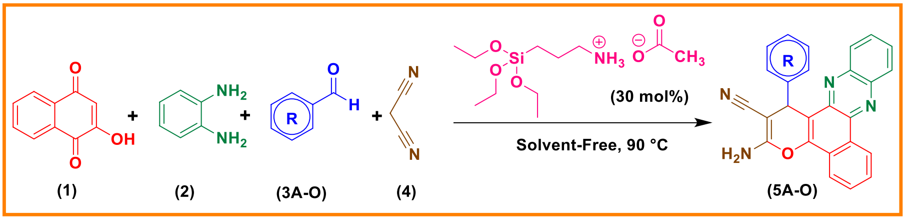


Fig. 2 Some biologically active derivatives of Phenazines



Scheme 1 Preparation of benzo[*a*]pyrano[*2,3-c*]phenazine derivatives in the presence of $[(EtO)_3Si(CH_2)_3N^+H_3][CH_3COO^-]$ as a basic ionic liquid catalyst

In continuation of our research on the synthesis and applications of homogenous and heterogeneous catalysts in organic chemistry [22, 23], here, we use the $[(EtO)_3Si(CH_2)_3N^+H_3][CH_3COO^-]$ as basic ionic liquid, and reusable catalyst for the one-pot synthesis of benzo[*a*]pyrano[*2,3-c*]phenazine derivatives by four-component condensation of 2-hydroxynaphthalene-1,4-dione, benzene-1,2-diamine, malononitrile and arylaldehydes at 90 °C under solvent-free conditions (Scheme 1).

2 Experimental

2.1 Materials and methods

All reagents were purchased from Merck or Aldrich and used without any further purification. The purities of the starting materials used in the our research were 2-hydroxy-1,4-naphthoquinone (98%), benzene-1,2-diamine (98%), malononitrile (99%), (3-aminopropyl)triethoxysilane (98%), and aromatic aldehydes (98–99%). All yields refer to isolated products after purification. Nuclear magnetic resonance (^{1}HNMR) and Carbon-13 nuclear magnetic resonance (^{13}CNMR) spectra were recorded using a Bruker Advance DPX 300 MHz instrument. The spectra were provided in DMSO-d_6 as deuterated solvent. Fourier Transform Infrared (FT-IR) spectra were recorded using a JASCO FT-IR 460 Plus spectrophotometer. Melting points were determined in open capillaries using a BUCHI 510 melting point apparatus. Thin layer chromatography (TLC) was performed on silica-gel Poly Gram SIL G/UV 254 plates.

2.2 Preparation of $[(EtO)_3Si(CH_2)_3N^+H_3][CH_3COO^-]$

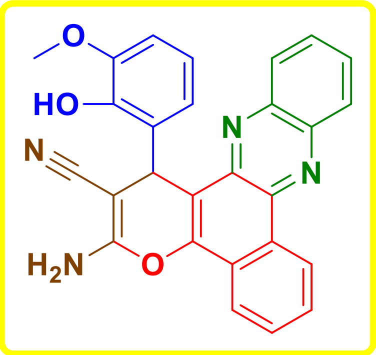
According to the literature [22], APTES ((3-aminopropyl)triethoxysilane) (10 mmol) was placed in a two necked flask equipped with a reflux condenser and a dropping funnel. The flask was placed in an ice bath. Under vigorous stirring with a magnetic stirring bar, acetic acid (10 mmol) was added dropwise to the flask in about 60 min. Stirring was continued for 24 h at room temperature, to obtain a viscous yellow liquid. The ionic liquid was prepared. The stable ionic liquid sample could be stored at room temperature for over 6 month. The ionic liquid was identified by FT-IR, ^{1}HNMR and ^{13}CNMR spectra [22].

