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Multicomponent Biginelli's synthesis of 3,4-Dihydropyrimidin-2(1H)-ones catalyzed by Phenyl phosphonic acid

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ABSTRACT

An efficient protocol has been developed for the Biginelli reaction using Phenyl phosphonic acid (PPA) as a novel acid catalyst by a three-component condensation of β -keto ester, aldehydes, and urea or thio-urea to give corresponding 3, 4-dihydropyrimidin-2(1H)-ones.

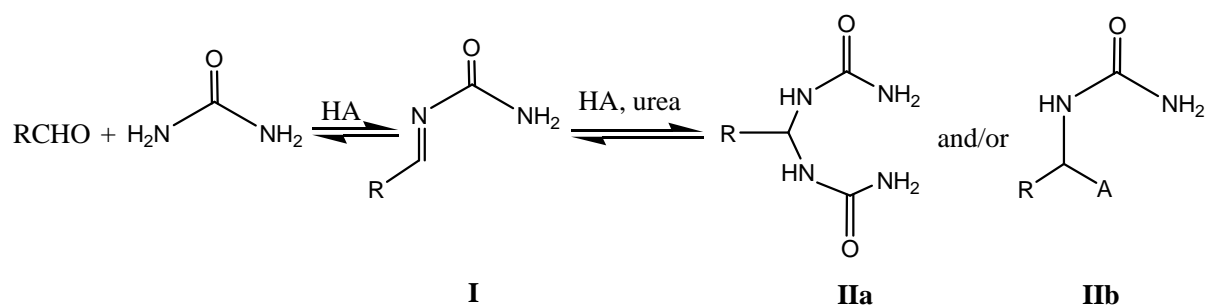
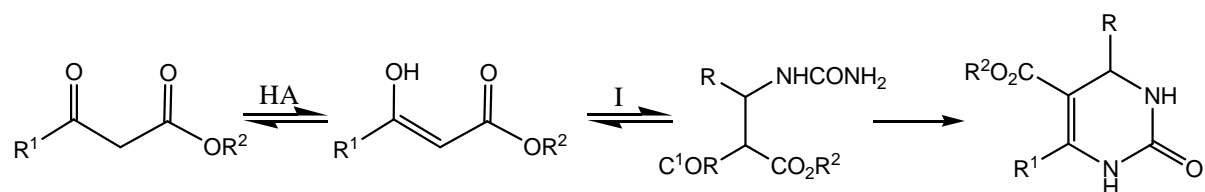
Key words: multicomponent reactions, Biginelli reaction, Phenyl phosphonic acid (PPA), 3, 4-dihydropyrimidin-2(1H)-ones, Bronsted acid.

INTRODUCTION

The protocol of green chemistry involves the ecofriendly transformations and environmental concerns in research and industry [1] using heterogeneous catalysts. In organic synthesis and medicinal chemistry multicomponent reactions are having the most important protocols [2]. The Biginelli reaction [3] is the most important and useful multicomponent reaction which offers an efficient way to access 3, 4-dihydropyrimidin-2(1H)-ones. The 3, 4-dihydropyrimidin-2(1H)-ones and their derivatives [4] are medicinally important [5] as calcium channel blockers, antihypertensive and anti-inflammatory agents and α -1-a-antagonists. These have recently emerged as important target molecules due to their therapeutic and pharmacological properties [6] such as antiviral [7], antimitotic [8], anticarcinogenic [9].

The first one pot-synthesis of 3, 4-dihydropyrimidine was reported by Biginelli in 1893 involves condensation of an aldehyde, β -keto ester and urea or thio-urea under acidic condition.

Recently several improved procedures [10] have been reported using Lewis acids as well as protic acids as promoters. The mechanism of Bronsted acid-mediated classical Biginelli reaction is shown in figure 1.

