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Phenylboronic acid as a mild and efficient catalyst for Biginelli reaction

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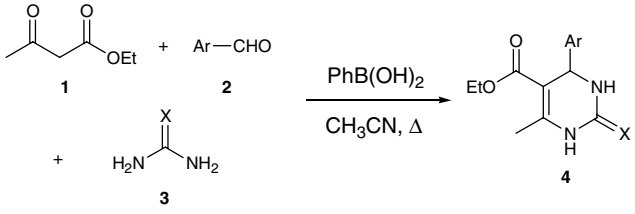
Abstract—The synthesis of 3,4-dihydropyrimidinone derivatives was achieved in good to excellent yields using phenylboronic acid as catalyst to promote the Biginelli three-component condensation of a diversity of aromatic aldehydes, ethyl acetoacetate and urea or thiourea.

1. Introduction

3,4-Dihydropyrimidinones (DHPMs) constitute a very important class of organic compounds due to their attractive pharmacological properties, including antiviral, antitumour, antibacterial activities. The dihydropyrimidinone core is also found in many natural products that explained the important efforts devoted to the synthesis of these heterocycles.[1] The one-pot, three-component Biginelli condensation provides certainly the most efficient access to DHMP derivatives due to its atom economy feature and the availability and the diversity of the building blocks engaged in this reaction (Scheme 1). In the past few years, the Biginelli reaction has received renewed interest and several improved procedures have been reported.[2] There is a variety of suitable reaction conditions, traditionally with strong Brønsted acid, but nowadays, more frequently, with Lewis acids, such as $LiClO_4$, $LaCl_3$–$7H_2O$, $InCl_3$, $Bi(OTf)_3$, $BiCl_3$, $Mn(OAc)_3$, $Cu(OTf)_2$, $FeCl_3$–$6H_2O$, $ZrCl_4$ or $SnCl_2{\cdot}2H_2O$, for example.[3] Other works have been devoted to the use of ionic liquids,[4] microwave irradiation,[5] solid phase reagents,[6] and polymer-supported catalysts.[7] The use of two boron compounds, Et_2OBF_3 in the presence of CuCl and acetic acid in refluxing THF[8] and boric acid in glacial acetic at 100 °C[9] has also been reported. Two asymmetric syntheses using $CeCl_3/InCl_3$ or $Yb(OTF)_3$ in the presence of chiral ligands were recently investigated.[10,11]



Scheme 1.

Boronic acids are effective catalysts for several organic transformations, such as Mukayama aldol condensation or amidation of carboxylic acids with amines, for example. The synthetic interest of these catalysts is greatly enhanced by the possible use of chiral derivatives, such as acyloxyboranes or alkyldichloroboranes. They have been successfully applied to asymmetric Diels Alder cycloadditions or enantioselective allylation reactions.[12] To our knowledge, neither boronic acid nor its derivatives have been hitherto tested as catalysts in the Biginelli reaction.

Keywords: Biginelli; Boronic acid; 3,4-Dihydropyrimidinone; Three-component condensation.
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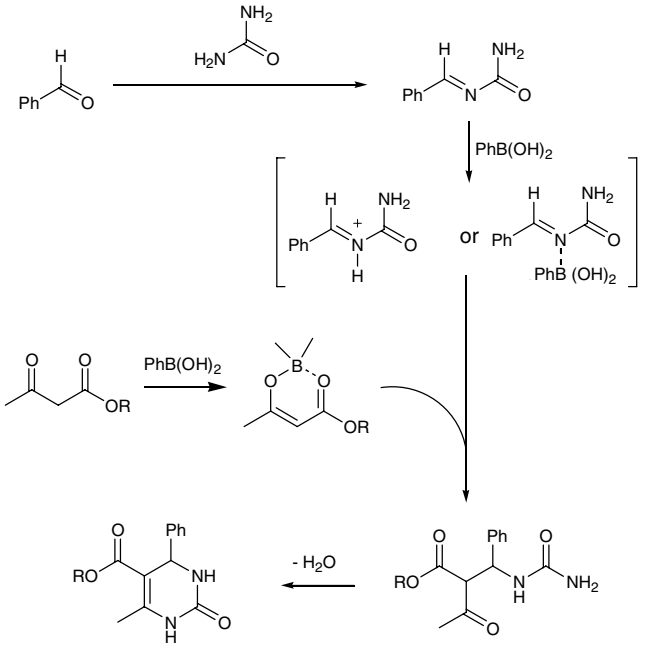
Table 1. Phenylboronic acid catalysed synthesis of dihydropyrimidinones **4**

