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Maleic acid as a versatile catalyst for one pot synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones and their thione analogues

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ABSTRACT

Maleic acid catalyzed 3,4-Dihydropyrimidin-2-(1H)-ones and their thione analogues have been synthesized by condensation of aromatic aldehydes, β-dicarbonyl compound and urea or thiourea in the presence of alcohol-water (2:1; v/v) under mild reaction conditions. The yields obtained were excellent. The use of very cheap non-hazardous catalyst, environmentally benign solvent and easy work-up are the perspectives advantageous aspects of the present method.

Key words: Biginelli reaction, maleic acid, non-hazardous catalyst, pyrimidine.

INTRODUCTION

The interest of dihydropyrimidines (DHPMs) and their derivatives have gained great deal of attention due to its widespread activities like calcium channel blockers, α-1a-antagonists and neuropeptide-Y (NPY) antagonists [1]. Recently, some alkaloids are being reported containing dihydropyrimidines, which are potent HIV inhibitors [2]. DHPMs and their sulphur analogues are pharmacologically important because of their antibacterial, antitumor and anti-inflammatory properties [3]. The biological activity of some recently isolated alkaloids has been attributed to the presence of dihydropyrimidinone moiety in the corresponding molecule [4].

Literature provides a number of methods for the synthesis of DHPMs and their derivatives. Biginelli reported the first synthesis of dihydropyrimidine by a simple one-pot condensation reaction of ethyl acetoacetate, benzaldehyde and urea. Later on, different modifications are reported for the synthesis of an array of substituted DHPMs. The use of different Lewis acid has been attempted, such as $FeCl_3$, BF_3-ethrate, $LaCl_3$, $ZnCl_2$, $ZrCl_4$, $BiCl_3$ etc [5]. Some metal-triflates like Yb $(OTf)_3$, Bi $(OTf)_3$, La $(OTf)_3$ are equally reported [6]. We have recently reported sulphamic acid as a catalyst for preparing DHPMs [7]. Oxalic acid is a versatile catalyst for one pot synthesis of 3, 4 – dihydropyrimidine has been also reported [8].

Most literature examples of Biginelli variants use simple β ketoester such as methyl acetoacetate in the condensation reactions. The efficacy of Biginelli's reaction is substrate dependent with the use of more highly functionalized or sterically encumbered ketoester leading to severely reduced yields. Existing synthetic strategies have shown a great deal of variability in yield depending upon the aryl aldehyde used. However, most of these methods are associated with expensive and toxic reagents or catalysts. These methods produce unsatisfactory output and incompatibility with other functional groups results into tedious work-up. Some of these methods are applicable for aromatic aldehydes only [9]. Thus there is a need for a simple and general procedure for one-pot synthesis of DHPMs and for

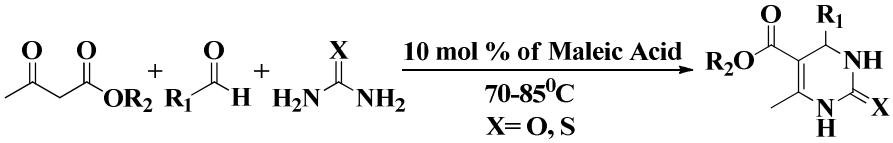
their thione analogues under mild conditions. In continuing with our research for the development of simple and novel methods for synthesis of different heterocyclic derivatives [10], we have developed a convenient method for the synthesis of DHPMs and their thione analogues using 10-mol% maleic acid as a catalyst in ethanol-water. In our present research, maleic acid catalyzes three component reaction which afforded uniform high yields regardless of ketoester or an aldehyde substituents. Maleic acid as a catalyst is very cheap and non-hazardous. It is very easy to handle. The reaction conditions are very simple. Apart from its simplicity, use of maleic acid in the reaction of one pot synthesis it has an ability to tolerate a variety of substituted β-ketoesters and arylaldehyde. Maleic acid or (Z)-butenedioic acid or cis-butenedioic acid or oxalic acid is an organic compound which is a dicarboxylic acid (a molecule with two carboxyl groups). It consists of an ethylene group flanked by two carboxylic acid groups. Maleic acid is the cis isomer of butenedioic acid, whereas fumaric acid is the trans isomer. Maleic acid is a less stable molecule than fumaric acid, e.g: the difference in heat of combustion is 22.7kJ/mol. The physical properties of maleic acid are very different from those of fumaric acid. Maleic acid is soluble in water, which is a greener feature, whereas fumaric acid is insoluble in water. The melting point of maleic acid (132^0C) is also much lower than that of fumaric acid (295^0C). Both properties of maleic acid can be explained on account of the inter-molecular hydrogen bonding [11], that takes place at the expense of intermolecular interactions. Maleic acid is commercially available as a crystalline solid or as an aqueous solution in 40% water. It is mainly used for making maleate salts of APIs such as cholrpheniramine and pheniramine maleate. It is also used to prevent vancidity of oils.

