Calcium Bromide is an Efficient Catalyst for Synthesis of Dihydropyrimidones under Microwave Condition

Pramod Kulkarni

Department of Chemistry, Hutatma Rajguru Mahavidyalaya, Rajgurunagar, Pune Maharashtra 410505, India

Corresponding email: pramodskulkarni3@gmail.com

Abstract:

An efficient and ecofriendly method was developed for synthesis of a series of dihydropyrimidinone derivatives through three-component one-pot cyclocondensation between substituted benzaldehydes, beta ketoester and urea/thiourea using calcium bromide as a catalyst under microwave irradiation in a solvent-free condition. The merits of this method is solvent free approach, low catalyst loading, shorter reaction time, simple workup procedure, catalyst is easily available, inexpensive and easy to handling. Using this procedure, we synthesized 25 different biologically active dihydropyrimidine.

Keywords: Calcium bromide, Dihydropyrimidones, Microwave, Solvent free

Introduction:

Over the years Dihydropyrimidinones (DHPMs) molecules and its derivatives attract many organic chemists due to their therapeutic and pharmacological properties [1]. Dihydropyrimidinones molecules is core backbone of several drugs used as calcium channel blockers [2], antihypertensive [3], anticancer agents [4], antidiabetic activity [5], antithrombotic agent [6], Carbonic anhydrase inhibitor [7], α_{1a}-adrenergic antagonists [8], neuropeptide Y (NPY) antagonists [9], antileishmanial [10]. These compounds also exhibit a broad range of biological activities [11] such as antiviral, antibacterial, anti-inflammatory, antioxidant, antitubleuer and FATP4 inhibitor properties. Pyrimidinone derivatives are found as core units in many marine alkaloids (batzelladine and carambine), which have been found to be potent to HIV-gp-120 CD4 inhibitors [12]. Due to the outstanding importance in pharmacological and biological activities, the synthesis of these compounds has become an important challenge in current years. The synthesis of these compounds firstly reported by the Biginelli in 1893, The Biginelli reaction, is a direct and simple approach for the synthesis of 3,4-dihydropyrimidinones by one-pot cyclocondensation of ethyl acetoacetate, benzaldehyde and urea in the presence of strong acid [13]. However, one serious shortcoming of this method is the low yield of the products. This has lead to the development of a multistep synthesis of Biginelli compounds that bring on higher yields, although missing the ease of the one pot synthesis [14]. Hence, the Biginelli reaction involving one step cyclocondensation for

the synthesis of dihydropyrimidinones has received renewed interest, and several improved protocols, mainly using Lewis acids as well as protic acids have been developed for accomplishing this reaction. In order to improve the efficiency of the Biginelli reaction, different catalysts such as $ZnCl_2$/TBAB [14], LiBr [15], $Cu(OTf)_2$ [16], $FeCl_3.6H_2O$, $NiCl_2.6H_2O$ [17], $Zr(H_2PO_4)_2$ [18], Sodium Selenate [19], Lanthanide Triflate [20], Indium (III) Chloride [21], $CdCl_2$ [22], silica sulphuric acid [23], mesoporous silica MCM-41 [24], *t*-BuOK [25], $Y(NO_3)_3.6H_2O$ [26], Iron (III) trifluoroacetate and trifluoromethanesulfonate [27], CaF_2 [28], PEG-embedded thiourea dioxide [29], 12-Molybdophosphoric acid [30], Chlorosulfonic acid [31], Nafion-H [32], Cobalt nitrate [33], Silica-gel [34], Silica-bonded *S*-Sulfonic acid [35], $NaIO_4$ [36], Aluminatesulfonic acid nanoparticles [37], trichloroisocyanuric acid [38], 1,3-Dichloro-5,5-dimethylhydantoin[39], Nano-$TiCl_4.SiO_2$ [40], $FePO_4.2H_2O$ [41], $LaCl_3/ClCH_2COOH$ [42] and so on. Other methods, for synthesis of dihydropyrimidiones are ionic liquid [43], microwave irradiation [44], and ultrasound [45]. Some other methods and biological activity of dihydropyrimidiones are described in review article published in 2012 by Suresh and Jagir S. Sandhu [46]. However, some of these catalyzed reactions conditions have certain shortcomings such as use of expensive reagents, heavy metal salts, strongly acidic conditions, use of toxic organic solvent, anhydrous conditions, preparation of catalysts require, high temperature, long reaction times, scope of reaction was limited to aromatic aldehydes. Due to increasing environmental perception in chemical research and Industry, the challenge for a sustainable environment calls for fair processes that can avoid using harmful organic solvents, or even better, do not need solvents at all, avoid usage of toxic metals or metal salts which affect on aquatic life's as well as cause soil pollution, avoid use of hazardous catalyst. Hence, due to the enormous biological importance of dihydropyrimidinones, the synthesis of these molecules is attracting most of the researcher to synthesize it. Thus, development of simple, effective, fair, high yielding and eco-friendly approaches using new catalysts for the synthesis of these molecules is an important task of organic chemists.

