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Synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones using camphor sulfonic acid as a catalyst under solvent-free conditions

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ABSTRACT

DL-10-Camphorsulfonic acid (CAS. No- 5872-088-2) was found to be a convenient catalyst for the synthesis of 3,4-dihydropyrimidin-2-(1H)-ones through a one-pot three-component reaction of aldehydes, alkyl acetoacetate, and urea at 80^{o}C under solvent-free conditions.

Keywords: One-pot synthesis, biginelli reaction, solvent-free condition, Camphorsulfonic acid.

INTRODUCTION

Over the years, dihydropyrimidinones (DHPMs) and their derivatives have displayed a captivating assortment in natural, synthetic, pharmacological, therapeutic and bioorganic chemistry mainly due to their wide range of biological activities[1–3], and they are being studied because of their activities as calcium channel blockers, antihypertensive agents, alpha-la-antagonists and neuropeptide Y(NPY) antagonists[4,5]. Moreover, dihydropyrimidinethiones have been suggested to be useful building blocks for synthesis of natural products, such as the batzelladine family of polycyclic marine alkaloids [6,7], of which batzelladine alkaloids have been found to be potent HIV gp-120-CD4 inhibitors[8,9].

Multi-component reactions are of increasing importance in organic and medicinal chemistry as they offer significant advantages over conventional linear-type syntheses, including high selectivity, good yields, milder reaction conditions and simple work-up. Thus, a vast number of diverse compounds can be obtained in parallel syntheses. New, efficient methods for rapid construction of potentially bio-active compounds are required, and multi-component reactions allow the construction of several bonds in a single operation. They are this gaining in importance as powerful tools for synthesizing complex, diverse molecules.

The most simple and straightforward procedure for the synthesis of DHPMs was first reported by the Italian chemist Pietro Biginelli in 1893, it involves a three-component one-pot condensation of benzaldehyde, ethyl acetoacetate and urea under strongly acidic conditions [10]. However, this reaction usually requires harsh conditions, long reaction times and affords low yields, particularly when substituted aromatic and aliphatic aldehydes are employed, which impede their applications. To overcome those disadvantages, several protocols for the synthesis of DHPMs have been developed to improve and modify this reaction by means of microwave irradiation[11,12], ultrasound irradiation[13], ionic liquids[14–16], and different types of acidic, base, metal oxide, nanoparticle, enzyme,

phasetransfer catalysts such as lanthanide triflate[17], H_3BO_3[18], VCl_3[19], $Sr(OTf)_2$[20], PPh_3[21],Indium(III) halides[22], nanomagnetic-supported sulfonic acid[23], Iron(III) tosylate[24], Bis[(L)prolinato-N,O]Zn-water[25], 1-glycyl-3-methyl imidazolium chloride copper(II) Complex[26], $KAl(SO_4)_2 \cdot 12H_2O$ supported on silica[27], $FeCl_3$-supported nanopore silica[28], SiO_2-$CuCl_2$[29],metal oxide-MWCNTs[30–32], $Fe_3O_3$and boehmite nanoparticle[33,34], nanosilica-supported tin(II)chloride35, graphite[36], trypsin[37], silica sulfuric acid[38], $Mn(OAc)_3 \cdot 2H_2O$[39],$Y(NO_3)_3 \cdot 6H_2O$[40], $In(OTf)_3$[41], $TaBr_5$[42], $Ce(NO_3)_3 \cdot 6H_2O$[43], silica chloride[44], HCOOH[45],ytterbium chloride[46], TBAB[47], Cl_3CCOOH[48] and so on. However, in spite of their potential utility, many of these reported one-pot protocols suffer from drawbacks such as the use of expensive reagents, volatile strong acidic conditions and long reaction times. Therefore, to avoid these limitations, the introduction of a milder and more efficient method accompanied with higher yields is needed.

