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Microwave-induced bismuth nitrate-catalyzed synthesis of dihydropyrimidones via Biginelli condensation under solventless conditions

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Abstract—Microwave-induced bismuth nitrate-catalyzed efficient and extremely rapid synthesis of 4-aryl-3,4-dihydropyrimidones via Biginelli condensation reaction has been developed in excellent yield.

Dihydropyrimidones have attracted immense interest as calcium channel blockers, antihypertensive agents, alpha-1a-antagonists,[1] and neuropeptide Y (NPY) antagonists.[2,3] The most important examples are batzelladine alkaloids, which are potent HIV group-120-CD4 inhibitors.[4] As a result of their medicinal properties, synthesis of the dihydropyrimidone nucleus has received much attention. The initial synthesis of dihydropyrimidone following Biginelli condensation has proved to be inefficient with 20–50% yield.[5] Recently, methods have been discovered to synthesize these types of heterocycles, however, they involve multiple sequences and hazardous conditions.[6] A few attractive methods are known, but most of them employ anhydrous reaction conditions and Lewis acids ($BF_3{\cdot}Et_2O$, $LiClO_4$, $InCl_3$, $ZrCl_4$, $NiCl_2{\cdot}6H_2O$, $BiCl_3$, $Bi(OTf)_3$, and $FeCl_3$).[7] Many of these methods are also time consuming. Therefore, development of an efficient, rapid, and catalytic method is necessary for the synthesis of this type of multifunctionalized rings. We report here a remarkably fast and simple microwave-induced bismuth nitrate-catalyzed synthesis of dihydropyrimidones through a three-component reaction under solventless conditions.

In a series of publications, we have demonstrated the versatility of bismuth nitrate-catalyzed organic reactions.[8] Bismuth nitrate is readily available at a very low cost. It is a stable and non-toxic crystalline solid. Our research has established that this reagent can act as an effective Lewis acid, and it can be used successfully in the presence of commercially available solvents without any drying or treatment. Several experimental conditions toward the preparation of dihydropyrimidones have been attempted (Table 1). The reactants (aldehyde **1**, urea **2**, and dicarbonyl compound **3**) and bismuth nitrate are mixed in the presence of an organic solvent (THF or ethanol) and heated under reflux for approximately 6 h. After the addition of crushed ice the solid product was filtered to isolate product **4** in excellent yield. A number of dihydropyrimidones were prepared following this method in good yield. It is remarkable to note that this reaction produces product even with 0.1 mol % of bismuth nitrate (Table 1, entries 21 and 22). Microwave-induced reactions using CEM Discover Lab-Mate and domestic microwave have also been performed under solventless conditions.[9] To our surprise, product **4** has been isolated in excellent yield within 4–5 min using 2 mol % of bismuth nitrate with four other substrates (Table 1, entries 14–18). However, the reaction did not proceed through stirring in a mortar and pestle (Table 1, entry 12), at high temperature in water (Table 1, entry 13), or room temperature in acetonitrile (Table 1, entry 19). In contrast to other available methods, this present method for the synthesis of dihydropyrimidione is extremely rapid and highly efficient. This is a novel, powerful, and economical one-pot procedure for the preparation of dihydropyrimidones.

Keywords: Biginelli condensation; Microwave; 4-Aryl-3,4-dihydropyrimidones; Bismuth nitrate; Solventless reaction.
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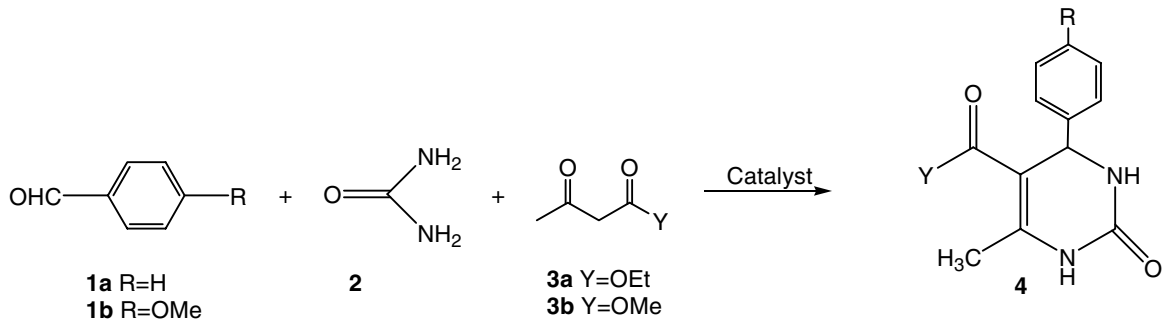
Table 1. Synthesis of 4-aryl-3,4-dihydropyrimidones