1. *Acyliminium ion formation step*2. *Addition, acyclization and dehydration steps*

The use of lithium salts [11], TMSI [12], reactions under ionic liquids [13], solid phase [14], polymer supported [15], heterogeneous catalysts, by silica's [16] and montmorillonites [17] or activation by ultrasound [18] and microwave [19] to prepare DHPMs have also been prepared. In recent years, many protocols are employed by the use of Lewis and Bronsted acids such as alumina supported MoO_3 [20], graphite supported lanthanum chloride [21], antimony (III) chloride [22], bismuth nitrate [23], iron (III) trifluoroacetate and trifluoromethane sulfonate [24], copper (II) tetrafluoroborate [25], TCCA [26], PSSA [27], Yttrium (III) nitrate hexahydrate [28], TaBr_5 [29], concentrated H_2SO_4 [30], H_3BO_3 [31], HBF_4 [32], chloroacetic acid [33], $p\text{-TsOH}$ [34], HCl [35], acetic acid [36], silica sulphuric acid [37], $\text{H}_3\text{PW}_{12}\text{O}_{40}$ [38], $\text{H}_3\text{PMo}_{12}\text{O}_{40}$ [39], $\text{Al}_2\text{O}_3/\text{MeSo}_3\text{H}$ [40] and chiral phosphoric acid [41] are reported.

However some microwave assisted Biginelli reactions reported by three component condensation reaction of aldehyde, ethyl acetoacetate and urea or thio-urea under Bronsted acid catalysis suffer from harsh conditions and show frequently low yields. In connection of our earlier work on phenyl boronic acid [42], here we like to introduce new Bronsted acid catalyst phenyl phosphonic acid (PPA) with an aldehyde, ethyl acetoacetate, urea or thio-urea which was mixed under reflux and the desired products are in excellent yields.

EXPERIMENTAL SECTION


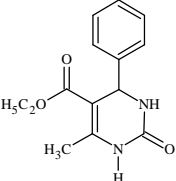
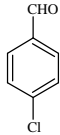
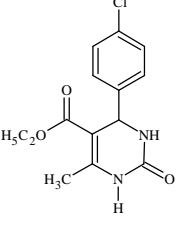
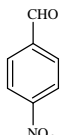
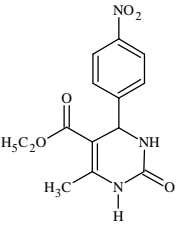
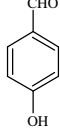
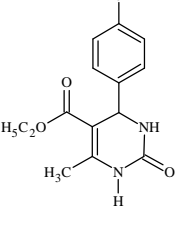
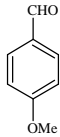
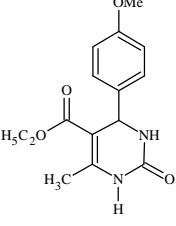
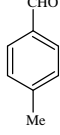
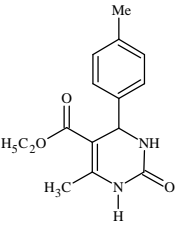
IR spectra were obtained using a Shimadzu FT-IR spectrophotometer. Mass spectra were determined on a Shimadzu GCMS-QP 1000 EX instrument. ^1H NMR spectra were recorded on a Bruker Avance Dpx-250. Melting points were observed in open capillary tubes in a circulating oil melting point apparatus.

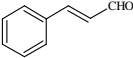
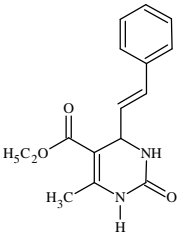
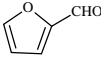
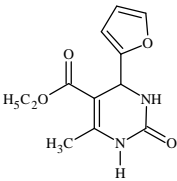
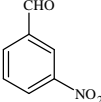
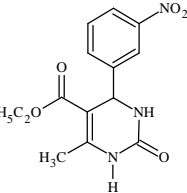

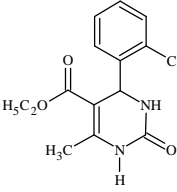
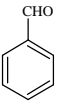
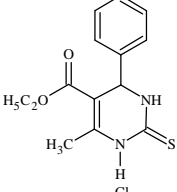
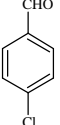
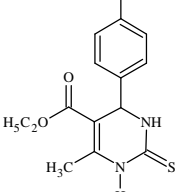
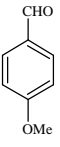
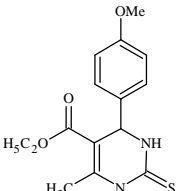
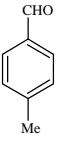
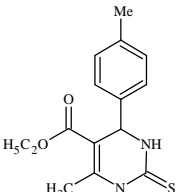
General Procedure

