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Mild basic ionic liquid catalyzed pseudo four component synthesis of 7,10-diaryl-7*H*-benzo[7,8]chromeno[2,3-d]pyrimidin-8-amine derivatives under solvent-free conditions

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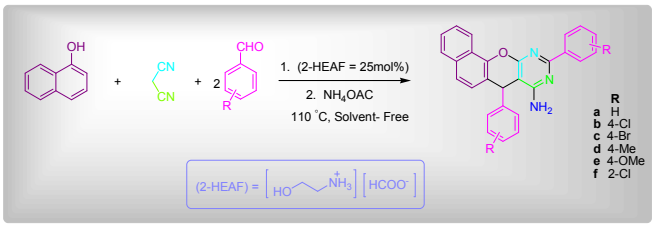
2-Hydroxyethylammonium formate [2-HEAF] as mild basic ionic liquid catalyzed the one-pot pseudo four component condensation reaction of aromatic aldehydes, α-naphthol, malononitrile, and ammonium acetate under thermal solvent-free conditions. This convenient and efficient procedure synthesized 7,10-diaryl-7*H*-benzo[7,8]chromeno[2,3-d]pyrimidin-8-amine derivatives in short reaction times and good yields.

Introduction

Chromene derivatives are an important class of compounds, widely present in plants, including edible vegetables and fruits [1]. Numerous bioactive natural products have been identified, and the presence of the chromene-based structure has been associated with the capacity to prevent disease [2]. Synthetic analogues have been developed over the years, some of them displaying remarkable effects as pharmaceuticals activities [3] such as anti-microbial [4], anti-inflammatory [5], analgesic [6], antiviral [7], antiproliferative [8], antibacterial [9], anticancer [10], antioxidants [11], antitumor [12]. Pyrimidine scaffold is the base of many bioactive molecules such as antimalarial [13], antibacterial [14], antitumor [15], anticancer [16], anti-inflammatory and antifungal agent [17]. Thus, synthetic methodologies for the synthesis of molecules containing chromene and pyrimidine rings are of particular interests for organic and medicinal chemists. Recently, antibacterial activity of 7,10-diaryl-7*H*-benzo[7,8]chromeno[2,3-d]pyrimidin-8-amine derivatives was studied by researchers [18].
Multi-component reactions (MCRs), because of their productivity, simple procedures, time-saving manner, convergence, and facile execution, are one of the best tools in combinatorial chemistry [19]. Herein, we report the one-pot pseudo four component synthesis of 7,10-diaryl-7*H*-benzo[7,8]chromeno[2,3-d]pyrimidin-8-amine derivatives using 2-hydroxyethylammonium formate [2-HEAF] ionic liquid as mild basic catalyst by the condensation of aromatic aldehydes, α-naphthol , malononitrile and ammonium acetate under solvent-free conditions (Scheme 1).



Scheme 1: The one-pot preparation of 7,10-diaryl-7*H*-benzo[7,8]chromeno[2,3-d]pyrimidin-8-amine derivatives

Results and discussion

First, to find optimization conditions, the solvent-free reaction of α-naphthol, malononitrile, benzaldehyde and ammonium acetate in the presence of [2-HEAF] as a catalyst was selected as a model. The reaction was carried out with different amount of the catalyst (15, 20, 25, 30, 40 mol %) and varieties temperature (80, 90, 100, 110, 120 °C) (Table 1). As it was shown from table 1, 25 mol % of [2-HEAF] as catalyst at 110 °C afforded 7,10-diphenyl-7*H*-benzo[7,8]chromeno[2,3-d]pyrimidin-8-amine in 36 min with 92% of yield.

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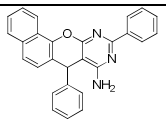
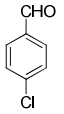
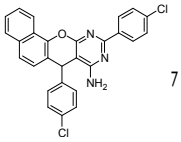
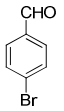
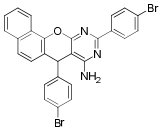
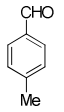
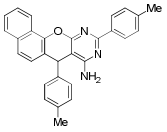
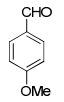
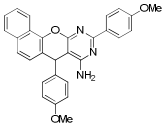
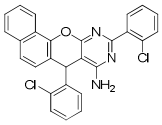
Table 1: Optimization conditions for the one-pot synthesis of 7,10-diphenyl-7*H*-benzo[7,8]chromeno[2,3-d]pyrimidin-8-amine in the presence of [2-HEAF] under solvent-free conditions