Entry	1	2	3	Catalyst	Method	Percent yield
1	**1a**[a]	**2**[a]	**3a**	$Bi(NO_3)_3$[a]	Reflux[a]	85
2	**1a**[a]	**2**[a]	**3a**	$BiCl_3$[a]	Reflux[a]	44
3	**1a**[a]	2[a]	**3a**	$Bi(OTf)_3$[a]	Reflux[a]	87
4	**1b**[a]	**2**[a]	**3a**	$BiCl_3$[a]	Reflux[a]	43
5	**1b**[a]	**2**[a]	**3a**	$Bi(NO_3)_3$[a]	Reflux[a]	80
6	**1b**[a]	**2**[a]	**3a**	$Bi(OTf)_3$[a]	Reflux[a]	84
7	**1a**[a]	**2**[a]	**3b**	$Bi(NO_3)_3$[a]	Reflux[a]	83
8	**1a**[a]	**2**[a]	**3b**	$Bi(OTf)_3$[a]	Reflux[a]	85
9	**1b**[a]	**2**[a]	**3b**	$Bi(NO_3)_3$[a]	Reflux[a]	81
10	**1b**[a]	**2**[a]	**3b**	$Bi(OTf)_3$[a]	Reflux[a]	82
11	**1a**[b]	**2**[b]	**3a**	$Bi(NO_3)_3$[b]	Reflux[b]	96
12	**1a**[c]	**2**[c]	**3a**	$Bi(NO_3)_3$[c]	Mortar and pestle[c]	13
13	**1a**[d]	**2**[d]	**3a**	$Bi(NO_3)_3$[d]	Reflux[d]	23
14	**1a**[e]	**2**[e]	**3a**	$Bi(NO_3)_3$[e]	MWI[e]	98
15	**1a**[e]	**2**[e]	**3b**	$Bi(NO_3)_3$[e]	MWI[e]	97
16	**1a**[e]	**2**[e]	**3a**	$Bi(NO_3)_3$[e]	MWI[e]	98
17	**1a**[e]	**2**[e]	**3b**	$Bi(NO_3)_3$[e]	MWI[e]	97
18	**1a**[f]	**2**[f]	**3a**	$Bi(NO_3)_3$[f]	MWI[f]	88
19	**1a**[g]	**2**[g]	**3a**	$Bi(NO_3)_3$[g]	RT[g]	18
20	**1a**[h]	2[h]	**3a**	$Bi(NO_3)_3$[h]	Reflux[h]	95
21	**1a**[i]	**2**[i]	**3a**	$Bi(NO_3)_3$[i]	Reflux[i]	91
22	**1a**[j]	**2**[j]	**3a**	$Bi(NO_3)_3$[j]	Steam bath[j]	75

The reactions were performed using 1:1.1:1.1 ratios (aldehyde, urea, keto ester, respectively).
[a] Substrates and 10 mol % of catalyst were refluxed in 2 mL of anhydrous THF for 6 h.
[b] Substrates and 10 mol % of catalyst were refluxed in 2 mL of anhydrous ethanol for 5 h.
[c] Substrates and 10 mol % of catalyst were mixed in a mortar and pestle for 2 h.
[d] Substrates and 10 mol % of catalyst were refluxed in 2 mL of ice water for 6 h.
[e] Substrates and 2 mol % of catalyst were microwaved in the CEM Discover Lab-Mate microwave for 4.5 min.
[f] Substrates and 2 mol % of catalyst were microwaved in a domestic microwave for 5 min.
[g] Substrates and 10 mol % of catalyst were stirred at room temperature in 2 mL of acetonitrile for 1 h.
[h] Substrates and 1 mol % of catalyst were refluxed in 2 mL of anhydrous ethanol for 7 h.
[i] Reaction was carried out on 10 mmol scale with 0.1 mol % of catalyst and 20 mL of anhydrous ethanol under reflux for 7 h.
[j] Reaction was carried out on 10 mmol scale with 0.1 mol % of catalyst under reflux in a steam bath for 2 h.

Different types of bismuth catalysts have been investigated. Although bismuth triflate produces product in comparable yield in the presence of anhydrous ethanol or tetrahydrofuran, it is an expensive and hygroscopic solid. Bismuth trichloride produces the product in low yield (Table 1, entries 2 and 4). However, Kaimal et al. reported synthesis of dihydropyrimidones using bismuth trichloride-catalyzed reaction in large excess of acetonitrile for 5 h (eight times less catalyst with respect to the substrate).[10] The reaction was highly efficient as indicated by the product yield. Our present bismuth nitrate-catalyzed reaction is much superior to the existing methods because of several reasons. For example, our microwave-induced reaction is a catalytic (100 times less catalyst with respect to the substrate) rapid (4–5 min) process performed in the absence of solvent Scheme 1.

The mechanism of the dihydropyrimidone formation has been investigated by Folkers and Johnson.[10,11] It has been hypothesized that the reaction proceeds through an acylimine intermediate. Following this explanation, it can be assumed that due to the presence of vacant d-orbital, bismuth salts may stabilize the acylimine intermediate and this intermediate complex may then react effectively with a β-ketoester. A cyclization and dehydration path may then follow to produce the dihydropyrimidone system as described in earlier



Scheme 1.

papers.[10,11] As a result of our long-term involvement in the use of imine in organic synthesis, we became interested to identify the formation of the acylimine intermediate.[12] Reaction of urea **2** with benzaldehyde **1a** was performed in the presence and absence of bismuth nitrate for 2–16 h under reflux temperature in benzene using a Dean Stark. However, formation of acylimine could not be detected.[10,11] The staring materials (urea and benzaldehyde) remain unreacted as evidenced from ^{1}H NMR study. On this basis, it seems that the mechanism of Biginelli reaction is complex and further work is necessary to determine the course of the reaction.

In conclusion we have demonstrated a new, mild, cost effective, catalytic, and highly efficient procedure for the synthesis of 4-aryl-3,4-dihydropyrimidones.[13] In contrast, most the available procedures require much longer reaction times, expensive and/or corrosive acids (catalytic or stoichiometric), dry reaction conditions, and dry solvents.

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13. A representative experimental procedure is described below: Microwave synthesis of 4-aryl-3,4-dihydropyrimidones: Aromatic aldehyde (1 mmol), β-ketoester (1.1 mmol), and urea (1.1 mmol) were mixed with bismuth nitrate (10 mg) and placed in a microwave reaction vial. The CEM Discover Lab-Mate microwave was programed to the following settings: 300 W, 100 °C, and reaction time of 4.5 min. After the reaction, ice water was added, which resulted in the precipitation of the solid product. This was crystallized (ether–hexane) to afford the pure product as described earlier.[14]
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