Tributyl Borate Mediated Biginelli Reaction: A Facile Microwave-Assisted Green Synthetic Strategy toward Dihydropyrimidinones

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Exploitation of a new boron-based catalyst, tributyl borate, for the formation of dihydropyrimidinones under solvent-free microwave-assisted conditions is described. The method is a simple, easy, fast, cost effective, and potentially green protocol for the formation of multi-functionalized pharmacologically active dihydropyrimidinones.

Dihydropyrimidinones (DHPMs), commonly known as Biginelli compounds, have received unprecedented attention due to their biological, pharmaceutical, and therapeutic properties.[1] Functionalized derivatives of these compounds have proved to be effective antimicrobial, antioxidant, antitumor, antiinflammatory, antihypertensive agents calcium channel blockers, HIV inhibitors, etc.[1–3] Several alkaloids which have shown useful pharmacological activity bearing the DHPMs moiety have been isolated from marine sources.[3] Thus, the synthesis of these highly active functional entities in a more elegant protocol has high significance.

Since the first report on the synthesis of DHPMs by Biginelli in 1893,[4] many improved procedures have been developed for their formation under conventional, microwave-assisted and ultrasonic pathways.[2,5–12] Most of these methods reported describe the use of Lewis acids and salts, which mainly contain heavy metals.[5] Other promoters include acetic acid,[6] ammonium chloride,[5f] poly(phosphate esters),[7] propylphosphonic anhydride,[8] hexafluorophosphate,[12] montmorillonite KSF clay,[9] etc. The boron-based catalysts reported so far are BF_3-etherate/CuCl/HOAc,[2a] boric acid in glacial acetic acid,[10] phenylboronic acid,[11] 1-butyl-3-methylimidazolium tetrafluoroborate,[12] etc.

Although many revised protocols are reported for the formation of dihydropyrimidinones, most of them suffer from low yields, long reaction times, and impurities. Here our effort is to devise a simple, high yielding, fast, easy, and potentially green protocol using the cheap eco-friendly reagent, tributyl borate. It is noteworthy that tributyl borate is a mild, efficient, cost-effective, and heavy metal free novel boron-based catalyst used for the first time to generate a DHPMs library under microwave-assisted solvent-free conditions.

The present investigations were initiated by exposing a mixture of methyl acetoacetate (1), urea (2), benzaldehyde (3), and tributyl borate to microwaves in the absence of a solvent for 3 min at a power of 390 W. An efficient reaction occurred and the dihydropyrimidinone (4) was obtained in 95% yield (Figure 1).

A number of 1,3-diketones, urea/thiourea, and aldehydes were found to be suitable substrates for DHPMs synthesis under these conditions and the results are summarized in Table 1. In the absence of tributyl borate it was found that the conversion was only 5–20% even after 30 min microwave irradiation. The same reaction was carried out under solution phase mode and the yields and time of the reaction were compared with that of the microwave-assisted method. A reasonable mechanism proposed for the reaction is shown in Figure 2.

The water scavenging nature of the reagent and the potential ability of the boron to coordinate with the diketones and the acyliminium salt are likely to be the driving forces for this condensation–cyclization reaction.

When tributyl borate is used, it is observed that aromatic aldehydes with both electron-donating and -withdrawing functional groups behave efficiently. The experimental procedure is very simple and the work up is easy as the number and quantity of the by-products formed are negligible. In most of the cases the products are obtained in the purest form by two- or three-step crystallization. In some cases (Entries 3, 7, and 11 in Table 1) column chromatography purification is needed.

The reaction was also found successful when carried out under reflux conditions in different solvents using tributyl borate as the catalyst. The results of optimization experiments considering the synthesis of **4** as a typical example are summarized in Table 2.

Among the different solvents and solvent mixtures tested, 1:1 DMF–methanol mixture was found to be the effective solvent system for the synthesis of dihydropyrimidinones both under reflux and room temperature stirring conditions.

