A Novel Cu-catalysed Three-component One-pot Synthesis of Dihydropyrimidin-2(1*H*)-ones Using Microwaves under Solvent-free Conditions

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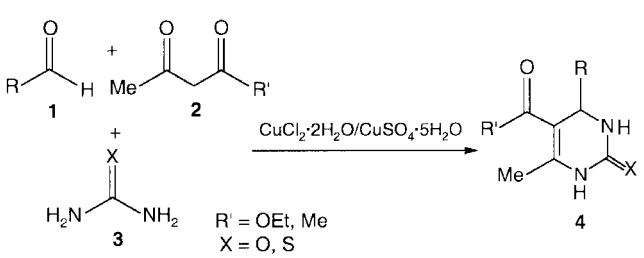
Abstract: Cupric chloride dihydrate catalyzes the three-component Biginelli condensation between an aldehyde, a β-ketoester and urea or thiourea under microwave irradiation in the absence of solvent to yield various substituted 3,4-dihydropyrimidin-2(1*H*)-ones. The reaction is also effective when performed at room temperature in acetonitrile or at 100 °C in a solvent free approach, without any side reactions as observed by Biginelli and others.

Key words: Biginelli condensation, cupric chloride, cupric sulphate, dihydropyrimidinones,, three-component reactions

In recent years attention has been focused particularly on dihydropyrimidinones (DHPMs), which are an important class of compounds due to their therapeutic and pharmacological properties.[1] They have emerged as integral backbones of several calcium channel blockers (e.g. nifedipine), antihypertensive agents and alpha-1a-antagonists and neuropeptide antagonists.[2] Alkaloids containing the dihydropyrimidine unit have been isolated from marine sources[3] and among these are the batzelladine alkaloids which were found to be potent HIV gp-120-CD4 inhibitors.[4] This is an impressive profile that bodes well for the interaction of this heterocyclic building block with a variety of biological targets of interests. Thus synthesis of this heterocyclic nucleus is of continuing interest. The most convenient Biginelli's one-pot reaction first described more than a century ago[1a] and reviewed[1b,c] recently involves condensation of an aldehyde, a β-dicarbonyl compound and urea or thiourea under strongly acidic conditions. However, the main drawback of Biginelli reaction is low yields[5] and sensitive functional groups are lost during the reaction conditions.[6] This has led to the discovery of multi-step strategies[7] that produce somewhat higher yields but lack the simplicity of the original Biginelli one-pot synthesis. Several improvement includes combination of Lewis acids with transition metal salts or $BF_3{\cdot}OEt_2$[8] or KSF[9] or InX_3[10] (X = Cl, Br) or CAN[11] or $Yb(OTf)_3$[12] and poly- phosphate ester[13] mediates Biginelli reaction was applied recently to greatly improve the yield of the process. Even during last two years several improved protocols[14] by the modification of the classical one-pot approach[8,9,13,15] and complex multi-step strategies[2a,7,16] have been published. But the practical application of these methods suffer from disadvantages such as the use of expensive or less easily available reagents, vigorous reaction conditions, prolonged standing and tedious manipulations in the isolation of the pure products. Therefore, a need still exists for versatile, simple and environmentally friendly processes whereby DHPMs may be obtained under milder conditions.

A very recent report by Sudalai and his co-workers[14b] prompted us to disclose our results on the three-component Biginelli reaction using cupric chloride dihydrate in a solvent-free condition under microwave irradiations. The reaction also proceeded efficiently at room temperature in acetonitrile and the corresponding DHPMs were obtained in 80–94% yields. Further, the condensation was found to be equally effective when $CuCl_2{\cdot}2H_2O$ was replaced by $CuSO_4{\cdot}5H_2O$ and the corresponding DHPMs were obtained in almost comparable yields. Sudalai et al. have synthesised various dihydropyrimidin-2(1*H*)-ones in 60–95% yields using expensive $Cu(OTf)_2$ and various other copper salts. Among the copper salts screened including $CuSO_4{\cdot}5H_2O$, $Cu(OTf)_2$ showed excellent activity in terms of yields in producing the required product at 25–70 °C in 4–12 hours. But with 5 mol% of cuprous chloride and copper sulphate, they got the corresponding DHPMs in 20% and 0% yields respectively. In contrast, we have performed the Biginelli reaction in presence of $CuCl_2{\cdot}2H_2O$ and $CuSO_4{\cdot}5H_2O$ in solvent free conditions, and isolated the corresponding DHPMs in 80–99% yields. The reaction was very fast when carried out under microwave irradiations (1–1.5 min) and took 1–2 hours on heating at 100 °C. We employed microwave energy because the potential application of microwave technology in organic synthesis[17] particularly in solid state is increasing rapidly due to its reaction simplicity, less polluting and minimum reaction time providing rapid access to large libraries of diverse small molecules (Scheme 1).



