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ORIGINAL ARTICLE

Microwave-assisted multicomponent reaction for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones and their corresponding 2(1*H*)-thiones using lanthanum oxide as a catalyst under solvent-free conditions

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KEYWORDS

3,4-Dihydropyrimidinone;
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Abstract An efficient synthesis of 3,4-dihydropyrimidinone derivatives using lanthanum oxide as a catalyst, from aldehydes, β-keto ester and urea/thiourea without solvent under the irradiation of microwave is described. Compared with classical Biginelli reaction conditions, this new method has the advantage of excellent yields and shorter reaction times.

1. Introduction

Dihydropyrimidinones (DHPMs) derivatives have exhibited important pharmacological properties such as antiviral, antibacterial, antitumor and antihypertensive activities (Rovnyak et al., 1995). Some have been successfully used as calcium channel blockers, α-1a-antagonists and neuropeptide Y (NPY) antagonists (Atwal et al., 1990). Several alkaloids, which contain the dihydropyrimidine core unit, have been isolated from marine sources. Most notable among these are the batzelladine alkaloids, which were found to be potent HIVgp-120-CD4 inhibitors (Snider et al., 1996). The Biginelli reaction is considered as an important multicomponent reaction for generating compounds with diverse medicinal applications.

The original one-pot synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones was first reported by Pietro Biginelli in 1893 performing the three component cyclocondensation reaction of ethyl acetoacetate, benzaldehyde and urea under Bronsted acid catalysis. However, this reaction suffers from the harsh conditions, high reaction times and frequently low yields (Biginelli, 1893). Therefore, the discovery of milder and practical routes for the synthesis of dihydropyrimidin-2(1*H*)-ones by the Biginelli reaction continues to attract the attention of researchers.

In recent years, new methods for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones have been developed by different groups. In order to improve the efficacy of the Biginelli reaction different Lewis catalyst such as $SbCl_3$ (Cepenec et al., 2007), $InBr_3$ (Fu et al., 2002), $Cu(NH_2SO_3)_2$ (Liu and Wang,

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2009), $H_3PMo_{12}O_{40}$ (Heravi et al., 2006), $ZrCl_4$ (Reddy et al., 2002), CaF_2 (Chitra and Pandiarajan, 2009), $LaCl_3{\cdot}7H_2O$ (Lu et al., 2001), lanthanide triflate (Ma et al., 2000) and ionic liquid (Peng and Deng, 2001) were reported.

During recent years, the chemistry of lanthanum and their use in organic synthesis have developed rapidly. Furthermore, their low toxicity and availability at a moderate price makes this element attractive for use in organic synthesis. The use of lanthanide(III) compounds as catalysts or promoters in organic synthesis has attracted great interest from many chemists (Molander, 1992). Lanthanide additives (or) complexes can enhance the reactivity and selectivity of many types of reaction, such as reduction (Nishino et al., 2002), carbon–carbon bond forming reactions (Kobayashi, 1999), aldol condensation (Kobayashi et al., 1993), Fridel–Crafts acylations (Kawada et al., 1994) and aza Diels–Alder reactions (Makioka et al., 1995).

Environmental concerns in research and industries to reduce the amount of pollutants produced, including organic solvents whose recovery is mandated by ever more strict laws. Hence, the challenges for a sustainable environment call for the use of clean procedures, which can avoid the use of harmful solvents. The emergence of microwave assisted solid phase synthesis (Varma, 1999) is a step forward in this direction. In this expeditious and solvent free approach the adsorbed reactants over solid supports are exposed to microwave irradiation. The coupling of a microwave heating mode with the use of solid has allowed the synthesis of several organic compounds with higher purity of products and very simplified ease of manipulation and work up (Katritzky and Singh, 2003).

It is of great practical importance to synthesize by Biginelli reaction DHPMs using easily separable solid catalysts having pore size large enough to allow the diffusion of large molecules, requiring short reaction time and particularly without any solvent, so that the synthesis is also environ-friendly producing little or no waste. The present investigation was undertaken for this purpose. Herein, we wish to report a simple and efficient method for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones and their corresponding thiones under solvent-free conditions using lanthanum oxide as a catalyst.

2. Experimental

2.1. Materials and methods

Benzaldehyde and substituted benzaldehydes (Aldrich chemicals) were used as received. Ethyl acetoacetate (AnalaR grade), urea/thiourea and lanthanum oxide were purchased from Merck and used as such.

