Polystyrene-supported AlCl3: A Highly Active and Reusable Heterogeneous Catalyst for the One-pot Synthesis of Dihydropyrimidinones
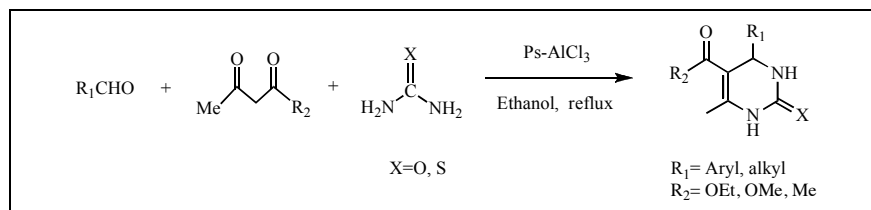
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An environmentally benign Biginelli protocol for the one-pot synthesis of substituted 3,4-dihydro-pyrimidin-2(1H)-ones using polystyrene supported aluminium chloride as catalyst has been achieved. This polymeric catalyst is stable and can be easily recovered and reused without obvious change in their efficiency.

INTRODUCTION

Dihydropyrimidinones (DHPMs) have attracted much attention in previous years due to the large range of biological activities such as calcium channel blockers, α-1a-adrenoaceptor-selective antagonists, anti-viral, anti-tumor, and anti-inflammatory drugs [1]. The simple and straightforward procedure for the synthesis of dihydropyrimidinones involves one-pot condensation of three components: ethyl acetoacetate, aldehyde, and urea, under strong acid conditions [2]. This procedure is known as the Biginelli reaction. The major drawback associated with this protocol is the low yield, particularly for substituted aromatic and aliphatic aldehydes [2].

Recently, many synthetic methods for preparing dihydropyrimidinones have been reported including classical conditions, with microwave and ultrasound irradiation and by using Lewis acids as well as protic acid promoters such as: H_2SO_4 [3], $BF_3.Et_2O/CuCl$ [4], $LaCl_3.7H_2O$ with catalytic concentrated HCl [5], $CeCl_3.7H_2O$ [6], $InCl_3$ [7], heteropolyacids [8], $BiCl_3$ [9], $Cu(OTf)_2$ [10], TMSCl [11], $LiClO_4$ [12], LiBr [13], $Ag_3PW_{12}O_{40}$ [14], phenylpyruvic acid [15], $FeCl_3.6H_2O/$ HCl [16] and silica sulfuric acid [17]. Acidic ionic liquids as effective catalysts for this transformation were also utilized [18]. However, some of the reported methods also suffer from drawbacks such as non-recyclability, harsh reaction conditions, long reaction times, the need of an additive, tedious work-up and environmental pollution. Moreover some of the methods are only practical for aromatic aldehydes. Therefore, a need still exists for versatile, simple and environment-friendly processes whereby DHPMs can be formed under milder and practical conditions.

Great efforts in catalysis research have been devoted in recent years to the introduction and application of effective and safe heterogeneous catalysts [19]. The utilization of polymer-supported catalyst offers several advantages in preparative procedures. Such catalysts are as active as their homogeneous counterparts while having the distinguishing characteristics of being easily separable from the reaction media, recyclability, greater selectivity, enhanced stability, easier handling, non-toxicity and low cost [20].

Previously, Neckers and co-workers used polystyrene supported $AlCl_3$, $Ps-AlCl_3$, as a catalyst in the condensation, esterification and acetalization of alcohols [21]. Recently, such catalyst was also found to be effective in Friedel-Crafts acylation [22], sulfonylation [23], tetrahydropyranylation [24] and dithioacetalization [25]. In continuation of our recent work on the use of polymer supported catalyst in organic reactions [26], we found that $Ps-AlCl_3$ was a good catalyst for the synthesis of DHPMs. Here we wish to report $Ps-AlCl_3$ as a reusable and effective catalyst for the one-pot synthesis of DHPMs under milder reaction conditions in moderate to high yields (Scheme 1)

