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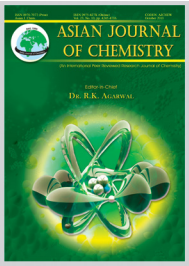

One-Pot Synthesis of 3,4-Dihydropyrimidin-2-(1*H*)-ones Using Nickel Chloride as a Catalyst

UTTAM B. MORE

Post-Graduate and Research Center, Department of Chemistry R.B. Narayanrao Borawake College, Shrirampur-413 709, India

*Corresponding author: E-mail: uttambmore@rediffmail.com

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An efficient one pot synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones from an aldehyde, β-ketoester and urea/thiourea, using nickel chloride pentahydrate is described. The protocol is described using three different sets of reaction conditions. The method provides much improved modification of original Biginelli reaction, in terms of high yield, short reaction time and simple workup procedure.

Key Words: Biginelli reaction, Nickel chloride pentahydrate, One-pot synthesis, Grinding.

INTRODUCTION

Biginelli reaction was first reported more than a century ago[1] and involves the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones (DHPMs) by a simple one-pot condensation reaction of ethyl acetoacetate, benzaldehyde and urea in ethanol. However, this one pot, one step protocol often provides only low or moderate yields of the desired target molecules. In past decade, dihydropyrimidin-2-(1*H*)-one derivatives have exhibited important pharmacological properties *e.g.* as the integral backbone of several calcium channel blocks, antihypertensive agents, α-1a-antagonists and neuropeptide Y(NPY) antagonists[2]. Therefore the discovery of milder and practical routes for synthesis of dihydropyrimidin-2-(1*H*)-ones by the Biginelli reaction continues to attract the attention of researchers. Several improved procedure for the preparation of 3,4-dihydropyrimidin-2-(1*H*)-ones (Biginelli compounds) have recently been reported, either by modification of the classical one-pot Biginelli approach itself[3,4] or by development of novel, but more complex multistep strategy[5]. In addition several combinatorial approaches towards 3,4-dihydropyrimidin-2-(1*H*)-ones have been advanced using solid-phase or fluorous phase reaction conditions[6]. Furthermore, several marine alkaloids with interesting biological activities containing the dihydropyrimidin-5-carboxylate core unit have recently been isolated[7]. Most notably among these are the batzelladine alkaloids, which were found to be potent HIV gp-120-CD4 inhibitors[8]. The recently reported BF_3-OEt_2 or polyphosphate ester mediated Biginelli reaction[9] requires long reaction time to achieve moderate to high yields of the products. More recently, the 3,4-dihydropyrimidin-2-ones has been synthesized by using lanthanum chloride[10], manganese acetate[11], cerium chloride[12], cuprous chloride[13], zinc tetrafluoroborate[14], *p*-TsOH[15] and Al_2O_3/Me_2SO_3H[16]. Many other methods involving microwave irradiation, ionic liquids, clay, solvent free and catalyst-free procedures are also reported[17]. These compounds have also been synthesized using *tetra*-butyl ammonium bromide (TBAB) as a phase-transfer catalyst[18]. However many of these methods are associated with harsh reaction conditions, expensive and toxic reagents, tedious work-up, stoichiometric amount of catalyst, long reaction times, unsatisfactory yields, incompatibility with other functional groups *etc*. Here we wish to report one-pot synthesis of 3,4 dihydropyrimidin-2-(1*H*) ones using $NiCl_2.5H_2O$ as a catalyst, which is cheap, commercial and readily available reagent. We have carried out the synthesis of 3,4 dihydropyrimidin-2-(1*H*)-ones in solvents, namely ethanol and water under reflux condition. We have also carried out the same reactions under solvent free conditions (grinding). For studying the generality of these processes, different examples illustrating different methods for the synthesis of dihydropyrimidin-2-(1*H*)-ones were studied and are summarized in Table-1. A variety of substituted aromatic aldehydes carrying either electron donating or withdrawing substituents afforded high yields of product in high purity. Thiourea has been used with similar success to yield the corresponding dihydropyrimidinethiones, which are also of much interest with regard to biological activity[19].