2.3 General Procedure for the Direct Synthesis of Benzo[*a*]pyrano[*2,3-c*]phenazine (5A–O) Derivatives Using $[(EtO)_3Si(CH_2)_3N^+H_3][CH_3COO^-]$ as Basic Ionic Liquid Catalyst

$[(EtO)_3Si(CH_2)_3N^+H_3][CH_3COO^-]$ (30 mol%) was added to a mixture of 2-hydroxynaphthalene-1,4-dione (1 mmol) and benzene-1,2-diamine (1 mmol) at 90 °C. After 5 min an orange solid of benzo[*a*]phenazine was formed. Then, aryl aldehydes (1 mmol), and malononitrile (1 mmol), were added to this obtained mixture. The progress of the reaction was monitored by TLC (petroleum benzene/ethyl acetate: 1/3). After completion of the reaction, ethanol (3 mL) was added to the reaction mixture and warmed mixture. Then, mixture was cooled, the ionic liquid as catalyst is dissolved in ethanol. The ethanol containing the catalyst is separated and then the resulting solid product was subsequently recrystallized from hot ethanol to give the pure solid. The synthesis of all the known products were approved by the comparison of their melting point, FT-IR, ^{1}HNMR and ^{13}CNMR spectra with those of authentic literature samples. The new products were identified by FT-IR, ^{1}HNMR and ^{13}CNMR spectra. The new unknown products are characterized as follows:

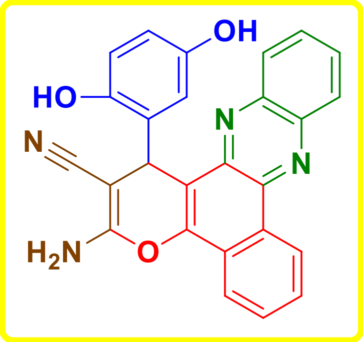
2.4 Experimental Characterization Data and Spectra of the New Compounds

3-Amino-1-(2-hydroxy-3-methoxyphenyl)-1*H*-benzo[*a*]pyrano[*2,3-c*]phenazine-2-carbonitrile (5E): Time: 55 min, Yield (%): 89%, M.p. (°C) (Observed): 267–269; IR (KBr) (ν_{max}/cm^{-1}): 3440, 3374, 3316, 3199, 3069, 2169, 1663, 1630, 1594, 1513, 1461, 1386, 1346, 1293, 1248, 1221, 1174, 1159, 1140, 1110, 1052, 953, 855, 826, 794, 771, 749, 735, 724, 656, 640, 621, 583, 554, 527, 476, 448, 413; ^{1}HNMR (300 MHz, DMSO-d_6): δ_H (ppm) 3.69 (3H, s, CH_3), 5.69 (1H, s, CH), 6.62 (1H, t, $J=7.2$ Hz, Ar–H), 6.69 (1H, d, $J=6.3$ Hz, Ar–H), 6.80 (1H, d, $J=6.3$ Hz, Ar–H), 7.22 (2H, s, NH_2), 7.87–7.98 (4H, m, Ar–H), 8.04–8.07 (1H, m, Ar–H), 8.18–8.21 (1H, m, Ar–H), 8.40 (1H, d, $J=7.8$ Hz, Ar–H), 8.88 (1H, s, OH), 9.13 (1H, d, $J=7.5$ Hz, Ar–H), ^{13}CNMR (75 MHz, DMSO-d_6): δ_C (ppm) 33.0, 56.0, 57.5, 110.4, 113.8, 119.0, 120.9, 121.9, 122.5, 125.2, 126.1, 128.9, 129.2, 130.1, 130.4, 130.8, 131.1, 131.7, 140.1, 140.3, 141.3, 141.6, 144.5, 147.1, 148.2, 160.6.

