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One-pot synthesis of 7-aryl-11,12-dihydrobenzo[h]pyrimido-[4,5-b]quinoline-8,10(7*H*,9*H*)-diones *via* three-component reaction in ionic liquid

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Abstract

A series of new 7-aryl-11,12-dihydrobenzo[h]pyrimido-[4,5-b]quinoline-8,10(7*H*,9*H*)-diones were synthesized *via* three-component reaction of aldehydes, 1-naphthylamine and barbituric acid in ionic liquid. The method provided several advantages such as easy work-up, high yields and environmentally benign procedure.

Keywords: Aldehyde; 1-Naphthylamine; Barbituric acid; Ionic liquid

7-Aryl-11,12-dihydrobenzo[h]pyrimido-[4,5-b]quinoline-8,10(7*H*,9*H*)-diones, a novel class of fused heterocyclic compounds, are incorporated by pyrimido-[4,5-b]quinoline-2,4(1*H*, 3*H*, 5*H*, 10*H*)-dione and [4,7]-phenantroline motifs, both of which possess various important bioactivities. For example, not only are pyrimido-[4,5-b]quinoline-2,4(1*H*, 3*H*, 5*H*, 10*H*)-dione derivatives antitumor, anticancer, antihypertensive, and antibacterial, they are also inhibitors of Kaposi's sarcoma-associated herpesvirus (KSHV) and topoisomerase, useful for the treatment of topoisomerase-associated diseases and disorders [1–3]. At the same time, [4,7]-phenantroline derivatives exhibit antitumor, anticancer, antiviral, antimalarial, antiinfective, cytotoxic activities, as well as being triple-helix DNA stabilizing agents [4–6]. Hence, it is promising that the fused scaffolds of pyrimido-[4,5-b]quinoline-2,4(1*H*, 3*H*, 5*H*, 10*H*)dione with [4,7]phenanthroline, *i.e.*, 7-aryl-11,12-dihydrobenzo[h]pyrimido-[4,5-b]quinoline-8,10(7*H*, 9*H*)-diones, may display novel or enhanced significant bioactivities. However, survey of the literature revealed that the synthesis of this important fused heterocyclic skeleton was neglected. Therefore, the investigation on the synthesis of 7-aryl-11,12-dihydrobenzo[h]pyrimido-[4,5-b]quinoline-8,10(7*H*,9*H*)-diones is of great necessity.

Multicomponent reactions (MCRs) are a powerful method for the synthesis of organic compounds, since the products are formed in a single step and diversity can be achieved by simply varying each component [7]. Due to their easy operations and good results, MCRs have attracted much attention [8,9].

In recent years, the room temperature ionic liquids are attracting increasing interest as a 'green' recyclable alternative to classical molecular solvents for synthetic organic chemistry [10–12]. To date, some important reactions

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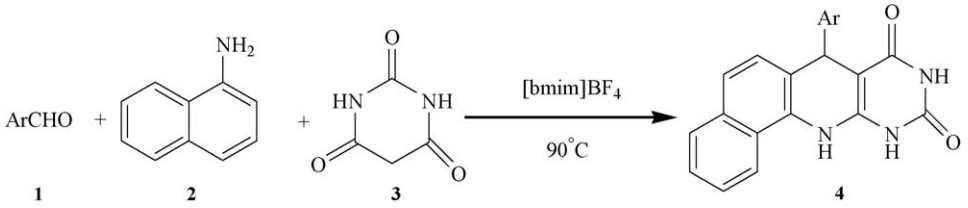

Scheme 1. The synthetic route of 7-aryl-11,12-dihydrobenzo[h]pyrimido-[4,5-b]quinoline-8,10(7*H*,9*H*)-diones.

have been carried out and investigated. Meanwhile, ionic liquids are able to generate an internal pressure and promote the association of reactants in the solvent cavity during the activation process [13,14]. Thus ionic liquids are well suited as reaction media for MCRs in which the entropy of the reaction is decreased in the transition state [15]. Herein we would like to report a novel procedure for the preparation of 7-aryl-11,12-dihydrobenzo[h]pyrimido-[4,5-b]quinoline-8,10(7*H*,9*H*)-diones (Scheme 1) through a three-component reaction of aldehydes **1**, 1-naphthylamine **2** and barbituric acid **3** in an ionic liquid.

First, we examined the efficiency of different solvents in the three-component reaction of aldehyde, 1-naphthylamine and barbituric acid. We found that the reaction occurred easily at 90 °C in ionic liquids and completed within 0.5 h to give product in high yields. It can be seen from Table 1 that the reactions using ionic liquids as the solvent resulted in higher yields and shorter reaction times than those using organic solvents. On the basis of the obtained results, [bmim]BF_4 was found to be superior in terms of low cost and high yield. Under these optimized reaction conditions, a series of 7-aryl-11,12-dihydrobenzo[h]pyrimido-[4,5-b]quinoline-8,10(7*H*,9*H*)-dione derivatives **4** were synthesized. The results are summarized in Table 2.

It was found out that the reaction of benzaldehyde (**1a**, 2 mmol), 1-naphthylamine (**2**, 2 mmol) and barbituric acid (**3**, 2 mmol) went smoothly in 2 mL of [bmim]BF_4 after being stirred for appropriate time at 90 °C (monitored by TLC). Upon completion, the mixture was added with 5 mL water. The precipitate was collected by suction and purified by recrystallization from EtOH to give the desired product 7-phenyl-11,12-dihydrobenzo[h]pyrimido-[4,5-b] quinoline-8,10(7*H*, 9*H*)-dione **4a** with a yield of 88% (Table 2, entry 1). The filtrate was concentrated under reduced pressure and dried at 100 °C to recover the ionic liquid for subsequent use.