2.2. Apparatus

All melting points were measured in open capillaries and are uncorrected. IR spectra were recorded using Avatar-330 FT-IR spectrophotometer using KBr pellets. ^1H and ^{13}C NMR spectra were recorded on a BRUKER AMX 500 MHz spectrometer in DMSO-d_6 using TMS an in internal standard. Elemental analyses were performed on a Perkin Elmer 240 CHN elemental analyzer. Microwave LG ECN: MG-395 WA/01, MOD: MG-395 WA model was used.

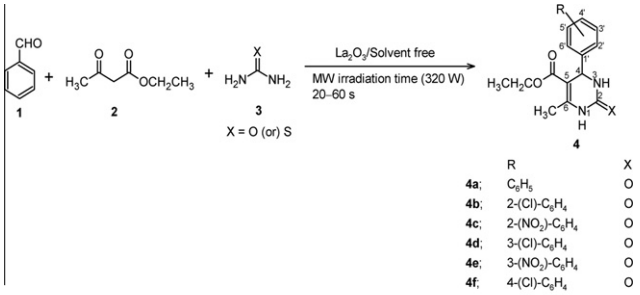
2.3. General procedure for preparation of 3,4-dihydropyrimidin-2(1H)-ones/thiones

A mixture of aromatic aldehydes (10 mmol), ethyl acetoacetate (10 mmol) and urea/thiourea (15 mmol) with La_2O_3 (10 mol%) without any solvent in a beaker (capacity 25 mL), placing the beaker containing the reaction mixture at the center of the microwave oven (320 W) and irradiating for a period of 5 s at a time. After every irradiation, the reaction vessel was removed from the microwave oven for a period of 10 s and the reaction mixture was stirred. The completion of the reaction was checked by TLC (ethyl acetate/hexane, 8:2). The total period of the MW irradiation ranges from 20 to 60 s. Then, the crude product from the reaction mixture was dissolved in ethyl acetate, the catalyst was separated by the filtration. The organic layer was washed with water and dried over anhydrous Na_2SO_4. Organic solvent was evaporated under reduced pressure and the resulting solid product was then crystallized from hot ethanol. The structure of the pure products was confirmed by FT-IR, ^1H NMR, ^{13}C NMR and elemental analysis. A variety of substituted benzaldehydes and urea/thiourea were used for this reaction.

3. Results and discussion

In a model reaction, ethyl acetoacetate (**2**) (10 mmol), benzaldehyde (**1**) (10 mmol), urea/thiourea (**3**) (15 mmol) and La_2O_3 (10 mol%) in micro oven gave the product in 98% yield (Scheme 1). A variety of substituted benzaldehydes and urea/thiourea were used for this reaction. The results are summarized in Table 1.

It was found that the reaction could go smoothly and the corresponding DHPMs were obtained in excellent yield (90–98%) when the mixture was irradiated at 320 W for 20–60 s. No product could be obtained when the reaction was carried out at room temperature for a long time even in the presence of 20 mol% La_2O_3. It was also found that the use of 10



	R	X
4a;	C_6H_5	O
4b;	2-(Cl)-C_6H_4	O
4c;	2-(NO_2)-C_6H_4	O
4d;	3-(Cl)-C_6H_4	O
4e;	3-(NO_2)-C_6H_4	O
4f;	4-(Cl)-C_6H_4	O
4g;	4-(CH_3O)-C_6H_4	O
4h;	4-(NO_2)-C_6H_4	O
4i;	4-(F)-C_6H_4	O
4j;	3,4,5-(CH_3O)-C_6H_2	O
4k;	C_6H_5	S
4l;	2-(Cl)-C_6H_4	S
4m;	2-(NO_2)-C_6H_4	S
4n;	3-(Cl)-C_6H_4	S
4o;	3-(NO_2)-C_6H_4	S
4p;	4-(Cl)-C_6H_4	S
4q;	4-(CH_3O)-C_6H_4	S
4r;	4-(NO_2)-C_6H_4	S
4s;	4-(F)-C_6H_4	S
4t;	3,4,5-(CH_3O)-C_6H_2	S

Scheme 1 Synthesis of 3,4-dihydropyrimidinones/thiones catalyzed by La_2O_3 under microwave irradiation and solvent-free condition.

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