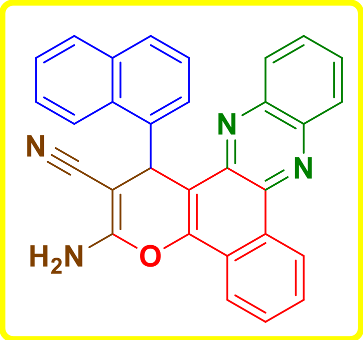


3-Amino-1-(2,5-dihydroxyphenyl)-1*H*-benzo[*a*]pyrano[*2,3-c*]phenazine-2-carbonitrile (5H): Time: 95 min, Yield (%): 92%, M.p. (°C) (Observed): > 280; IR (KBr) (ν_{max}/cm^{-1}):

3425, 3338, 3059, 2940, 2821, 2750, 2719, 2598, 2191, 1662, 1631, 1594, 1526, 1484, 1461, 1404, 1348, 1325, 1292, 1222, 1139, 1084, 1052, 1004, 916, 854, 762, 723, 698, 641, 618, 583, 554, 528, 503, 450; ^{1}HNMR (300 MHz, DMSO-*d*$_6$): δ_H (ppm) 6.07 (1H, s, CH), 6.37 (1H, s, Ar–H), 7.22 (2H, s, NH_2), 7.37 (1H, d, $J = 6.6$ Hz, Ar–H), 8.16 (3H, s, Ar–H), 8.33 (6H, s, Ar–H), 8.87 (1H, s, OH), 9.08 (1H, s, OH); ^{13}CNMR (75 MHz, DMSO-*d*$_6$): δ_C (ppm) 33.0, 57.5, 110.4, 113.8, 119.0, 120.9, 121.9, 122.5, 125.2, 126.1, 128.9, 129.5, 129.2, 130.1, 130.4, 130.8, 131.1, 131.7, 140.1, 140.3, 141.3, 141.6, 144.5, 147.1, 148.2, 160.6.



3-Amino-1-(naphthalen-1-yl)-1*H*-benzo[*a*]pyrano[*2,3-c*]phenazine-2-carbonitrile (5L): Time: 35 min, Yield (%): 95%, M.p. (°C) (Observed): > 280; IR (KBr) (ν_{max}/cm^{-1}): 3465, 3356, 3171, 3087, 3054, 3039, 2184, 1659, 1621, 1590, 1495, 1471, 1398, 1383, 1328, 1291, 1262, 1222, 1162, 1106, 1053, 1022, 950, 860, 779, 754, 667, 637, 610, 545, 449, 424, 404; ^{1}HNMR (300 MHz, DMSO-*d*$_6$): δ_H (ppm) 6.33 (1H, s, CH), 7.22–7.30 (2H, t, m, Ar–H), 7.34 (2H, s, NH_2), 7.55–7.69 (3H, m, Ar–H), 7.77–7.83 (2H, s, Ar–H), 7.85–7.95 (2H, m, Ar–H), 7.97–8.02 (1H, m, Ar–H), 8.05–8.07 (1H, m, Ar–H), 8.22 (1H, d, $J = 8.1$ Hz, Ar–H), 8.49 (1H, d, $J = 7.2$, Ar–H), 8.89 (1H, d, $J = 8.84$ Hz, Ar–H), 9.22 (1H, d, $J = 7.8$ Hz, Ar–H); ^{13}CNMR (75 MHz, DMSO-*d*$_6$): δ_C (ppm) 35.6, 55.9, 82.8, 112.1, 114.5, 122.5, 122.7, 125.2, 125.4, 126.1, 126.2, 128.9, 129.0, 129.2, 129.5, 130.2, 130.4, 130.9, 131.0, 132.3, 136.1, 140.1, 140.2, 141.4, 142.0, 144.0, 146.6, 148.2, 152.6, 158.1.

