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Research Article

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Microwave assisted Biginelli's synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones using 1, 3, 5-triazine-2, 4, 6-triyltrisulfamic acid as heterogeneous and recyclable catalyst

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ABSTRACT

A microwave assisted three-component condensation of β-keto ester, aldehydes, and urea or thio-urea catalysed by TTSA to a biologically active 3,4-dihydropyrimidin-2(1H)-ones is described. The reactions were completed in short time, simple work up procedure, and the catalyst could be recovered by mere filtration and recycled for five consecutive runs without significant loss of activity.

Key words: Microwave, Heterogeneous catalyst, Biginelli reaction, TTSA, Multicomponent reactions (MCRs), 3,4-dihydropyrimidin-2(1H)-ones.

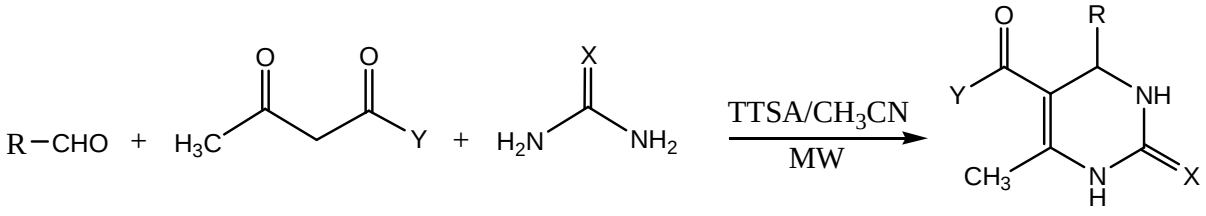
INTRODUCTION

The eco-friendly transformations and environmental concerns in research and industry [1] using heterogeneous catalysts is of considerable importance among the researchers. Multicomponent reactions (MCRs) are having the most important protocols [2] in organic synthesis and medicinal chemistry. The Biginelli reaction [3] is the most important and useful multicomponent reaction which offers an efficient way to access 3, 4-dihydropyrimidin-2(1H)-ones. The 3,4-dihydropyrimidin-2(1H)-ones and their derivatives [4] are medicinally important [5] as calcium channel blockers, antihypertensive and anti-inflammatory agents and α 1-a antagonists. These have recently emerged as important target molecules due to their therapeutic and pharmacological properties [6] such as antiviral [7], antimitotic [8], anticarcinogenic [9]. More recently Suresh and J. S. Sandhu [10] has reviewed the accounts regarding the past, present and future of the Biginelli reactions with respective of its critical perspective.

Biginelli in 1893, reported the first one pot- synthesis of 3,4-dihydropyrimidines by condensation of an aldehyde, β-keto ester and urea or thio-urea under acidic condition [3]. Several procedures [10] have been reported using homogeneous as well as heterogeneous catalysts as promoters. Furthermore, several alkaloids containing the dihydropyrimidine nucleus obtained from marine sources are well known to show interesting biological activities. [10] Owing to the wide synthetic utility and potential applications, the synthesis of this heterocyclic nucleus is of much importance. A number of improved methods[11] involving the use of transition-metal-based catalysts/reagents, ionic liquids, polymer immobilized reagents, microwave, and ultrasound irradiation have been recently reported for their synthesis.

In continuation of our ongoing research work [12-13] and considering the medicinal importance of 3, 4-Dihydropyrimidin-2(1H)-ones search of an efficient methodology for its synthesis, we have synthesised the tilted compounds by the multicomponent condensation of aldehyde, with ethyl acetoacetate, urea or thio-urea in

acetonitrile under reflux using a recyclable and heterogeneous TTSA as catalyst. However recently we came across the literature [14] which reported the Biginelli reaction using the above catalyst without solvent by conventional heating at 80°C. Therefore we further extended our research to the rapid synthesis of 3, 4-Dihydropyrimidin-2(1H)-ones under microwave irradiation without solvent. Here in we wish to demonstrate the results obtained for the remarkably faster condensation of a variety of aldehyde with ethyl acetoacetate, and urea/thio-urea using TTSA as heterogeneous and recyclable catalyst in acetonitrile by microwave irradiation without solvent.



