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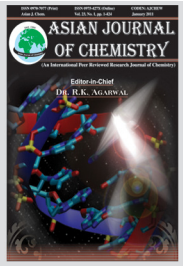

A Simple and New Method for the Synthesis of Dihydropyrimidinones by Biginelli Reaction

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Borax/phosphorous oxychloride (BPO) is found to be a new efficient catalyst for three component coupling of β-dicarbonyl compounds, aldehydes and urea (or thiourea) to afford the corresponding dihydropyrimidinones or their sulfur analogues. The reaction proceeds efficiently under solvent-free conditions with excellent yields.

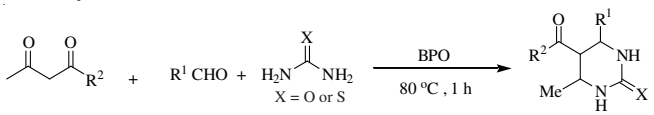
Key Words: Dihydropyrimidinones, Biginelli reaction, Multicomponent reactions, Borax.

INTRODUCTION

Multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry[1,2]. The strategies of multicomponent reactions offer significant advantages over conventional linear-type syntheses for their high degree of atom economy, convergence, ease of execution and broad applications characters. Multicomponent reactions are particularly useful to generate diverse chemical libraries of 'druglike' molecules for biological screening[3,4]. In such reactions, three or more reactants come together in a single reaction vessel to form new products that contain portions of all the components. The three-component Biginelli reaction is attractive, since the resulting dihydropyrimidinone (DHPM) scaffold displays a wide range of biological activity as antiviral, antitumor, antibacterial, antiinflammatory[5,6] calcium channel blockers, antihypertensive agents[7] and as α_{1a} and enoceptor-selective antagonists[8]. Several marine alkaloids containing the dihydropyrimidinone core unit have shown interesting biological properties. In particular, batzelladine alkaloids have been found to be potent HIV gp-120-CD4 inhibitors[9]. The original Biginelli protocol for the preparation of dihydropyrimidinones consisted of heating a mixture of the three components included β-ketoester, aldehyde and urea in ethanol containing a catalytic amount of HCl[10].

Many reagents have been reported in the literature for this reaction including, $InCl_3$[11], *p*-TsOH[12], $Bi(OTf)_3$[13], $BF_3.OEt_2$[14], ionic liquids (BMIm.PF_6 and BMIm.BF_4)[15], I_2[16], NBS[17], polyaniline-bismoclite complex[18], heteropoly acid[19], sulfated zirconia[20], $Sr(NO_3)_2$[21], iron(III) trifluoroacetate[22], trichloroisocyanuric acid[23], $SbCl_3$[24] PS-PEG bound sulfonic acid[25] and mesoporous aluminosilicate[26], are also used. Many of these protocols involve expensive reagents, strongly acidic conditions, long reaction times, unsatisfactory yields and incompatibility with other functional groups.

Surface-mediated solid phase reactions are of growing interest[27], because of their ease of set-up and work-up, mild reaction conditions, rate of the reaction, selectivity, high yields, lack of solvent and the low cost of the reactions in comparison with their homogeneous counterparts. This paper reports a new study on the Biginelli reaction catalyzed by $Na_2B_4O_7$/$POCl_3$(BPO). It is found that borax (anhydrous)-supported $POCl_3$ under solvent-free conditions was capable of producing high yields of dihydropyrimidinone from Biginelli reaction (**Scheme-I**). The work on borax/phosphorous oxychloride (BPO) is reported recently[28].



Scheme-I

EXPERIMENTAL

Preparation of BPO: A mixture of $POCl_3$ (3 g) and anhydrous borax (2 g) were combined in a mortar and pestle by grinding them together until a fine, homogeneous powder was obtained (15-20 min).

General procedure for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones and -thiones: 0.15 g BPO was added to a 25 mL round-bottomed flask containing aldehyde (2 mmol), β-ketoester or β-diketone (2 mmol) and urea or thiourea (3 mmol). The reaction mixture was heated with stirring at 80 ºC

in an oil bath for 1 h (completion of the reaction was monitored by TLC). After completion (100 % conversion using aldehyde as the blank reactant), the reaction mixture was cooled to reach room temperature and the precipitate was washed with cold water (2 × 20 mL). The crude product was recrystallized from an appropriate solvent. The obtained products were identified by comparison of their spectral and physical data with authentic samples.

