Bull. Chem. Soc. Ethiop. **2009**, 23(1), 141-144.
Printed in Ethiopia
ISSN 1011-3924

SHORT COMMUNICATION

EFFICIENT SODIUM SELENATE-CATALYZED SYNTHESIS OF 3,4-DIHYDRO-2(1*H*)-PYRIMIDINONES AND –THIONES UNDER SOLVENT-FREE CONDITIONS

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(Received July 17, 2008; revised August 26, 2008)

ABSTRACT. Sodium selenate efficiently catalyzes the three-component Biginelli reaction of an aldehyde, a,β-keto ester and urea or thiourea under solvent-free conditions to afford the corresponding 3,4-dihydropyrimidin-2(1*H*)-ones or –thiones in excellent yields.

KEY WORDS: Dihydropyrimidinones, Sodium selenate, Biginelli reaction, Three component reaction

INTRODUCTION

Dihydropyrimidinone derivatives have attracted considerable interest in recent times because of their promising activities as calcium channel blockers, antihypertensive agents and antagonists [1, 2]. Moreover, several alkaloids containing the dihydropyrimidine unit have been isolated from marine sources, which also exhibit interesting biological properties [3]. Thus, synthesis of this heterocyclic nucleus is of much current importance. The most simple and straightforward procedure, reported by Biginelli in 1893, involves one-pot condensation of ethyl acetoacetate, benzaldehyde and urea under strongly acidic conditions [4, 5]. However, one serious drawback of Biginelli's reaction is low yields in the case of substituted aromatic and aliphatic aldehydes [6, 7]. This has led to the development of multi-step strategies that produce somewhat higher overall yields but lack the simplicity of the one-pot, one-step synthesis [7, 8]. The art of performing efficient chemical transformation coupling three or more components in a single operation by a catalytic process avoiding stoichiometric toxic reagents, large amount of solvents and expensive purification technique, represents a fundamental target of the modern organic synthesis [9]. Thus, Biginelli's reaction for the synthesis of dihydropyrimidinone has received renewed interest and several improved procedures have recently been reported [5, 10-17] although some of these methods involve strong Lewis acids such as BF_3 [14], protic acids such as HCl [17], AcOH [14] and additives [14]. Consequently, there are scopes for further renovation toward milder reaction conditions, variations of substituents in all three components and better yields. Our own work also found sodium selenate to be a very efficient catalyst for three components coupling reactions [18]. We wish to report here another remarkable catalytic activity of sodium selenate for the one-pot condensation of ethyl acetoacetate, aldehyde and urea or thiourea to dihydropyrimidin-2(1H)- ones or thiones.

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EXPERIMENTAL

All the products are known compounds and were characterized by mp, IR, ^{1}H NMR and GC/MS. Melting points were measured by using the capillary tube method with an electrothermal 9200 apparatus. ^{1}H NMR spectra were recorded on a Bruker AQS AVANCE-300 MHz spectrometer using TMS as an internal standard ($CDCl_3$ solution). IR spectra were recorded as KBr disk on the FT-IR Bruker Tensor 27. GC/MS spectra were recorded on an Agilent Technologies 6890 network GC system and an Agilent 5973 network mass selective detector. Thin layer chromatography (TLC) on commercial aluminum-backed plates of silica gel, 60 F254 was used to monitor the progress of reactions. All the products were characterized by spectra and physical data.

General procedure for the synthesis of 4-aryl-3,4-dihydropyrimidin-2(1H)-one or thione

A mixture of aldehyde (2 mmol), ethylacetoacetate (2 mmol), urea or thiourea (3 mmol) and Na_2SeO_4 (0.05 g) was heated with stirring at 80 ˚C for 1.5 h. The mixture was cooled to reach room temperature and the reaction mixture was poured onto crushed ice. The solid product was filtered and washed with cold water (2 × 20 mL). The solid was dried and recrystallised from hot ethanol to afford pure product. At the end of the reaction, the catalyst remaining in the aqueous phase can be recovered by removing the water by heating and washed with diethyl ether, dried at 80 ºC for 1 h, and reused in another reaction. The recycled catalyst was used for three reactions without observation of appreciable loss in its catalytic activities.

