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An efficient and solvent-free one-pot synthesis of 1,4-dihydropyridines under microwave irradiation

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Abstract

An efficient synthesis of 1,4-dihydropyridines using lanthanum oxide as a catalyst from aldehydes, β-ketoester and ammonium acetate without solvent under the irradiation of microwave is described. Compared with the classical Hantzsch reaction, this new method has the advantage of good yield (90–98%) and short reaction time (40–80 s).

Keywords: Hantzsch reaction; 1,4-Dihydropyridine; Microwave; Solvent free; Lanthanum oxide

There is always something new on the old topic of the Hantzsch reaction since Arthur Hantzsch first reported it in 1882 [1]. This is mainly due to the fact that it offers an efficient way to prepare the 1,4-dihydropyridines (1,4-DHPs) which exhibit significant biological activities in the treatment of cardiovascular disease as calcium channel blockers [2]. A number of dihydropyridine calcium antagonists have been introduced as potential drugs for the treatment of congestive heart failure and angina pectoris [3]. They also function as neuroprotectants, as anti-platelet treatment of aggregators and are important in Alzheimer's disease as anti-ischaemic agents [4]. The classical method for the synthesis of 1,4-DHPs is one-pot condensation of aldehydes with ethyl acetoacetate and ammonia either in acetic acid or by refluxing in ethanol. However, the yield of 1,4-DHP obtained by Hantzsch method is generally low [1]. Recently, many synthetic methods have been developed to improve and modify this reaction by using silica gel/$NaHSO_4$ [5], $AlCl_3{\cdot}6H_2O$ [6], TMSI [7], $HClO_4$–SiO_2 [8], triphenylphosphine [9], ionic liquid [10] and 3,4,5-trifluorobenzeneboronic acid [11]. These methods however, involve long reaction time, harsh reaction conditions, tedious work-up procedure, give unsatisfactory yield with other side products, the use of large quantity of volatile organic solvents.

However, most of the researchers have been focused on the modification and optimization of the Hantzsch reaction to maximize reaction conversion, minimize reaction time and offer high purity of 1,4-DHPs. Thus, the development of an efficient and versatile method for the preparation of Hantzsch 1,4-DHPs is an active ongoing research area and there is scope for further improvements towards short reaction time and high yield.

During the last decade, lanthanide additives (or) complexes are found to enhance the reactivity and selectivity of many reactions, such as reduction [12], carbon–carbon bond forming reactions [13], aldol condensation [14], Friedel–Crafts acylations [15], aza Diels–Alder reactions [16] and many diverse reactions [17]. In this letter, we would like to

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report a simple effective approach to the Hantzsch reaction products using La_2O_3 as a catalyst under microwave irradiation with solvent free conditions.

1. Experimental

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 AC 300 MHz spectrometer in $CDCl_3$ using TMS an internal standard. Elemental analyses were performed on a Perkin Elmer 240 CHN elemental analyzer. Microwave LG MS–1947C AC–230 V/50 Hz model was used.

A mixture of aldehyde (**1**) (5 mmol), ethyl acetoacetate (**2**) (10 mmol), ammonium acetate (**3**) (10 mmol) and lanthanum oxide (10 mol%) without solvent in a beaker (capacity 25 mL) kept at the center of the microwave oven (320 W) and irradiation for a period of 10 s was maintained. After every irradiation (10 s), the reaction vessel was removed from the microwave oven and stirred the reaction mixture. The completion of the reaction was checked by TLC (ethylacetate:hexane, 8:2). The total period of microwave irradiation was in the range of 40–80 s. The reaction mixture was then extracted with ethylacetate and the catalyst was separated by the filtration. The organic layer then washed with water and dried over anhydrous Na_2SO_4. Organic solvent was evaporated under reduced pressure and solid compound, which was crystallized from absolute ethanol is identified as 1,4-DHPs in excellent yield. The obtained products were confirmed by FT-IR, ^1H and ^{13}C NMR and elemental analysis.

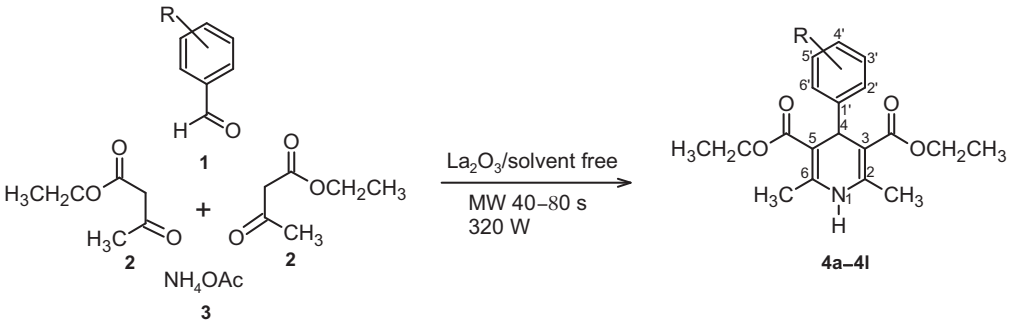
2. Results and discussion

In a model reaction, benzaldehyde (**1**) (5 mmol), ethyl acetoacetate (**2**) (10 mmol), ammonium acetate (**3**) (10 mmol) and La_2O_3 (10 mol%) are irradiated in microoven gave the product in 98% yield (Scheme 1).

We have studied the effect of catalyst by varying amount of catalyst 4, 6, 8, 10 and 12 mol% (Table 1). From the above studies we found that 10 mol% La_2O_3 was to be the optimum and this amount of catalyst was fixed for all substituents. We also screened a number of different catalysts for this reaction. The reaction was carried out in the presence of Nafion-H, amberlite-IR-120, silica–sulfuric acid, zeolite, KH_2PO_4 or BF_3 OEt_2 under microwave irradiation gave low yield even after prolonged reaction time. However, when the same reaction was conducted under microwave irradiation using La_2O_3 as a catalyst, result in excellent yield with short reaction time (Table 2, entry 7). Table 3 compares the efficiency of present method with the efficiency of other methods in the synthesis of 1,4-DHPs.

Encouraged by this result, a series of aldehydes were examined under optimized conditions and the results are shown in Table 4. It is seen that several aromatic aldehydes bearing either electron-releasing or electron-withdrawing substituents in *meta* and *para* position afford high yield. Here, we have found that the reactions of aromatic aldehydes having electron-withdrawing groups are rapid as compared to the reaction of aldehydes having electron-donating groups. We have not tried this method for aliphatic aldehydes.

Spectral data and elemental analysis for selected compounds:



Scheme 1. La_2O_3 catalyzed synthesis of 1,4-dihydropyridines under microwave irradiation.