Scheme 1

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In a typical procedure, a mixture of ethyl acetoacetate (1.30 g, 10 mmol), benzaldehyde (1.06 g, 10 mmol), urea (0.6 g, 10 mmol) and cupric chloride dihydrate (0.17 g, 1 mmol) was placed in an Erlenmeyer flask and heated in a microwave oven at power 60%, (operating at 2450 MHz frequency) for 1.5 minutes. After completion (monitored by TLC), the reaction was cooled to room temperature and poured into water (30 mL). The solid separated was filtered, washed with water and then recrystallised from ethanol to afford pure **4a**, mp 201–202 °C (lit.[18] mp 202 °C) in 98% yield. Similarly other substituted aldehydes, β-dicarbonyl compounds and urea were reacted together to produce the corresponding dihydropyrimidin-2(1*H*)-ones. The results are summarized in Table 1. Under this condition, the yields were significantly improved to 80–99% and the reaction time was reduced dramatically. A number of substituted aromatic, aliphatic and heterocyclic aldehydes have been employed successfully. Acetylacetone and thiourea were also used with similar success to provide the corresponding 3,4-dihydropyrimidin-2(1*H*)-

Table 1 $CuCl_2{\cdot}2H_2O/CuSO_4{\cdot}5H_2O$ Catalysed Synthesis of Dihydropyrimidin-2-(1*H*)-ones **4**

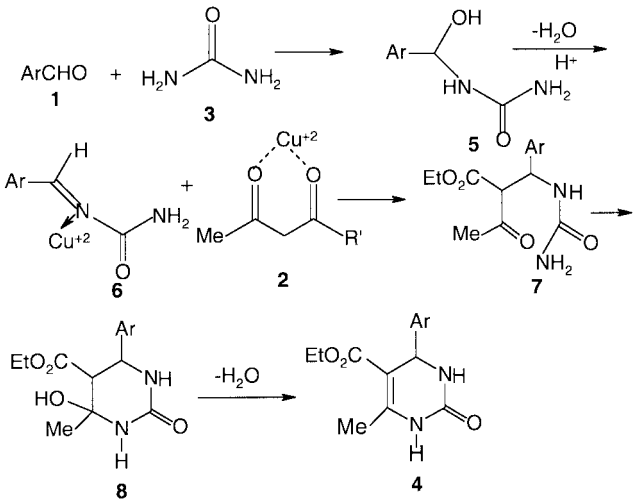
Entry	Products[a]	R^1	R^2	X	Catalyst	Reaction[b] time (min) thermal	Yield[c] (%)	Reaction[b] time (min) microwave	Yield[c] (%)	Mp (°C)	Lit. mp (°C)
1	**4a**	Ph	OEt	O	$CuCl_2{\cdot}2H_2O$	60	96	1	98	200–202	202–204[14b]
2	**4b**	4-ClC_6H_4	OEt	O	$CuCl_2{\cdot}2H_2O$	60	97	1	96	215–216	213–215[8]
3	**4c**	4-$MeOC_6H_4$	OEt	O	$CuCl_2{\cdot}2H_2O$	60	96	1.5	99	198–200	201–202[14b]
4	**4d**	4-$NO_2C_6H_4$	OEt	O	$CuCl_2{\cdot}2H_2O$	60	90	1	92	206–208	207–208[14b]
5	**4e**	4-$CH_3C_6H_4$	OEt	O	$CuCl_2{\cdot}2H_2O$	60	95	1	97	214–215	215–216[14b]
6	**4f**	2-Furyl	OEt	O	$CuCl_2{\cdot}2H_2O$	60	80	1.5	82	208–209	209–211[14b]
7	**4g**	3-$NO_2C_6H_4$	OEt	O	$CuCl_2{\cdot}2H_2O$	60	86	1.5	88	227–228	226–227[22a]
8	**4h**	C_6H_4-CH=CH	OEt	O	$CuCl_2{\cdot}2H_2O$	100	82	1	85	231–232	232–235[12]
9	**4i**	*n*-Bu	OEt	O	$CuCl_2{\cdot}2H_2O$	110	80	1.5	80	156–157	157–158[12]
10	**4j**	$(CH_3)_2CH$-	OEt	O	$CuCl_2{\cdot}2H_2O$	112	80	1.5	82	190–192	194–195[12]
11	**4k**	Ph	OEt	S	$CuCl_2{\cdot}2H_2O$	60	97	1.5	88	208–209	208–210[14b]
12	**4l**	4-ClC_6H_4	OEt	S	$CuCl_2{\cdot}2H_2O$	75	95	1.5	97	191–192	192–195[14b]
13	**4m**	2-Thienyl	OEt	S	$CuCl_2{\cdot}2H_2O$	60	92	1.5	90	214–216	215–217[14b]
14	**4n**	Ph	CH_3	O	$CuCl_2{\cdot}2H_2O$	60	96	2	98	207–209	209–212[8]
15	**4o**	4-MeC_6H_4	CH_3	O	$CuCl_2{\cdot}2H_2O$	65	93	1.5	95	192–193	192–194[14b]
16	**4p**	4-$NO_2C_6H_4$	CH_3	O	$CuCl_2{\cdot}2H_2O$	60	80	1.5	80	236–238	235–237[14b]
17	**4a**	Ph	OEt	O	$CuSO_4{\cdot}5H_2O$	70	96	1	98	200–202	202–204[14b]
18	**4b**	4-ClC_6H_4	OEt	O	$CuSO_4{\cdot}5H_2O$	60	97	1	96	215–216	213–215[8]
19	**4c**	4-$MeOC_6H_4$	OEt	O	$CuSO_4{\cdot}5H_2O$	70	96	1.5	99	198–200	201–202[14b]
20	**4d**	4-$NO_2C_6H_4$	OEt	O	$CuSO_4{\cdot}5H_2O$	70	90	1	92	206–208	207–208[14b]
21	**4f**	2-Furyl	OEt	O	$CuSO_4{\cdot}5H_2O$	70	80	1.5	82	208–209	209–211[14b]
22	**4h**	C_6H_4-CH=CH	OEt	O	$CuSO_4{\cdot}5H_2O$	110	82	1	85	231–232	232–235[12]
23	**4i**	*n*-Bu	OEt	O	$CuSO_4{\cdot}5H_2O$	110	85	1.5	88	156–157	157–158[12]
24	**4k**	Ph	OEt	S	$CuSO_4{\cdot}5H_2O$	70	97	1.5	88	208–209	208–210[14b]
25	**4n**	Ph	CH_3	O	$CuSO_4{\cdot}5H_2O$	70	96	2	98	207–209	209–212[8]
26	**4p**	4-$NO_2C_6H_4$	CH_3	O	$CuSO_4{\cdot}5H_2O$	70	80	1.5	80	236–238	235–237[14b]

