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Research Article

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One-Pot Synthesis of 3, 4-Dihydropyrimidin-2(1H)-Ones Catalyzed by Barium Chloride

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ABSTRACT

The three component condensation of an aldehyde, β-dicarbonyl and urea (or thiourea) using barium chloride in the presence of nitric acid has been investigated. The 3,4-dihydropyrimidin-2(1H)-one derivatives were synthesized in high yields at short reaction times. Barium chloride is one of the useful and inexpensive catalysts that can be easily separated and are not contaminated by products. The activity of the recycled $BaCl_2$ was examined and it was seen that the catalyst displayed very good reusability. This method offers several advantages including high yields, environmental friendliness, short reaction times, cheapness of catalyst, simple work up procedure and easy isolation, which make it a useful process for synthesis of dihydropyrimidones as well as the thio derivatives.

Keywords: 3, 4-Dihydropyrimidin-2(1H)-one; Synthesis; Barium chloride

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INTRODUCTION

In 1893, the Italian chemist Pietro Biginelli reported a cyclocondensation reaction between ethylacetoacetate, benzaldehyde, and urea to obtain a heterocyclic system of 3,4-dihydropyrimidinones (DHPMs), which is known as Biginelli reaction [1]. Pyrimidines belong to an important class of organic compounds with significant therapeutic and medicinal properties [2,3]. Some of them have antiviral, antitumor, antibacterial and anti-inflammatory activity [4-9]. In addition, the batzelladine alkaloids containing the pyrimidine core unit inhibit the binding of HIV envelop protein gp-120 to human CD_4 cells and therefore, are potential new lead for AIDS therapy [10,11].

Due to the importance of this compound in the biological system, the study of synthesis of 3,4-dihydropyrimidin-2(1H)-one derivatives has attracted the attention of several research groups. Up to now, numerous methods have been developed for the modification of Biginelli reaction. Various catalysts and reaction conditions have been studied [12]. Although some of the reported procedures prepare a wide range of 3,4-dihydropyrimidin-2(1H)-ones, most of them have several disadvantages such as low selectivity, cumbersome workup, long reaction times, low yields of products and use of expensive catalysts.

Herein $BaCl_2$ was employed as a useful catalyst for the synthesis of 3,4-dihydropyrimidin-2(1H)-one derivatives via one-pot three component condensation of an aldehyde, β-dicarbonyl and urea (or thiourea) under reflux or solvent free conditions in high yields. Barium chloride is one of the useful and inexpensive catalysts that can be easily separated and are not contaminated by products. In recent years synthesis of 5-ester 3, 4-dihydropyrimidin-2(1H)-ones by barium chloride and SiO_2 under solvent free conditions have been reported. [13,14] The present study describes a convenient and efficient method for the synthesis of 5-ester or 5-keto 3,4-dihydropyrimidin-2(1H)-ones one / thione derivatives by barium chloride under reflux condition.

EXPERIMENTAL SECTION

Materials

All materials are commercial reagent grades and were prepared from Merk or Fluka. All products were known and their physical and spectroscopic data were compared with those of authentic samples [15-20].

Instruments used

Melting points were determined with Barnstead Electrothermal and are uncorrected. The FT-IR spectra were recorded as KBr pellets on a Shimadzu FT-IR 8000 spectrometer; ^{1}HNMR data were obtained using a Bruker Avance Ultra-Shield 400 MHz spectrometer in $CDCl_3$.

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

A mixture of ethyl acetoacetate or acetylacetone (5 mmol), aldehyde (5 mmol), urea (7.5 mmol), $BaCl_2$ $2H_2O$ (0.5 mmol), HNO_3 (1 drop) in CH_3CN (10 cc) was heated and stirred under reflux conditions for the times reported in Tables 3. The progress of reaction was followed by TLC. After the reaction was completed, the mixture was cooled to room temperature and crushed ice was added. The precipitate was filtered, washed with cold water and dried under vacuum. The product was purified by recrystallization from petroleum ether and ethanol.

RESULTS AND DISCUSSION

A long series of 3, 4-dihydropyrimidin-2(1H)-one / thione derivatives were synthesized via one-pot three component condensation of an aldehyde, ethyl acetoacetate / acetylacetone), urea / thiourea. As a model reaction, we studied the three-component barium chloride catalyzed Biginelli condensation by examining the conditions required for the reaction involving benzaldehyde, urea and ethyl acetoacetate to afford the corresponding 3,4-dihydropyrimidone. The reaction was performed in different solvents such as EtOAc, H_2O, CH_3CN, EtOH and MeOH. The best result was obtained in acetonitrile after 4 hours (Table 1). In order to show effect of catalyst, the different amounts of barium chloride and nitric acid was used in this reaction. As we show in Table 2, in the absence of any catalyst the yield of product was very low after 4 h.