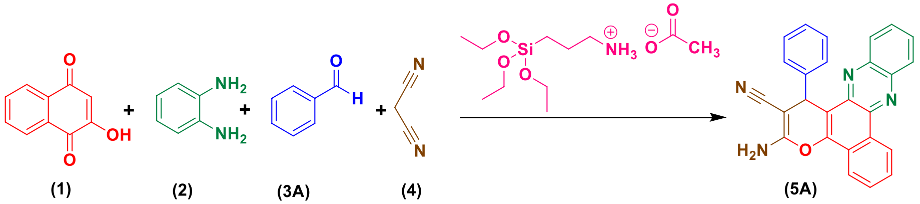


2.5 Optimization of the Reaction Conditions for Prepation of Phenazine Derivatives

To evaluate the activity of the $[(EtO)_3Si(CH_2)_3N^+H_3][CH_3COO^-]$ as ionic liquid, at first, the one-pot and four-component reaction of 2-hydroxynaphthalene-1,4-dione (1 mmol), benzene-1,2-diamine (1 mmol), benzaldehyde (1 mmol), and malononitrile (1 mmol) as a model reaction was selected. The model was examined in different solvents such as H_2O, EtOH, DMF, toluene, and solvent-free under various temperatures conditions in the presence of $[(EtO)_3Si(CH_2)_3N^+H_3][CH_3COO^-]$ (30 mol%) as catalyst (Table 1). The best result was obtained at 90 °C under solvent-free conditions (Table 1, Entry **12**).

Next, the model reaction was tested at different amount of $[(EtO)_3Si(CH_2)_3N^+H_3][CH_3COO^-]$ (10, 20, 30, 40, 50 mol%) at 90 °C under solvent-free conditions. The best results were obtained at 90 °C under solvent-free conditions in the presence of 30 mol% of $[(EtO)_3Si(CH_2)_3N^+H_3][CH_3COO^-]$ as catalyst (Fig. 3).

Table 1 Optimization of reaction conditions for preparation of 3-amino-1-phenyl-1*H*-benzo[*a*]pyrano[*2,3*-*c*]phenazine-2-carbonitrile[a] (5A) in the presence of $[(EtO)_3Si(CH_2)_3N^+H_3][CH_3COO^-]$ as catalyst in different solvents and various amount of the catalyst under several temperature



Entry	Catalyst	Amount of catalyst (mol%)	Solvent (3 mL)	Temp. (°C)	Time (min)	Yield (%)[b]
1	–	–	–	r.t	360	–
2	–	–	–	100	360	–
3	–	–	H_2O	r.t	360	–
4	–	–	H_2O	Reflux	360	Trace
5	Ionic Liquids	30 mol%	H_2O	r.t	360	Trace
6	Ionic Liquids	30 mol%	H_2O	Reflux	360	33
7	Ionic Liquids	30 mol%	–	r.t	360	27
8	Ionic Liquids	30 mol%	Solvent-Free	50	240	53
9	Ionic Liquids	30 mol%	Solvent-Free	60	180	71
10	Ionic Liquids	30 mol%	Solvent-Free	70	120	88
11	Ionic Liquids	30 mol%	Solvent-Free	80	90	92
12	**Ionic Liquids**	**30 mol%**	**Solvent-Free**	**90**	**45**	**93**
13	Ionic Liquids	30 mol%	Solvent-Free	100	40	90
14	Ionic Liquids	30 mol%	DMF	100	180	38
15	Ionic Liquids	30 mol%	Toluene	100	360	Trace
16	Ionic Liquids	30 mol%	EtOH	r.t	360	Trace
17	Ionic Liquids	30 mol%	EtOH	Reflux	50	95

[a] Based on reaction of 2-hydroxynaphthalene-1,4-dione (1 mmol), benzene-1,2-diamine (1 mmol) benzaldehyde (1 mmol), and malononitrile (1 mmol)

