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Multicomponent solvent free synthesis of 3, 4-dihydropyrimidine-2-[*1H*]-one and 3, 4-dihydropyrimidine-2-[*1H*]-thione

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Abstract

A one pot, multicomponent condensation of an aldehyde, ethylacetoacetate, and urea/thiourea for the synthesis of 3,4-dihydropyrimidine-2-[*1H*]-thione/one (DHPMs) under solvent free conditions using $CuSO_4.5H_2O$ in high yields is described. The present methodology offers several advantages such as high yields, short reaction times, simple operation and easy workup.

Keywords: $CuSO_4.5H_2O$ catalyst, 3,4 - dihydropyrimidine – 2 – [*1H*] -thione/one (DHPMs), solvent free.

Introduction

Multicomponent reactions (MCRs) due to their convergence, productivity, facile execution and generally high yields of products have attained considerable attention from the view of synthetic chemistry. MCRs led to interesting heterocyclic skelton, which are of useful medicinal importance [1-8]. Development of a simple, safe, ecofriendly and economic synthetic route for generating libraries of biologically active molecule, are one of the major challenges in organic synthesis. Dihydropyrimidine-2-[*1H*]-one (DHPMs) are among such type of molecules which belongs to a class of with significant therapeutic and medicinal properties [9], like antiviral, antitumor, antibacterial and anti-inflamatory activity[10-12]. In addition, DHPMs are also known to have other pharmacological properties such as calcium channel modulators, mitotic kinesin inhibitors and hepatisis B virus replication inhibitors, blood platelets aggregation inhibitor, cardiovascular activity etc. [13]. Due to these potential applications of 3, 4-dihydropyrmidin-2-[*1H*]-ones, it is necessary to find a versatile, simple and ecofriendly process. A survey of literature reveals that numerous methods for the synthesis of DHPMs using lanthanidetriflate [14], indium halides [15], indiumtriflate [16], iodine [17], strontium(II) triflate [18], fluorapatite [19], zirconium tetrachloride [20], ferric chloride [21], cobaltous chloride [22], zinc chloride [23], lithium bromide [24], montmorillonite [25], alumina supported MoO_3 [26] have been reported.

Many of these methodologies are associated with one another drawbacks such as expensive catalysts, acidic conditions, hard reaction conditions, tedious workup, stoichiometric amounts of catalysts, long reaction times, incompatibility with other functional groups etc. In view of these drawbacks development of a general, efficient and green method for the synthesis of DHPMs is still needed. Therefore in continuation to our work on the synthesis of DHPMs [22], we hereby report one pot synthesis of Dihydropyrimidine-2-[*1H*]-one/thione (DHPMs) using $CuSO_4.5H_2O$ as an inexpensive and easily available reagent (**Scheme 1**).

Material and methods:

Materials were obtained from commercial suppliers and were used without further purifications. Melting points are uncorrected and were recorded in open end capillaries. H^1 NMR spectra were recorded in $CDCl_3$ solution on a Bruker 300 MHz spectrometer, chemical shifts (delta) are reported in ppm relative to TMS as internal standard. The IR spectra were obtained on a Perkin-Elmer spectrometer.

General Procedure: In a flask aromatic aldehyde (1mmole), ethylacetaacete (1mmole) and urea (1.5mmole)/thiourea (1 mmole) were taken and refluxed for stipulated time without any solvent in presence of $CuSO_4.5H_2O$. After refluxing add 5 ml of methanol and pour it in to ice cold water with continuous stirring, product separate out, filter it and recrystalised from

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ethanol.

Spectral data of some selected compounds:

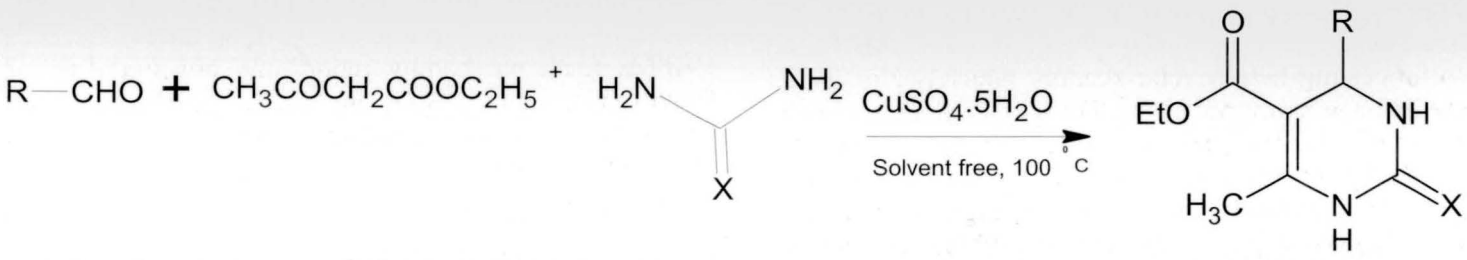
5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidine-2-[*1H*]-one,4a. colourless solid, m.p. 202-04; IR (KBr): 3240, 1722, 1705, 1649 cm^{-1}; ^1H NMR: 9.12 (s, 1H), 7.66 (s, 1H), 7.16-7.28 (m, 5H), 5.10 (d, 1H), 3.94 (q,2H), 2.18 (s, 3H), 1.04 (t,3H).

