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Sirirat Chancharunee [a], Pilaiwan Pinhom [a], Manat Pohmakotr [b] & Patrick Perlmutter [c]

[a] Chemistry Department, Faculty of Science, Chiangmai University, Chiangmai, Thailand

[b] Chemistry Department, Faculty of Science, Mahidol University, Bangkok, Thailand

[c] School of Chemistry and the Centre for Green Chemistry, Monash University, Victoria, Australia

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One-Pot Synthesis of 3,4-Dihydropyrimidine-2-(1*H*)-ones Using CsF–Celite as Catalyst

Sirirat Chancharunee,[1] Pilaiwan Pinhom,[1] Manat Pohmakotr,[2] and Patrick Perlmutter[3]

[1]Chemistry Department, Faculty of Science, Chiangmai University, Chiangmai, Thailand

[2]Chemistry Department, Faculty of Science, Mahidol University, Bangkok, Thailand

[3]School of Chemistry and the Centre for Green Chemistry, Monash University, Victoria, Australia

Abstract: A facile, efficient, and environmentally benign procedure for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones via the cyclocondensation reaction of aromatic aldehyde, ethyl acetoaceate, and urea catalyzed by CsF–Celite was developed. This environmentally friendly method is superior to previous methods with respect to reaction time, yield, and workup.

Keywords: Celite, cesium fluoride, dihydropyrimidinones, green chemistry, multicomponent reaction

In recent years, dihydropyrimidinones (DHPMs, **4** and **5**, Scheme 1) and their derivatives have attracted considerable interest because of their diverse therapeutic and pharmacological profiles, which include antihypertensive, antiviral, antifungal, antibacterial, and antitumor action.[1] 4-Aryl-3,4-dihydropyrimidinones, which have a structure similar to 4-aryl-1,4-dihydropyridines, also exhibited calcium channel modulating activity.[2] The structurally related marine alkaloids batzelladine A and B have been found to be potent HIV gp-120CD4 inhibitors.[3]

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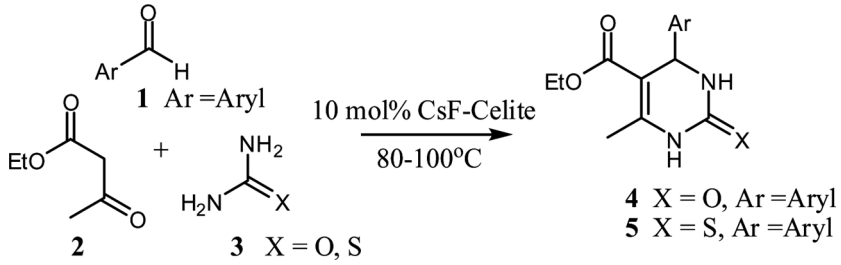
Address correspondence to Sirirat Chancharunee, Chemistry Department, Faculty of Science, Chiangmai University, Chiangmai 50220, Thailand. E-mail: siriratc@chiangmai.ac.th



Scheme 1. Preparation of compounds **4** and **5**.

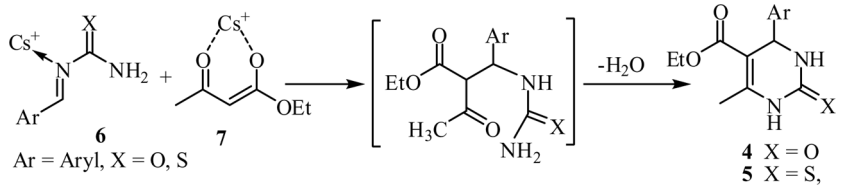
Additionally, monastrol (5g, X = S, Ar = 3-OHC_6H_5) has been identified as a novel anticancer drug.[4] The classical synthesis of DHPMs, the "Biginelli reaction,"[5] involves the one-pot, multicomponent condensation of a β-ketoester, an aldehyde, and urea under strongly acidic conditions. In addition to strong acid, these reactions require long reaction times, usually resulting in low yields. Several modified and improved procedures for the one-pot synthesis of dihydropyrimidinones have been reported, employing a range of catalysts and promoters, including $BF_3 \cdot OEt_2$,[6] polyphosphate ester (PPE),[7] $CeCl_3$,[8] $InCl_3$,[9] $FeCl_3$,[10] and montmorillonite–KSF clay.[11] However, many of these methods have drawbacks such as long reaction times, harsh reaction conditions, the use of stoichiometric reagents and toxic, flammable solvents, difficult workups, or low yields of products.

