A NEW KEY FOR OLD LOCK: GLYCEROL, AS AN OH-ACID, CATALYZED ONE-POT THREE-COMPONENT AND FULLY GREEN SYNTHESIS OF 3,4-DIHYDROPYRIMIDIN-2(1*H*)-ONE AND -THIONES

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Keywords: Organic OH-acid**,** reusable catalyst, glycerol, dihydropyrimidin-2(1*H*)thione, dihydropyrimidin-2(1*H*)one.

Synthesis of 3,4-dihydropyrimidin-2(1*H*)-one and 3,4-dihydropyrimidin-2(1*H*)-thione derivatives from aldehydes, ethyl acetoacetate and urea or thiourea using glycerol as an organo OH-acid, green and reusable catalyst is reported. The practical and simple protocol led to excellent yields of the dihydropyrimidin-2(1H)-one and thiones under mild reaction conditions and within short span of reaction times with easy reaction workup by maintaining excellent atom economy.

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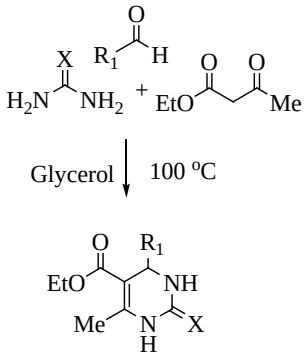
INTRODUCTION

Aryl-3,4-dihydropyrimidines derivatives (DHPMs) have received great attention because of their wide range of therapeutic and pharmacological properties, such as antiviral,[7] antitumor, antibacterial and antifungal,[8] anti-inflammatory,[9] antihypertensive agents, and neuropeptide Y (NPY) antagonists.[10] Furthermore, these compounds have emerged as the integral backbones of several calcium-channel blockers.[11] Also, several alkaloids containing the dihydropyrimidine were isolated from marine sources, for example, of these are the batzelladine alkaloids, which are found to be potent HIVgp-120-CD4 inhibitors.[12,13] After the classic Biginelli approach to 3,4-dihydropyrimidinones, the development of multistep synthetic strategies that produce relatively higher yields was demand. So, various protocols for synthesis of 3,4-dihydropyrimidines were explored by varying components and catalysts.[14]



R_1 = 3-(NO_2)-C_6H_4, 2-(OH)-C_6H_4, 4-$N(Me)_2$-C_6H_4, Ph-CH=CH, C_4H_4O; X= O, S

Scheme 1. Preparation of DHPMs in glycerol as a solvent.

In this communication, we report glycerol as an organic OH-acid, green and reusable catalyst for the synthesis of DHPMs via a one-pot three component condensation of aldehydes, ethyl acetoacetate, urea and thiourea at 100 °C (Scheme 1).

EXPERIMENTAL

Melting points were measured by using the capillary tube method with an electro thermal 9200 apparatus. IR spectra were recorded on a Perkin Elmer FT-IR spectrometer between 4000-400 cm^{-1}. ^{1}HNMR spectra were obtained on Bruker DRX- 300 MHZ NMR instrument. Analytical TLC of all reactions was performed on Merck precoated plates (silica gel 60 F-254 on aluminium). Elemental analyses of the new products were done using a Vario EL III apparatus. Their results are in good agreement with the calculated values.

General procedure for the synthesis of arylidene pyrimidinones using glycerol

A mixture of the 2.0 mmol aldehyde, 2.0 mmol, 0.26 g ethyl acetoacetate (2.0 mmol), 5.0 mmol, 0.072 g or 0.0913 g urea or thiourea and 1 cm^3 glycerol was heated in an oil bath at 100 °C for the specified times. The reaction was monitered by TLC (ethyl acetate/n-hexane, 1:2). After completion of the reaction, crushed ice was added and stirred for 10 min. The product was collected by filtration, washed with water and then crystallized from methanol to afford the pure product.