Application of maleic acid as a weak acid (dicarboxylic acid) in chemical synthesis promoted us to use it as catalyst for dihydropyrimidine, which is commonly known as Biginelli cyclo-condensation and its application for various dihydropyrimidines. Surprisingly the results were encouraging in terms of reaction time, yield and purity. Hence we reported a simple, cost effective and efficient method for synthesis of dihydropyrimidines using Maleic acid as a catalytic promoter, 1, 3- dicarbonyl compound, urea or thiourea in Ethanol: water and aromatic / aliphatic aldehyde reacted well in a short time to result into desired dihydropyrimidine with an excellent yield. The methodology has been extended for a series of substituted dihydropyrimidines and their analogues.

MATERIALS AND METHODS

2.1 General method for Maleic acid mediated synthesis of dihydropyrimidine (4a-r)

A reaction mixture of alcohol: water 30ml (2:1), β ketoester. (0.01mole), aldehyde aromatic/aliphatic (0.01mole), urea (0.02 mol), maleic acid (0.01 mol) was heated to 70-85^0C for 100 min. Reaction completion was checked on TLC. After completion of the reaction, alcohol was distilled off below 50^0C and allowed to cool at room temperature. A solution of sodium carbonate 30 ml was added to the reaction mixture to afford the crystalline product which was further collected by filtration, rinsed with ethyl acetate and dried in vacuum to afford the desired product (4a-r) as a crystalline solid (Scheme 1).



Scheme 1: Synthesis of dihydropyrimidin

2.2 Spectral evaluation of compounds (4a-r)

Ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4a)

IR (KBr cm^{-1}): 3300 (N-H), 3045 (=CH), 1270 (C-N), 1705 (C=O), 1650 (C=O) cm^{-1}; **^{1}H-NMR (DMSO-d_6):** 8.25 (s, 1H, NH), 7.6 (s, 1H, NH), 7.10-7.30 (m, 5H, Ar-H), 5.12 (s, 1H), 4.20 (2H, OCH_2), 2.29 (s, 3H, CH_3), 1.30 (s, 3H, CH_3); **Mass (ES/MS):** 261 (m+1).

Ethyl 4-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4b)

IR (KBr cm^{-1}): 3300 (N-H), 3045 (=CH), 1350 (C-N), 1700 (C=O), 1630 (C=O), 600 (C-Cl) cm^{-1}; **^{1}H-NMR (DMSO-d_6):** 6 (s, 1H, NH), 6 (s, 1H, NH), 7.33-7.36 (m, 4H, Ar-H), 5.12 (s, 1H), 4.20 (2H, OCH_2), 2.25 (s, 3H, CH_3), 1.27 (s, 3H, CH_3); **Mass (ES/MS):** 293 (m+1).

Ethyl 4-(4-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4c)
IR (KBr cm^{-1}): 3360 (N-H), 3300 (O-H), 3010 (=CH), 1270 (C-N), 1730 (C=O), 1645 (C=O) cm^{-1}; **^{1}H-NMR (DMSO-d_6):** 6 (s, 1H, NH), 6 (s, 1H, NH), 6.60-7.03 (m, 4H, Ar-H), 5.11 (s, 1H), 4.1 (2H, OCH_2), 2.24 (s, 3H, CH_3), 1.27 (s, 3H, CH_3); **Mass (ES/MS):** 275.09 (m+1).