Scheme 1
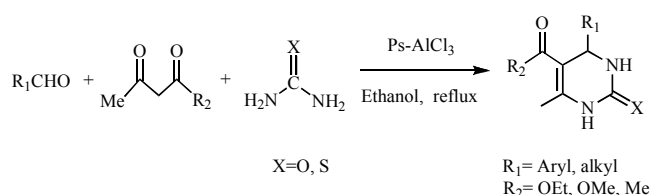
RESULTS AND DISCUSSION

To explore the use of polystyrene supported aluminum chloride as a catalyst, reaction of benzaldehyde, ethyl acetoacetate and urea was investigated under different conditions. The results are summarized in Table 1.

Table 1

Ps–AlCl$_3$ catalyzed condensation of benzaldehyde, urea and ethyl acetoacetate under different reaction conditions

Entry	Solvent	Catalyst (mol %)	Yield[a] (%)
1	Toluene	10	42
2	Cyclohexane	10	<5
3	CH$_2$Cl$_2$	10	15
4	CH$_3$CN	10	75
5	H$_2$O	10	NR
6	CH$_3$CH$_2$OH	-	NR
7	CH$_3$CH$_2$OH	5	62
8[b]	CH$_3$CH$_2$OH	10	89, 85, 83, 78, 77
9	CH$_3$CH$_2$OH	20	88
10[c]	CH$_3$CH$_2$OH	-	NR
11[d]	CH$_3$CH$_2$OH	10	NR

[a] Isolated Yields. [b] Catalyst was reused for five times. [c] Ps was used as catalyst. [d] Catalyst was filtrated after 15 minutes.

It was found that the reaction is affected by various solvents. The results indicated that toluene, cyclohexane and dichloromethane are unsuitable for the reaction. Solvents such as ethanol and acetonitrile proved to be effective. No reaction occurred when H$_2$O was used as solvent (Table 1, entry 5), perhaps because of the aggregation of the catalyst caused by its hydrophobic nature, leading to the inadequate access of substrates to the active sites of the catalyst [23]. Moreover, our study showed that the best results were observed when the molar ratio of aldehyde, ethyl acetoacetate and urea was 1:1:1.5. In addition, we found that the yields were obviously affected with different amount of catalyst. No reaction occurred without catalyst, while 10 mol% of Ps–AlCl$_3$ was sufficient and excessive amount of catalyst did not increase the yields significantly (Table 1, entries 6-9). The recyclability of catalyst was also examined according to the typical experiment conditions. We obtained the desired product in 89%, 85%, 83%, 78% and 77% yields in sequence runs, respectively (Table 1, entry 8).

To confirm the activity of polymer supported AlCl$_3$, a control experiment was carried out by using polystyrene alone under the same experiment conditions. No product was isolated when using the polystyrene as catalyst (Table 1, entry 10), which indicated that polystyrene itself didn't promote the reaction. Good yield was obtained when using aluminium chloride as catalyst, however, more

catalyst as well as an additive was needed [27]. Meanwhile, to find out whether the reaction took place in the solid matrix of Ps-AlCl$_3$ or aluminium chloride simply released into ethanol is responsible for the reaction, Ps-AlCl$_3$ was refluxed in ethanol for 15 minutes, and then filtered off. Then reactants were added to the filtrate and refluxed for 3h, no reaction took place (Table 1, entry 11). These results could deduce that the reaction takes place in the solid matrix and the release of AlCl$_3$ is negligible.

Under the optimized conditions, we examined the generality of this procedure, a series of Biginelli compounds were synthesized. The results are listed in Table 2.

