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Research Article

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Green approach for synthesizing Pyrimido pyrimidine moieties using TBAB

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ABSTRACT

An efficient and direct procedure for the synthesis of pyrimido[4,5-d] pyrimidine derivatives from three component condensation of an aromatic aldehyde, urea/ thiourea and barbituric acid was carried out by using aqueous tetrabutyl ammonium bromide (TBAB) under solvent-free microwave conditions, which devoids hazards of solution phase reactions. The reaction time has been brought down from minutes to seconds with improved yield as compared to reported method.

Key words: Barbituric acid, Tetrabutyl ammonium bromide, microwave.

INTRODUCTION

The application of ionic liquids as alternative reaction media was frequently reported in literature during recent years [1–5]. Properties of ionic liquids such as solubility, solvation strength, acidity, and coordination were selectively varied and in most cases successfully validated. Whereas microwave-assisted reactions are known for their short reaction times [6-8] This advantage results from the way in which substances are heated in the microwave field.

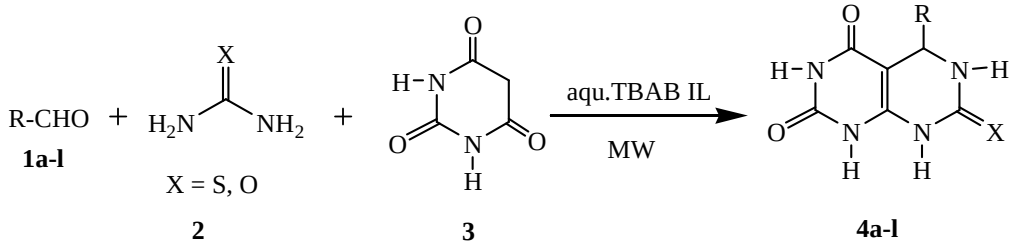
Microwaves directly excite polar molecules (dipole relaxation) and ions. (ionic conduction) On the macroscopic scale, the substance or substance mixture heats up, which is induced through friction of molecules or ions with each other. Therefore, the presence of ions and/or polar molecules is necessary for substances to be heated in the microwave field. Ionic liquids fulfill both requirements and should be principally suitable for energy dissipation with microwaves.

In multi-component reaction (MCR), three or more components combine in one pot process to afford a single product [9]. These reactions, by virtue of their convergence, low energy consumption, minimum waste production, facile execution, high selectivity and productivity, represent an important platform for the design and discovery of various drugs and drug related molecules [10,11] Pyrimido[4,5-d]pyrimidine derivatives are well known as bronchodilators [12], vasodilators [13], antiallergic [14], antihypertensive [15], and anticancer [16] agents. Therefore, lot of efforts have been made toward the synthetic manipulation of uracil for the preparation of pyrimido[4,5-d]pyrimidine derivatives, which usually requires forcing conditions, long reaction times and complex synthetic pathways [17]. The promising methods for the synthesis of pyrimido [4,5-d]pyrimidine involve multistep syntheses starting from 1,3-disubstituted cyanouracils [18], polymer bound 2-(alkylsulfanyl)-4-aminopyrimidine-5-carbonitriles [19], aza-Wittig-type reactions Using iminophosphoranes of 5-aminouracils [20] and reacting 6-[(dimethylamino) methylene] aminouracils with various heterocumulenes [21].

Synthetic alternatives are many and varied and have resorted to harsh conditions, *e. g.* the use of PTSA (*p*-toluenesulfonic acid) as catalyst, using $POCl_3$ with DMF as a solvent [22]. Additionally, reagents for these procedures are not readily or commercially available which is a key deficiency in developing conditions for library synthesis. Therefore, there is a need to develop more efficient and sustainable chemical process for the synthesis of

pyrimido [4,5-d]pyrimidines.

As part of our ongoing program of developing environmentally benign synthetic methods for pharmacologically important heterocyclic skeletons, we explored a green multicomponent reaction (MCR) protocol using aqu. IL Tetrabutylammonium bromide. Herein, we report a simple, rapid and one-pot aqu. IL mediated procedure for the synthesis of pyrimido[4,5-d] pyrimidines in high yield and purity (scheme 1).



