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Poly(ethylene)glycol/ AlCl_3 as a new and efficient system for multicomponent Biginelli-type synthesis of pyrimidinone derivatives

Abstract: Biginelli condensation of aldehydes, cyclopentanone and urea or thiourea in poly(ethylene)glycol 400, at 45°C in the presence of aluminum chloride as a highly efficient catalyst has been developed. The reaction is very fast, clean and environmentally benign for the synthesis of a vast variety of pyrimidinone derivatives.

Keywords: aluminum chloride; Biginelli condensation; poly(ethylene)glycol; pyrimidinone.

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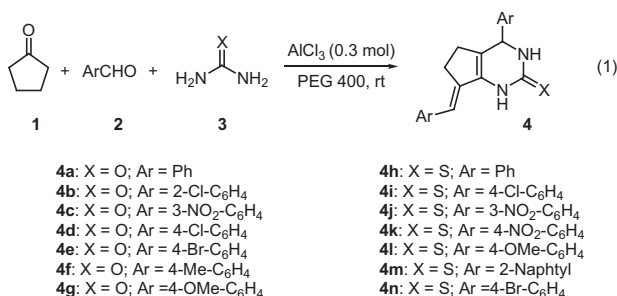
Introduction

Multicomponent reactions (MCRs) are important transformations in organic and medicinal chemistry [1–4]. These types of condensation reactions provide a fast and easy access to a variety of polyheterocyclic compounds of therapeutic and pharmacological properties [5–7]. The Biginelli reaction is a three-component reaction which involves an α -ketoester, an urea or thiourea, and an aldehyde to produce 3,4-dihydro-2(1H)-pyrimidinones [6]. Many of such compounds show interesting bioactivity [8–11] or are used as substrates to prepare heterocyclic products with pharmacological properties [12]. These reasons have motivated researchers to extend the scope of the method to other 1,3-dicarbonyl compounds such as β -diamides [13], cyclic diketones [14] and β -ketolactones [15]. Another modification has been focused on the use of different acidic catalysts, mostly in the presence of a polar solvent. Formerly, the Biginelli reaction suffered from the need of harsh conditions to afford acceptable yields. Recently, the development of mild Lewis acid [8, 9, 10, 16] and heteropolyacid [17] catalysts has considerably improved the yield of the reaction. In the presence of such catalysts, the reaction is relatively facile, leading to high yields of dihydropyrimidinones. These catalysts include InCl_3 [8], BiCl_3 [10], phenylpyruvic acid [14], $\text{Al}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$

[18], H_2SO_4 [19], $\text{BF}_3 \cdot \text{Et}_2\text{O}/\text{CuCl}$ [20], $\text{LaCl}_3 \cdot 7\text{H}_2\text{O}$ in the presence of concentrated HCl [21], $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ [22], heteropolyacids [23], $\text{Cu}(\text{OTf})_2$ [24], TMSCl [25], LiClO_4 [26], LiBr [27], InBr_3 [28], $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}/\text{HCl}$ [29], TMSI [30], Brønsted acidic ionic liquid [31], ionic liquid [32] and base catalyst [33]. They have been used with success in ethanol, acetic acid, tetrahydrofuran, acetonitrile or *N,N*-dimethylformamide.

Results and discussion

In continuation of our studies on developing inexpensive and environmentally benign methodologies for organic reactions especially with the use of poly(ethylene)glycol 400 (PEG 400) as a green and reusable solvent [34–40], we now report for the first time aluminum chloride catalyzed Biginelli condensation reaction of cyclopentanone with a vast variety of aldehydes with both urea or thiourea using PEG 400 as the reaction medium (Equation 1). The versatility of aluminum chloride and the environmentally benign nature of PEG encouraged us to couple them and study their utility for pyrimidinone synthesis reaction. To the best of our knowledge, there are no literature reports on Biginelli condensation under these conditions.