MATERIALS AND METHODS

All ^{1}H NMR spectra were recorded on 400 MHz Varian FT-NMR spectrometers. All chemical shifts are given as δ value with reference to Tetra methyl silane (TMS) as an internal standard. The chemicals and solvents were purchased from commercial suppliers either from Aldrich, Spectrochem and they were used without purification prior to use.

Camphorsulfonic acid catalyzed synthesis of 3,4-dihydropyrimidin-2-(1H)-ones derivatives.
To a mixture of aldehyde (1 mmol), ethyl acetoacetate (1 mmol), urea (1 mmol) and Camphor sulfonic acid (20 mol%) was stirred at 80 °C under solvent-free condition for 5 h. The completion of the reaction was monitored by TLC. After cooling, the reaction mixture was poured in to crushed ice and stirred for 30 min. The separated solid was filtered under suction, washed with cold water thoroughly and then recrystallized from methanol to afford the pure product. All products are known compounds, which were characterized by mp, IR and ^{1}H-NMR spectra. The results are summarized in Table- 02.

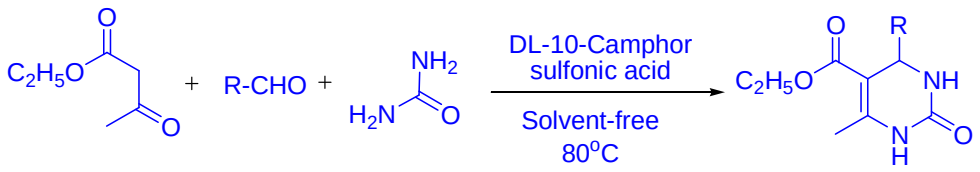
Characterization data for selected compounds:
Ethyl 1,2,3,4-tetrahydro-6-methyl-2-oxo-4-phenylpyrimidine-5-carboxylate (entry-1): This compound was obtained as Off-white solid; ^{1}H NMR (DMSO-d_6): δ 1.10 (t, *J*= 7.2 Hz, 3H), 2.35 (s, 3H), 3.90 (q, *J*= 7.2 Hz, 2H), 5.25 (s, 1H), 7.18-7.40 (m, 5H), 7.90 (br s, 1H), 9.45 (br s, 1 H); IR (KBr, Cm^{-1}): 3320, 3119, 1689, 1660.

Ethyl 1,2,3,4-tetrahydro-4-(4-methoxyphenyl)-6-methyl-2-oxopyrimidine-5-carboxylate (entry-3): This compound was obtained as Off-white solid; ^{1}H NMR (DMSO-d_6): δ 1.09 (t, *J*= 7.2 Hz, 3H), 2.20 (s, 3H), 3.61 (s, 3H), 3.89 (q, *J*= 7.2 Hz, 2H), 5.26 (s, 1H), 7.14 (d, *J*= 8.2 Hz, 2H), 7.34 (d, *J*= 8.2 Hz, 2H), 7.91 (br s, 1H), 9.46 (br s, 1 H); IR (KBr, Cm^{-1}): 3323, 3210, 1698, 1668.

ethyl 1,2,3,4-tetrahydro-4-(4-hydroxyphenyl)-6-methyl-2-oxopyrimidine-5-carboxylate (entry-6): This compound was obtained as white solid; ^{1}H NMR (DMSO-d_6): δ 1.11 (t, *J*= 7.2 Hz, 3H), 2.21 (s, 3H), 3.87 (q, *J*= 7.2 Hz, 2H), 5.25 (s, 1H), 7.21 (d, *J*= 8.2 Hz, 2H), 7.46 (d, *J*= 8.2 Hz, 2H), 7.86 (br s, 1H), 9.20 (br s, 1 H), 9.47 (s, 1H); IR (KBr, Cm^{-1}): 3389, 3316, 3201, 1696, 1670.