Scheme 1

EXPERIMENTAL SECTION

General procedure for the synthesis of pyrimido[4,5-d] pyrimidine derivatives

Method A (Conventional synthesis):
To the mixture of barbituric acid **3** (1mmol), an aromatic aldehyde **1a–l** (1mmol) and urea/thiourea **2a/2b** (1mmol), 3ml of aqu. TBAB (1:1) were added. The reaction mixture was kept on heating at 110^{o}C-120^{o}C for an appropriate time with constant stirring. The solid obtained was isolated by filtration, washed with water and dried.

Method B (Microwave-assisted synthesis):
An equimolar amounts of barbituric acid **3** (1mmol), an aromatic aldehyde **1a–l** (1mmol), urea/thiourea **2a/2b** (1mmol), and 3 mL of aqu. TBAB (1:1) were mixed thoroughly in a mortar. The reaction mixture was then transferred to 100 mL conical flask and was then irradiated in a domestic microwave in a domestic microwave oven for specific time as shown in (Table 2), at low power (150W). The progress of the reaction was monitored at regular intervals of time. Upon completion, the reaction mixture was cooled and the product was isolated by filtration, washed with cold water, dried and then recrystallized from ethanol to afford pyrimido[4,5-d]pyrimidine in pure form.

Spectral data of some representative compounds

5,6-Dihydro-5-phenylpyrimido[4,5-d]pyrimidine-2,4,7(1*H*,2*H*,8*H*)Trione(4a), Yellow colored solid, M. p. 172-174°C; IR (KBr): 3416, 3323, 3221,2983, 1735, 1697, 1647, 1496, 1419,1232, 758,702 cm^{-1}; ^{1}HNMR (400MHz , $CDCl_3$): 5.49 (s, 1H, ArCH), 7.51-7.76(m, 5H, ArH), 7.55, (s, 1H, NH), 10.16(s, 1H, NH), 11.26 (s, 1H, NH), 11.63(s, 1H, NH), *m/e* = 259 [M^{+}].

5,6-dihydro-5-(4-chlorophenyl)pyrimido[4,5-d]pyrimidine-2,4,7(1*H*,3*H*,8*H*)trione(4c),White solid; m. p. 296 - 298°C; **IR** (KBr): 484, 3223, 3090, 1760, 1705, 1673, 1644, 1575 cm^{-1}.^{1}HNMR (400 MHz, DMSO-d_6): δ 11.27 (s, 1H, NH), 10.98 (s, 2H,NH), 8.26 (s, 1H, NH), 7.61 (d, *J* = 8.0 Hz, 2H, arom. H), 7.26 (d, *J* = 8.0 Hz, 2H, arom. H), 4.90 (s, 1H, 5H); *m/e* = 292.03 [M+].

5,6-dihydro-5-(4-nitrophenyl)pyrimido[4,5-d]pyrimidine-2,4,7(1*H*,3*H*,8*H*)-trione (4i),
IR (KBr): 3382, 3191, 3087, 2965, 2856, 1650,1515 cm^{-1}; ^{1}HNMR (400MHz, DMSO-d_6): 11.40(s, 1H, NH), 11.20 (s, 2H, NH), 10.18 (s, 1H, NH),8.20-8.40 (m, 4H,H_{arom}), 6.12 (s,1H, 5H); *m/e* = 304 [M^{+}].

5,6-dihydro-5-(2-Hydroxyphenyl)pyrimido[4,5-d]pyrimidine-7-thioxo-2,4(1*H*,3*H*,8*H*)-dione (6b), White solid; m. p. 200-202°C; **IR** (KBr): 3446, 3222, 3080, 1697, 1650, 1582 cm^{-1}; ^{1}HNMR (400 MHz, DMSO-d_6): δ 11.96 (s, 1H, NH), 10.97 (s, 2H, NH), 8.29(s, 1H, NH) 7.23-7.30 (m, 4H, arom. H), 4.89 (s, 1H, 5H); *m/e* = 290 [M^{+Na}] 313.