Table 1: Synthesis of ethyl-6- methyl-4-phenyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate in the presence of $BaCl_2$ / HNO_3 in various solvents

Entry	Solvent	Yield (%)[a]	Time (h)
1	CH3CN	93	4
2	EtOH	72	4
3	MeOH	61	4
4	H2O	0	4
5	EtOAc	40	4
6	CH3CN/H2O (3:1)	53	4

[a]Isolated yield

Table 2: Influence amount of catalyst on the yield of ethyl-6-methyl-4-phenyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate in refluxing acetonitrile

Entry	BaCl2 (mol %)	HNO3 (drop)	Time (h)	Yield (%)[a]
1	10	1	4	93
2	5	1	4	72
3	10	2	4	70
4	15	1	4	93
5	0	1	4	43
6	10	0	4	50

[a]Isolated yield

According to the data of Tables 1 and 2, 5 mmol of β-dicarbonyl ,5 mmol of aldehyde, and 7.5 mmol urea (or thiourea) using 0.5 mmol barium chloride in the presence one drop of nitric acid in 10 cc of acetonitrile were chosen as the optimized reaction conditions for synthesis of 3,4-dihydropyrimidin-2(1H)-one (or thione) derivatives (Figure 1).

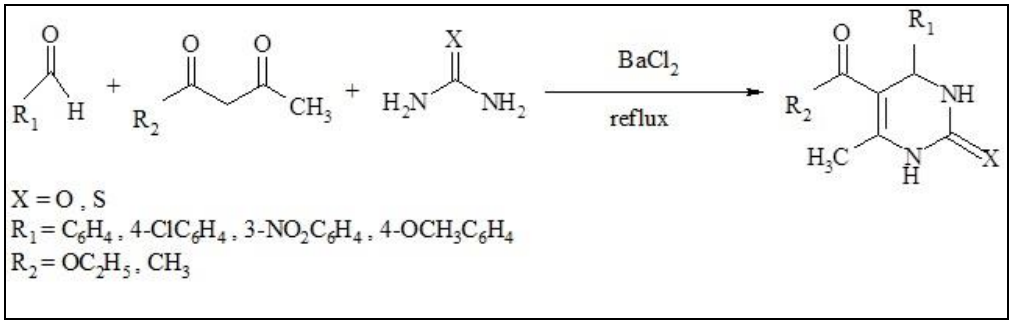

Figure 1: Synthesis of 3,4-dihydropyrimidin-2(1H)-one(or thione) derivatives using barium chloride

The results of one-pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones catalyzed by barium chloride are summarized in Table 3.

Table 3: Synthesis of 3, 4-dihydropyrimidin-2(1H)-one (or thione) derivatives using barium chloride under reflux condition

Comp.	R1	R2	X	Yield (%)[a]	Time (h)
1a	ph	OEt	O	93	3.5
1b	4-ClC6H4	OEt	O	70	3
1c	3-NO2C6H4	OEt	O	68	3.75
1d	4-OCH3C6H4	OEt	O	85	2
1e	Ph	OEt	S	73	3.5
1f	4-ClC6H4	OEt	S	72	3
1g	3-NO2C6H4	OEt	S	52	4
1h	4-OCH3C6H4	OEt	S	80	2
1i	Ph	Me	O	78	3.75
1j	4-ClC6H4	Me	O	80	3
1k	3-NO2C6H4	Me	O	64	4
1l	4-OCH3C6H4	Me	O	82	2

[a]**Isolated yield**

Various aromatic aldehydes carrying either electron-releasing or electron-withdrawing substituents afforded good to excellent yields of the products. Thiourea was used with similar success to provide the corresponding 3, 4-dihydropyrimidin-2(1H)-thiones which are also of interest with regard to their biological activities [19]. The presented data in Table 3 indicate that barium chloride in the presence of nitric acid is a highly efficient catalyst in the synthesis of dihydropyrimidones. The electron-withdrawing in substituted benzaldehydes lead to the products in shorter reaction times than the electron releasing substituted benzaldehydes under reflux condition.

The activity of the recycled $BaCl_2$ was examined in the synthesis of ethyl-6- methyl-4-phenyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate. The recovered catalyst dried prior to use and tested for its activity in the subsequent run and fresh catalyst was not added. We obtained desired product in 93%, 90%, 89% and 89% yields after 1-4 runs respectively. So, it was seen that the catalyst displayed very good reusability.

CONCLUSIONS

In summary, we have described a simple and general method for the synthesis of dihydropyrimidones by using a reusable catalyst. This method offers several advantages including high yields, environmental friendliness, short

reaction times, cheapness of catalyst, simple work up procedure and easy isolation, which make it a useful process for synthesis of dihydropyrimidones as well as the thio derivatives.

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