[a] All the compounds were characterized by IR, NMR, MS and mp.
[b] At r.t., the reaction time is 2–3 h and the yield is 80–94%.
[c] Isolated yields.

thiones.[19] Thus variation in all three components have been accommodated very comfortably. This condensation procedure is fairly general and several functionalities including nitro, chloro, hydroxyl, methoxy and conjugated carbon-carbon double bond do survive during the course of the reaction. However, under the present reaction condition β-ketoaldehyde do not produce the corresponding dihydropyrimidinones, instead they lead to multiple products. Meanwhile, even for aliphatic aldehyde such as butyraldehyde and *iso*-butyraldehyde which normally show extremely poor yields in the Biginelli reaction, the corresponding dihydropyrimidinones could be obtain in 80–82% yields[20] (Table 1). Acid sensitive aldehydes such as furfural also worked well without the formation of any side products. Roughly 0.1 equivalent of $CuCl_2$ was found to be sufficient for these reactions and use of less than 0.1 equivalent was not optimal one. The use of large amount of $CuCl_2 \cdot 2H_2O$ is also found to be not fruitful i.e. does not increase the yields. Notably, with $CuSO_4$, 0.05 equivalent of the catalyst was sufficient to perform the condensation. Also, the reagents employed for this process were inexpensive and anhydrous conditions were not required. All the reactions were very fast, clean and high yielding using 1 or 0.5 mol% of the catalyst. In a recent solvent-free approach[12] by Yang et al. the heterogeneous mixture of β-ketoesters, aldehydes and urea were refluxed for 10 hours in the presence of 30 mol% of $CeCl_3 \cdot 7H_2O$ to get the corresponding DHPMs in 65–80% yields. In contrast, using $CuCl_2 \cdot 2H_2O$ or $CuSO_4 \cdot 5H_2O$ in a solvent-free approach we got the corresponding DHPMs in 80–99% yields when carried out in a microwave oven or by heating the heterogeneous mixture at 100 °C.

Recently, the mechanism of the Biginelli reaction was studied in detail by Kappe.[13,21] He proposed and established that the first step in this reaction was the formation of acylimine intermediate from aldehyde and urea. Subsequent addition of the β-keto ester enolate to the acylimine followed by cyclodehydration would afford dihydropyrimidinones **4**. Owing to the empty orbital in the copper ion a complex **6** can be formed through a co-ordinative bond and stabilized by copper. A tentative mechanism for the copper promoted Biginelli condensation is shown in Scheme 2.

In conclusion, the present method discloses a new and simple modification of the Biginelli reaction by using inexpensive $CuCl_2 \cdot 2H_2O$ or $CuSO_4 \cdot 5H_2O$ as a catalyst in solvent-free conditions under microwave irradiations. The yield of the DHPMs can be increased from 20–50%[8] to 80–99% while the reaction time was reduced dramatically from 18–48 hours to 1–1.5 minutes. It not only led to economical automation but also reduces hazardous pollution to achieve environmentally friendly processes. This Cu-catalysed one-pot synthesis of DHPMs is therefore, simple, high yielding, time saving and environment friendly. In addition to its simplicity and selectivity this reaction has one salient feature in its ability to tolerate a variety of aldehydes and constitute a useful alternative to the commonly accepted procedures.



Scheme 2

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