Entry	Catalyst (mol %)	Temp (°C)	Time (min)		Yield (%)[a]
			Step1	Step2	
1	25	80	10	50	68
2	25	90	9	46	76
3	25	100	7	43	82
4	25	110	5	31	92
5	25	120	4	31	93
6	15	110	7	44	83
7	20	110	6	37	90
8	25	110	5	31	92
9	30	110	3	28	92
10	40	110	2	26	93

[a] Yields refer to the isolated pure product. Based on the reaction of α-naphthol, malononitrile, benzaldehyde and ammonium acetate.

Next, pseudo four component condensation of aromatic aldehydes, α-naphthol, malononitrile and ammonium acetate under optimized conditions for preparation of 7,10-diaryl-7*H*-benzo[7,8]chromeno[2,3-d]pyrimidin-8-amine derivatives were investigated (Table 2). The wide ranges of substituted and structurally diverse aldehydes (aromatic aldehydes carrying electron-donating or electron-withdrawing substituent) synthesize the corresponding products in high to excellent yields using the mentioned ionic liquid as catalyst (Table 2). There was no effect in the reaction time and the yield of the corresponding products when electron donating groups or electron-withdrawing groups on banzaldehydes were used. Our observation can be confirmed with only one catalyst which reported in the literature [18]. We also examined aliphatic aldehydes such as *n*-heptanal and *n*-octanal instead of benzaldehydes in the reaction. All the starting materials were intact and none of the desired products, or by-products were formed after 24 h.

Table 2: Synthesis of 7,10-diaryl-7*H*-benzo[7,8]chromeno[2,3-d]pyrimidin-8-amine derivatives catalyzed by (2-HEAF)

Entry	Aldehyde	Product	Time (min)		Yield (%)a	M.P/MP [ref](°C)
			Step1	Step2		
1			5	31	92	175-176/ 176-178 [18]
2			7	38	91	192-194/ 194-196 [18]
3			6	34	89	232-234/ 234-236 [18]
4			6	34	93	212-214/ 212-214 [18]
5			8	42	91	165-167/ 164-166 [18]
6			8	49	90	189-191/ 188-190 [18]

[a] Yield refer to the isolated pure product. All known products have been reported previously in the literature and were characterized by comparison of IR and NMR spectra with authentic samples [18].

The proposed mechanism for the preparation of 7,10-diphenyl-7*H*-benzo[7,8]chromeno[2,3-d]pyrimidin-8-amine from bezaldehyde, α-naphthol, malononitrile and ammonium acetate using weak basic ionic liquids as a catalyst is described in Scheme 2. According to literature [18], 2-benzylidenemalononitrile, containing the electron-poor C-C double bond, is formed by Knoevenagel addition of malononitrile to benzaldehyde in the presence basic ionic liquids as catalyst. Then, 2-benzylidenemalononitrile has been attacked by α-naphthol in the presence of weak basic ionic liquids, which leads to the 2-amino-4*H*-chromeno-3-carbonitrile. In the continuation of the catalytic cycle, 2-amino-4*H*-chromeno-3-carbonitrile reacts with other benzaldehyde to give imine 5 as intermediate, which it reacts with ammonium acetate to form intermediate 6, followed by cyclization and aromatization to afford the corresponding products.