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

IR [KBr] υ(cm^{-1}): 3331, 3101, 2966, 1710, 1689, 1631, 1525, 1456, 1347, 1317, 1266, 1225, 1088, 901, 808, 794, 739, 685. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.11 (t, J = 7.5 Hz, 3H), 2.26 (s, 3H), 4.01 (q, J = 7.5 Hz, 2H), 5.28 (d, J = 3.0 Hz, 1H), 7.61-7.70 (m, 2H), 7.87 (s, 1H, NH), 8.07-8.13 (m, 2H), 9.34 (s, 1H, NH).

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

IR [KBr] υ(cm^{-1}): 3246, 3116, 2926, 1721, 1702, 1650, 1527, 1457, 1366, 1289, 1222, 1169, 1093, 785. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.12 (t, J = 7.5 Hz, 3H, CH_3), 2.21(s, 3H, CH_3), 2.83 (s, 6H, $N(CH_3)_2$), 4.0 (q, J = 7.5 Hz, 2H, -OCH_2), 5.02 (s, 1H, CH), 6.65 (d, J = 9.1 Hz, 2H, arom), 7.03 (d, J = 9.1 Hz, 2H, arom), 7.55 (s, 1H, NH), 9.0 (s, 1H, NH).

Ethyl 4-(furan-2-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

IR [KBr] υ(cm^{-1}): 3347, 2982, 1698, 1650, 1489, 1370, 1332, 1302, 1263, 1211, 1122, 1096, 1050, 1022, 806, 750, 730. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.2 (t, J = 7.0 Hz, 3H), 3.6 (s, 3H), 3.8 (q, J = 7.0 Hz, 2H), 6.1 (d, J = 3.0 Hz, 2H), 6.3 (q, J = 2 Hz, 1H), 7.6 (s, 1H), 7.8 (s, 1H, NH), 9.3 (s, 1H, NH).

Ethyl (E)-6-methyl-2-oxo-4-styryl-1,2,3,4-tetrahydropyrimidine-5-carboxylate

IR [KBr] υ(cm^{-1}): 3244, 3113, 2977, 1723, 1652, 1451, 1286, 1228, 1095, 967, 778, 692. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.21 (t, J = 7.0 Hz, 3H), 2.34 (s, 3H), 4.11 (q, J = 7.05 Hz, 2H), 4.73 (d, J = 4.80 Hz, 1H), 6.21 (d, J = 6.0 Hz, 1H), 6.37 (d, J = 15.9 Hz, 1H), 7.19-7.40 (m, 5H), 7.52 (s, 1H, NH), 9.11 (s, 1H, NH).

Ethyl 4-(2-hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

IR [KBr] υ(cm^{-1}): 3364, 3166, 3084, 2948, 1727, 1610, 1589, 1564, 1491, 1475, 1371, 1323, 1223, 1187, 1152. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.04 (t, J = 7.2 Hz, 3H), 2.15 (s, 3H), 4.10 (d, 1H), 4.22 (q, J = 7.2 Hz, 2H), 4.22 (s, 1H), 6.81-7.21 (m, 4H), 8.46 (s, 1H, NH), 9.57 (s, 1H, NH).

Ethyl 4-(4-(dimethylamino)phenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

IR [KBr] υ(cm^{-1}): 3296, 3177, 2989, 1662, 1575, 1523, 1458, 1370, 1332, 1287, 1180, 1113, 943, 814, 771, 572. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.11 (t, J = 7.0 Hz, 3H), 2.28 (s, 3H), 2.85 (s, 6H), 3.97 (q, J = 7.0 Hz, 2H), 5.04 (d, J = 3.2 Hz, 1H), 6.66 (d, J = 8.5 Hz, 2H), 7.01 (d, J = 8.5 Hz, 2H), 9.55 (s, 1H, NH), 10.24 (s, 1H, NH).

