Oxalic Acid as a versatile catalyst for one pot facile synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones and their thione Analogues

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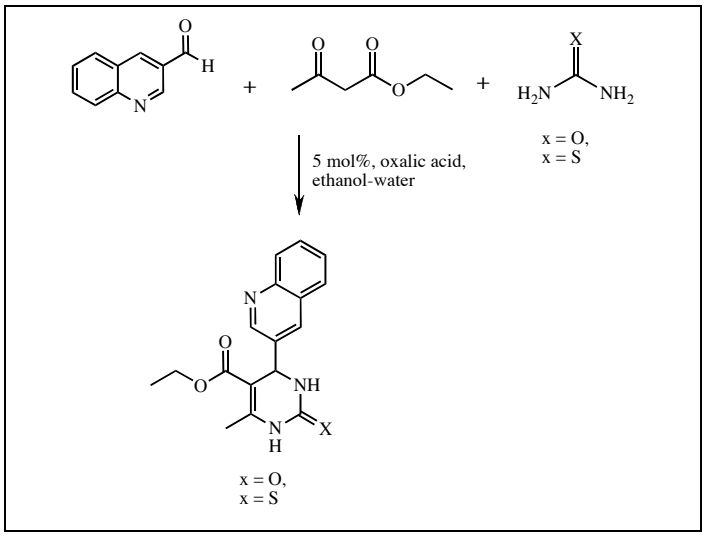

3,4-Dihydropyrimidin-2-(*1*H)-ones and their thione analogues are synthesized from the condensation of aromatic aldehydes, β-dicarbonyl compound and urea or thiourea in presence of 5 mol% of oxalic acid in ethanol-water (1:2 ; v/v) under mild reaction conditions. The yields obtained are better and also the use of very inexpensive catalyst, environmentally benign solvent and easy work-up are the advantageous aspects of the present method.

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INTRODUCTION

The interest of dihydropyrimidones (DHPMs) and their derivatives stem from their widespread activities like calcium channel blockers, α-1a-antagonists and neuropeptide-Y (NPY) antagonists [1]. Recently, some alkaloids are reported containing dihydropyrimidones, which are potent HIV gp 120-CD_4 inhibitors [2]. DHPMs and their sulphur analogues are pharmacologically important because of their antibacterial, antitumour and anti-inflammatory properties [3]. The literature reveals a number of methods for the synthesis of DHPMs and their derivatives. Biginelli [4] reported the first synthesis of dihydropyrimidines by a simple one-pot condensation reaction of ethyl acetoacetate, benzaldehyde and urea. Later, different modifications are reported for the synthesis of array of substituted DHPMs. The use of different Lewis acid has 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 also reported [6]. We have recently reported sulphamic acid as a catalyst for preparing DHPMs [7]. However, most of these methods are associated with expensive and toxic reagents or catalysts, unsatisfactory yields, incompatibility with other functional groups and involve tedious work-up. Some of methods are applicable for aromatic aldehydes only [8]. Thus, there is still need of a simple and general procedure for one-pot synthesis of DHPMs and their thione analogues under mild conditions. In continuation with our research for the development of simple and novel methods for synthesis of different heterocycles [9], we have developed a convenient method for the synthesis of DHPMs and their thione analogues using 5 mol% oxalic acid as a catalyst in ethanol-water.

Oxalic acid is the only possible compound in which two carboxylic groups are joined directly; and hence supposed to be one of the strongest organic acid. The use of oxalic acid as a catalyst was reported for the de-protection of ketal to give the corresponding aldehydes or ketones [10]. It was also used for isomerization of Δ^5-cholesten-3-one to Δ^4-cholesten-3-one [11] and oxalic acid is also used for the dealumination of zeolite [12]. To our knowledge, further use of the strong acidic property of oxalic acid is not explored. We have used oxalic acid (5 mol%) as a catalyst for synthesis of array of substituted DHPMs and

their thione analogues in ethanol-water under mild conditions.