EXPERIMENTAL

All chemicals were of analytical grade. Solvents and aldehydes were distilled before use. Melting points and boiling points were determined by open capillary method and are uncorrected.

TABLE-1
$NiCl_2.5H_2O$ CATALYZED SYNTHESIS OF DIHYDROPYRIMIDIN-2-(*1H*)-ONES

Entry	Aldehyde	Z	Yield (%)			m.p. (^{0}C)	
			Ethanol reflux	Water reflux	Solvent free (grinding)	Found	Reported
a	Ph-CHO	O	93	76	93	203-204	202-203[11]
b	2-(OH)-C_6H_4	O	83	72	90	198-199	199-200[14]
c	4-(OH)-C_6H_4	O	86	75	88	228-229	227-228[11]
d	4-(OCH_3)-C_6H_4	O	92	86	94	202-203	203-204[16]
e	3-(OH)4-(OCH_3)-C_6H_3	O	83	73	89	98-99	98-100[11]
f	4-(CH_3)-C_6H_4	O	79	75	91	168-169	169-171[16]
g	4-(Cl)-C_6H_4	O	90	76	88	210-211	212-213[11]
h	4-(NO_2)-C_6H_4	O	84	73	86	208-209	209-210[13]
i	2,4-(OCH_3)$_2$-C_6H_3	O	75	78	85	159-160	158-160[11]
j	3,4-(OCH_3)$_2$-C_6H_3	O	82	80	87	176-177	177[11]
k	2-(NO_2)-C_6H_4	O	84	79	81	206-207	206-208[11]
l	Ph-CHO	S	51	-	88	208-209	208-210[16]
m	4-(Cl)-C_6H_4	S	-	-	65	192-193	192-194[13]
n	4-(NO_2)-C_6H_4	S	-	-	71	108-109	109-111[13]
o	3-(OH)-C_6H_4	S	-	-	85	183-184	183-184[16]
p	3-(NO_2)-C_6H_4	S	-	-	82	206-207	206-208[16]

General procedure for synthesis of 3, 4 dihydropyrimidin-2(1*H*)-ones

Method I (reflux method): A mixture of ethyl acetoacetate (10 mmol), an aromatic aldehyde (10 mmol) and urea/thiourea (20 mmol) and 5-6 drops of conc. HCl in ethanol (5 mL) or water (15 mL) was heated under reflux in the presences of $NiCl_2.5H_2O$ (1.4 mmol) for 2 to 3 h (monitored by TLC, hexane:ethyl acetate, 9:1). The reaction mixture after being cooled to room temperature was poured onto crushed ice and stirred for 5-10 min. The solid separated was filtered under suction, washed with ice-cold water (50 mL) and then recrystallized from hot ethanol to afford pure product (Table- 1).

Method II (grinding method): A mixture of ethyl acetoacetate (10 mmol), an aromatic aldehyde (10 mmol) and urea/thiourea (20 mmol), $NiCl_2.5H_2O$ (1.4 mmol) and 5-6 drops of conc. HCl, was ground together for 2-5 min using mortar and pestle. The initial syrupy mixture solidifies within 5-20 min, which was kept over night. The solid was washed with cold water and recrystallized from hot ethanol to afford pure product (**Scheme-I**).

The synthesized compounds were characterized[11,13,16] by their physical constants, TLC and spectroscopic (PMR and IR) techniques with those reported in literature. The spectroscopic data for some compounds is given below.