RESULTS AND DISCUSSION

The catalytic activity of camphorsulfonic acid was first investigated using three-component reaction of benzaldehyde, ethyl acetoacetate, and urea as a model reaction. After carrying out the reaction at different conditions (Table-01), the best results have been obtained with 20 mol% camphorsulfonic acid at 80^{o}C after 5 hrs with 82% yield under solvent-free conditions. One important aspect of green chemistry is the elimination of solvents in chemical processes or the replacement of hazardous solvents with relatively benign solvents. Our initial work started with screening of solvent and catalyst loading so as to identify optimal reaction conditions for the synthesis of dihydropyrimidin-2(1*H*)-one derivatives. The solvents acetone, acetonitrile, ethanol, toluene and methanol were examined and reaction with no solvent at 80^{o}C was found to be the most successful. We also evaluated the amount of camphorsulfonic acid required for the reaction, and it is concluded that 20 mol% of catalyst is sufficient to promote the reaction.



Scheme-1: Camphorsulfonic acid catalyzed synthesis of 3,4-dihydropyrimidin-2 (1H)-ones

Table-1: Optimization of the reaction conditions[a]

S.No	Solvent	Time(hr)	Temp(^{O}C)	Camphorsulfonic acid	Yield (%)[b]
01	Acetone	10	55	20 mol%	47
02	Acetonitrile	10	80	20 mol%	71
03	MeOH	10	65	20 mol%	62
04	EtOH	10	80	20 mol%	70
05	Toluene	10	100	20 mol%	48
06	Solvent-free	15	80	20 mol%	81
07	Solvent-free	10	80	20 mol%	80
08	Solvent-free	05	80	20 mol%	82
09	Solvent-free	05	80	10 mol%	71
10	Solvent-free	10	80	No catalyst	49

[a]Reaction conditions: benzaldehyde (1.0 mmol), ethyl acetoacetate (1.0 mmol), urea (1.0 mmol) mol%) used. [b]Isolated yield.

In order to study the scope of the procedure, a series of DHPMs were synthesized with the optimized conditions. The results are listed in Table-2. In all cases studied, the three-component reaction proceeded smoothly to give the corresponding DHPMs in excellent yields. Most importantly, aromatic aldehydes carrying either electron donating or electron withdrawing substituents reacted very well to give the corresponding DHPMs with high purity in good yields. Notably, this procedure is compatible with a wide range of functional groups such as methoxy, halides, hydroxy, *etc*. Beside those above, some sensitive groups also showed to be well tolerated by this method. For instance, furfuraldehyde also afford the corresponding products in excellent yields as well.

Table-1: Camphorsulfonic acid catalyzed one-pot synthesis of 3,4-dihydropyrimidin-2-(1H)-ones under solvent-free conditions[a].

Entry	R-aldehyde	Yield %	Melting range ^{o}C	
			Found	Reported
01	-C_6H_5	82	201-204	202-205[49]
02	2-OMe-C_6H_4-	80	257-259	260[50]
03	4-OMe-C_6H_4-	84	201-203	202-204[49]
04	2-Cl-C_6H_4-	79	218-221	221-223[51]
05	4-Cl-C_6H_4-	76	208-211	210-212[49]
06	4-OH-C_6H_4-	77	232-234	231-233[51]
07	4-Br-C_6H_4-	81	211-213	215[52]
08	3-Me-C_6H_4-	80	222-225	224-226[51]
09	4-Me-C_6H_4-	78	213-216	214-216[49]
10	2-Furfural	78	200-203	202-204[53]

[a]Reaction conditions: aldehyde (1.0 mmol), ethyl acetoacetate (1.0 mmol), urea (1.0 mmol) and camphor sulfonic acid (20 mol%) was stirred for 5h at 80^{o}Cunder solvent-free condition. [b]Isolated yield. All compounds are matched with their authentic data.

CONCLUSION

In conclusion, we have demonstrated that the use of camphorsulfonic acid for the synthesis of 3,4-dihydropyrimidin-2-(1H)-ones has been described through the Biginelli reaction at 80^{o}C under solvent-free conditions. This method offers several advantages including high yields, short reaction times, solvent-free condition, usage of cheap catalyst, a simple work-up procedure.

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