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NOTE

Synthesis of 4-Aryl-substituted 3,4-Dihydropyrimidin-2-ones Under Microwave Irradiation and Solvent-Free Condition

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4-Aryl-substituted 3,4-dihydropyrimidin-2-ones are synthesized in high yields using zinc iodide as a mild catalyst under microwave irradiation and solvent-free condition by one-pot cyclocondensation reaction. This is a simple, mild, rapid and environmentally benign method of the synthesis of the DHPMs.

Key Words: Biginelli, Dihydropyrimidinones, Microwave irradiation, Solvent-free conditions.

In the past decade, dihydropyrimidine derivatives exhibited important pharmacological properties, as the integral backbone of several calcium channel blockers, a hypertensive agents, α-la-antagonists and neuropeptide Y (NPY) antagonists[1]. Furthermore, several marine alkaloids with interesting biological activities containing the dihydropyrimidine-5-carboxylate core unit have recently been isolated[2]. Most notably among these are the batzelladine alkaloids, which were found to be potent HIV group-120-CD4 inhibitors[3].

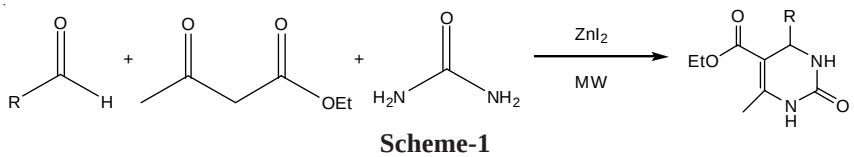
The Biginelli reaction, first reported more than a century ago and recently reviewed[1b], involves the acid-catalyzed cyclocondensation reaction of ethyl acetoacetate, benzaldehyde and urea. This reaction is carried out by simply heating a mixture of the above three components dissolved in ethanol with a catalytic amount of hydrochloric acid at reflux temperature for 18 h. However, this one-pot, one step protocol often provides only low to moderate yields of the desired target molecules (20-50 %) in particular when substituted aromatic or aliphatic aldehydes are employed. Therefore, the discovery of milder and practical routes for the synthesis of dihydorpyrimidin-2-ones by the Biginelli reaction continues to attract the attention of researchers.

Recently, several improved procedures for the preparation of dihydropyrimidines have been reported, either by modification of the classical one-pot Biginelli approach itself or by the development of novel but complex multi-step strategies[4]. Some new catalysts have been reported, such as a number of Lewis acids (*e.g.* LiBr[5], $FeCl_3 \cdot 6H_2O$[6], $Bf_3 \cdot OEt_2$[7], $ZrCl_4$[8], $BiCl_3$[9], $Mn(OAc)_3 \cdot 2H_2O$[10], $LaCl_3 \cdot H_2O$[11], $InCl_3$[12], $Cu(OTf)_2$[13], $In(OTf)_3$[14], lanthanide triflates[15], $ZnCl_2$[16], $NiCl_2 \cdot 6H_2O$[17], $MgBr_2$[18], $CeCl_3 \cdot 7H_2O$[19], $CdCl_2$[20], $InBr_3$[21], *etc.*), I_2[22], HTMA[23], L-Proline[24], SiO_2-$NaHSO_4$[25]. In addition, new technologies, such as microwave irradiation[26], ultrasonic[27], ionic liquid[26d] and solid-state synthesis[28], also have been used in the Biginelli reaction.

Previous reported synthetic methods normally required prolonged reaction times and high temperature with moderate yields, so it is important to explore

mild, rapid and higher yielding protocol at ambient temperature. Though microwave irradiation technology has been used in Biginelli reaction and it reached high yields, those reactions are not perfect and they also suffer from drawbacks, such as high temperature (normal temperature is above 100ºC) or prolonged time (more than 2 h) or poisonous solvent (CH_3CN).

Herein, a practical route for the cyclocondensation reaction under microwave irradiation and solvent-free conditions using zinc iodide as a mild catalyst (**Scheme-I**) is reported. Compared to other methods, the present one is rapid (3-7 min), mild (room temperature), environmentally friendly (solvent-free) and high yields (78-88%) (Table-1). This route is a simple but effective modification of the Biginelli reaction while preserve the original one-pot strategy. Though zinc iodide has been used in the Biginelli reaction as a catalyst[29], it is a traditional reaction that reacted at 80ºC under high pressure for 4 h use poisonous CH_3CN as the solvent and its yield is only 77 %.



Scheme-1

TABLE-1
ZnI_2 CATALYZED BIGINELLI REACTION UNDER MICROWAVE IRRADIATION AND SOLVENT-FREE CONDITION (P = 600 W)

Entry	R	Time (min)	Yield (%)
1	Ph	3	88
2	4-CH_3-C_6H_4	5	81
3	3-OCH_3-C_6H_4	5	85
4	4-OCH_3-C_6H_4	5	80
5	2-OH-C_6H_4	5	78
6	2-Cl-C_6H_4	5	82
7	4-OH-3-OMe-C_6H_3	7	86
8	4-NO_2-C_6H_4	7	85
9	3,4-OMe_2-C_6H_3	5	84
10	3-Br-C_6H_4	5	78

Considering the environmentally benignancy and taking full advantage of this new technology, we try to accomplish this Biginelli reaction under solvent-free and microwave irradiation condition. First, it was found the Biginelli reaction of benzaldehyde, ethyl acetoacetate and carbamide could be catalyzed by zinc iodide under microwave irradiation and solvent-free condition and the desired product was obtained in high yield (88%). Similarly, various aromatic aldehydes reacted well under the same conditions to give the corresponding DHPMs in moderate to excellent yields. The most advantage of this method is the reaction time that had been shortened from hours to several min.

In summary, a mild, rapid and convenient method for the three-component, one-pot Biginelli-like reaction catalyzed with ZnI_2 under the microwave irradiation and solvent-free condition has been discovered. This method shortened the

reaction time prominently, and it spurned the use of poisonous solvent. So, it is a useful amelioration of the Biginelli reaction.

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