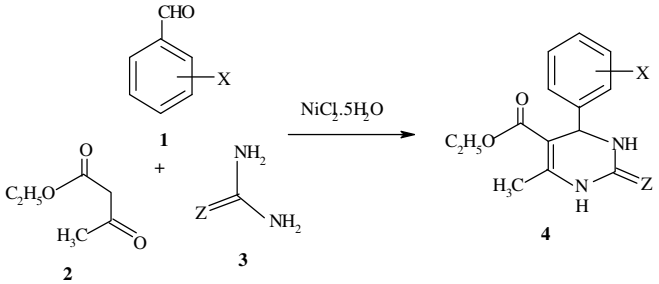
Spectral analysis:

5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2-(1*H*)-one (4a): IR (KBr, ν_{max}, cm^{-1}): 3292, 3116, 1725, 1700, 1677, 722; ^{1}H NMR (300 MHz): δ 1.24 (t, *J* = 7.2 Hz, 3H), 2.31 (s, 3H), 4.02 (q, *J* = 7.3 Hz, 2H), 5.22 (d, 1H), 5.84 (s, 1H), 7.16-7.24 (m, 5H), 8.30 (s, 1H).

5-Ethoxycarbonyl-6-methyl-4-(4-methoxyphenyl)-3, 4-dihydropyrimidin-2-(1*H*)-one (4d): IR (KBr, ν_{max}, cm^{-1}): 3294, 1724, 1642, 1290, 722; ^{1}H NMR (300 MHz): δ 1.11 (t, 2H), 2.26 (s, 3H), 3.74 (s, 3H), 4.01 (q, 2H), 5.24 (s, 1H), 6.92 (d, 2H), 7.21 (d, 2H), 7.72 (s, 1H), 8.28 (s, 1H).

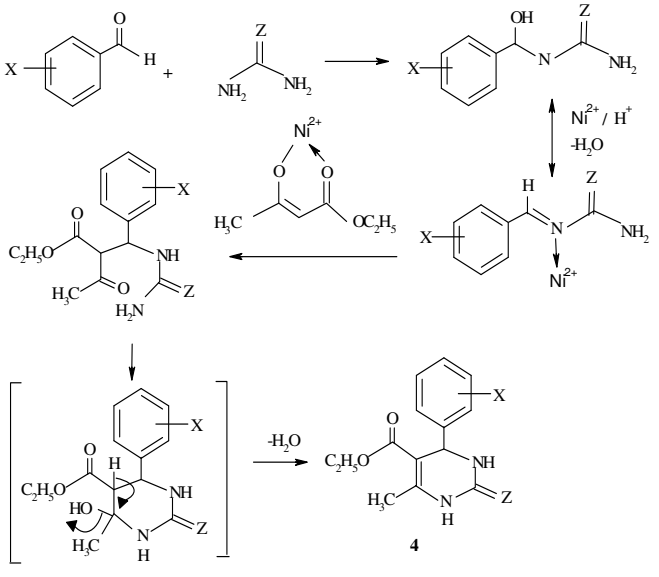
5-Ethoxycarbonyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2-(1*H*)-one (4h): IR (KBr, ν_{max}, cm^{-1}): 3294, 1726, 1702, 1647, 1370, 722; ^{1}H NMR (300 MHz): δ 1.04 (t, 3H), 2.22 (s, 3H), 3.92 (q, 2H), 5.24 (s, 1H), 7.51 (d, 2H), 7.84 (s, 1H), 8.21 (d, 2H), 8.34 (s, 1H).

5-Ethoxycarbonyl-6-methyl-4-(3,4-dimethoxyphenyl)-3,4-dihydropyrimidin-2-(1*H*)-one (4j): IR (KBr, ν_{max}, cm^{-1}): 3300, 1710, 1651, 1613, 1290, 722; ^{1}H NMR (300 MHz): δ 1.20 (t, 3H), 2.30 (s, 3H), 3.85(s, 6H), 4.10 (q, 2H), 5.27 (s, 1H), 6.80 (m, 3H), 7.18 (s, 1H), 8.65 (s, 1H).



Scheme-I Synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones

Mechanism:



RESULTS AND DISCUSSION

The present procedure provides an efficient and improved modification of Biginelli reaction. The isolation of the product is simple and higher yields are obtained. It is found that using thiourea, all the aldehydes reacted under solvent free (grinding) method, whereas some aldehydes (entry m-p) reacted successfully with grinding method. The grinding method was found to be better on the basis of yield and purity of products.

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