Entry	Product	Ar	X	Yields (%)	Mp (°C) [Lit.]
1	**4a**	C_6H_5	O	87	200–202 [202–204][8]
2	**4b**	3-Cl–C_6H_4	O	76	195–196 [193–195][8]
3	**4c**	3,5-Cl_2–C_6H_3	O	80	>300
4	**4d**	3,4-Cl_2–$C_6H_{3,5}$	O	78	>300
5	**4e**	4-MeO–C_6H_4	O	97	202–203 [201–203][8]
6	**4f**	4-HO–C_6H_4	O	91	198–200 [198–200][13]
7	**4g**	4-Me–C_6H_4	O	70	213–214 [215–216][14]
8	**4h**	3-Me–C_6H_4	O	75	204–205 [207–208][15]
9	**4i**	3-NO_2–C_6H_4	O	75	227–228 [229–231][14]
10	**4j**	2-Thienyl	O	82	207–208 [207–208][16]
11	**4k**	C_6H_5	S	60	204–205 [206–207][16]
12	**4l**	4-MeO–C_6H_4	S	75	150–152 [150–152][14]



Scheme 2.

In the following, we report our preliminary investigations dealing with the use of a boronic acid, $PhB(OH)_2$, a commercially available, nontoxic and cheap reagent, as catalyst in these synthetically useful three-component condensation (Scheme 1).

The optimised conditions utilise a 1:1:1.5:0.1 ratio of ethyl acetoacetate **1**, aldehyde **2**, urea **3** and phenylboronic in acetonitrile as solvent at reflux temperature (Table 1). Aromatic aldehydes carrying either electron-donating or electron-withdrawing substituents afforded high yields of products (entries 1–9). Acid sensitive aldehydes, such as 2-thiophenecarboxaldehyde, reacted without the formation of any side product and gave the 3,4-dihydropyrimidinone derivative in 82% yield (entry 10). Thiourea has also been frequently employed to provide the 3,4-dihydropyrimidinethiones. In our experimental conditions, the cyclisation took place in moderate to good yields (entries 11 and 12). With 2-methylpropanal, an aliphatic aldehyde, the corresponding 3,4-dihydroxypyrimidinone was formed in very low yield (20%) that was currently observed in the classical Biginelli reaction conditions.

These results suggest a mechanism wherein the in situ acylimine intermediate, generated from the aldehyde and urea, is activated, either by protonation or coordination with boron, the phenyl boronic acid being able to act as a Lewis or a Brønsted acid.[12] It was followed by the addition to the boron enolate derived from ethyl acetoacetate,[17] cyclisation and dehydration (Scheme 2).

In conclusion, we have developed a simple and efficient method for a one-pot three-component synthesis of 3,4-dihydropyridiminone derivatives using phenylboronic acid as catalyst in refluxing acetonitrile and neutral media. Further studies to confirm our mechanistic hypothesis and to extend these results to chiral organoboranes derivatives are underway.

2. Experimental

General procedure for the synthesis of 3,4-dihydropyrimidinones **4**. A solution of ethyl acetoacetate **1** (2 mmol), aldehyde **2** (2 mmol), urea **3** (3 mmol) and phenylboronic acid (0.2 mmol) in acetonitrile (10 ml) was heated under reflux for 18 h. The reaction mixture was poured into crushed ice with stirring. The crude product was filtered, washed with 95% ethanol, dried and recrystallised from hot ethanol to give **4**. All compounds are fully characterised by mp, IR, ^1H and ^{13}C spectroscopy.

Selected data for **4e**: 5-Ethoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one. Mp: 202–203 °C; IR (KBr): 3246, 3111, 2985, 2956, 2931, 1730, 1703, 1651, 1514. ^1H NMR (DMSO-d_6): δ 9.14 (s, 1H, NH); 7.67 (s, 1H, NH); 7.15 (d, $J = 8.6$ Hz, 2H); 6.88 (d, $J = 8.7$ Hz, 2H); 5.10 (d, $J = 3.2$ Hz, 1H); 3.98 (q, $J = 7.1$ Hz, 2H, OCH_2); 3.74 (s, 3H, OCH_3); 1.10 (t, $J = 7.1$ Hz, 3H, CH_3). ^{13}C (DMSO-d_6): δ 165.8; 158.8; 152.6; 148.4; 137.4; 127.8; 114.1; 100.0; 59.6, 55.4; 53.7; 18.1; 14.5.

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