[b] Isolated yields after purification

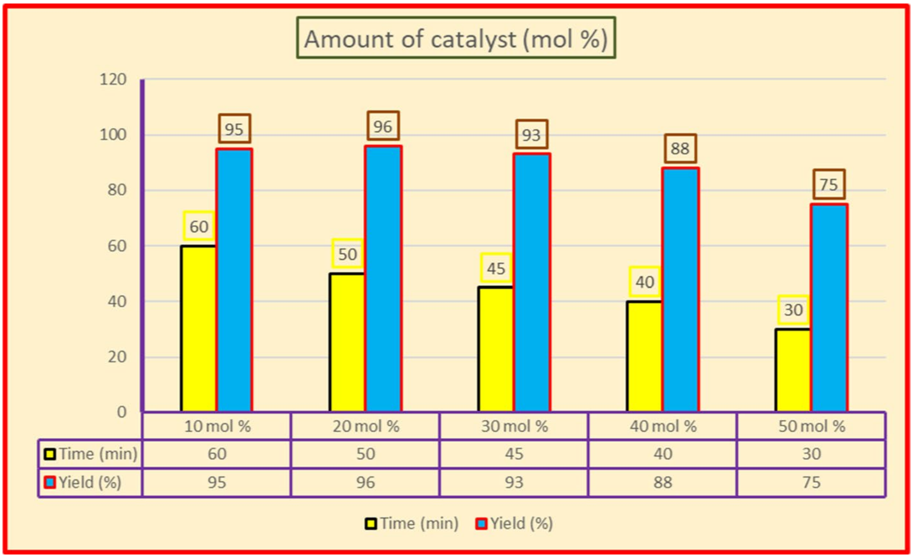


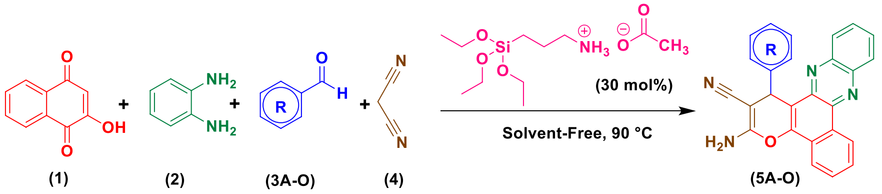
Fig. 3 The study of reaction model in the presence of different amounts of $[(EtO)_3Si(CH_2)_3N^+H_3][CH_3COO^-]$ as ionic liquid

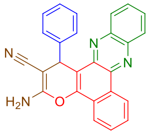
After optimization of the reaction conditions, to investigate the efficiency and the scope of the procedure, numerous benzo[*a*]pyrano[*2,3-c*]phenazine derivatives were produced by the one-pot four-component condensation reaction between aromatic aldehydes with 2-hydroxynaphthalene-1,4-dione, benzene-1,2-diamine, and malononitrile using basic ionic liquid $[(EtO)_3Si(CH_2)_3N^+H_3][CH_3COO^-]$ at 90 °C under solvent-free reaction conditions. The results are displayed in Table 2. The effect of substituents on the aromatic ring was assessed strong in terms of yields under these reaction conditions. Both categories of aromatic aldehydes counting electron-releasing and electron-withdrawing substituents on their aromatic ring gained the appropriate products in high to excellent yields in short reaction time. The reaction times of aromatic aldehydes having electron withdrawing groups was rather faster than that of electron donating groups.

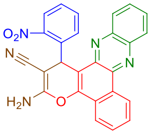
According to the literature [23–25], The proposed mechanism for product formation is shown in Scheme 2. First, benzene-1,2-diamine (1) condenses with 2-hydroxynaphthalene-1,4-dione (2) and provides 6*H*-benzo[*a*]phenazin-5-one (A) [26]. The reaction of intermediate (A) with aryl aldehydes (3) in the presence of basic ionic liquids as catalysts under Knoevenagel condensation cause to form intermediate (B), which reacts in the presence of ionic liquids as catalysts with malononitrile (4) to form Michael adduct intermediate (C), then the intermediate (C) undergo the cyclization, and 1,3-hydrogen shift cause to prepare finally the desired products (Scheme 2).

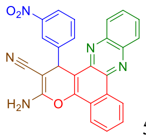
Reusability of the catalysts is important in green environmental chemistry. For this purpose, we studied, the reaction of 2-hydroxynaphthalene-1,4-dione (1 mmol) and benzene-1,2-diamine (1 mmol), benzaldehyde (1 mmol) and malononitrile (1 mmol) as a model under solvent-free conditions at 90 °C. After completion of reactions, ionic liquid as catalyst was soluble in EtOH and could be recovered and reused conveniently after removing ethanol under vacuum at 70 °C for 2 h. The recovered catalyst was reused for at least five runs without any loss of its activity (Fig. 4).