From the pharmaceutical point of view, a significant advantage of the method is that it does not involve the use of any heavy metal species. Further even acid sensitive aldehydes

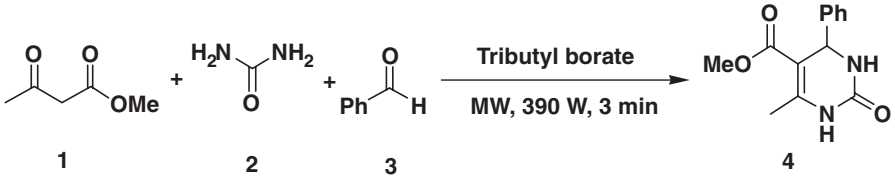

Figure 1. Reaction of methyl acetoacetate, urea, and benzaldehyde in the presence of tributyl borate.

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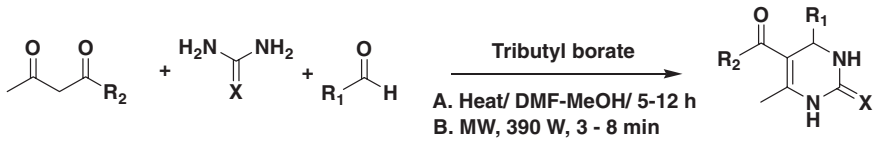
Table 1. Formation of DHPMs Catalyzed by Tributyl Borate



Entry	R_1	R_2	X	Time		Yield/%		Melting point/°C	
				A[a]/h	B[a]/min	A[a]	B[a]	Exptl.	Reported[b]
1	C_6H_5	Me	O	5	3	80	91	235–236	233–236[5f]
2	4-OMe-C_6H_4	Me	O	7	4	72	87	174–176	178–180[5i]
3	2-Cl-C_6H_4	Me	O	8	8	63	82	259–260	257–258[1d]
4	C_6H_5	OEt	O	6	4	78	93	202–203	202–204[5c]
5	4-OMe-C_6H_4	OEt	O	9	7	70	86	204–205	201–203[5a]
6	2-OH-C_6H_4	OEt	O	10	6	68	69	198–200	201–203[5h]
7	4-OH-3-OMe-C_6H_3	OEt	O	8	5	65	79	235–236	232–233[5g]
8	Furyl	OEt	O	7	3	60	75	206–207	205–206[2d]
9	4-OH-C_6H_4	OEt	O	9	4	59	76	228–231	225–229[5c,6]
10	4-NMe_2-C_6H_4	OEt	O	5	2	58	83	258–260	256–258[2d]
11	3-NO_2-C_6H_4	OEt	O	11	8	61	72	227–229	229–231[11]
12	2-Naphthyl	OEt	O	12	3	60	81	247–249	248–250[6]
13	C_6H_5	OMe	O	5	4	85	95	206–207	207–210[5f]
14	4-OMe-C_6H_4	OMe	O	6	4	70	83	188–191	191–193[5f]
15	2-Cl-C_6H_4	OMe	O	8	6	55	71	247–249	252–253[5f]
16	3-NO_2-C_6H_4	OMe	O	8	7	59	77	278–280	279–280[5f]
17	C_6H_5	OEt	S	6	4	78	95	205–207	206–207[8,11]
18	4-OMe-C_6H_4	OEt	S	9	6	61	74	141–143	138–140[5f]
19	C_6H_5	Me	S	6	7	58	87	217–219	220–222[8]
20	C_6H_5	C_6H_5	O	10	4	61	89	204–206	203–204[5i]
21	4-OMe-C_6H_4	C_6H_5	O	7	5	55	82	222–224	218–220[5i]

a) A: Reflux method and B: Microwave-assisted method. b) References.

