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Research Article

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An efficient synthesis of biologically active 7-aryl-11,12-dihydrobenzo[*H*]pyrimido-[*4,5-b*]quinoline-8,10 (*7H,9H*)-diones

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ABSTRACT

Organocatalyst has been used as a green catalyst for the synthesis of 7-aryl-11,12-dihydrobenzo[h]pyrimido-[4,5-b]quinoline-8,10(7H,9H)-diones via a one-pot three component condensation reaction of aromatic aldehydes, 1-naphthyl amine and barbuturic acid in solvent water. The environmentally benign, mild reaction conditions and excellent yields of desired products are some of the agreeable features of the method.

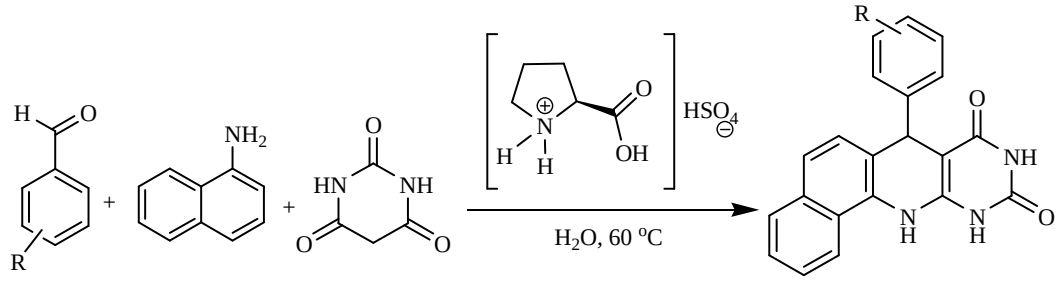
Keywords: One-pot synthesis, Organocatalyst, Pyrimido-quinolinedione, Aromatic aldehyde, Barbuturic acid, 1-Naphthylamine.

INTRODUCTION

7-Aryl-11,12-dihydrobenzo[h]pyrimido-[4,5-b]quinoline-8,10(7H,9H)-diones, a new class of fused heterocycles, are included by pyrimido-[4,5-b]quinoline-2,4(1H,3H,5H,10H)-dione and [4,7]-phenantroline pattern, both of which having a variety of significant bioactivities. Such as pyrimido-[4,5-b]quinoline-2,4(1H,3H,5H,10H)-diones are having anticancer, antitumor, antibacterial and antihypertensive activities as well as act as 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, phenantroline derivatives exhibit anticancer, antitumor, antimalarial, antiviral, antiinfective, cytotoxic activities, as well as being triple-helix DNA stabilizing agents [4-6]. Therefore, it is hopeful that the moiety of pyrimido-[4,5-b]quinoline-2,4(1H,3H,5H,10H)dione with phenanthroline, i.e., 7-aryl-11,12-dihydrobenzo [h]pyrimido-[4,5-b]quinoline-8,10(7H, 9H)-diones, may reveals a improved noteworthy bioactivities. However, literature survey shows that the synthesis of this vital fused heterocyclic moiety was ignored. Therefore, the study on the synthesis of 7-aryl-11,12-dihydrobenzo[h]pyrimido-[4,5-b]quinoline-8,10(7H,9H)-diones is of enormous necessity.

Multi-component reactions (MCRs) are a potent method for the synthesis of organic molecules, since the products are produced in a one step and variety can be achieved by simply varying each component [7]. Due to their simple operations and good results, MCRs have attracted much attention [8,9].

Due to our attention in organocatalyzed synthesis [10-12] herein we report successful method for synthesis of 7-aryl-11,12-dihydrobenzo[h]pyrimido-[4,5-b] quinoline-8,10(7H,9H)-diones in excellent yields using pyrrolidine based organocatalyst.



1a-j **2** **3** **4a-j**

Scheme 1

EXPERIMENTAL SECTION

All solvents were used as commercial anhydrous grade without further purification. The column chromatography was carried out over silica gel (80-120 mesh). Melting points were determined in open capillary tube and are uncorrected. ^{1}H spectra were recorded on a Bruker 300 MHz spectrometer in $CDCl_3$ solvent and TMS as an internal standard. ^{13}C NMR spectra were recorded on a Bruker-300 MHz spectrometer in $CDCl_3$ solvent. Mass spectra were taken on Polaris-Q Thermoscintific GC-MS.

General procedure for synthesis of 7-aryl-11,12-dihydrobenzo[h]pyrimido-[4,5-b]quinoline-8,10(7H,9H)-diones: Aromatic aldehyde (2 mmol), 1-naphthylamine (2 mmol), barbituric acid (2 mmol) were added to a 50 mL round bottom flask containing Proline based organocatalyst (15 mol %) in solvent water. The mixture was then stirred at 60 ^{o}C for appropriate time (monitored by TLC) as indicated in table 2. After completion of the reaction, the precipitate was collected by suction and purified by crystallization from ethyl alcohol to give desired products. The crude obtained product was purified by column chromatography using silica gel mesh 80-120 to afford the pure product.

7-(4-methoxyphenyl)-11,12-dihydrobenzo[h]pyrimido-[4,5-b]quinoline-8,10(7H, 9H)-dione (4c): ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.60 (s, 3H, OCH_3), 5.24 (s, 1H, CH), 6.69-7.60 (m, 10H, Ar-H), 9.20 (s, 1H, NH), 10.28 (s, 1H, NH), 10.82 (s, 1H, NH); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 40.2, 53.4, 78.8, 110.2, 114.1, 116.5, 118.8, 120.2, 123.4, 126.0, 128.0, 129.9, 132.5, 134.8, 137.1, 139.5, 148.9, 151.5, 157.8, 162.7; GC-MS (m/z): 371 (M^+).