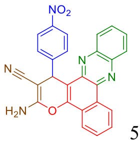
Table 2 Synthesis of benzo[*a*]pyrano[*2,3-c*]phenazine[a] in the precence of $[(EtO)_3Si(CH_2)_3N^+H_3][CH_3COO^-]$ as catalyst

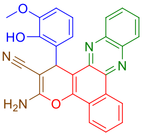


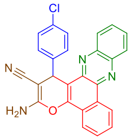

5A
Time: 45 min, Yield (%)[b]: 93 %
M.P (°C) (Observed): >280
M.P (°C) (Literature): 301-302 [24]

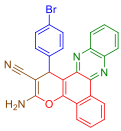

5B
Time: 35 min, Yield (%)[b]: 98 %
M.P (°C) (Observed): 278-280
M.P (°C) (Literature): 279-283 [25]

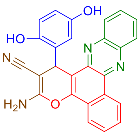

5C
Time: 40 min, Yield (%)[b]: 93 %
M.P (°C) (Observed): 279-280
M.P (°C) (Literature): 280 [26]

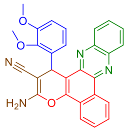

5D
Time: 40 min, Yield (%)[b]: 91 %
M.P (°C) (Observed): 279-281
M.P (°C) (Literature): 282-283 [26]

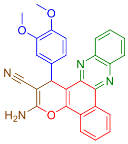

5E
Time: 55 min, Yield (%)[b]: 89 %
M.P (°C) (Observed): 267-269
New

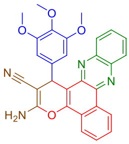

5F
Time: 25 min, Yield (%)[b]: 97 %
M.P (°C) (Observed): >280
M.P (°C) (Literature): 290-291 [24]

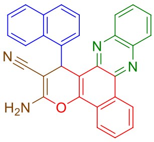

5G
Time: 45 min, Yield (%)[b]: 94 %
M.P (°C) (Observed): >280
M.P (°C) (Literature): 285-286 [24]

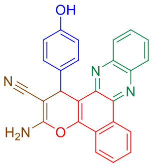

5H
Time: 95 min, Yield (%)[b]: 92 %
M.P (°C) (Observed): >280
New

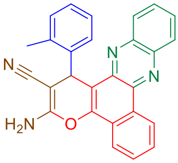

5I
Time: 60 min, Yield (%)[b]: 96 %
M.P (°C) (Observed): >280
M.P (°C) (Literature): 295 [26]

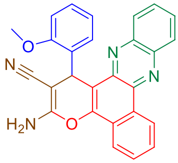

5J
Time: 75 min, Yield (%)[b]: 92 %
M.P (°C) (Observed): 276-277
M.P (°C) (Literature): 275-277 [27]


5K
Time: 80 min, Yield (%)[b]: 96 %
M.P (°C) (Observed): 249-251
M.P (°C) (Literature): 253-254 [24]


5L
Time: 35 min, Yield (%)[b]: 95 %
M.P (°C) (Observed): >280
New


5M
Time: 70 min, Yield (%)[b]: 89 %
M.P (°C) (Observed): 248-250
M.P (°C) (Literature): 251-252 [27]


5N
Time: 55 min, Yield (%)[b]: 94 %
M.P (°C) (Observed): 259-261
M.P (°C) (Literature): 256-260 [25]


5O
Time: 50 min, Yield (%)[b]: 92 %
M.P (°C) (Observed): 271-273
M.P (°C) (Literature): 273 [26]

