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Tin oxide nanoparticle catalyzed one-pot synthesis of 3, 4 dihydropyrimidinones

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ABSTRACT

Tin oxide nano particle is an efficient, inexpensive, and readily available catalyst for the three components one-pot condensation reaction of an aldehyde, urea/thiourea and 1, 3-dicarbonyl compounds to afford the corresponding dihydropyrimidinones in high yield. This technique is non-polluting method and does not employ any toxic reagents, quantifying it as a green approach to this cyclocondensation reaction. Compared with the classical Biginelli reaction conditions, this new method has the advantage of excellent yield and shorter reaction time. All the compounds have been characterized by Elemental analysis, IR, ^{1}H NMR and ^{13}C NMR Spectra.

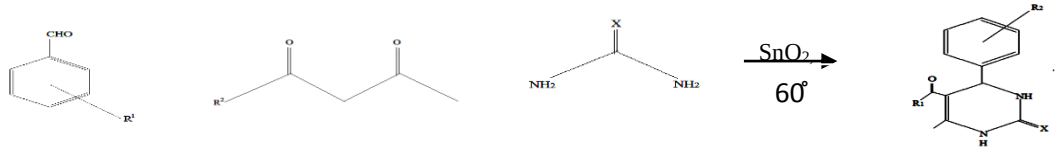
Keywords: Nanoparticles, Dihydropyrimidinones, Biginelli reaction, cyclocondensation, NMR spectra

INTRODUCTION

Many dihydropyrimidinones and their derivatives are pharmacologically important as calcium channel blockers, antihypertensive agents and α-1a antagonists. 3,4-Dihydropyrimidinones, denoted as Biginelli compounds and their derivatives are highly important heterocyclic units in the realm of natural and synthetic organic chemistry that possess diverse therapeutic and pharmacological properties, including anti-viral, anti-tumor, anti-bacterial and anti-inflammatory activities.

Also, several alkaloids containing the dihydropyrimidine nucleus isolated from marine sources have been found to possess interesting biological activities. Owing to the wide range of pharmacological and biological activities, the synthesis of these compounds has become an important target in current years. The Biginelli reaction, first reported in 1893, is a direct and simple approach for the synthesis of 3,4-dihydropyrimidinones by one-pot cyclocondensation of ethyl acetoacetate, benzaldehyde and urea in the presence of strong acid. However, one serious drawback of this method is the low yield of the product, particularly in case of substituted aromatic and aliphatic aldehydes. This has led to the development of more complex multistep strategies that produce somewhat higher overall yields but lack the simplicity of the one-pot Biginelli protocol. This has led to the recent disclosure of several one-pot methodologies for the synthesis of DHPMs derivatives involving the use of a number catalysts such as $InCl_3$, ASA, P_2O_5, PWA,$Yb(OTf)_3$, $SrCl_2.6H_2O$-HCl, $ZnCl_2$, LiBr, $Cu(OTf)_2$, $CuCl_2.2H_2O$-HCl, [bmim] BF_4-immobilized Cu(II) acetylacetonate, [bmim] $FeCl_4$, 1,1,3,3-tetramethylgaunidinium trifluoroacetate, $GaCl_3$ etc. However, many of these methods also suffer from drawbacks, such as involvement of expensive reagents, acidic conditions, solvent mediated reactions, longer reaction time, non-reproducible yields and environmental pollution. Development of non-polluting synthetic methodologies for organic reactions is one of the latest challenges to the organic chemists. In continuation of our research work we wish to report a clean, simple and single step cyclocondensation reaction of aldehydes, 1,3-dicarbonyl compounds and urea/thiourea in the presence of Tin oxide nanoparticle as a catalyst with high yield. (Scheme 1).

Scheme 1. Synthesis of 2,3 dihydropyrimidione derivatives



MATERIALS AND METHODS

The course of reaction and the purity were ascertained by performing TLC. Melting points were determined in open capillaries. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX 400 spectrometer operating at 400.13 MHz for ^{1}H and 100.62 MHz for ^{13}C in DMSO-d_6. All NMR measurements were made using 5 mm tubes. For recording ^{1}H NMR spectra, solutions were prepared by dissolving about 10 mg of the compound in 0.5 ml of the solvent. For recording ^{13}C spectra, solutions were prepared by dissolving about 50 mg of the compound in 0.5 ml of the solvent. IR spectra were recorded in KBr discs on an Avatar (300 FT-IR) Thermo Nicolet spectrometer. Elemental analysis were carried out on an Elementar Vario EL III analyzer. Thin layer chromatography was performed on silica gel G (Merck).