1 **2** **3** **4**

Y= OEt, R= Alkyl or Ar, X = O or S

Scheme 1: Biginelli reaction

EXPERIMENTAL SECTION

3.1 Material and Characterization

Melting points were observed in open capillary tubes in a circulating oil melting point apparatus. FTIR spectra were recorded on Perkin Elmer Spectrometer, ^{1}H NMR spectra were recorded with Bruker AVANCE 400 MHz NMR spectrometer in $CDCl_3$, mass spectra were recorded with micromass Q- Tof Micro (TQF MS EF +).

3.1 General Procedure

To a equimolar mixture (2 mmol each) of aldehyde **1**, β-keto ester **2** and urea or thio-urea **3** in acetonitrile, catalytic amount of TTSA (3 mol%) was added and the contents were irradiated to microwave (450 wt) at the interval of 10 sec. After completion of the reaction as monitored by TLC (2-4 minute), the reaction mixture was filtered to remove the catalyst and the filtrate was poured into ice-cold water and stirred for 15-20 minutes. Then the contents were filtered, washed with cold water (20 ml) to remove excess urea if any. The solid so obtained was the corresponding 3,4-dihydropyrimidin-(2H)-one **4**. It was then recrystallized by hot ethanol to get essentially pure products (**Scheme 1**). Further used catalyst is washed with acetonitrile, dried and recycled for another condensation. Product formations were confirmed by the comparison with authentic sample, physical constants, IR, ^{1}H-NMR spectral and Mass analysis.

3.1.1 Ethyl-4-(4-chlorophenyl)-6-methyl-2-*oxo*–1,2,3,4–tetrahydro-5-pyrimidine carboxylate (4b). Solid, mp 201 °C ; IR (KBr): 3242 (–NH–), 2979 (C–H), 1706, 1647 (C=O),783 (C–Cl); 1H NMR (400 MHz, DMSO-d6) :(1.2, t, 3H), (2.2, s, 3H), (3.6, s, 1H), (4.1, q, 2H), (5.3, s, 2H), (7.2, 7.4,m, 4H);Mass:295 (M^+ 1)

3.1.2 Ethyl-4-(4-chlorophenyl)-6-methyl-2-thi*oxo*–1,2,3,4–tetrahydro-5-pyrimidine carboxylate (4l). Yellowish solid, mp 189 °C ; IR (KBr): 3226 (– NH–), 2983 (C–H),1710 (C=O), 1672 (C=S), 746 (C–Cl); 1H NMR (400 MHz, DMSO-d6):1.1 (t, 3H, -CH_3), 2.3 (s, 3H, -CH_3), 3.1 (s, 1H, -CH-), 4.1 (q, 2H, -CH_2-),5.1 (s, 2H, 2 NH), 7.2 , 7.3 (m, 4H, Ar–H); Mass: 311 (M^+1),

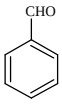
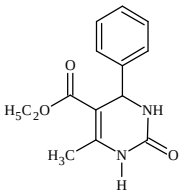
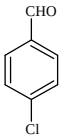
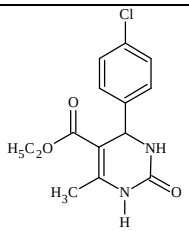
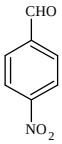
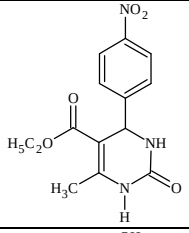
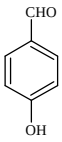
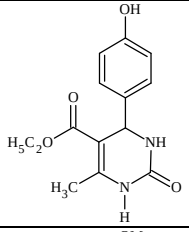
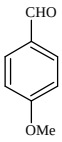
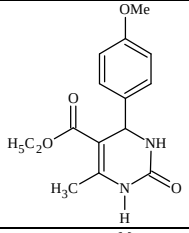
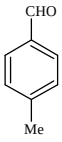
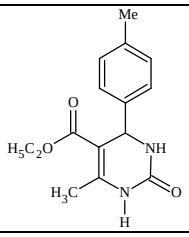
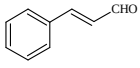
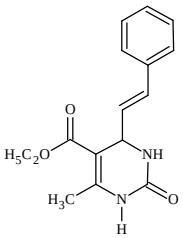
RESULTS AND DISCUSSION