Ethyl 6-methyl-4-(3-nitrophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

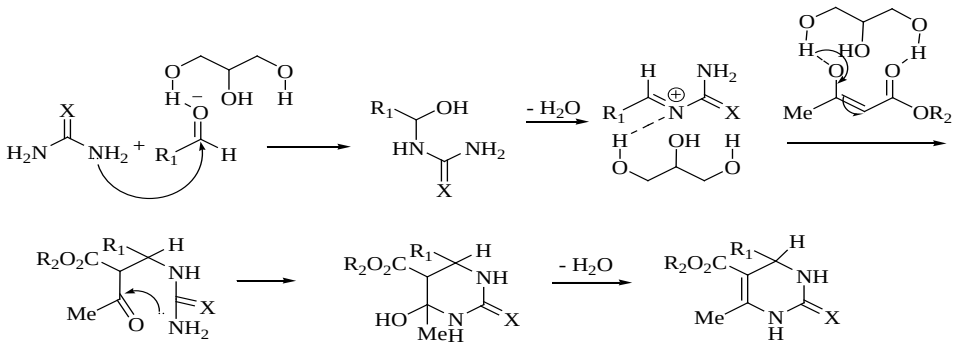
IR [KBr] υ(cm^{-1}): 3087, 2987, 1729, 1661, 1628, 1528, 1400, 1351, 1299, 1209, 1103, 1045, 1019, 812, 734, 678. ^{1}H NMR (250 MHz, DMSO-d_6) δ: 1.13 (t, J = 7.1 Hz, 3H), 2.34 (s, 3H), 4.05 (q, J = 7.1Hz, 2H), 5.36 (d, J = 3.6 Hz, 1H), 7.70-7.72 (m, 2H), 8.10-8.11 (m, 1H), 8.17-8.20 (m, 1H), 9.81 (s, 1H, NH), 10.55 (s, 1H, NH).

RESULTS AND DISCUSSION

On basis of our previous investigation that synthesis of dihydropyrimidinones need to temperature and acidic condition as mention in introduction section. Thus the authors decided to set up a model reaction to achieve a fully green procedure for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-one and -thione derivatives in the presence of glycerol as green solvent and organic OH-acid catalyst.

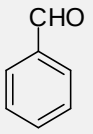
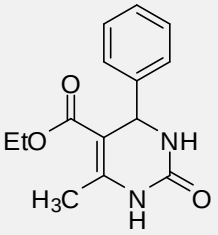
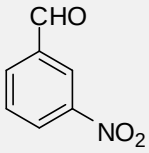
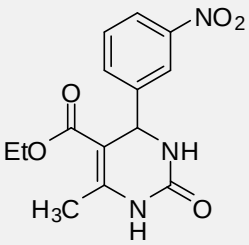
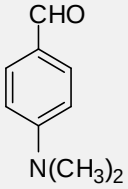
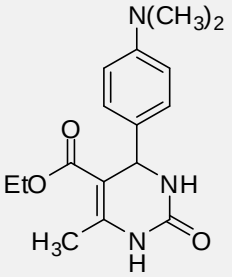
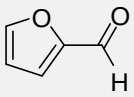
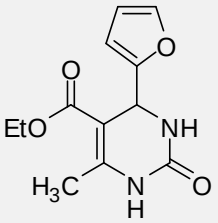
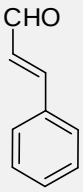
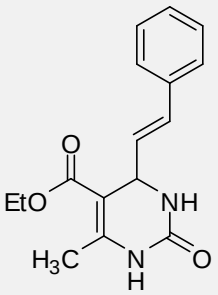
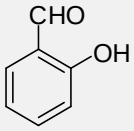
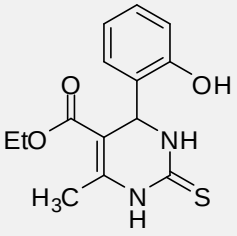
Then the synthesis of compound 5-(ethoxycarbonyl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-ones(Table 1) was selected as a model reaction to determine suitable reaction conditions. The reaction was carried out by employing benzaldehyde (2.0 mmol), ethyl acetoacetate (2.0 mmol),urea (5.0 mmol) and different amount of glycerol (5.0, 4.0, 3.0 and 1.0 ml) at 100 °C. Found that increasing amount of glycerol does not effect to yield and rection time, therefore, we selected 1.0 ml of glycerol as green organic OH-acid catalyst for this reaction. To generalize of this method the reaction of ethyl acetoacetate with different kinds of aromatic aldehydes and urea/thiourea using glycerol as catalyst at 100 °C was examined.