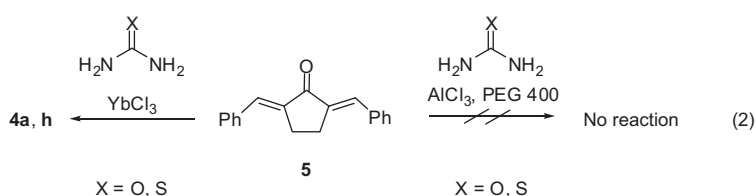


At the beginning, we studied the reaction under solvent-free conditions in the presence of 0–0.4 mmol AlCl_3 as catalyst. TLC analysis showed that the best quantity of AlCl_3 is 0.3 mmol. Owing to low yields (0–46%), we decided to perform the reaction in a solvent to potentially increase the obtained yields. We tested CHCl_3 , CH_2Cl_2 , Et_2O , CH_3CN , EtOH , THF and PEG as solvents for Biginelli condensations of cyclopentanone, benzaldehyde and urea in the presence

of 0.3 mmol AlCl_3 as catalyst. The results showed that this reaction is highly solvent-dependent. It does not work at all in ethanol. It seems that alcohols with low molecular weight are not suitable choices as solvents for the reactions catalyzed by AlCl_3 because they can react readily with Lewis acid. In addition, the reaction does not work well in chloroform, dichloromethane, diethyl ether or tetrahydrofuran (yields in the range of 25–65%). Fortunately, in the case of PEG 400 as solvent, the yield is excellent (91%).

The Biginelli condensation of cyclopentanone, benzaldehyde and urea in PEG 400 as solvent in the presence of different amounts of AlCl_3 as catalyst (0.0–0.4 mmol) at room temperature was performed. Similarly to the solvent-free conditions, the amount of 0.3 mmol of AlCl_3 as catalyst is optimal to give yield of 91%. The effect of temperature on the Biginelli condensation of cyclopentanone, benzaldehyde and urea in presence of 0.3 mmol AlCl_3 in PEG 400 as solvent was studied. Reaction was performed at 45°C, 60°C and 80°C. With increases in the temperature up to 45°C, the yield was also increased up to yield 94%. However, a further rise in temperature to 80°C caused a decrease in yield, from 89% at 60°C to 84% at 80°C. In summary, the optimal temperature for this reaction is 45°C.

The reaction works easily for a vast variety of aldehydes with both electron-donating and electron-withdrawing groups with both urea and thiourea to give corresponding pyrimidinone derivatives in good to excellent yields. The new compounds characterized by FT-IR, ^1H NMR, ^{13}C NMR and CHN analysis (Experimental section). However, it should be noted that the reaction time for aldehydes with electron-withdrawing groups is considerably longer (**4b–4e** vs. **4f**, **4g**). High yields for the reaction of electron-rich aldehydes have been noted [41]. In their proposed mechanism, Zhang et al. [41] have suggested aldol condensation between cyclopentanone and aldehyde to produce corresponding α,α' -bis(substituted benzylidene)cyclopentanone **5**. Then this intermediate product would react with urea or thiourea to produce desired pyrimidinone **4a,h** [41] (Equation 2). Concerning this proposed mechanism, we expected that compound **5** would also undergo reaction with urea or thiourea under our conditions to produce pyrimidinone **4**. However, compound **4** was not found in the reaction mixture, which suggests that the mechanism of this transformation requires additional studies.



Conclusion

Efficient conditions for the synthesis of pyrimidinone derivatives using Biginelli reaction by condensation of cyclopentanone with different aldehydes and urea and/or thiourea in the presence of AlCl_3 in PEG as a green and reusable solvent are reported. This protocol is a low cost procedure that is also user and environmentally friendly.

Experimental

General

Chemicals were purchased from Merck and Aldrich chemical companies. Thin layer chromatography (TLC) on commercial aluminum backed plates of silica gel 60 F254 was used to monitor the progress of reactions. Melting points were recorded on a Thermo Scientific 9100 apparatus. The FT-IR spectra were taken on a Perkin-Elmer, model 783, spectrophotometer in KBr pellets. The ^1H NMR spectra (300 MHz) and ^{13}C NMR spectra (75 MHz) were recorded in $\text{DMSO}-d_6$ on a Bruker AMX-300 spectrometer. Elemental analyses were performed on a Perkin-Elmer CHN analyzer, 2400 series II.