The advancement of microwave assisted reaction in organic synthesis has improved the speed, reduced cost, reduced energy spent making it a sustainable process and is commonly publicized as "green chemistry" process whose applications are encouraged to minimize the use of non renewable resources as well as polluting solvent, to reduce generation of inferior products which are frequently toxic and to burn down the emission of harmful gases [47]. During last 25 years a significant number of ~ 5000 publications using microwave-assisted organic transformations are published [48]. Application of microwave in

organic synthesis is well documented in Literature and some reviews are published on organic transformation mediated by microwave irradiation [48, 49, 50].

Calcium bromide is the calcium salt of hydrobromic acid. Calcium bromide is obtained by the interaction of bromine and milk of the lime in the presence of ammonia. It is readily soluble in water and absolute ethanol [51]. It is thermally and chemically stable. Use of calcium bromide in organic synthesis is very rare [52].

Results and Discussion:

Microwave-enhanced chemistry is based along the efficient heating of materials by "microwave dielectric heating" effects. This phenomenon is dependent on the power of a specific material (solvent or reagent) to absorb microwave energy and convert into heat. The electric component of an electromagnetic field causes heating by two primary mechanisms: depolarization and ionic conduction. Radiation of the sample at microwave frequencies results in the dipoles or ions aligning in the applied electric field. As the applied field oscillates the dipole or ion field attempts, or realign itself with the alternating electric field and in the process, energy is lost in the form of heat through molecular friction and dielectric loss. The quantity of the heat generated by this process is immediately linked to the power of the matrix to adjust itself with the frequency of the given field. If the dipole does not have adequate time to realign or reorients too quickly with the applied field, no heating occurs [49]. Calcium bromide is polar covalent molecules due to high electronegative difference between calcium and bromine. The binding electron pair in calcium and bromine is pulled towards bromine atom, forming a diploe within the molecule. Due to this dipole calcium bromide absorbs microwave energy and converts into heat. This generated heat used to bring reaction between urea, benzaldehyde and ethyl acetoacetaete.

To lead off the reaction conditions for the calcium bromide catalyzed Biginelli condensation under microwaves, the reaction of benzaldehyde with ethyl acetoacetate and urea was taken as a model reaction (Scheme 1).

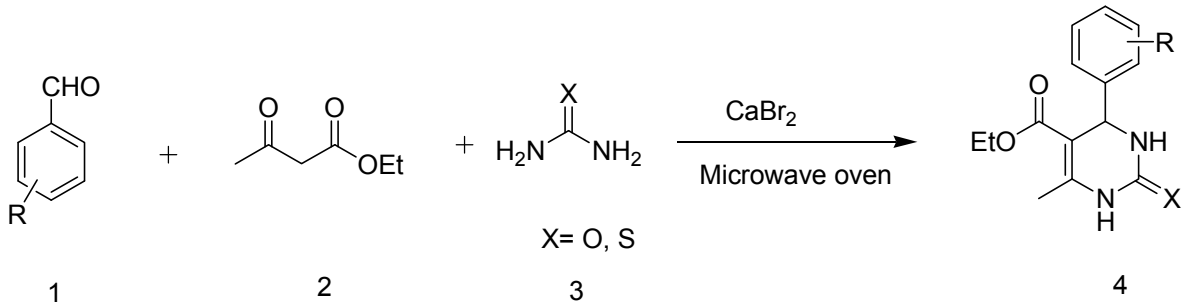
I tested to optimize the reaction conditions by changing the quantities of calcium bromide from 0 mole% - 20 mole%. It was noted that the condensation reaction can be efficiently carried out by taking 2mol% of the catalyst at 400w, in a short time span of only 1.5 to 3 minutes, which is much lesser and yield is high as compared to other catalysts using more than 5 to 20mol%. A further increase in the catalyst amount does not show any noticeable increase in the product yield (Table 1).

Table 1. Optimising amount of catalysts for synthesis of dihydropyrimidiones[a]

Entry	Amount of catalyst in mol%	Time in Minutes	% Yield[b]
1	0	15	25
2	0.5	10	41
3	1	5	52
4	2	2	94
5	5	2	95
6	10	1.5	95
7	15	1.5	95
8	20	1.5	94

a: Reaction Condition: 1mmol of Benzaldehyde, 1mmol of ethyl acetoacetate, 1mmol of urea, 0.02mmol of calcium bromide under irradiated in microwave, b: isolated yield after purification

In order to study the scope of this protocol, a series of DHPMs were synthesized using aromatic aldehydes carrying both electron donating or withdrawing substituens and heterocyclic aldehydes were subjected to reaction with β-keto esters, urea / or thiourea under the optimized reaction conditions. Thiourea has been used with similar success to provide the corresponding dihydropyrimidin-2(1H)-thiones which are also of much interest with regard to biological activity. The reaction proceeds smoothly to give the corresponding dihydropyrimidiones in excellent yields and the results are given in Table 2.