Consequently, the search for new catalysts and cleaner methods using less hazardous reagents and environmentally friendly conditions, such as solvent-free conditions, is of considerable interest. In this report, we disclose our preliminary results employing CsF–Celite–catalyzed Biginelli synthesis of DHPMs under solvent-free conditions. The preparation of the CsF–Celite was carried out in the same manner as described by Hayat et al.[12] To establish the optimal conditions for our new method, we carried out a set of experiments, varying the reaction time, amount of catalyst, and the quantities of urea. The best conditions to prepare the dihydropyrimidinone **4** were achieved when 10 mol% of CsF–Celite, 1 equivalent of both aldehyde and ethyl acetoacetate, and 1.3 equivalents of urea were mixed and heated together. Excellent yields, after recrystallization from ethanol, were obtained (Table 1, entry 1). Decreasing the catalyst concentration resulted in lower yields under the same conditions (Table 1, entry 2). On the other hand, higher amounts of catalyst did not improve the yield significantly (Table 1, entry 3). To ascertain the generality of this procedure, several examples were studied, and the results are summarized in Table 1. All synthesized compounds were characterized by NMR spectroscopy and melting point.

Table 1. CsF–Celite catalyzed synthesis of dihydropyrimidin-2(1*H*)-ones (DHPMs)

Entry	Ar in **4** and **5**	X	T (°C)	Reaction time[a] (h)	Yield[b] (%)	Mp (°C)	Lit. mp (°C)
1	**4a**, Ar = C_6H_5	O	80	1	95 (94,95,95)[c]	201–203	202–203[13]
2	**4a**, Ar = C_6H_5	O	80	1	92[d]	201–203	202–203[13]
3	**4a**, Ar = C_6H_5	O	80	1	96[e]	201–203	202–203[13]
4	**4b**, Ar = 4-$NO_2C_6H_4$	O	80	3	95	207–208	208–209[13]
5	**4c**, Ar = 4-$CH_3OC_6H_4$	O	80	3	97	202–203	200–201[13]
6	**4d**, Ar = 4-$(CH_3)_2NC_6H_4$	O	80	2	97	255–258	257–258[14]
7	**4e**, Ar = 4-ClC_6H_4	O	110	3	93	213–215	214–215[14]
8	**4f**, Ar = 2-ClC_6H_4	O	80	3	95	215–216	215–217[14]
9	**5a**, Ar = C_6H_5	S	80	1	96	208–210	207–209[13]
10	**5b**, Ar = 4-$NO_2C_6H_4$	S	80	3	94	107–108	109–111[15]
11	**5c**, Ar = 4-$CH_3OC_6H_4$	S	80	2	98	148–150	150–151[13]
12	**5d**, Ar = 4-$(CH_3)_2NC_6H_4$	S	80	3	96	198–200	196–198[16]
13	**5e**, Ar = 4-ClC_6H_4	S	80	2	95	194–196	192–194[15]
14	**5f**, Ar = 2-ClC_6H_4	S	80	2	92	165–167	164–165[16]
15	**5g**, Ar = 3-HOC_6H_4	S	80	3	94	182–184	184–185[13]

[a]The reactions were monitored by TLC for disappearance of starting aldehyde.
[b]Yields of isolated and recrystallized product from EtOH.
[c]Three consecutive condensations catalyzed by recycled CsF–Celite (10 mol%).
[d]Reaction catalyzed by CsF–Celite (5 mol%).
[e]Reaction catalyzed by CsF–Celite (15 mol%).