General procedure for preparation of pyrimidinones **4a–n**

A mixture of aldehyde (1 mmol), ketone (1 mmol), urea or thiourea (1.2 mmol) and AlCl_3 (0.3 mmol) in PEG (2 mL) was stirred at 45°C for a period of time indicated below. After completion of the reaction, as monitored by TLC, distilled water (4 mL) was added. The solid precipitate was filtered and washed with absolute ethanol or ethyl acetate (3 mL) and acetone (2 mL) and dried in air.

As an alternative work-up procedure, the reaction mixture was cooled in a dry ice-acetone bath to precipitate the PEG 400 and organic products were extracted with ether. The ether layer was washed with water (2 mL) and dried over MgSO_4 . The organic solvent was removed under reduced pressure to give the crude product **4a–n**. The product was crystallized from ethanol.

(7E)-7-Benzylidene-3,4,6,7-tetrahydro-4-phenyl-1H-cyclopenta[d]pyrimidin-2(5H)-one (4a) Yellow solid; yield 94%; mp 238–240°C; (lit mp 236–239°C [25]); reaction time 2.5 h.

(7E)-7-(2-Chlorobenzylidene)-4-(2-chlorophenyl)-3,4,6,7-tetrahydro-1H-cyclopenta[d]pyrimidin-2(5H)-one (4b) Yellow solid; yield 86%; mp 228–231°C; (lit mp 232–234°C [25]); reaction time 5.5 h.

(7E)-7-(3-Nitrobenzylidene)-3,4,6,7-tetrahydro-4-(3-nitrophenyl)-1H-cyclopenta[d]pyrimidin-2(5H)-one (4c) Brown solid; yield 84%; mp 233–235°C; (lit mp 235–239°C [25]); reaction time 4.2 h.

(7E)-7-(4-Chlorobenzylidene)-4-(4-chlorophenyl)-3,4,6,7-tetrahydro-1H-cyclopenta[d]pyrimidin-2(5H)-one (4d) Yellow-green solid; yield 89%; mp 250–253°C; (lit mp 252–255°C [25]); reaction time 4.5 h.

(7E)-7-(4-Bromobenzylidene)-4-(4-bromophenyl)-3,4,6,7-tetrahydro-1H-cyclopenta[d]pyrimidin-2(5H)-one (4e) Yellow solid; yield 96%; mp 219–222°C; (lit mp 221–222°C [41]); reaction time 3.5 h.

(7E)-7-(4-Methylbenzylidene)-4-(4-methylphenyl)-3,4,6,7-tetrahydro-1H-cyclopenta[d]pyrimidin-2(5H)-one (4f) Dark yellow solid; yield 96%; mp 241–243°C; (lit mp 238–241°C [25]); reaction time 2.2 h.

(7E)-7-(4-Methoxybenzylidene)-4-(4-methoxyphenyl)-3,4,6,7-tetrahydro-1H-cyclopenta[d]pyrimidin-2(5H)-one (4g) Yellow solid; yield 95%; mp 254–257°C; (lit mp 250–252°C [25]); reaction time 2 h.

(7E)-7-Benzylidene-3,4,6,7-tetrahydro-4-phenyl-1H-cyclopenta[d]pyrimidine-2(5H)-thione (4h) Pink solid; yield 96%; mp 218–221°C; (lit mp 219–223°C [25]); reaction time 1 h.

(7E)-7-(4-Chlorobenzylidene)-4-(4-chlorophenyl)-3,4,6,7-tetrahydro-1H-cyclopenta[d]pyrimidine-2(5H)-thione (4i) Light red solid; yield 90%; mp 223–225°C; (lit mp 226–228°C [25]); reaction time 2.3 h.

(7E)-7-(3-Nitrobenzylidene)-3,4,6,7-tetrahydro-4-(3-nitrophenyl)-1H-cyclopenta[d]pyrimidine-2(5H)-thione (4j) Dark brown solid; yield 92%; mp 309–312°C; (lit mp 313–317°C [25]); reaction time 3 h.