RESULTS AND DISCUSSION

In recent years, there has been an increasing interest in reactions that proceed in the absence of solvents due to their reduced pollution, low costs and simplicity in process and handling[29]. Here we wish to report the capacity of BPO as catalysts for the one-pot synthesis of 3,4-dihydropyrimidinones or their sulfur analogues under solvent-free reactions.

After some experimentation with respect to the amount of catalyst (Table-1, entries 6-9) and reaction temperature (Table-1, entries 4-6), the optimal conditions have been established[27]. It is interesting to note that reaction was not observed in the presence of $POCl_3$ and borax separately (Table-1, entries 2,3).

TABLE-1
DIFFERENT REACTION CONDITIONS FOR CONDENSATION OF BENZALDEHYDE (2 mmol), ETHYL ACETOACETATE (2 mmol) AND UREA (3 mmol).

Entry	Catalyst (g)	Temperature (ºC)	Time (h)	Yield (%)
1	-	80	10.0	20
2	$POCl_3$ (0.20)	80	10.0	0
3	Borax (0.20)	80	5.0	30
4	BPO (0.20)	Room temperature	5.0	45
5	BPO (0.20)	60	2.5	67
6	BPO (0.20)	80	1.0	96
7	BPO (0.15)	80	1.0	94
8	BPO (0.05)	80	1.0	73
9	BPO (0.10)	80	1.0	82

To generalize this methodology, we subjected a series of other substituted aromatic, carrying either electron-donating or -withdrawing substituent, aliphatic and heterocyclic aldehydes to obtained the corresponding dihydropyrimidinones under the optimized reaction conditions (Table-2).

Many of the pharmacologically relevant substitution patterns of the aromatic ring could be introduced with high efficiency. Furthermore, the experimental results showed that besides ethyl acetoacetate, acetylacetate and methyl acetoacetate could also be used and the corresponding dihydropyrimidinones were produced in high to excellent yields (Table-2 entries 12-19). Thiourea has been used with similar success to provide the corresponding thio-derivatives of dihydropyrimidinones which are also of much interest with respect to their biological activities[5] (Table-2, entries 20-24). Noteworthy is recently identified lead compound, monastrol (Table-2, entry 22), of a new class of anticancer agents that act as cell division (mitosis) blockers[30]. This method utilizes readily available low cost reagents affording high yields of dihydropyrimidinones, in short reaction times, for a variety of compounds.

Conclusion

In conclusion, this report discloses a simple modification of the Biginelli dihydropyrimidinone synthesis. Excellent yields, low cost and easy availability of the catalyst, environmentally friendly procedure, easy work-up and timesaving process under solvent-free conditions are some of the salient feature of this reaction. Further, studies for the application of this method as catalyst for several reactions are under investigation in our laboratory.

TABLE-2
BPO CATALYZED SYNTHESIS OF DIHYDROPYRIMIDIN-2(1H)-ONES AND THIONES (DHPMs)

Entry	R^1	R^2	X	Yield (%)
1	C_6H_5	OEt	O	94
2	4-$CH_3OC_6H_4$	OEt	O	96
3	2-ClC_6H_4	OEt	O	91
4	4-ClC_6H_4	OEt	O	90
5	3-$NO_2C_6H_4$	OEt	O	87
6	PhCH=CH	OEt	O	86
7		OEt	O	83
8		OEt	O	81
9	4-OHC_6H_4	OEt	O	94
10	*n*-C_3H_7	OEt	O	62[b]
11	*n*- C_5H_{11}	OEt	O	65[b]
12	C_6H_5	Me	O	90
13	4-$CH_3OC_6H_4$	Me	O	91
14	4-$NO_2C_6H_4$	Me	O	86
15	C_6H_5	OMe	O	94
16	4-ClC_6H_4	OMe	O	90
17	4-$CH_3OC_6H_4$	OMe	O	92
18	4-$CH_3C_6H_4$	OMe	O	94
19	2-ClC_6H_4	OMe	O	89
20	C_6H_5	OEt	S	91
21		OEt	S	80
22	3-HOC_6H_4	OEt	S	92
23	4-$CH_3OC_6H_4$	OEt	S	93
24	4-$NO_2C_6H_4$	OEt	S	86

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