Synthesis of 1,4-dihydropyridine Derivatives *via* One Pot Multicomponent Condensation in Water

Arash Ghorbani-Choghamarani* and Masoomeh Norouzi

Department of Chemistry, Faculty of Science, Ilam University, P.O. Box 69315516, Ilam, Iran

Received March 15, 2013: Revised June 08, 2013: Accepted June 10, 2013

Abstract: A facile and efficient one-pot preparation of a new series of 1,4-dihydropyridines has been reported *via* a three-component reaction of *nano* aluminum nitride, aromatic aldehydes and benzyl-3-oxobutanoate or 2-methoxyethyl-3-oxobutanoateat 80 °C in water. Using this methodology, Hantzsch1,4-dihydropyridine derivatives were synthesized in a simple pathway without the use of a catalyst or an organic solvent.

Keywords: 1,4-Dihydropyridine, Hantzsch reaction, One-pot condensation, Multicomponent, Aluminum nitride.

INTRODUCTION

Multi-component reactions (MCRs) have emerged as an efficient and powerful tool in modern synthetic organic chemistry allowing the facile creation of several new bonds in a one-pot transformation [1]. The sequencing of multicomponent reactions (MCRs) and subsequent cyclization reactions is a powerful stratagem for the rapid synthesis of diverse heterocyclic structures [2].

As a one-pot reaction, MCRs generally afford good yields and are fundamentally different from two-component and stepwise reactions in several aspects and permit a rapid access to combinatorial libraries of complex organic molecules for an efficient lead structure identification and optimization in drug discovery [3].

Hantzsch 1,4-dihydropyridines (1,4-DHPs) are a very important class of compounds which can be found in numerous biologically active compounds. For example, some of these compounds are calcium-channel modulators blocker and show antihypertensive effects [4].

Also these heterocyclic compounds are interesting example of a useful scaffold, because of their ability to act as NAD(P)H analog of 1,4-dihydronicotinamide.

Interestingly, these heterocycles have been found to be the structural feature of several compounds belonging to different bio-active classes such as vasodilator, antitumor, bronchodilator, analgesic, anti-inflammatory, antithrombotic, anticonvulsant, hepato-protective, radioprotective, antiatherosclerotic, and antidiabetic agents. They were also reported to exhibit anticancer, antitubercular, antibacterial, and antiviral, activities. 1,4-DHPs are also known to act as HIV protease inhibitors and chemosensitizersin MDR tumor therapy [5-12].

*Address correspondence to this author at the Department of Chemistry, Faculty of Science, Ilam University, P.O. Box 69315516, Ilam, Iran; Tel/Fax: +98 841 2227022; E-mails: arashghch58@yahoo.com or a.ghorbani@mail.ilam.ac.ir

These examples clearly show the remarkable potential of new dihydropyridine derivatives as a source of valuable drug candidates, due to the potential importance of 1,4-dihydropyridyl compounds from a pharmaceutical, industrial and synthetic point of view [13].

Dihydropyridines are also important because of their applications in synthesis. Thus, some types of 1,4-dihydropyridines behave as mimics of the coenzymes NADH and NADPH and can therefore be employed as hydrogen transfer reagents. Furthermore, dihydropyridines have also been widely used as synthetic intermediates especially in the preparation of libraries of alkaloid-like compounds and related heterocyclic systems [14].

Dihydropyridines are often obtained by reduction of pyridinium salts, which in turn need to be prepared by *N*-alkylation of pyridines. A better approach would be one based on the direct construction of the dihydropyridine framework from acyclic precursors. The best known of these dihydropyridine syntheses is the Hantzsch reaction involving a multicomponent condensation of an aldehyde with a 1,3-dicarbonyl compound and ammonia [15-19].

RESULTS & DISCUSSION

In continuing our investigations on the synthetic organic reactions [20-23], in efforts to develop an efficient and environmentally-friendly procedure for the synthesis of 1,4-dihydropyridine derivatives, we have decided to prepare a new type of 1,4-dihydropyridines **4a-h** *via* one-pot and three-component condensation of *nano* aluminum nitride, a variety of aldehydes and 1,3-dicarbonyl compounds. It was found that benzyl-3-oxobutanoate **2** or 2-methoxyethyl-3-oxobutanoate **3** could be condensed with aromatic aldehydes **1a-e** and *nano* aluminum nitride (as a source of ammonia) to smoothly afford 1,4-dihydropyridines with excellent yields at 80°C in water solvent (Scheme **1**).