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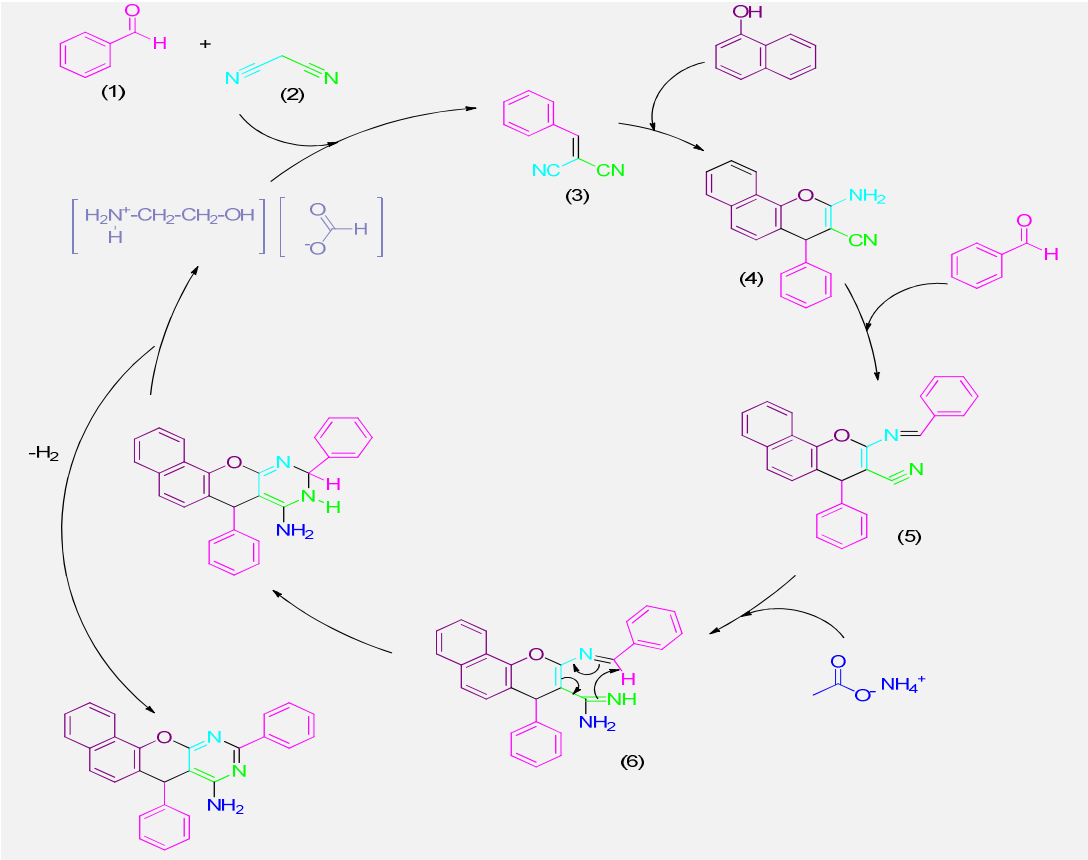

Scheme 2: Plausible mechanism for the catalytic synthesis of 7,10-diphenyl-7H-benzo[7,8]chromeno[2,3-d] pyrimidin-8-amine derivatives

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We also investigated the recycling of the ionic liquids under solvent-free conditions using a model reaction of α-naphthol, malononitrile, benzaldehyde and ammonium acetate for the preparation of 7,10-diphenyl-7*H*-benzo[7,8]chromeno[2,3-d] pyrimidin-8-amine in the presence of [2-HEAF] (Table 2, Entry 1). After completion of the reaction, water was added and the precipitated mixture was filtered off for separation of crude products. After washing the solid products with water completely, the water containing ionic liquid (IL is soluble in water) was evaporated under reduced pressure and ionic liquid was recovered and reused (Fig. 1). The recovered catalysts were reused four runs without any loss of its activities.

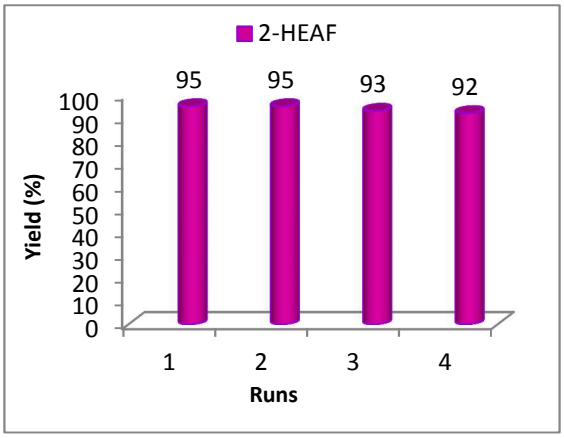

Figure 1: The Investigation of the reusability of the ionic liquids under solvent-free conditions using a model reaction of α-naphthol, malononitrile, benzaldehyde and ammonium acetate in the presence of [2-HEAF] as catalyst

In order to show the accessibility of the present work (4-CRs) in comparison with only one catalyst which reported in the literature. We summarized some of the results for the preparation of 7,10-diphenyl-7*H*-benzo[7,8]chromeno[2,3-d] pyrimidin-8-amine in Table 3. The results show that ionic liquid [2-HEAF] is the most efficient catalyst with respect to the reaction time and in terms of obtained yield.