4-(4-chlorophenyl)-5-ethoxy carbonyl-6-methyl-3,4-dihydo pyrimidin-2-[*1H*]-one, 4b: colourless solid, m.p. 212-14 °C; IR (KBr): 3242, 1723, 1704, 1649 cm^{-1}; ^1H NMR: 9.20 (s, 1H), 7. (s, 1H), 7.16-7.28 (m, 4H), 5.10 (d, 1H), 3.94 (q,2H), 2.18 (s, 3H), 1.04 (t,3H).

5-ethoxycarbonyl-6-methyl-4-(4-methoxyphenyl -3, 4-dihydro pyrimidine-2-[*1H*]-thione 4i: light yellow solid, m.p. 140-42°C; IR (KBr): 3445, 3315, 3175, 2965, 1667, 1617, 1575, 1510 cm^{-1}, ^1H NMR: 9.60 (s,1H), 6.87-7.09 (m, 4H), 5.10 (d, 1H), 3.96 (q,2H), 2.28 (s, 3H) 1.08 (t, 3H)

Results and discussion:

In order to determine the most appropriate reaction conditions, the reaction is carried out in different solvents like ethanol, methanol, acetonitirle etc. and under solvent free condition. It was found that solvent free synthesis of DHPMs is superior to solution phase strategy in terms of yield as well as reaction time. Also to evaluate the catalytic efficiency of $CuSO_4.5H_2O$, initially a model study was carried out on the synthesis of 5-ethoxycarbonyl-6-methyl-4-phenyl -3,4-dihydropyrimidine-2-[1*H*]-one **4a**. Further investigation was for optimum amount of catalyst for the efficient production of the DHPMs and found that 5mol% of $CuSO_4.5H_2O$ is sufficient to catalyse the reaction. Decrease in the amount of catalyst affects the product yield inversely and the reaction time increases. Increase in amount of catalyst did not provide any fruitful results. In a typical experimental procedure, mixture of ethyl acetoacetate (1 mmole), Benzaldehyde (1 mmole), urea/thiourea (1.5 mmole) and $CuSO_4.5H_2O$ (5mol %) were taken in a flask and heated at 100°C. After completion (*vide* TLC), the reaction was cooled to room temperature, added 5 ml MeOH to it and then poured it in ice cold water. The solid thus obtained was recrystalised form ethanol to afford pure **4a**, m.p. 202-04°C in 85% yield. ^1H NMR spectrum of **4a** shows signals at 9.12 (s, NH), 7.16-7.28 (m, 5H), 5.10 (d, 1H), 3.94 (q, 2H), 2.18 (s, 3H), 1.04 (t,3H). IR (KBr) shows absorption band at 3240 cm^{-1} for NH and absorption band at 1722 and 1705 shows the presence of Carbonyl group. Spectral data of **4a** fully supports the structure assigned to it. After optimizing the conditions, we next examined the generality of this procedure to other substrates using ethylacetoacetate, different aromatic aldehydes and urea/thiourea. The results are summarised in **Table 1**. Aromatic aldehydes carrying different functional groups were subjected to the reaction and in all cases the desired product were obtained in high yields.



1 2 3 4

X=O or S, R= C_6H_5, 4-Cl C_6H_4, 3-NO_2 C_6H_4, 4-OH C_6H_4, 4-OCH_3 C_6H_4

Scheme 1

Table 1 - $CuSO_4.5H_2O$ catalysed synthesis of dihydropyridiones and dihydropyrimidionethione under solvent free conditions

S. No.	R	X	Reaction time (hr)	Yield (%)	Melting point (°C)
4a	C_6H_5	O	3.2	85	202-204
4b	4-Cl C_6H_4	O	4	78	212-14
4c	3-NO_2 C_6H_4	O	3.8	75	225-27
4d	4-OH C_6H_4	O	5	83	225-27
4e	4-OCH_3 C_6H_4	O	4.2	74	199-201
4f	C_6H_5	S	3.6	82	200-02
4g	4-Cl C_6H_4	S	4.5	74	182-83
4h	3-NO_2 C_6H_4	S	4.2	75	195-96
4i	4-OCH_3 C_6H_4	S	5	70	140-42

Conclusion:

In conclusion, a highly efficient method for the synthesis of DHPMs derivatives has been developed. The attractive features of this method are its simplicity, in-expensive and environmental benign solvent free conditions.

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