General Procedure for the Synthesis of Dihydropyrimidinones: A solution of aldehyde (10 mmol), 1,3-dicarbonyl compound (10 mmol) and urea/thiourea (15 mmol) was heated to reflux (40°C) in ethanol in the presence of tin oxide nanoparticles (0.5g) for 60 min.. The progress of the reaction was monitored by TLC. After the completion of the reaction, the mixture was cooled to room temperature and poured into crushed ice. The crude product containing also the catalyst was collected on a Buchner funnel by filtration. The mixture of the product and the catalyst was digested in ethanol (40 ml). The undissolved catalyst was removed by filtration. The crude product was obtained by evaporation of ethanol and further purified by recrystallization from hot ethanol to afford pure dihydropyrimidin-2(H)-thiones. The catalyst could be reused in the next run. All the products were characterized by Mass spectra, IR, ^{1}H NMR and ^{13}C NMR spectra.

The synthesized compounds have been identified by comparison of spectral data (IR, ^{1}H NMR and ^{13}C NMR) and mp with those reported.

RESULTS AND DISCUSSION

The model reaction of benzaldehyde (10 mmol), ethyl acetoacetate (10 mmol), urea (15 mmol) and tin oxide nanoparticles (0.5g) was heated to reflux (40°C) in the presence of ethanol gave the product in 95% yield (Scheme 1). Under these conditions, the yields were significantly raised (90-95% vs for the classical Biginelli method) and the reaction time was shortened from 18 hours to 60 minutes. To the best of our knowledge, there are no earlier reports of tin oxide as catalyst for biginelli reaction.

Tin oxide nanoparicles showed a relatively good activity in terms of yield in producing the required product and short reaction time and also it is a reusable catalyst which could be 5 reused in the another reaction. It is one of the most suitable catalyst for the selective construction of heterocyclic ring system, in particular for the synthesis of 3,4-dihydropyrimidin-2(1H)- thiones. Reusability of the catalyst was next checked by the same model reaction for 5 times. The results are summarized in Table 1.

Table.1.Yields of dihydropyrimidin-2(1H)-thione 4a for successive runs

Run	Reaction time (min.)	Yield (%)	m.p. (°C)
1	60	95	201-202
2	60	95	202-203
3	60	93	201-202
4	60	93	201-202
5	60	92	201-202

A wide range of structurally varied dicarbonyl compound aldehyde and urea are coupled together by this procedure to produce the corresponding dihydropyrimidinones. The results are reported in Table 2. Both iketone and ketoester participated in this reaction readily. A variety of substituted aromatic aldehydes have been subjected to this condensation very efficiently. Aromatic aldehydes carrying either electron-donating or electron-withdrawing substituents afforded high yields of products in high purity. Another important feature of this procedure is the survival of a variety of functional groups such as hydroxy, halides, etc under the reaction conditions. This method utilizes readily available reagents at low cost and also affords high yields of DHPMs in very short reaction times. The mechanism for Biginelli condensation is well explored in the literature.

In all cases, the purity of the product was confirmed by Mass spectra. The structures of the pure products were confirmed by IR, ^{1}H NMR and ^{13}C NMR spectral data.

Table.2.Synthesis of dihydropyrimidines catalyzed by Tin oxide nanoparticles

Entry	R^1	R^2	Time (min.)	Yield (%)	m.p. (°C)
1	H	OC_2H_5	45	90	201-202
2	H	OCH_3	50	90	264-265
3	4-OCH_3	OCH_3	55	91	200-201
4	4-CH_3	OCH_3	60	92	257-258
5	4-Cl	OCH_3	60	90	259-260
6	2-Cl	OCH_3	65	92	283-284
7	4-F	OCH_3	60	95	259-260

CONCLUSION

In summary, this report discloses a new and simple modification of the Biginelli dihydropyrimidinones synthesis. By using tin oxide nanoparticles as a catalyst, the yields of the one-pot Biginelli reaction can be increased from 20 to 50% to 90-95% while the reaction 7 time was shortened from 18 to 60 minutes. This approach is nonpolluting and does not employ any toxic materials, quantifying it as a green approach to this cyclocondensation reaction. This tin oxide catalytic one-pot synthesis of dihydropyrimidinones is a simple, high yielding, time saving and environmentally friendly process.

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