5,6-dihydro-5-(4-methoxyphenyl)pyrimido[4,5-d]pyrimidine-7-thioxo-2,4(1*H*,3*H*,8*H*)-dione (6b), Yellow solid; m. p. > 300°C, IR (KBr): 3452, 3211, 1720, 1698, 1655, 1560 cm^{-1}. ^{1}HNMR (400 MHz, DMSO-d6): δ 11.29 (s, 1H, NH), 10.99 (s, 2H, NH), 8.31 (s, 1H, NH), 7.22 (d, *J* = 7.0 Hz, 2H, arom. H), 7.16(d, *J* = 7.0 Hz, 2H, arom. H), 4.88 (s, 1H, 5-H), 3.83 (s, 3H, OCH_3); *m/e* = 305 [M^{+}].

RESULTS AND DISCUSSION

To search for an appropriate solvent for the synthesis of pyrimido [4,5-d] pyrimidines under microwave irradiation, the model reaction of barbituric acid (1 mmol), p-methoxy benzaldehyde (1mmol) and urea (1mmol) was examined using water, glycol, DMF, THF, ethanol, [Bmim]BF_4, [Bmim]Cl, [Bmim]PF_6, and Tetrabutyl ammonium bromide as solvents under MW irradiation (150W) conditions as shown in Table1. The reaction proceeded efficiently when aqu. Tetrabutyl ammonium bromide was used as solvent resulting in higher yields in comparison to the other solvents used. Inspired by this result, aqu.TBAB (table 1, entry **10**) was then used as solvent for all further MW assisted pyrimido [4,5-d] pyrimidine derivative synthesis.

Table 1: Solvent optimization for the synthesis of compound (4d) under microwave irradiation at low power (150W)

Entry	Solvent	Time (min)	Yield (%)
1	Water	5	70
2	Glycol	5	75
3	DMF	7	70
4	THF	---	---
5	Ethanol	8	60
6	[Bmim]BF4	6	78
7	[Bmim]Cl	6.5	80
8	[Bmim]PF6	7	75
9	TBAB	3	85
10	aqu. TBAB (1:1)	1	85

To optimize the reaction temperature under conventional heating, the synthesis of **4d** was performed in aqu. TBAB at temperatures ranging from 110 to 120^{o}C and also at low powers of microwaves (100, 150W). It was observed that the time needed to reach the temp. at 110 to 120^{o}C by conventional heating method was too long. Whereas Microwave irradiation at 150W using 2-3 mL of aqu. TBAB furnished the highest yield of pyrimido [4,5-*d*] pyrimidines in less time. (Table 2) Thus a microwave power of 150W was chosen as the optimal one. The ease of separation of pyrimido [4,5-d] pyrimidine derivatives from the reaction media is the foremost advantage of this process in aqueous TBAB media. Similarly, thiourea (1mmol) in place of urea was taken to get 5-aryl-1,3,5,6,8-pentahydro-7-thioxo-pyrimido [4,5-d] pyrimidine-2,4-diones.

Thus thiourea proved here as one of the ingredients with similar success to provide the corresponding pyrimido [4,5-*d*] pyrimidine thiones which are also of interest with respect to their biological activities. Moreover, for comparision, classical heating conditions were also applied for the synthesis of all products as summarized in Table 2. It was found that the reaction proceeds efficiently under MW irradiation with a reduction in time from hours to minutes to seconds in comparison to the conventional one with appreciable yield enhancement. In addition, looking at the success of this approach, as no extra catalyst was required for the proposed protocol, it was thought worthwhile to attempt the reactions without any solvent or catalyst, but no proper results were obtained; only some charring was observed on prolonged heating.

Table 2: Comparative study data for the synthesis of pyrimido [4,5-d] pyrimidine derivatives under conventional and microwave assisted method using aqu. TBAB

Entry	R	X	Product	Method A		Method B	
				Time (h)	Yield (%)	Time (sec.)	Yield (%)
1	Ph	O	4a	3.0	80	32	95
2	2-OH-C_6H_4	O	4b	4.5	70	37	96
3	4-Cl-C_6H_4	O	4c	5.0	72	32	96
4	4-OMe-C_6H_4	O	4d	5.0	76	37	97
5	4-CH_3-C_6H_4	O	4e	4.0	75	37	96
6	4-NO_2-C_6H_4	O	4f	3.5	73	32	70
7	C_6H_5	S	4g	2.5	80	32	95
8	2-OH-C_6H_4	S	4h	5.0	74	37	94
9	4-Cl-C_6H_4	S	4i	3.5	80	27	97
10	4-OMe-C_6H_4	S	4j	3.0	75	42	96
11	4-Br-C_6H_4	S	4k	3.0	76	32	87
12	4-$N(Me)_2$-C_6H_4	S	4l	3.2	78	37	88