Scheme 1 Synthesis of Dihydropyrimidinone using calcium bromide as catalyst under microwave irradiation

Table 2. Synthesis of substituted dihydropyrimidinones/thiones using calcium bromide as a catalyst under microwave condition[a]

Entry	Aldehyde	X	Product (4)	Time in minutes	% Yield[b]	M. P. [Ref]
1	Benzaldehyde	O	**4a**	1.5	94	201-203[44]
2	4-chlorobenzaldehyde	O	**4b**	2	91	213-214[43]
3	4-methoxybenzaldehyde	O	**4c**	2.5	89	206-209[33]
4	4-bromobenzaldehyde	O	**4d**	2	86	233-235[42]
5	4-hydroxybenzaldehyde	O	**4e**	2	87	196-198[33]
6	4-nitrobenzaldehyde	O	**4f**	2	82	211[40]
7	4-N,N-dimethylbenzaldehyde	O	**4g**	3	79	249-251[40]
8	4-methylbenzaldehyde	O	**4h**	2.2	91	216-217[33]
9	3-hydroxybenzaldehyde	O	**4i**	1.3	92	166-168[45]
10	3-nitrobenzaldehyde	O	**4j**	1.4	90	227-228[44]
11	3-bromobenzaldehyde	O	**4k**	1.2	89	187-188[33]
12	2-hydroxybenzaldehyde	O	**4l**	3.3	81	201-202[42]
13	2-nitrobenzaldehyde	O	**4m**	3.5	72	205-207[44]
14	2-chlorobenzaldehyde	O	**4n**	3.5	74	215-216[44]
15	Cinnmaldehyde	O	**4o**	3.4	82	231-232[33]
16	Furfural aldehyde	O	**4p**	2.3	85	203-204[31]
17	3,4-dihydroxybenzaldehyde	O	**4q**	2.4	88	241-243[18]
18	$CH_3CH_2CH_2CHO$	O	**4r**	2.3	85	179-181[44]
19	4-chlorobenzaldehyde	S	**4s**	2	91	191-193[43]
20	4-methoxybenzaldehyde	S	**4t**	2.4	87	193-194[33]
21	2-hydroxybenzaldehyde	S	**4u**	2.5	76	241-244[43]
22	2,4-dimethoxybenzaldehyde	O	**4v**	3	88	212-214[18]
23	3,4-dichlorobenzaldehyde	O	**4w**	2.4	89	223-225[43]
24	3-methoxybenzaldehyde	S	**4x**	3	90	153-154[43]
25	4-N,N-dimethylbenzaldehyde	S	**4y**	3.2	82	209-211[45]

a: Reaction condition: 1mmol of substituted benzaldehyde, 1mmol of ethyl acetoacetate, 1mmol of urea/thiourea, 0.02mmol of calcium bromide under microwave irradiation; b: isolated yield after purification

Notably, this protocol is compatible with a wide range of functional groups such as methoxy, halides, nitro, hydroxyl, *N, N*-dimethyl-, and acid sensitive compound like cinnamaldehyde, furfural aldehyde could afford the corresponding products in excellent yield as well.

Conclusion:

In summary, here I reported an efficient synthesis of dihydropyrimidinones and dihydropyrimidinthiones using calcium bromide as a catalyst under microwave condition. The mild reaction conditions, rapid formation of product, high yields, inexpensive and easily available catalyst, are some notable merits of this method. Moreover, compatibility with the environment, more efficiency and easy separation of catalyst after synthesis are considered as another merit of this method. Most importantly, absence of organic solvents and use of microwave irradiation as an alternative energy source which obey principles number two and five out of the twelve principles of green chemistry, due to this, method contributes it to the development of green technology.

Experimental:

All reagents, chemicals and solvents were purchased from Loba, Merck, SRL and Sigma Aldrich. Microwave reactions were carried out using an unmodified household microwave oven (Onida MO20CJP27B) at 400W power level. Calcium bromide was purchased from Loba Chemicals. TLC (pre-coated silica gel 60 F254) was used to monitor the progress of the reaction. Melting points were recorded by open capillary method and are uncorrected. IR spectra were recorded as KBr pellets using shizmude FTIR. The ^{1}HNMR spectra were obtained on a Bruker DRX-300 Avance instrument using DMSO *d6* as solvent and TMS as internal standard at 300MHZ. All products are known compounds and their authenticity was ensured on the basis of spectroscopic data and on comparison with authentic samples.

General Procedure for the Synthesis of Dihydropyrimidinones and Thiones: A mixture of aldehyde (1mmol), ethyl acetoacetate (1mmol), urea or thiourea (1mmol) and calcium bromide (0.02mmol, 2mol %) in a reaction flask was stirred well, kept in microwave oven. The reaction mixture was irradiated in microwave oven at 400W for 2 minutes. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture

was cooled, added to 20mL ice cold water, solid was precipitated, filtered on a suction pump, washed with water and dried. A pure sample was obtained by recrystallization from ethanol.

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