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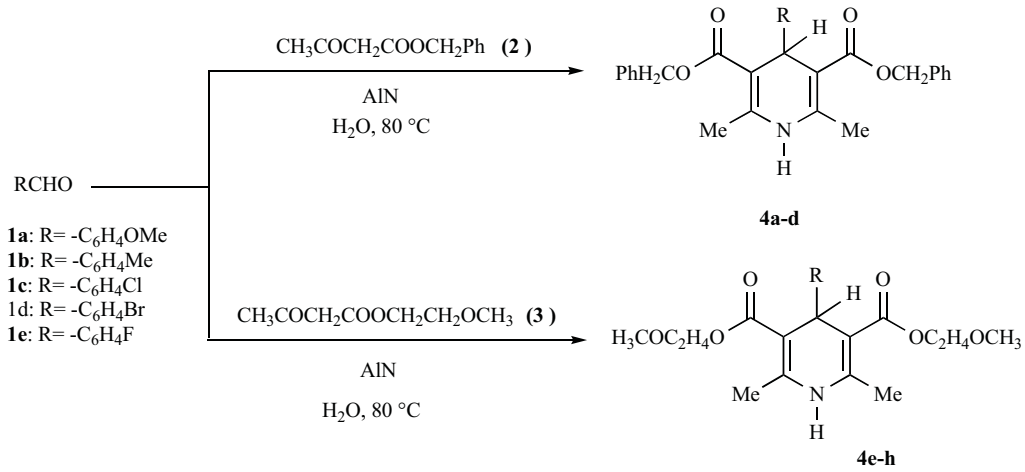


Scheme 1. Synthesis of 1,4-dihydropyridine derivatives.

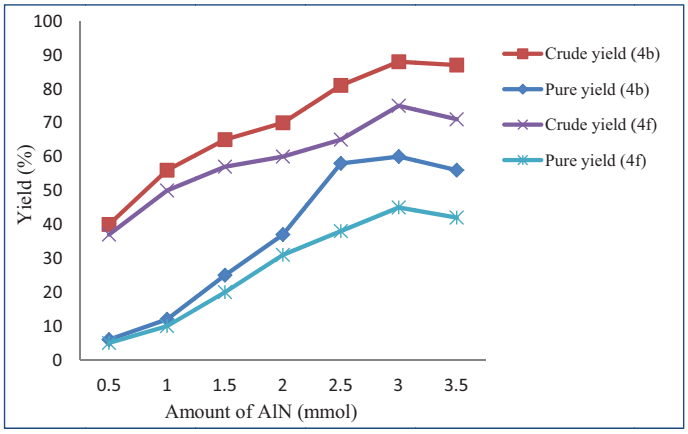


Fig. (1). Optimization of the amount of aluminum nitride for the synthesis of 1,4-dihydropyridine derivatives.

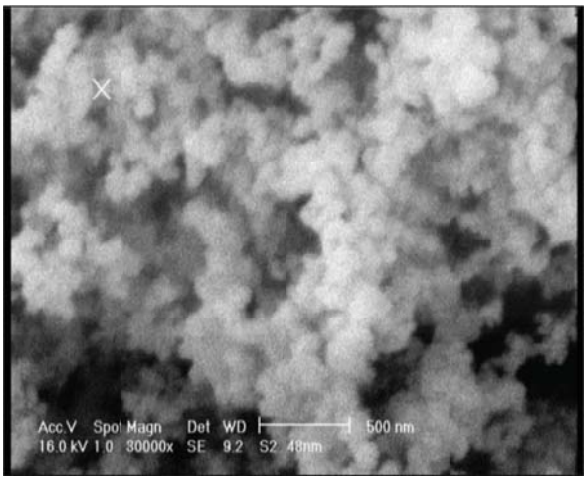


Fig. (2). SEM image of nano aluminium nitride.

To study the conditional aspects of Hantzch reaction we used aluminum nitride as alternative nitrogen source to improve the reaction conditions.