Method A : Conventional heating (110-120^{o}C) Method B : Micowave heating at (150W)

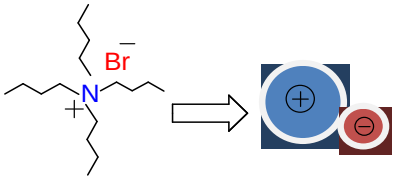
The structures of the products were assigned on the basis of the spectral data. In the ^{1}HNMR spectra, the disappearance of the diagnostic signal due to the methylene protons of barbituric acid at δ 3.8 ppm indicates the condensation of the active methylene group with the aromatic aldehydes used. Following the mechanism, this

intermediate then condenses with urea/thiourea furnishing the required products 4a-l, which is confirmed by the appearance of a singlet at δ 4.9 ppm assigned to 5-H.

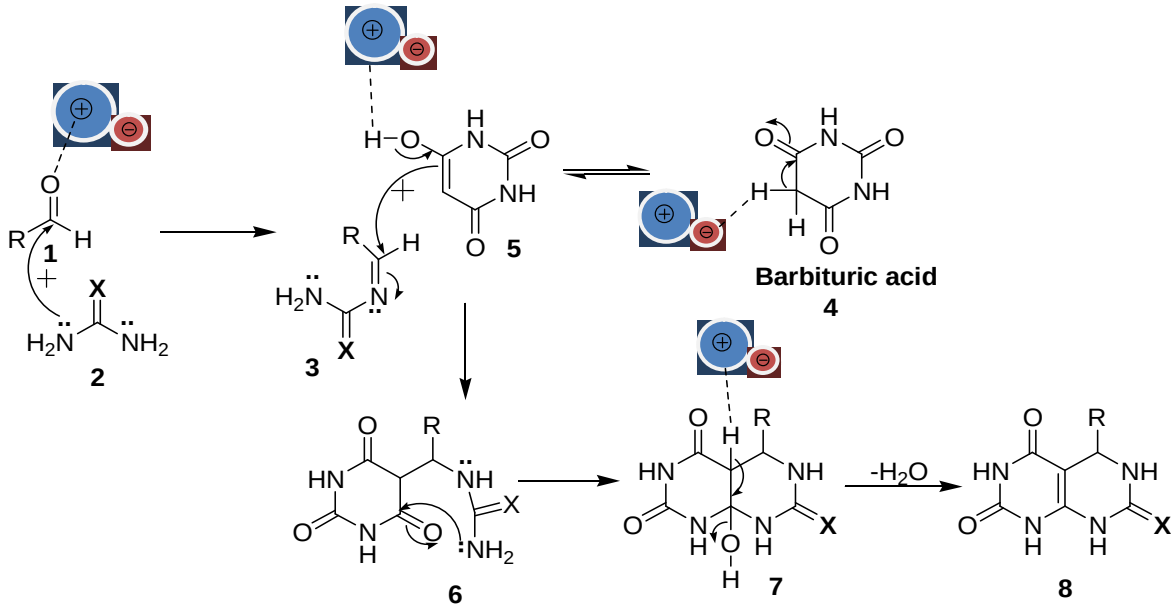
CONCLUSION

In brief, a practically convenient and eco-friendly synthesis of pyrimido [4,5-*d*] pyrimidines has been developed in an aqueous TBAB medium without using any catalyst, without use of hazardous organic solvents and corrosive acids or bases. Water-insoluble solid products obtained in short time are found to be essentially pure and in very high yield. This simple single-step reaction has the ability to withstand the variations in the 1,3-diketone and carbonyl part also. This direct strategy could find broader interest for the synthesis of compound libraries having in common a heterocyclic pyrimido [4,5-*d*] pyrimidine moiety.

Tetrabutyl ammonium bromide mediated, probable mechanism for the synthesis of Pyrimido [4,5-d] pyrimidine derivatives



Tetrabutyl ammonium bromide Ionic liquid



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