As can be seen from Table 2, a variety of aromatic, aliphatic aldehydes underwent three-component condensation smoothly to afford a wide range of substituted dihydropyrimidinones. Aromatic aldehydes with either electron-donating or electron-withdrawing substituents in the *ortho*, *meta* and *para* positions such as nitro, hydroxyl, halide, alkoxyl, alkylamino, afforded the corresponding dihydropyrimidinones in moderate to high yields. This method is even effective with aliphatic aldehydes by prolonging reaction time to 6 h, which normally show extremely low conversions in the Biginelli reaction (Table 2, entries 14-16). Nevertheless, this protocol has its limitations. Aldehydes, which are sensitive to acid such as furfural, were not suitable for carrying out the Biginelli reaction under these conditions (Table 2, entry 23). Thiourea has been used in a similar way to produce the corresponding thio derivatives of dihydropyrimidinones, which are also of much interest with respect to their biological activities (Table 2, entries 17-22). Using methyl acetoacetate and acetylacetone instead of ethyl acetoacetate, the desired products were also obtained in high yields (Table 2, entries 2-3). Unlike most of the reported methods, this procedure does not require any additives or activators or anhydrous conditions. This procedure not only preserves the simplicity of the Biginelli reaction, but also produces good yields of the products with high purity.

As to the reaction process, it was presumed that the reaction may proceed *via* acylimine intermediate [36], formed from the aldehyde and urea and stabilized by aluminium chloride. Subsequent addition of β-diketoester enolate to the acylimine, followed by cyclization and dehydration, afforded the corresponding dihydro-pyrimidinones (Scheme 2).

CONCLUSION

In conclusion, the present procedure provides an efficient and improved modification of the Biginelli reaction. The significant advantages of this methodology are mild reaction conditions, high yields, short reaction

Table 2

Ps-AlCl$_3$ catalyzed Biginelli reaction of aldehydes, β-ketoesters and urea or thiourea.

Entry	R$_1$	R$_2$	X	Yield[a] (%)	Mp(°C) Found (lit) [ref]
1	C$_6$H$_5$	OEt	O	89	203-204 (202-204) [4]
2	C$_6$H$_5$	OMe	O	90	208-210 (209-212) [4]
3	C$_6$H$_5$	CH$_3$	O	84	230-232 (233-236) [28]
4	4-CH$_3$C$_6$H$_4$	OEt	O	90	205-206 (204-205) [29]
5	2-CH$_3$C$_6$H$_4$	OEt	O	85	207-208 (208-210) [30]
6	4-HOC$_6$H$_4$	OEt	O	82	234-236 (235-236) [29]
7	4-CH$_3$OC$_6$H$_4$	OEt	O	91	203-204 (201-203) [4]
8	2-CH$_3$OC$_6$H$_4$	OEt	O	83	257-258 (259-260) [31]
9	4-NMe$_2$C$_6$H$_4$	OEt	O	63	253-254 (251-252) [29]
10	4-ClC$_6$H$_4$	OEt	O	87	212-214 (213-215) [4]
11	2-ClC$_6$H$_4$	OEt	O	84	216-218 (215-218) [31]
12	3-ClC$_6$H$_4$	OEt	O	85	194-196 (195-197) [32]
13	4-NO$_2$C$_6$H$_4$	OEt	O	86	208-210 (208-211) [4]
14[b]	n-C$_2$H$_5$	OEt	O	78	178-183 (179-181) [33]
15[b]	n-C$_3$H$_7$	OEt	O	76	155-157 (157-158) [34]
16[b]	cyclohexyl	OEt	O	82	233-235 (235-236) [14]
17	C$_6$H$_5$	OEt	S	84	209-210 (207-208) [35]
18	4-CH$_3$C$_6$H$_4$	OEt	S	86	190-192 (192-194) [35]
19	4-ClC$_6$H$_4$	OEt	S	85	208-210 (209-210) [35]
20	4-NMe$_2$C$_6$H$_4$	OEt	S	59	208-209 (209-210) [35]
21	4-HOC$_6$H$_4$	OEt	S	77	202-204 (202-203) [29]
22	4-CH$_3$OC$_6$H$_4$	OEt	S	85	150-152 (150-152) [14]
23	2-Furyl	OEt	O	-	-

[a] Isolated Yields. [b] Refluxed for 6h.