5-Ethoxycarbonyl- 4-phenyl-6-methyl -3,4-dihydropyrimidin-2(1H)-one (4a)

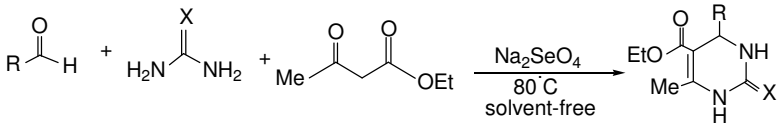
M.p. 202-204 ˚C; IR (KBr) (ν_{max}, cm^{-1}): 3244, 1724, 1639; ^{1}H NMR ($CDC1_3$, 300 MHz) δ_H (ppm): 1.1 (t, 3H, CH_3*-CH_2O), 2.24 (s, 3H, CH_3), 4.01 (q, 2H, OCH_2), 5.16 (s, 1H, CH), 7.21-7.30 (m, 5H, aromatic CH), 7.76 (s, 1H, NH), 9.24 (s, 1H, NH); GC/MS (m/z): 260 (M^+).

5-Ethoxycarbonyl- 4-(4-nitro-pheny)l-6-methyl-3,4-dihydropyrimidin-2(1H)-one (4d)

M.p. 209-210 ˚C; IR (KBr) (ν_{max}, cm^{-1}): 3250, 1720, 1636; ^{1}H NMR ($CDC1_3$, 300 MHz) δ_H (ppm): 1.1 (t, 3H, CH_3*-CH_2O), 2.27 (s, 3H, CH_3), 3.98 (q, 2H, OCH_2), 5.20 (s, 1H, CH), 7.51 (d, 2H, aromatic CH), 7.89 (s, 1H, NH), 8.01 (d, 2H, aromatic CH), 9.33 (s, 1H, NH); GC/MS (m/z): 305 (M^+).

RESULTS AND DISCUSSION

As part of our program aimed at developing new selective and environmental friendly methodologies for the preparation of fine chemicals [19-21], we performed the synthesis of dihydropyrimidin-2(1H)-ones or -thiones through a three-component reaction employing sodium selenate as a catalyst. This reaction proceeded smoothly and rapidly to give the corresponding dihydropyrimidinones in good yields (Table 1). The best condition to prepare the dihydropyrimidinones or thiones were achieved when 0.05 g of sodium selenate, 3 equivalent of urea (or thiourea), 2 equivalent of both ethylaceto acetate and aldehyde were heated under solvent-free conditions for 1.5 h, affording the desired product (Scheme 1). We found that this method is effective with a variety of substituted aromatic aldehydes independently of the nature of the substituents in the aromatic ring, representing an improvement to the classical Biginelli's methodologies.



1 **2** **3** **4**

Scheme 1

Table 1. Sodium selenate catalyzed synthesis of dihydropyrimidinones and thiones.

Entry	R	X	Product	Time (h)	M.p. (^{0}C)		Yield (%)[a]
					Observed	Reported	
1	Ph	O	**4a**	1.5	202-204	201-203 [22]	80
2	4-Me-Ph	O	**4b**	1.5	213-214	214-215 [14]	75
3	4-MeO-Ph	O	**4c**	1.5	199-202	199-201 [22]	76
4	4-NO_2-Ph	O	**4d**	1.5	209-210	209-211 [14]	70
5	4-Cl-Ph	O	**4e**	1.5	215-216	214-215 [14]	78
6	3-NO_2-Ph	O	**4f**	1.5	228-229	227-229 [23]	70
7	Ph	S	**4g**	1.5	208-209	208-209 [24]	77
8	4-Cl-Ph	S	**4h**	1.5	208-209	209-210 [25]	75

[a] Isolated yields.

In order to show the merit of the present work in comparison with some reported protocols, we compared the results of the synthesis of 5-ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (entry 1 in Table 1) in the presence of, sulfuric acid, zeolite, $BF_3.OEt_2$/CuCl, montmorillonite KSF, with sodium selenate with respect to the reaction times (Table 2). The yield of product in the presence of sodium selenate is comparable with these catalysts. However, reaction in the presence of these catalysts, required longer reaction times than sodium selenate.

Table 2. Comparison the results of the synthesis of 5-ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydro-pyrimidin-2(1*H*)-one using different catalysts.

Entry	Catalyst	Time (h)	Yield (%)	References
1	Sulfuric acid	18	71	[4]
2	Zeolite	12	80	[26]
3	$BF_3.OEt_2$/CuCl	18	94	[27]
4	Montmorillonite KSF	48	82	[16]
5	Sodium selenate	1.5	80	This work

CONCLUSIONS

We have developed a simple, efficient, and green protocol for the synthesis of dihydropyrimidinones using sodium selenate as a reusable catalyst. The short reaction times, simple work-up in isolation of the products in high yields with high purity, mild reaction conditions are features of this new procedure.

ACKNOWLEDGMENT

The authors gratefully acknowledge partial financial support from the research council of Alzahra University.

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