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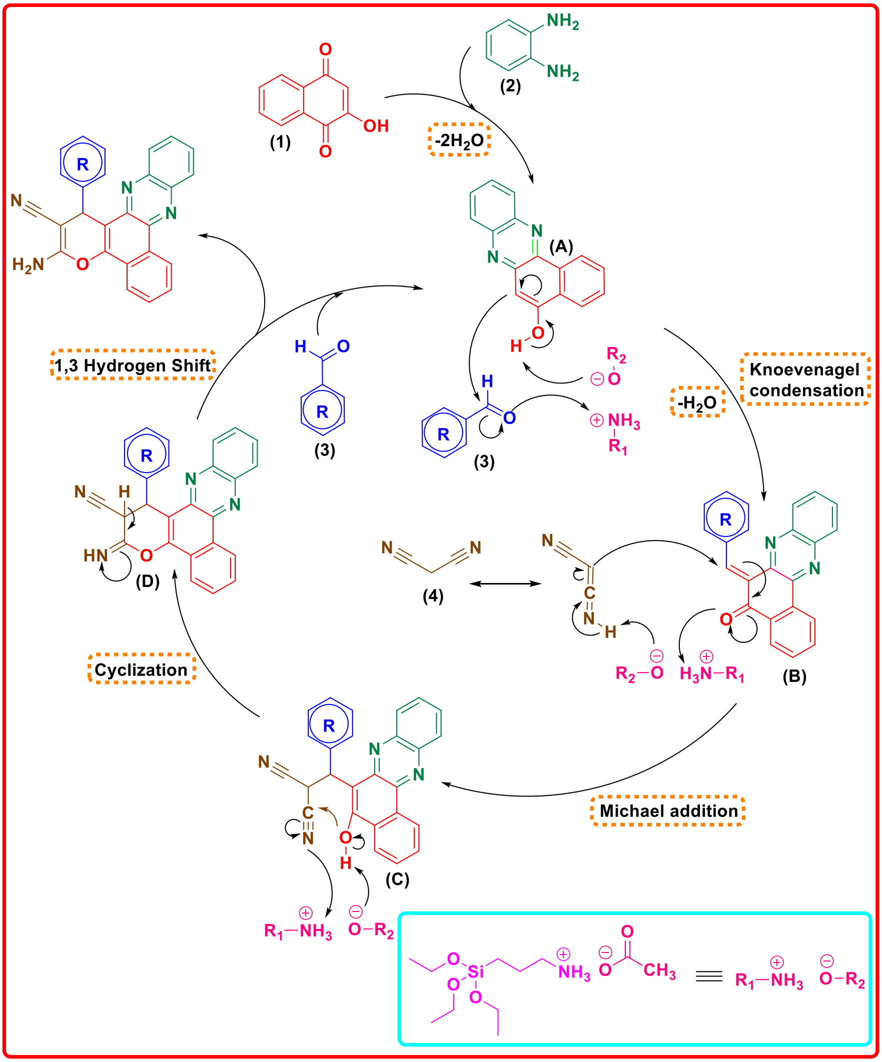
[a] Reaction conditions: 2-hydroxynaphthalene-1,4-dione (1 mmol), benzene-1,2-diamine (1 mmol), aldehyde (1 mmol), and malononitrile (1 mmol), and 30 mol% of 3-(triethoxysilyl)propane-1-aminium formate in 90 °C. [b] Isolated yields after purification.

Table 2 (continued)