Scheme 2
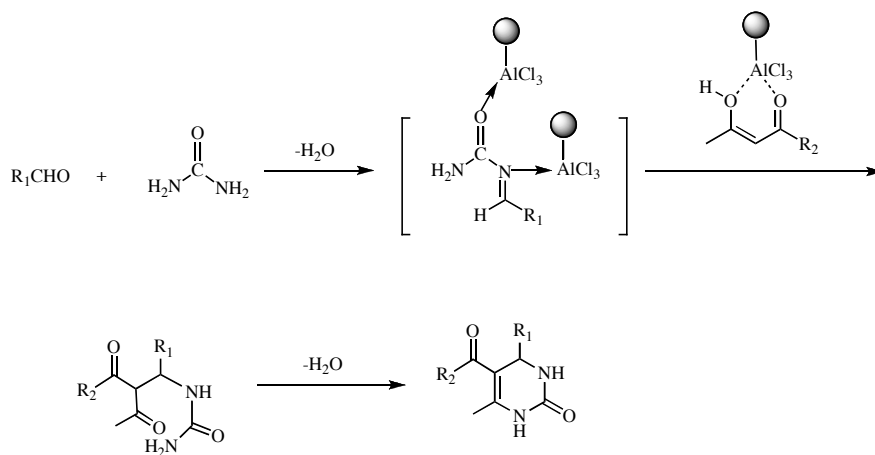
times, simple work-up procedures and low cost. In addition, the use of Ps–AlCl$_3$ has resulted in a reduction in the unwanted and hazardous waste that is produced during conventional homogeneous process. Most importantly, such catalyst is rather easy to prepare and handle and can be recovered and reused without significant loss of its activity.

EXPERIMENTAL

Chemicals used were obtained from commercial suppliers and used without further purifications. Melting points were determined on a Shimadzu DSC-50 thermal analyzer. IR spectra were recorded on a Bomem MB154S infrared analyzer. ^{1}H NMR was recorded with a Bruker Advance RX500 spectrometer. Inductively coupled plasma (ICP) spectra were measured on an Ultima2C apparatus.

Typical Procedure for Preparation of Ps–AlCl$_3$ [21]. Anhydrous AlCl$_3$ (4.5 g) was added to polystyrene (8% divinyl benzene, 3.5 g) in carbon disulfide (25 mL). The mixture was stirred under reflux for 1 h, cooled and then water (50 mL) was cautiously added to hydrolyze the excess AlCl$_3$. The mixture was stirred until the deep orange color disappeared and the catalyst became light yellow. The catalyst was collected by filtration and washed with water (350 mL) and then with ether (30 mL), acetone (30 mL) and ether (30 mL), then dried at 80 °C

under vacuum overnight. Complex formation was demonstrated by a new bond at 1629 cm^{-1} in the IR spectrum. The aluminium content of Ps–AlCl$_3$ was 2.11% analyzed by ICP analysis and the loading capacity of aluminium chloride was calculated to be 0.78 mmol/g.

Typical procedure for the synthesis of 3,4-dihydro-pyrimidin-2(1*H*)-ones. A mixture of benzaldehyde (1.06 g, 10 mmol), ethyl acetoacetate (1.30 g, 10 mmol), urea (0.9 g, 15 mmol) and Ps–AlCl$_3$ (1.28 g, 1 mmol of AlCl$_3$) in ethanol (10 mL) was refluxed for 3 h. After completion of reaction, hot ethanol was added to the mixture; the catalyst was filtrated off and washed with ether (15 mL×2). The filtrate was concentrated on a rotary evaporator under reduced pressure and the solid product obtained was washed with water (20 mL×2), and recrystallized from ethanol or ethyl acetate/*n*-hexane to give 5-ethoxy-carbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one in 89% yield, mp 203-204 °C (202-204 °C) [4]. Other aldehydes were reacted with urea and β-dicarbonyl compound similarly. The products were characterized by mp, IR, and ^{1}H NMR and they are also compared with respect to authentic compounds available in literature.

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