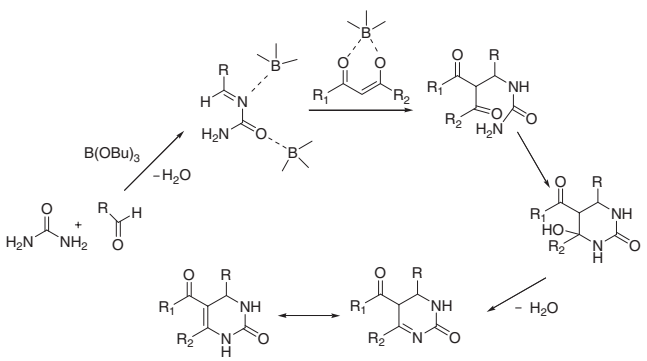


Figure 2. Feasible mechanism for dihydropyrimidinones formation in the presence of tributyl borate, $[B(OBu)_3]$.

like 2-furaldehyde and cinnamaldehyde can be used for the DHPM formation under the present experimental conditions, with good yield.

In conclusion, we have developed an expeditious environmentally benign route for the synthesis of dihydropyrimidinones under microwave-assisted conditions exploring the utility of a novel boron-based catalyst, tributyl borate in the Biginelli multicomponent reaction. It proved to be a successful, economic, and clean catalyst, as it conforms to any diketones, aldehydes, and urea derivatives for the formation of the DHPMs (Table 1). A comparative study of the microwave method with that of the reflux method shows that the former is the more efficient method. This method has the added benefit of generating the bioactive DHPM units in a metal-free environment, which is valuable to pharmaceutical industries.

Table 2. Optimization Experiments under Reflux Conditions

Sl.No	Solvent	Time/h		Yield/%	
		A[a]	C[a]	A[a]	C[a]
1	Methanol	10	18	68	38
2	Ethanol	12	20	73	35
3	Ethyl acetate	10	18	68	32
4	Acetonitrile	13	24	65	42
5	Toluene	14	26	52	12
6	DMF	9	16	79	41
7	DMF–MeOH (1:1)	8	15	82	48

a) A: Reflux conditions and C: Stirring at room temp.

Experimental

All the chemicals used were of synthetic grade and purified and perfectly dried before use. All the compounds were characterized by comparing their melting points, IR, NMR, and HRMS data with those reported in the literature. The melting points were determined using a GUNF melting point apparatus and are uncorrected. The IR spectra were recorded on a JASCO FT/IR-4100 spectrophotometer in KBr pellets, NMR spectra recorded on a BRUKER AVANCE DPX 300 MHz spectrometer using TMS as

internal standard and high-resolution mass spectra recorded on a JEOL JMS600 instrument. Microwave irradiation was done using a modified Microwave Assisted Reacting System, MARS 5 Version 194A02 (CEM Corporation, USA).

Synthetic Procedure. Representative Procedure for the Synthesis of 4 under Microwave-Assisted Condition: Methyl acetoacetate (0.69 g, 6 mmol), urea (0.48 g, 8 mmol), benzaldehyde (0.53 g, 5 mmol), and tributyl borate (1.4 g, 6 mmol) are taken in a loosely stoppered borosil vessel and irradiated at a power level of 390 W in a microwave reactor for 3 min, intermittently (6 × 30 s). The reaction mixture is transferred into crushed ice and stirred vigorously for 30 min. The solid separated is vacuum filtered, washed repeatedly with ice-cold ethyl acetate–light petroleum mixture (1:1) and finally with distilled water. The product **4** thus obtained is dried under vacuum and re-crystallized from ethanol for pure crystals. The yield is 95%, melting point: 206–207 °C.

Representative Procedure for the Synthesis of 4 under Reflux Solution Phase Mode: Methyl acetoacetate (0.69 g, 6 mmol), urea (0.48 g, 8 mmol), benzaldehyde (0.53 g, 5 mmol), and tributyl borate (0.48 g, 2 mmol) are mixed in 5 mL dry solvent and stirred at room temperature/refluxed for specified time as is described in Table 1. The reaction mixture is then poured into crushed ice and stirred vigorously for 1 h keeping the temperature below 5 °C. The solid separated out is vacuum filtered, washed repeatedly with ice-cold ethyl acetate and finally with distilled water. The crude product obtained is dried under vacuum and re-crystallized from ethanol for pure crystals.

Similar procedures have been adopted for the synthesis of other compounds under the experimental conditions mentioned in Table 1.

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