(7E)-7-(4-Nitrobenzylidene)-3,4,6,7-tetrahydro-4-(4-nitrophenyl)-1H-cyclopenta[d]pyrimidine-2(5H)-thione (4k) Brown

solid; yield 79%; mp 199–202°C; (lit mp 203–207°C [25]); reaction time 3.25 h.

7-(4-Methoxybenzylidene)-4-(4-methoxyphenyl)-3,4,6,7-tetrahydro-1H-cyclopenta[d]pyrimidin-2(5H)-thione (4l) Light yellow solid; yield 93%; mp 218–220°C; reaction time 0.75 h; IR: ν 3851, 3566, 1541, 1508, 1245, 1174, 1026 cm^{-1} ; ^1H NMR: δ 9.98 (1H, s, NH), 8.90 (1H, s, HC=), 6.90–7.29 (8H, m, CH), 6.84 (1H, s, NH), 5.11 (1H, s, CH), 3.73–3.74 (6H, OMe), 2.77 (2H, s, CH_2), 2.41–2.42 (1H, d, CH_2), 2.03–2.07 (1H, d, CH_2); ^{13}C NMR: δ 173.9, 158.9, 157.7, 135.5, 134.5, 133.9, 130.3, 129.3, 127.9, 120.1, 117.2, 114.0, 57.3, 28.4, 27.8. Anal. Calcd for $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_2\text{S}$: C, 69.81; H, 5.86; N, 7.40. Found: C, 69.92; H, 5.70; N, 7.61.

4-(Naphthalen-2-yl)-7-(naphthalen-2-ylmethylene)-3,4,6,7-tetrahydro-1H-cyclopenta[d]pyrimidin-2(5H)-thione (4m) Red solid; yield 82%; mp 238–240°C; reaction time 0.5 h; IR: ν 3392, 3322, 1544, 1483, 1191, 820, 746 cm^{-1} ; ^1H NMR: δ 10.22 (1H, s, NH), 9.13 (1H, s, HC=), 7.41–7.99 (14H, m, CH), 7.14 (1H, s, NH), 5.41 (1H, s, CH), 2.84–3.02 (2H, m, CH_2), 2.44–2.52 (1H, m, CH_2), 2.05–2.12 (1H, m, CH_2); ^{13}C NMR: δ 174.4, 139.6, 138.6, 135.3, 134.2, 133.2, 132.8, 132.6, 131.5, 128.6, 127.9, 127.6, 127.4, 126.7, 126.5, 126.2, 124.8, 125.2, 121.3, 117.9, 58.2, 28.5, 28.1. Anal. Calcd for $\text{C}_{28}\text{H}_{22}\text{N}_2\text{S}$: C, 80.35; H, 5.30; N, 6.69. Found: C, 80.48; H, 5.42; N, 6.79.

7-(4-Bromobenzylidene)-4-(4-bromophenyl)-3,4,6,7-tetrahydro-1H-cyclopenta[d]pyrimidin-2(5H)-thione (4n) Yellow solid; yield 86%; mp 226–228°C; reaction time 1.5 h; IR: ν 3240, 2920, 1672, 1558, 1489, 1186, 1090, 872 cm^{-1} ; ^1H NMR: δ 10.12 (1H, s, NH), 9.03 (1H, s, HC=), 7.07–7.59 (8H, m, CH), 6.90 (1H, s, NH), 5.23 (1H, s, CH), 2.72–2.88 (2H, m, CH_2), 2.39–2.53 (1H, m, CH_2), 2.02–2.09 (1H, m, CH_2); ^{13}C NMR: δ 174.4, 141.1, 138.7, 136.5, 134.0, 132.4, 130.5, 129.6, 128.8, 128.6, 121.3, 116.7, 69.8, 57.1, 28.3, 27.9. Anal. Calcd for $\text{C}_{20}\text{H}_{16}\text{Br}_2\text{N}_2\text{S}$: C, 50.44; H, 3.39; N, 5.88. Found: C, 50.31; H, 3.47; N, 5.64.

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