7-(2-hydroxyphenyl)-11,12-dihydrobenzo[h]pyrimido-[4,5-b]quinoline-8,10(7H, 9H)-dione (4i): ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.48 (s,1H, CH); 6.72-7.80 (m, 10H, Ar-H); 9.25 (s, 1H, NH); 9.82 (s, 1H, OH); 10.18 (s, 1H, NH); 10.69 (s, 1H, NH); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 31.5, 78.5, 110.2, 115.9, 117.9, 118.8, 120.2, 121.9, 123.8, 124.5, 125.7, 127.2, 129.5, 131.3, 132.4, 134.2, 141.2, 150.8, 153.1, 156.3, 163.9.; GC-MS (m/z): 357 (M^+).

RESULTS AND DISCUSSION

In continuation of our interest in synthesis of heterocycles [13-15], herein we describe the synthesis of 7-aryl-11,12-dihydrobenzo[h]pyrimido-[4,5-b]quinoline-8,10(7H,9H)-diones in presence of catalytic amount of pyrrolidine based organocatalyst. The synthesis of 7-aryl-11,12-dihydrobenzo[h]pyrimido-[4,5-b]quinoline-8,10(7H,9H)-diones was accomplished by a one-pot three-component reaction of aromatic aldehydes, 1-naphthyl amine and barbituric acid using catalyst in solvent ethanol under ambient temperature. Initially, we focused on optimization of suitable solvent and catalyst loading for the model reaction of 4-chloro benzaldehyde, 1-naphthyl amine and barbituric acid. Various solvents were screened to test the efficiency of organocatalyst (10 mol%), as shown in table **1**, it is noteworthy to reveal that the agreeable result was observed in the solvent water. Furthermore the reaction in solvents ethanol and methanol afforded 58 % and 49% yield respectively. In the non-polar solvent chloroform and dichloromethane desired product was obtained in lower yields. Therefore we continued our studies in the solvent water.

Afterward, we studied the effect of catalyst loading on the model reaction. It was examined that amount of the catalyst plays a major role in determining the desired product yield. On decreasing catalyst concentration to 5 mol%, reaction offered lower yield 51% with elongated reaction time. When catalyst loading was enhanced to 15 mol%, an

improved result was obtained. The reaction was completed within 20 minutes and afforded 92% yield of the desired product. Therefore, the finest optimized reaction condition was accomplished at the catalyst loading of pyrrolidine based organocatalyst to 15 mol% in water. More increase in the catalyst loading to 20 mol% did not show an enhancement in the product yield or reaction time. The model reaction in absence of catalyst in solvent water showed abridged performance with respect to the yield and reaction time.

Table 1: Optimization of the solvent and catalyst concentration for the synthesis of Pyrimido quinoline dione derivatives

Entry	Pyrrolidine based organocatalyst (mol %)	Solvent	Time (min)	Yield[a] (%)
1	10	Ethanol	50	58
2	10	Methanol	70	49
3	10	Water	35	78
4	10	Chloroform	110	34
5	10	DCM	100	36
6	5	Water	45	64
7	**15**	**Water**	**20**	**92**
8	20	Water	20	82
9	-	Water	120	32

[a]Conditions: 4-Chloro benzaldehyde (2 mmol), 1-naphthylamine (2 mmol), barbituric acid (2 mmol), pyrrolidine based organocatalyst (mol %), Solvent (10 mL) at 60 ^{O}C. Reaction was monitored by thin layer-chromatography. [b]Isolated yield

Table 2: Pyrrolidine based organocatalyzed one-pot synthesis of 7-aryl-11,12-dihydrobenzo[h]pyrimido-[4,5-b]quinoline-8,10(7H,9H)-diones[a]

Entry	R	Products	Time (min)	Mp. (^{o}C)	Yield (%)[b]
1	4-OH	4a	28	315-316	85
2	4-F	4b	22	305-307	84
3	4-OCH_3	4c	25	310-312	91
4	3,4,5-OCH_3	4d	30	230-232	87
5	3,4-OCH_3	4e	25	240-242	89
6	-H	4f	25	260-263	82
7	4-Cl	4g	20	322-324	92
8	3-OCH_3,4-OH	4h	30	295-297	90
9	2-OH	4i	25	299-300	88
10	3-NO_2	4j	22	290-292	84

[a]Conditions: Aromatic aldehyde (2 mmol), 1-naphthylamine (2 mmol), barbituric acid (2 mmol), pyrrolidine based organocatalyst (15 mol %), Water (10 mL) at 60 ^{O}C. Reaction was monitored by thin layer-chromatography. [b]Isolated yield

To study the scope of the reaction after the optimization of reaction condition, we have examined a wide range of aromatic aldehydes with 1-naphthylamine and barbituric acid to obtain the corresponding 7-aryl-11,12-dihydrobenzo[h]pyrimido-[4,5-b]quinoline-8,10(7H,9H)-diones in excellent yields (Table 2, entry 1-10). The reaction proceeded smoothly with aromatic aldehyde having electron-withdrawing or electron-releasing substituents.

CONCLUSION

In conclusion, we have developed a convenient one-pot protocol for the synthesis of 7-aryl-11,12-dihydrobenzo[h]pyrimido-[4,5-b]quinoline-8,10(7H,9H)-diones by the condensation of aromatic aldehydes, 1-naphthylamine and barbituric acid in presence of pyrrolidine based organocatalyst at 60 ^{o}C. The remarkable features of this protocol are use of environmentally benign reaction solvents and catalyst, easy to accomplish, mild reaction condition and excellent yields of 7-aryl-11,12-dihydrobenzo[h]pyrimido-[4,5-b]quinoline-8,10(7H,9H)-diones.

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