Scheme 2. Cs^+ activation in three-component coupling for Biginelli reaction.

Aromatic aldehydes containing either electron-donating or electron-withdrawing substituents reacted well under the reaction conditions to give the corresponding DHPMs in high to quantitative yields. In all cases examined, the condensation reactions were very clean, leading to DHPM in short reaction times (1–3 h).

The feasibility of recovery and reuse of the catalyst in the present methodology was also examined by using benzaldehyde as a model substrate (Table 1, entry 1). The catalyst was recovered by filtration during the recrystallization procedure, dried under reduced pressure, and then reused for three cycles. It was found that catalyst activity remains almost the same. This in turn makes the method more economical. This method not only preserved the simplicity of Biginelli's one-pot condensation but also remarkably improved the yields (92–98%) of DHPMs in shorter reaction times.

This reaction may proceed via imine intermediate **6**, formed by the reaction of the aldehyde and urea and stabilized by Cs^+. Subsequent nucleophilic addition of β-diketoeaster enolate to the imine, followed by cyclization and dehydration, afford the corresponding 3,4-dihydropyrimidin-2(1*H*)-ones **4** and **5** (Scheme 2).

In conclusion, we have demonstrated a new and efficient synthetic methodology for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones and their thio analogs under solvent-free conditions using a catalytic amount of CsF–Celite. The procedure afforded 3,4-dihydro-pyrimidones within a shorter period, in high purities, and with improved yields compared with the classical solution-phase reaction. Moreover, the simplicity of the procedure, ease of separation/reuse of the catalyst because of its heterogeneous nature, and ease of workup make this method an attractive synthetic tool for Biginelli condensation.

EXPERIMENTAL

Melting points were determined on a MelTemp melting-point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were obtained on Bruker

Avance 400 (400 MHz, ^{1}H; 100 MHz, ^{13}C) spectrometers. All spectra were taken in d_6-DMSO, and the chemical shifts are given in parts per million (ppm) with respect to tetramethylsilane (TMS) used as internal standard. Aldehyde, ethylacetoacetate, Celite® 521, urea, and thiourea were all commercial products and were purified before use.

Preparation of CsF–Celite

The CsF–Celite was prepared by stirring an aqueous solution of CsF (15.2 g in 300 ml of distilled water) with 10 g of Celite 521 at room temperature for 1 h, and water was removed under reduced pressure. The remaining solid was shaken with 100 ml of acetonitrile, and the solid was collected on a filter. The CsF–Celite was dried under vacuum and kept in a desiccator.

General Procedure for the Synthesis of Compounds 4 and 5

Aldehydes (1 mmol), ethyl acetoacetate (1 mmol), urea (1.3 mmol), and CsF–Celite (10 mol%) were mixed together in a 10-mL round-bottomed flask and heated at 80–110 °C for the appropriate time (Table 1). The reaction was monitored by thin-layer chromatography (TLC) until completion. The products were recrystallized from ethyl alcohol.

All 3,4-dihydropyrimidin-2(*1H*)-one derivatives are known compounds and were characterized by ^{1}H NMR spectroscopy and their melting points. Selected data for 5-ethoxycarbonyl-4-(3-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-thione (**5g**, X = S, Ar = 3-OHC_6H_5, Table 1, entry 15) are as follows: mp 182–184 °C (lit. mp 182–184 °C).[13] ^{1}H NMR (DMSO-d_6) δ, 1.11 (t, $J = 7.1$ Hz, 3H), 2.26 (s, 3H), 4.01 (q, $J = 7.1$ Hz, 2H), 5.07 (d, $J = 3.5$ Hz, 1H), 6.62–6.64 (m, 3H), 7.09–7.12 (m, 1H), 9.44 (s, 1H, OH), 9.59 (br s, 1H, NH), 10.28 (br s, NH).

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