Several aromatic aldehydes (Table 1) carrying either electron releasing or electron withdrawing sustituents in the ortho, meta and para positions afforded high yields of the products. An important feature of this procedure is the survival of variety of functional groups such as ether, nitro groups, and halides under the reaction conditions. Thiourea also reacts under similar conditions to give their corresponding 3, 4-dihydropyrimido-2(1H)thiones. The proposed mechanism for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-one and thione derivatives in the glycerol media has been shown in Scheme 2.



Scheme 2. Suggested mechanism for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-one/thiones.

Table 1. Synthesis of 3,4-dihydropyrimidin-2(1*H*)-one and thion derivatives in the presence of glycerol.

Entry	Aldehyde	X	Product	Time, h	Yield, %	M. P. °C Found; Reported[ref]
1		O		2.0	85	202-203 203-204[15]
2		O		1.0	80	224-227 225-227[15]
3		O		3.5	70	254-257 257-259[15]
4		O		3.0	65	203-205 206-208[16]
5		O		1.0	68	237-240 240-242[16]
6		S		1.0	35	237-239 240-241[17]

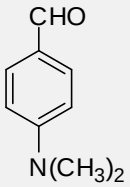
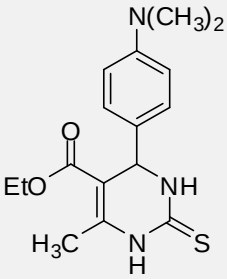
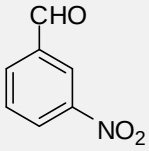
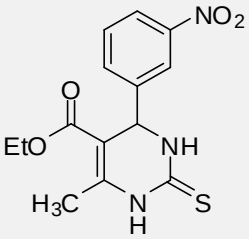
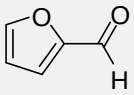
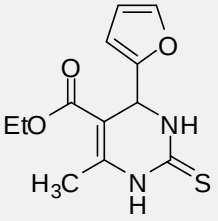
7		S		2.0	60	204-207 206-208[15]
8		S		2.0	65	203-205 206-209[15]
9		S		1.5	30	180-182 185[16]

Table 2. Comparison of efficiency of various catalysts in synthesis of ethyl 6-methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate.

	Entry	Catalyst	Mol % / g mL^{-1}	Temp., ° C	Time, h	Yield, %	Ref.
	1	Cl_3CCOOH	20 %	70	0.33	93	[18]
	2	$Al(NO_3)_3.9H_2O$	15 %	Reflux	9.0	70	[21]
	3	Na_2SeO_4	0.05 g	80	1.5	70	[20]
	4	[Btto][*p*-TSA]	5.0 %	90	0.5	92	[21]
	5	Al_2O_3/CH_3SO_3H	0.1 g	60	0.58	92	[22]
	6	*p*-$NH_2C_6H_4SO_3H$	0.01 g	100	0.83	90	[23]
	7	Silica triflate	0.03 g	90	0.08	85	[24]
	8	SiO_2-NPs	5.0 %	80	0.66	78	[25]
	9	$HClO_4$-SiO_2	0.50 g	110	0.36	92	[26]
	10	$Co(NO_3)_2.6H_2O$	15 %	80	0.23	93	[27]
	11	$Ce(NO_3)_3.6H_2O$	5.0 %	80	0.41	89	[28]
	12	SiO_2-Cl	2.5 %	80	3.0	91	[29]
	13	Glycerol	1.0 mL	100	1.0	80	This work

In order to show the merit of the present work, we compared the results of the synthesis of ethyl 6-methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (Entry 1 in Table l) with some previously reported catalysts. The yield of product in the presence of glycerol is comparable to the reported catalysts. However, reaction in the presence of these catalysts required less catalyst than this work (Table 2).

CONCLUSION

In continuation of our earlier work, carried to develop convenient synthetic protocols for the synthesis of bioactive heterocycles[30-32] by employing green tools and considering the above urgent need to provide convenient rapid route for the DHPMs, here we report for the first time the Biginelli reaction by subjecting substituted quinoline methoxy benzaldehydes, ethyl acetoacetate, urea and thiourea in glycerol medium and catalyst for obtaining new DHPMs.

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