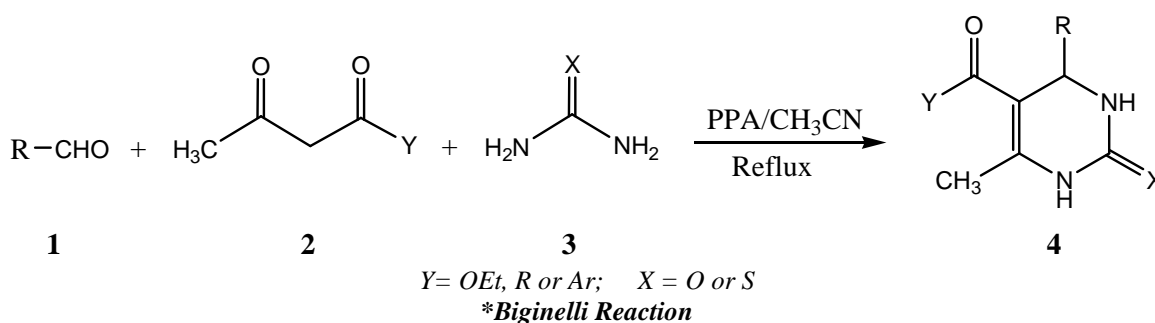
To a mixture of aldehyde **1** (2 mmol), β -keto ester **2** (2 mmol) and urea or thio-urea **3** (2 mmol) in acetonitrile, catalytic amount of phenyl phosphonic acid (10 mol %) was added and the contents were refluxed for 8 hours. After completion of the reaction as monitored by TLC, the reaction mixture is poured into ice-cold water and stirred for 10-15 minutes. The contents of the flask were then filtered, washed with cold water (20 ml) to remove excess urea. The solid so

obtained was the corresponding 3, 4-dihydropyrimidin-(2H)-one **4**. It was then recrystallized by hot ethanol to get the pure product (Scheme 1).

Table 1: Phenyl phosphonic acid catalyzed Synthesis of 3, 4 – dihydro pyrimidines using different aldehydes

Entry	Aldehyde	Product	Reflux Yield (%)	MP (^o C)
1			97	201
2			94	213
3			90	208
4			90	227
5			93	200
6			86	215

7			90	230
8			88	201
9			84	228
10			87	216
11			72	204
12			74	180
13			69	135
14			65	135



RESULTS AND DISCUSSION

The generality of the reaction with phenyl phosphonic acid catalysed Biginelli reaction is explored. The desired dihydropyrimidine derivatives were obtained with 10 mol % of phenyl phosphonic acid and one equivalent of each of the three components aldehyde **1**, ethyl acetoacetate **2** and urea or thio-urea **3** which were refluxed in CH₃CN for 8 hours in moderate to excellent yields (Table 1).

The scope of the aldehyde component was first investigated by the reaction with urea (entries 1 to 10) and thus aldehydes bearing different types of substituents underwent the reaction in good to excellent yields. Thio-urea used in similar way afforded corresponding dihydropyrimidine-2(1H)-ones in moderate to good yields (entries 11 to 14) which are possessing great interest with regard to their biological activities (e.g. monastrol **18**) [43]. The reaction conversion and product outcome shown the effect of the substituent on the aldehyde. The products which has an electron donating substituent attached at different position of the aromatic ring was produced higher yields with that of the electron withdrawing substituent's showing moderate yield.

CONCLUSION

In summary, we have developed the ability of phenyl phosphonic acid a new and mild Bronsted acid promoter for the Bigenlli reaction in the synthesis of the medicinally important 3, 4-dihydropyrimidin-2(1H)-ones.

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