A variety of aldehydes were then tried to determine the scope and generality of this method and the results are listed in Table 2. To our delight, the following reaction went smoothly under this reaction conditions to afford the corresponding products in high yields. All the products **4a–1** are new compounds, which were identified by IR, ^{1}H NMR, mass spectroscopy and elemental analysis [16].

The ionic liquid plays the dual role of solvent and promoter. Just 2 mL ionic liquid is sufficient to push the reaction forward. More amounts of the ionic liquid did not improve the results to a greater extent. The high polarity of ionic liquids made the condensation more efficiently. It should also be noted that [bmim]BF_4 as reaction medium could be recovered easily and reused for several times without any decrease in terms of efficiency in the reaction.

From the results of Table 2, it is obvious this protocol could be applied to various aromatic aldehydes with electron-withdrawing groups or electron-donating groups. Besides, the results suggest that the substrates bearing electron-

Table 1
Solvent optimization for the synthesis of **4d**.

Entry[a]	Solvent	Temperature (°C)	Time (h)	Yield[b] (%)
1	[bmim]BF_4	90	0.5	92
2	[bmim]PF_6	90	0.5	88
3	[bmim]Br	90	0.5	90
4	EtOH	Reflux	10	20
5	AcOH	Reflux	10	35
6	CH_3CN	Reflux	10	23
7	H_2O	90	24	0

[a] All reaction were run with 4-fluorobenzaldehyde (2 mmol), 1-naphthylamine (2 mmol), barbituric acid (2 mmol), and 2 mL solvent.
[b] Isolated yield.

Table 2
Preparation of **4** in ionic liquid [bmim]BF_4.

Entry	Ar	Product	Time (min)	Yield[a] (%)
1	C_6H_5–	**4a**	30	88
2	4-Cl–C_6H_4–	**4b**	30	90
3	4-MeO–C_6H_4–	**4c**	40	77
4	4-F–C_6H_4–	**4d**	30	92
5	4-OH–C_6H_4–	**4e**	40	82
6	4-CH_3–C_6H_4–	**4f**	45	79
7	4-NO_2–C_6H_4–	**4g**	30	91
8	3-Br–C_6H_4–	**4h**	30	92
9	4-OH–3-OCH_3–C_6H_3–	**4i**	30	76
10	2-Cl–C_6H_4–	**4j**	30	89
11	2,4-Cl_2–C_6H_3–	**4k**	30	91
12	2-OH–C_6H_4–	**4l**	30	85

[a] Isolated yield.

withdrawing groups have higher reactivity (higher yields and shorter reaction time) than those bearing electron-donating groups. So, it is concluded that the electronic nature of the substituents on aldehydes has some effect on this reaction. It seems that the electron-withdrawing groups in aldehydes enhanced the electropositive property of β–C in the intermediates yielded from the Knoevenagel condensation of aldehydes **1** with barbituric acid **3**, which facilitated the nucleophilic attack thereafter.

In summary, a series of 7-aryl-11,12-dihydrobenzo[h]pyrimido-[4,5-b]quinoline-8,10(7*H*,9*H*)-diones were synthesized in ionic liquid [bmim]BF_4. The procedure offers several advantages including high yields, operational simplicity, cleaner reactions, minimal environmental impact, and provides a useful and attractive protocol for the synthesis of these compounds.

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[16] A typical procedure for the preparation of **4a**−**4l**: Aldehyde (**1**, 2 mmol), 1-naphthylamine (**2**, 2 mmol), barbituric acid (**3**, 2 mmol) were added to a 20 mL round bottom flask containing 2 mL [bmim]BF_4. The mixture was then stirred at 90 °C for appropriate time (monitored by TLC). After completion of the reaction, the reaction mixture was added with 5 mL water. The precipitate was collected by suction and purified by recrystallization from EtOH to give products **4**. The filtrate was concentrated under reduced pressure and dried at 100 °C to recover the ionic liquid for subsequent use. Some selected data: **4c**: mp >300 °C; ^{1}H NMR (DMSO-d_6, 500 MHz,): δ 3.44 (s, 3H, OCH_3); 5.13 (s, 1H, CH); 6.75–7.95 (m, 10H, Ar–H); 9.09 (s, 1H, NH); 10.03 (s, 1H, NH); 10.69 (s, 1H, NH); IR (KBr, cm^{-1}): ν_{max} 3267, 3076, 2834, 1715, 1608, 1550, 1509, 1461, 1399, 1252, 1176, 1108, 1031, 810; MS (EI, 70 eV) (*m*/*z*, %): 371 (M^+, 9.0), 368 (41.7), 369 (100), 264 (33.5), 207 (21.4); Anal. Calcd.

for $C_{22}H_{17}N_3O_3$: C, 71.15; H, 4.61; N, 11.31; Found C, 71.31; H, 4.57; N, 11.21. **4l**: mp >300 °C; ^{1}H NMR (DMSO-d_6, 500 MHz,): δ 5.56 (s, 1H, CH); 6.60–7.92 (m, 10H, Ar–H); 9.08 (s, 1H, NH); 9.69 (s, 1H, OH); 10.06 (s, 1H, NH); 10.77 (s, 1H, NH); IR (KBr, cm^{-1}) ν_{max}: 3345, 3210, 3042, 1705, 1601, 1551, 1458, 1401, 1353, 1268, 1216, 1126, 1031, 802; MS (EI, 70 eV) (*m*/*z*, %): 357 (M^+, 4.0), 263 (100), 165 (31.0), 193 (56.6), 220 (40.8), 94 (14.6); Anal. Calcd. for $C_{21}H_{15}N_3O_3$: C, 70.58; H, 4.23; N, 11.76; Found C, 70.66; H, 4.19; N, 11.62.