RESULTS AND DISCUSSION

Firstly, we studied the catalytic property of oxalic acid for the synthesis of ethyl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyridimidine-5-carboxylate (**4a**) using benzaldehyde, urea, ethyl acetoacetate substrates in various solvents like THF, acetonitrile, ethanol, benzene. Among the results obtained, use of 5 mol% oxalic acid in ethanol-water gave the better yield (98%) for the synthesis of **4a** (Table 1)**.** The use of environmental benign solvent such as water has received very much attention in 'Green Chemistry'. To study this aspect, the reaction was carried out for synthesis of **4a** using 5 mol% oxalic acid and corresponding substrates in water. The reaction was found to be sluggish and it may be due to lower solubility of substrates. To avoid this problem, the ethanol-water (1:2; v/v) solvent was used and found to be effective for synthesis of **4a** (98% in 45 min). The methodology was extended for synthesis of array of DHPMs using different aliphatic, aromatic and heterocyclic aldehydes and results are summarized in Table 2. Better yields were obtained for the 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 as well as aliphatic aldehydes. Using 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 an advantageous aspect of this method. It includes pouring the reaction mass in ice-water to precipitate the solid, which could be collected by filtration to give the corresponding DHPM with better yield.

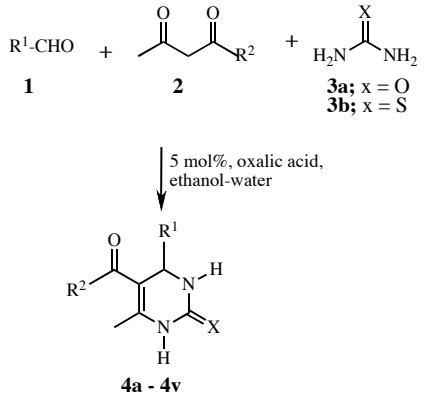
Table 1

Optimization of reaction conditions and the quantity of oxalic acid for the synthesis of ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyridimidine-5 carboxylate (**4a**).

Solvent	Mol % of oxalic acid	Reaction time (min)	Yield* (%)
THF	20	60	85
Acetonitrile	20	90	85
Ethanol	20	30	90
THF-water (1:1)	20	70	85
Acetonitrile-water (1:1)	20	70	92
Ethanol-water (1:2)	20	45	98
Ethanol-water (1:2)	15	45	98
Ethanol-water (1:2)	10	45	98
Ethanol-water (1:2)	5	45	98
Ethanol-water (1:2)	2.5	80	90

* Yields refer to isolated pure products.

Scheme 1



Although, the detailed mechanism of this reaction is not clear, probably as proposed for Lewis acid, the reaction involves the *in situ* formation of acylimine intermediate by the reaction of urea or thiourea and aldehyde, which undergoes the subsequent addition to the β-carbonyl compounds followed by cyclization and dehydration to yield corresponding DHPM [13].

In conclusion, DHPMs and their thione derivatives were efficiently synthesized with better yields using 5 mol% oxalic acid. For all the presented reactions, the ethanol-water solvent was used which is relatively environmentally benign and supporting to Green Chemistry. The advantages of the reported method are the use of cheap catalyst, easy work-up, and better yields. Hence the utility of oxalic acid catalyst for synthesis DHPMs and their thione derivatives would be precious addition to available methods.

EXPERIMENTAL

Typical experimental procedure for the synthesis of Ethyl 6-Methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyridimidine-5-carboxylate (4a). A mixture of ethyl acetoacetate (1.3 g m, 10 mmol), benzaldehyde (1.1 gm, 10 mmol), urea (0.72 gm, 12

Table 2

Oxalic Acid-catalyzed synthesis of DHPM and thione derivatives at 70°C.