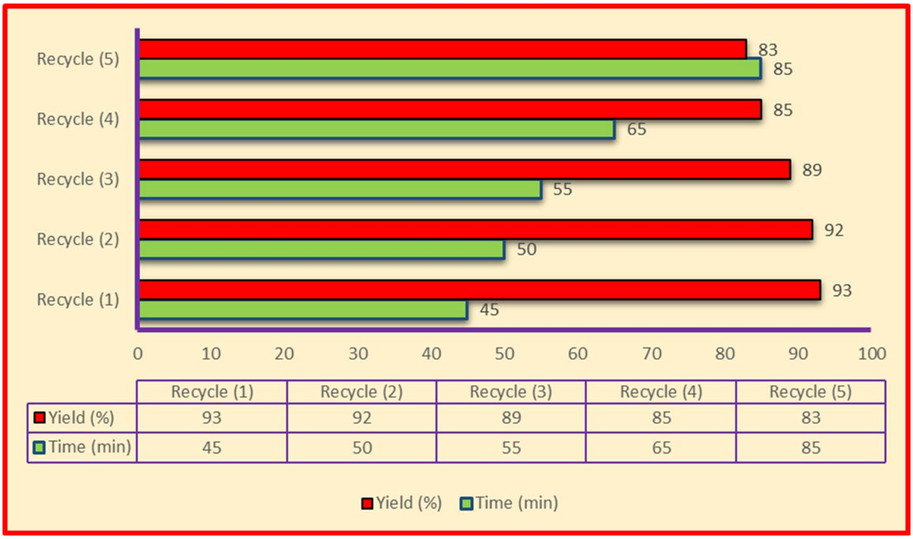
[a]Reaction conditions: 2-hydroxynaphthalene-1,4-dione (1 mmol), benzene-1,2-diamine (1 mmol), aldehyde (1 mmol), and malononitrile (1 mmol), and 30 mol% of 3-(triethoxysilyl)propane-1-aminium formate in 90 °C

[b]Isolated yields after purification.



Scheme 2. Mechanism for the synthesis of benzo[*a*]pyrano[*2,3-c*]phenazine derivatives in the presence of $[(EtO)_3Si(CH_2)_3N^+H_3][CH_3COO^-]$ as basic ionic liquid as catalyst

We also compared this method for preparation of benzo[*a*]pyrano[*2,3-c*]phenazine derivatives with various catalysts in literature (Table 3). We observed that our reported method, using $[(EtO)_3Si(CH_2)_3N^+H_3][CH_3COO^-]$ as the catalyst, is simple, effective,



	Recycle (1)	Recycle (2)	Recycle (3)	Recycle (4)	Recycle (5)
🟥Yield (%)	93	92	89	85	83
🟩Time (min)	45	50	55	65	85

Fig. 4 The recycling of the $[(EtO)_3Si(CH_2)_3N^+H_3][CH_3COO^-]$ as new catalyst

Table 3 Comparison result of $[(EtO)_3Si(CH_2)_3N^+H_3][CH_3COO^-]$ with other reported catalysts in the literature for preparation of benzo[*a*]pyrano-[*2,3-c*]phenazine

Entry	Catalyst	Solvent	Temp(°C)	Time (min)	Yield (%)	Refs.
1	Theophylline	water	70	180	89	[27]
2	GO-HPG-SO_3H	Solvent free	100	30	95	[28]
3	DABCO	EtOH	Reflux	600	60	[29]
4	Fulvic acid	H_2O	60	120	95	[30]
5	β-Cyclodextrin	EtOH:H_2O	70	60	89	[31]
6	[Co (TPPABr)]CBr_3	EtOH	Reflux	35	86	[32]
7	Nano-Fe_3O_4@chitosan	EtOH	Reflux	90	86	[33]
8	PEG	PEG	100	240	85	[34]
9	Cu-guanine-SBA-15	PEG	120	300	82	[35]
10	**$[(EtO)_3Si(CH_2)_3N^+H_3][CH_3COO^-]$**	**Solvent free**	**90**	**45**	**93**	**–**

applicable and comparable with many catalytic systems for the synthesis of benzo[*a*]pyrano[*2,3-c*]phenazine derivatives (Table 3, Entry **10**).

3 Conclusions

The four-component and one-pot synthesis of benzo[*a*]pyrano[*2,3-c*]phenazine derivatives was achieved in a simple, and green manner conditions in the presence of ionic liquid, $[(EtO)_3Si(CH_2)_3N^+H_3][CH_3COO^-]$, as catalyst. The phenazine derivatives were obtained in excellent yields. Recyclability of ionic liquid, easy work-up, and uses environment-friendly reaction conditions are advantages of this effective MCR protocol.

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Authors' Contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by FS, and HRS.

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Data Availability The data that support the findings of this study are available in the supplementary material of this article.

Declarations

Competing interests The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethical Approval This article does not contain any studies with human or animal subjects performed by any of the authors.

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