Ethyl 4-butyl-6-mehyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4d)
IR (KBr cm^{-1}): 3500 (N-H), 3080(=CH), 1260 (C-N), 1730 (C=O), 1600 (C=O) cm^{-1}; **^{1}H-NMR (DMSO-d_6):** 7.06 (s, 1H, NH), 7.2 (s, 1H, NH), 1.50 (2H, CH_2),1.20 (2H, CH_2), 1.35 (2H, CH_2), 0.8 (3H, CH_3), 4.25 (s, 1H), 4.1 (2H, OCH_2), 2.26 (s, 3H, CH_3), 1.28 (s, 3H, CH_3); **Mass (ES/MS):** 239.01 (m+1).

Ethyl 6- methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4e)
IR (KBr cm^{-1}): 3400 (N-H), 3045 (=CH), 1305 (C-N), 1710 (C=O), 1635 (C=O) cm^{-1}; **^{1}H-NMR (DMSO-d_6):** 8.25 (s, 1H, NH), 7.5 (s, 1H, NH), 7.45-8.07 (m, 4H, Ar-H), 5.14 (s, 1H), 4.29 (2H, OCH_2), 2.25 (s, 3H, CH_3), 1.29 (s, 3H, CH_3); **Mass (ES/MS):** 304.79(m+1).

Ethyl 6-methyl-2-oxo-4-(pyridin-4-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4f)
IR (KBr cm^{-1}): 3400 (N-H), 3100 (=CH), 1280 (C-N),, 1700 (C=O), 1645 (C=O) cm^{-1}; **^{1}H-NMR (DMSO-d_6):** 9.38 (s, 1H, NH), 7.2-8.50 (m, 4H, Ar-H) , 7.85 (s, 1H, NH), 5.15 (s, 1H), 4.00 (2H, OCH_2), 2.27 (s, 3H, CH_3), 1.09 (s, 3H, CH_3); **Mass (ES/MS):** 262 (m-1).

Ethyl 4-(2-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4g)
IR (KBr cm^{-1}): 3420 (N-H), 3045 (=CH), 1260 (C-N), 1730 (C=O), 1635 (C=O), 630 (C-Cl) cm^{-1}; **^{1}H-NMR (DMSO-d_6):** 7.6 (s, 1H, NH), 6 (s, 1H, NH), 7.10-7.39 (m, 4H, Ar-H), 5.14 (s, 1H), 4.18 (2H, OCH_2), 2.25 (s, 3H, CH_3), 1.31 (s, 3H, CH_3); **Mass (ES/MS):** 293.2 (m+1).

Ethyl 4-(furan-2-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4h)
IR (KBr cm^{-1}): 3300 (N-H), 3100 (=CH), 1260 (C-N),, 1700 (C=O), 1630 (C=O) cm^{-1}; **^{1}H-NMR (DMSO-d_6):** 6 (s, 1H, NH), 7.2 (s, 1H, NH), 6.28-7.60 (t, 3H), 5.74 (s, 1H), 4.1 (2H, OCH_2), 2.27 (s, 3H, CH_3), 1.33 (s, 3H, CH_3); **Mass (ES/MS):** 249.2 (m+1).

Methyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4i)
IR (KBR cm^{-1}): 3360 (N-H), 1310 (C-N), 3090 (=CH), 1715 (C=O), 1655 (C=O) cm^{-1}; **^{1}H-NMR (DMSO-d_6):** 9.15 (s, 1H, NH), 7.2-7.31 (m, 5H, Ar-H), 5.9 (s, 1H, NH), 5.12 (s, 1H), 3.6 (s, 3H, OCH_3), 2.20 (s, 3H, CH_3); **Mass (ES/MS):** 247 (m+1).

Methyl 6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4j)
IR (KBR cm^{-1}): 3310 (N-H), 1270 (C-N), 3100 (=CH), 1730 (C=O), 1630 (C=O) cm^{-1}; **^{1}H-NMR (DMSO-d_6):** 8.25 (s, 1H, NH), 7.5-8.1 (m, 4H, Ar-H), 7.5 (s, 1H, NH), 5.14 (s, 1H), 3.75 (s, 3H, OCH_3), 2.28 (s, 3H, CH_3); **Mass (ES/MS):** 290.01 (m+1).