Table 3: Comparison the results of 2-hydroxyethylammonium formate with 1-butyl-3 methylimidazolium tetrafluoroborate ([bmim]BF_4) in the synthesis of 7,10-diphenyl-7*H*-benzo[7,8]chromeno[2,3-d] pyrimidin-8-amine

Entry	Catalyst	Amount of the catalyst (mol %)	Conditions	Time (min)	Yield % [ref]
1	[bmim]BF_4	20	TEA/DMF; 100℃	90	92 [18]
2	2-HEAF	25	Solvent-Free; 110℃	36	92 The present work

Experimental

All reagents were purchased from Merck and Aldrich and used without further purification. The weak basic ionic liquid [2-HEAF] as a catalyst was prepared according to the reported procedure [20]. 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 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.

2.1. Preparation of the ionic liquid [2-HEAF]
2-Aminoethanol (119.8 g, 0.2 mol) was placed in a two necked flask equipped with a reflux condenser and a dropping funnel. The flask was mounted in an ice bath. Under vigorous stirring with a magnetic stirring bar, 76 ml (0.2 mol) formic acid was added dropwise to the flask in about 45 min. Stirring was continued for 24 h at room temperature, to obtain a viscous clear liquid [20].

2.2. General procedure for the one-pot synthesis of 7,10-diaryl-7H-benzo[7,8]chromeno[2,3-d]pyrimidin-8-amine derivatives under solvent-free conditions
[2-HEAF] as mild basic ionic liquid (0.25 mmol) was added to a mixture of α-naphthol (1 mmol), malononitrile (1 mmol), and aromatic aldehydes (2 mmol) and the reaction mixture was stirred at 110 ^oC in an oil bath. The completion of the reaction was monitored by TLC (Step1). After completion of the step 1 (single spot on TLC), ammonium acetate (5 mmol) was added at the same temperature (110 ^oC) and the reaction was monitored by TLC for appropriate time (Step 2). After completion of the reaction, the reaction mixture was cooled to room temperature and 20 mL of water was added. The solid separated was filtered, washed with ether, dried and purified by column chromatography using silica gel (eluent: $CHCl_3$:MeOH 9:1). All of the desired products were characterized by comparison of their physical data with those of known compounds.

Selected spectral data for some known products are given below:

7,10-Diphenyl-7H-benzo[7,8]chromeno[2,3-d]pyrimidin-8-amine: [mp: 175-176 ^oC]; IR (KBr): 3695, 3475, 3055, 1650, 1259 Cm-1; ^1H NMR (300 MHz, DMSO-d_6): δ 5/42 (s, 1H, pyran- CH), 6.96 (s, 2H, -NH_2), 7.18–7.96 (m, 15H, Ar-H), 8.38 (d, 1H, ArH-1); ^{13}C NMR (75 MHz, DMSO- d_6): δ 44.0, 108.2, 118.6, 120.7, 121.8, 126.2, 126.8, 127.1, 127.9, 128.7, 129.2, 129.8, 130.2, 130.9, 131.4, 133.4, 135.2, 144.2, 151.6, 159.3, 167.4, 174.9 .
7,10-Di-(4-chlorophenyl)-7H-benzo[7,8]chromeno[2,3-d]pyrimidin-8-amine: [mp: 192-194 ^oC]; IR (KBr): 3700, 3390, 3065, 1649, 1259 Cm-1 ; ^1H NMR (300 MHz, DMSO- d_6): δ 5.44 (s, 1H, pyran -CH), 6.94 (s, 2H, -NH_2), 7.20–8.02 (m, 13H, Ar-H), 8.38 (d, 1H, ArH-1); ^{13}C NMR (75 MHz, DMSO-d_6): δ 44.2, 108.3, 118.6, 120.9, 122.0, 126.2, 126.6, 127.2, 128.6, 129.1, 130.1, 130.8, 131.0, 131.9, 132.7, 134.1, 136.3, 143.7, 151.8, 159.5, 167.8, 175.0 .
7,10-Di-(4-bromophenyl)-7H-benzo[7,8]chromeno[2,3-d]pyrimidin-8-amine: [mp: 232-234 ^oC]; ^1H NMR (300 MHz, DMSO- d_6): δ 5.48 (s, 1H, pyran -CH), 6.96 (s, 2H, -NH_2), 7.20–8.06 (m, 13H, Ar-H), 8.34 (d, 1H, ArH-1); ^{13}C NMR (75 MHz, DMSO- d_6): δ 44.4, 108.8, 118.9, 120.9, 122.0, 122.8, 125.4, 126.4, 126.9, 127.4, 128.7, 129.3, 130.8, 131.7, 132.2, 134.3, 135.1, 144.5, 151.9, 159.6, 168.0, 175.2 .
7,10-Di-(4-methylphenyl)-7H-benzo[7,8]chromeno[2,3-d]pyrimidin-8-amine: [mp: 212-214 ^oC]; ^1H NMR (300 MHz,