Entry	R^1	R^2	X	Time (min)	Yield (%)	M.P. (°C) Found	Reported [ref.]
4a	C_6H_5	C_2H_5O	O	45	98	200-201	200-202 [14]
4b	4-$NO_2C_6H_4$	C_2H_5O	O	30	95	204-206	205-207 [14]
4c	4-ClC_6H_4	C_2H_5O	O	30	95	211-213	210-212 [5a]
4d	4-OHC_6H_4	C_2H_5O	O	40	95	230	228 [14]
4e	$CH_3CH_2CH_2CH_2$	C_2H_5O	O	40	89	159-161	157-158 [5a]
4f	3-$NO_2C_6H_4$	C_2H_5O	O	40	93	227-229	225-227 [5a]
4g	2-ClC_6H_4	C_2H_5O	O	45	90	218-220	216-218 [14]
4h	2- furyl	C_2H_5O	O	40	89	203-205	203-205 [5a]
4i	C_6H_5	CH_3O	O	40	95	212-214	209-216 [14]
4j	4-$NO_2C_6H_4$	CH_3O	O	45	90	238-240	235-237 [14]
4k	3-$NO_2C_6H_4$	CH_3O	O	40	90	239-240(d)	240-241(d) [14]
4l	2-ClC_6H_4	CH_3O	O	45	88	225-227	226-229 [16]
4m	4-ClC_6H_4	CH_3	O	30	88	232-235	233-235 [16]
4n	4-OHC_6H_4	CH_3	O	40	90	231-233	230 [16]
4o	3-$NO_2C_6H_4$	CH_3	O	35	90	267-268(d)	267-269 [5c]
4p	C_6H_5	C_2H_5O	S	45	95	210-212	208-210 16]
4q	3-$NO_2C_6H_4$	CH_3	S	40	93	210-212	208-210 [16]
4r	4-OHC_6H_4	CH_3	S	40	93	210-212	208-210 [16]
4s	C_6H_5	C_2H_5O	S	45	95	210-212	208-210 [16]
4t	Quinoline 3-carbaldehyde	C_2H_5O	O	40	93	209-211	-
4u	Quinoline 3-carbaldehyde	C_2H_5O	S	40	89	231-233	-
4v	CH_3	C_2H_5O	O	06	85	189-191	194-195 [5c]

* Yields refer to isolated pure products.

mmol) and oxalic acid (46 mg, 0.5 mmol) in water-ethanol (9 ml, 2:1; v/v) was heated at 70 °C till completion of reaction [TLC, ethyl acetate - hexane (8:2; v/v)]. Then, the reaction mixture was poured in ice water and the precipitated solid was collected by filtration, washed with water and dried. The crude product was recrystallized from ethanol to give the corresponding pure product 4a. White solid, mp 200 - 201 °C; ^{1}H NMR (DMSO-d_6): δ=9.18(s, 1H), 7.74(s, 1H,), 7.22(m, 5H), 5.14 (d, J = 3.6 Hz, 1H), 3.4(q, J=6.9 Hz, 2H), 2.24(s, 3H), 1.09 (t, J=6.9 Hz, 3H); mass (ES/MS): m/z 260 (M - H).

Ethyl-6-methyl-2-oxo-4-(quinolin-3-yl)-1,2,3,4-tetrahydro-pyrimidine-5-carboxylate(4t). White solid, mp 209 - 211 °C; ^{1}H NMR (DMSO-d_6): δ = 8.8(s, 1H), 8.1(d, 1H), 7.8(s, 1H), 7.5-7.6(m, 2H), 7.42 (t, 1H), 5.8 (bs, 2H), 5.32(s, 1H), 4.1(q, 2H), 1.71(s, 3H), 1.3 (t, 3H); mass (ES/MS): m/z 310(M - H); anal. Cald for $C_{17}H_{17}N_3O_3$: C, 65.58; H, 5.50; N, 13.50. Found: C, 65.61; H, 5.48; N, 13.52.

Ethyl-6-methyl-4-(quinolin-3-yl)-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylate (4u). White solid, mp 231 – 233 °C; ^{1}H NMR (DMSO-d_6): δ = 8.8(s, 1H), 8.1(d, 1H), 7.8(s, 1H), 7.5-7.6(m, 2H), 7.42 (t, 1H), 5.2(bs, 2H), 4.71(s, 1H), 4.1(q, 2H), 1.70(s, 3H), 1.3 (t, 3H); mass (ES/MS): m/z 326(M - H); anal. Cald for $C_{17}H_{17}N_3O_2S$: C, 62.36; H, 5.23; N, 12.83. Found: C, 62.41; H, 5.24; N, 12.81.

Using similar procedure other DHPMs and their thione derivatives were synthesized [Table 2]. All the synthesized compounds were characterized using mass, and ^{1}H NMR. Also the melting points of synthesized compounds were compared with the corresponding reported melting points in literature [9d,5a,14,15].

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