Methyl 6-methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4k)
IR (KBR cm^{-1}): 3300 (N-H), 1260 (C-N), 3010 (=CH), 1730 (C=O), 1630 (C=O) cm^{-1}; **^{1}H-NMR (DMSO-d_6):** 9.15 (s, 1H, NH), 7.4-8.1 (m, 4H, Ar-H), 7.5 (s, 1H, NH), 5.14 (s, 1H), 3.77 (s, 3H, OCH_3), 2.28 (s, 3H, CH_3); **Mass (ES/MS):** 290 (m+1).

Methyl 4-(2-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4l)
IR (KBR cm^{-1}): 3500 (N-H), 1270 (C-N), 3090 (=CH), 1700 (C=O), 1650 (C=O), 750 (C-Cl) cm^{-1}; **^{1}H-NMR (DMSO-d_6):** 6 (s, 1H, NH), 7.19-7.62 (m, 4H, Ar-H), 7.2 (s, 1H, NH), 5.12 (s, 1H), 3.70 (s, 3H, OCH_3), 2.29 (s, 3H, CH_3); **Mass (ES/MS):** 279.62 (m+1).

Methyl 4-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4m)
IR (KBR cm^{-1}): 3045 (N-H), 1270 (C-N), 3100 (=CH), 1730 (C=O), 1630 (C=O), 620 (C-Cl) cm^{-1}; **^{1}H-NMR (DMSO-d_6):** 7.5 (s, 1H, NH), 7.32-7.36 (m, 4H, Ar-H), 6 (s, 1H, NH), 5.13 (s, 1H), 3.75 (s, 3H, OCH_3), 2.25 (s, 3H, CH_3); **Mass (ES/MS):** 279.9 (m+1).

Ethyl 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4n)
IR (KBR cm^{-1}): 3500 (N-H), 3086 (=CH), 1310 (C-N), 1710 (C=O), 1678 (C=O) cm^{-1}; **^{1}H-NMR (DMSO-d_6):** 12.25 (s, 1H, NH), 7.20-7.32 (m, 5H, Ar-H), 6.9 (s, 1H, NH), 5.1 (s, 1H), 4.1 (2H, OCH_2), 2.20 (3H, CH_3), 1.25 (3H, CH_3); **Mass (ES/MS):** m/z 277 (m+1).

Methyl 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4o)
IR (KBR cm^{-1}): 3440 (N-H), 3010 (=CH), 1260 (C-N), 1730 (C=O), 1635 (C=O) cm^{-1}; **^{1}H-NMR (DMSO-d_6):**13.1 (s, 1H, NH), 7.2-7.32 (m, 5H, Ar-H), 5.8 (s, 1H, NH), 5.2 (s, 1H), 3.70 (s, 3H, OCH_3), 2.2 (s, 3H, CH_3); **Mass (ES/MS):** 263 (m+1).

Methyl 6-methyl-4-(3-nitrophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4p)
IR (KBR cm^{-1}): 3420 (N-H), 3045 (=CH), 1305 (C-N), 1710 (C=O), 1650 (C=O) cm^{-1}; **^{1}H-NMR (DMSO-d_6):**12.75 (s, 1H, NH), 7.4-8.01 (m, 4H, Ar-H), 6 (s, 1H, NH), 5.3 (s, 1H), 3.75 (s, 3H, OCH_3), 2.24 (s, 3H, CH_3); **Mass (ES/MS):** 309.01 (m-1).

Methyl 4-(4-hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4q)
IR (KBR cm^{-1}): 3360 (N-H), 3300 (OH), 3010 (=CH), 1250 (C-N), 1700 (C=O), 1678 (C=O) cm^{-1}; **^{1}H-NMR (DMSO-d_6):**13.5 (s, 1H, NH), 5.2-7.4 (m, 5H, Ar-H), 5.9 (s, 1H, NH), 5.1 (s, 1H), 3.70 (s, 3H, OCH_3), 2.28 (s, 3H, CH_3); **Mass (ES/MS):** 277.3 (m+1).

Ethyl-6-methyl-2-oxo-4-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4r)
IR (KBR cm^{-1}): 3500 (N-H), 3100 (=CH), 1350 (C-N), 1705 (C=O), 1650 (C=O) cm^{-1}; **^{1}H-NMR (DMSO-d_6):**6 (s, 1H, NH), 7.1-7.5 (m, 4H, Ar-H), 5.9 (s, 1H, NH), 5.15 (s, 1H), 4.2 (s, 3H, OCH_3), 1.27 (s, 3H, CH_3), 2.24 (S, 3H, CH_3); **Mass (ES/MS):** 228.1 (m+1).