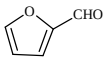
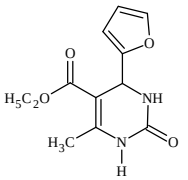
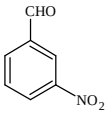
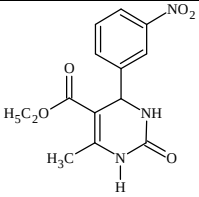
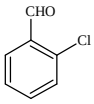
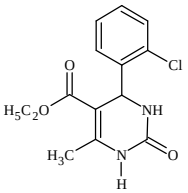
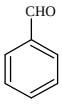
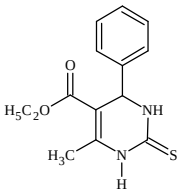
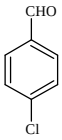
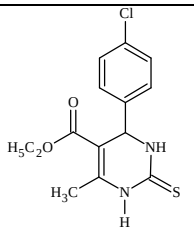
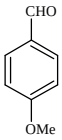
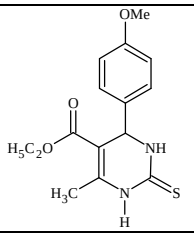
After establishing the optimal conditions, we report herein the results and generality of the microwave assisted TTSA catalysed Biginelli reaction (**Table 1**). The desired dihydropyrimidine derivatives were obtained with 3 mol % of TTSA and one equivalent of each of the three components aldehyde **1**, ethyl acetoacetate **2** and urea or thio-urea **3.** The neat mixture was irradiated to microwave (450 wt) at the interval of 10 sec. After each cycle of microwave exposure the contents were stirred by glass rod and TLC was taken to check conversion of reaction in good to excellent yields (Table 1). The protocol is applicable for both aliphatic as well aromatic aldehydes very well.

The scope of the aldehyde component was first investigated by the reaction with urea (entries 1 to 10) and thus aldehydes bearing different types of substituents underwent the reaction in good to excellent yields. Thio-urea used in similar way afforded corresponding dihydropyrimidine-2(1H)-ones in moderate to good yields (entries 11 to 13).The reaction conversion and product outcome showed the effect of the substituent on the aldehyde. Aromatic

aldehydes with substituents carrying electron-withdrawing groups reacted faster than the aromatic aldehydes with electron releasing groups reflected in terms of yield of the products. The product which has an electron withdrawing substituent attached at different position of the aromatic ring was produced higher yields with that of the electrondonating substituents.

Table 1 : Microwave assisted synthesis of 3,4 – dihydropyrimidines using TTSA.

Entry of Product	Aldehyde	Product	MW Yield (%)	MP (ºC)	MP (ºC)$^{Lit.}$
4a			95	201	202-204[15]
4b			94	213	210-212[15]
4c			96	208	212-214[15]
4d			90	227	225-226[16]
4e			93	200	202-204[15]
4f			90	215	215-216[17]
4g			90	230	229-232[18]

4h			88	201	202-204[19]
4i			89	228	226-227[23]
4j			86	216	216-218[22]
4k			72	207	208-209[21]
4l			74	179	180-182[19]
4m			69	135	136-138[19]

CONCLUSION

Heterogeneous Catalyst, TTSA having three active acidic sites was synthesized successfully and utilised together with microwave irradiation for the three-component condensation of β-keto ester, aldehydes, and urea or thio-urea to the corresponding biologically active 3,4-dihydropyrimidin-2(1H)-ones. The protocol was found to be rapid, simple, eco-friendly and high product yielding. The catalyst is recovered by simple filtration and recycled.

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