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DMSO- d_6): δ 2.24 (s, 6H, -CH_3), δ 5.38 (s, 1H, pyran -CH), 6.88 (s, 2H, -NH_2), 7.10–7.86 (m, 13H, Ar-H), 8.30 (d, 1H, Ar-H) ; ^{13}C NMR (75 MHz, DMSO- d_6): δ 28.2, 43.4, 108.3, 118.4, 120.6, 121.7, 126.1, 126.9, 127.1, 128.4, 129.0, 129.8, 130.2, 131.2, 132.3, 133.6, 137.2, 140.7, 142.4, 151.3, 159.1, 167.3, 174.8 .

7,10-Di-(4-methoxyphenyl)-7H-benzo[7,8]chromeno[2,3-d]pyrimidin-8-amine: [mp: 165-167 °C]; ^{1}H NMR (300 MHz, DMSO- d_6): δ 3.58 (s, 6H, -OCH_3), δ 5.40 (s, 1H, pyran -CH), 6.90 (s, 2H, -NH_2), 7.12–7.94 (m, 13H, Ar-H), 8.32 (d, 1H, Ar-H) ; ^{13}C NMR (75 MHz, DMSO- d_6): δ 44.2, 58.3, 108.4, 116.7, 118.5, 120.7, 121.8, 125.3, 126.2, 126.9, 127.3, 128.7, 129.3, 130.3, 131.4, 134.0, 137.9, 152.3, 159.2, 160.1, 162.3, 168.2, 175.2 .

7,10-Di-(2-chlorophenyl)-7H-benzo[7,8]chromeno[2,3-d]pyrimidin-8-amine: [mp: 189-191 °C]; IR (KBr): 3690, 3385, 3055, 1654, 1269 Cm-1; ^{1}H NMR (300 MHz, DMSO- d_6): δ 5.42 (s, 1H, pyran -CH), 6.95 (s, 2H, -NH_2), 7.15–7.94 (m, 13H, Ar-H), 8.36 (d, 1H, ArH-1); ^{13}C NMR (75 MHz, DMSO- d_6): δ 38.4, 108.9, 118.7, 120.7, 122.3, 126.2, 126.9, 127.4, 128.5, 129.1, 129.4, 129.8, 130.4, 131.2, 131.8, 132.6, 133.5, 134.4, 135.3, 140.4, 145.2, 151.7, 159.2, 167.8, 174.9 .

Conclusions

In this research, the basic ionic liquid [2-HEAF] was used for one-pot preparation of 7,10-diaryl-7*H*-benzo [7,8]chromeno[2,3-d]pyrimidin-8-amine derivatives under thermal solvent-free conditions for the first time. The attractive features of this protocol are efficient procedure, cleaner reaction, use of inexpensive and reusable ionic liquid as catalysts. Satisfactory yields of products, as well as a simple experimental, isolation and purification of the products make it a useful protocol for the synthesis of this class of compounds.

Acknowledgements

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Graphical Abstract

Mild basic ionic liquid catalyzed pseudo four component synthesis of 7,10-diaryl-7*H*-benzo[7,8]chromeno[2,3-d]pyrimidin-8-amine derivatives under solvent-free conditions

H.R. Shaterian*, S. Noura

2-Hydroxyethylammonium formate [2-HEAF] as basic ionic liquid catalyzed the one-pot pseudo four component condensation reaction of aromatic aldehydes, α-naphthol, malononitrile, and ammonium acetate under thermal solvent-free conditions. This convenient and efficient procedure synthesized 7,10-diaryl-7*H*-benzo[7,8]chromeno[2,3-d]pyrimidin-8-amine derivatives in short reaction times and good yields.