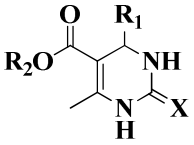
RESULTS AND DISCUSSION

Synthesis of the dihydropyrimidine analogous has been performed initially by using benzaldehyde, ethyl acetoacetate, urea & 20%, 10%, 5% (entry 5-7, Table I) mole of maleic acid. Synthesis of the same analogue (4a) was checked with different solvents (Table I). Among the results obtained, use of 10 % mol maleic acid in ethanol: water gave better yield (90%) **(**Table I**).** To study this aspect, the reaction was carried out for a synthesis of (4a) using 10 mol% maleic acid and corresponding substrates in water. The reaction was found to be sluggish and it may be due to the less solubility of substrates. To avoid this problem, the ethanol-water (2:1, v/v) was used as solvent and found to be effective for synthesis of 4a i.e (95%, in 100minutes). The methodology was extended for synthesis of series of DHPMs using different aliphatic, aromatic and heterocyclic aldehydes and results are summarized in Table II. Better yields were obtained for synthesis of all the DHPM derivatives. All synthesized derivatives were characterized using mass and ^{1}H NMR. The present method was found to be effective for both electron-donating and electron-withdrawing substituted aromatic aldehydes and as well as aliphatic aldehydes. Using the similar reaction conditions, the thione analogues of DHPMs were also synthesized from thiourea, β-dicarbonyl compound and aromatic or aliphatic aldehydes. The easy work-up of the reaction was also the advantageous aspect of this method. It includes the quenching the reaction mass in 5% sodium carbonate ice-water with stirring to precipitate the solid, which was collected by filtration to give the corresponding DHPM with better yield and quality. We specially want to note that, no further purification was required as well as no side product was observed.

Table I: Optimization of reaction conditions and quantity of maleic acid for the synthesis of *Ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4a)*

Entry	Solvent	Mol % of maleic acid	Reaction time (min)	Yield (%)
1	THF	10	150	81
2	Acetonitrile	10	120	84
3	Ethanol	10	120	85
4	Ethanol: Water (2:1)	10	100	90
5	THF: Water (1:2)	20	120	80
6	THF: Water (1:2)	10	120	82
7	THF: Water (1:5)	05	120	84

Table II: Physical data of 3,4-dihydropyrimidin-2-(1H)-Ones and Analogues



Entry	R_1	R_2	X	Time (min)	(%)Yield
4a	C_6H_5	C_2H_5	O	100	95
4b	4-ClC_6H_4	C_2H_5	O	100	90
4c	4-OHC_6H_4	C_2H_5	O	105	91
4d	$CH_3CH_2CH_2CH_2$-	C_2H_5	O	115	78
4e	3-$NO_2C_6H_4$	C_2H_5	O	120	92
4f	4-Pyridine	C_2H_5	O	100	84
4g	2-ClC_6H_4	C_2H_5	O	110	87
4h	2-furyl	C_2H_5	O	115	89
4i	C_6H_5	CH_3	O	90	92
4j	4-$NO_2C_6H_4$	CH_3	O	85	88
4k	3-$NO_2C_6H_4$	CH_3	O	100	90
4l	2-ClC_6H_4	CH_3	O	90	84
4m	4-ClC_6H_4	CH_3	O	100	93
4n	C_6H_5	C_2H_5	S	100	94
4o	C_6H_5	CH_3	S	100	88
4p	3-$NO_2C_6H_4$	CH_3	S	95	90
4q	4-OHC_6H_4	CH_3	S	100	93
4r	4-$CF_3C_6H_4$	C_2H_5	O	95	92

CONCLUSION

In summary, we have disclosed a new and simple modification of the Biginelli dihydropyrimidine synthesis. DHPMs and their thione derivatives were efficiently synthesized with better yields using 10-mol% Maleic acid. For all the presented reactions, the ethanol-water solvent was used which is relatively environmentally benign and supporting to Green Chemistry. Use of cheap non-hazardous catalyst with easy work-up, and better yields are the perspective advantages of this reported method. Hence the use of maleic acid as a catalyst, for synthesis DHPMs and their thione derivatives is a precious addition to the available methods.

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