Initially, in order to determine the optimal amount of aluminum nitride, the reaction of 1 mmol of 4-bromobenzaldehyde **1d** or 4-methoxybenzaldehyde **1a**, 2.2 mmol of benzyl-3-oxobutanoate **2** or 2-methoxyethyl-3-oxobutanoate **3** in the presence of different amounts of *nano* aluminum nitride in water (5 mL) at 80°C was conducted. The results of the preparation of dibenzyl 4-(4-bromophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate **4b** and bis(2-methoxyethyl) 1,4-dihydro-4-(4-methoxyphenyl)-2,6-dimethylpyridine-3,5-dicarboxylate **4f** as a function of the amounts of aluminum nitride are shown in (Fig. **1**).

In view of these results, the optimal value for aluminum nitride was 3 mmol, which was subsequently applied for all cases.

The morphology of aluminium nitride was also observed by scanning electron microscopy (Fig. **2**). SEM image showed diameters of approximately 40nm.

Eventually, these optimized conditions were applied to the reaction of a variety of aldehydes and benzyl-3-oxobutanoate **2** or 2-methoxyethyl-3-oxobutanoate **3,** aluminum nitride and water in a sealed tube at 80°C, for 6 h, (There was no increase in the yield of the product after longer reaction times). The results for these condensations are summarized in (Table **1**).

In all cases, crude products were obtained by extracting the reaction mixtures with dichloromethane, and then purified by preparative TLC.

Table 1. One-pot Synthesis of 1,4-dihydropyridine Derivatives [a]

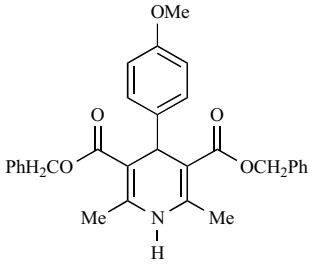
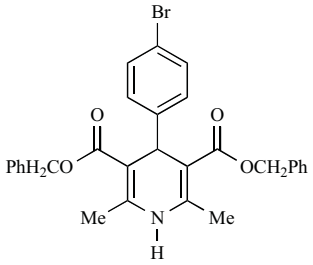
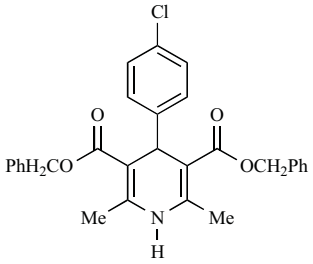
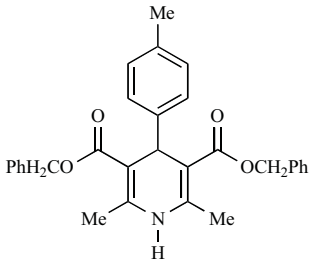
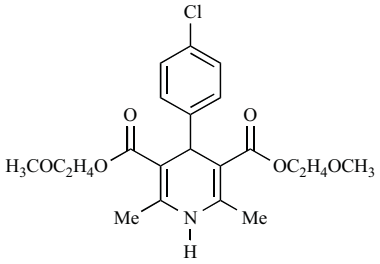
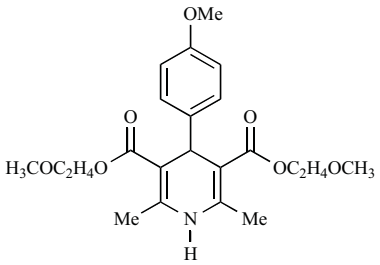
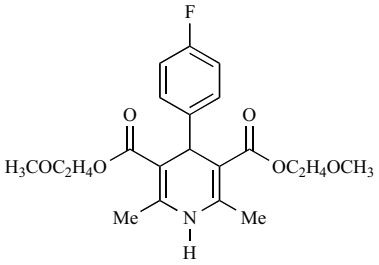
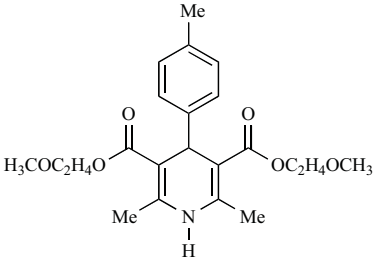
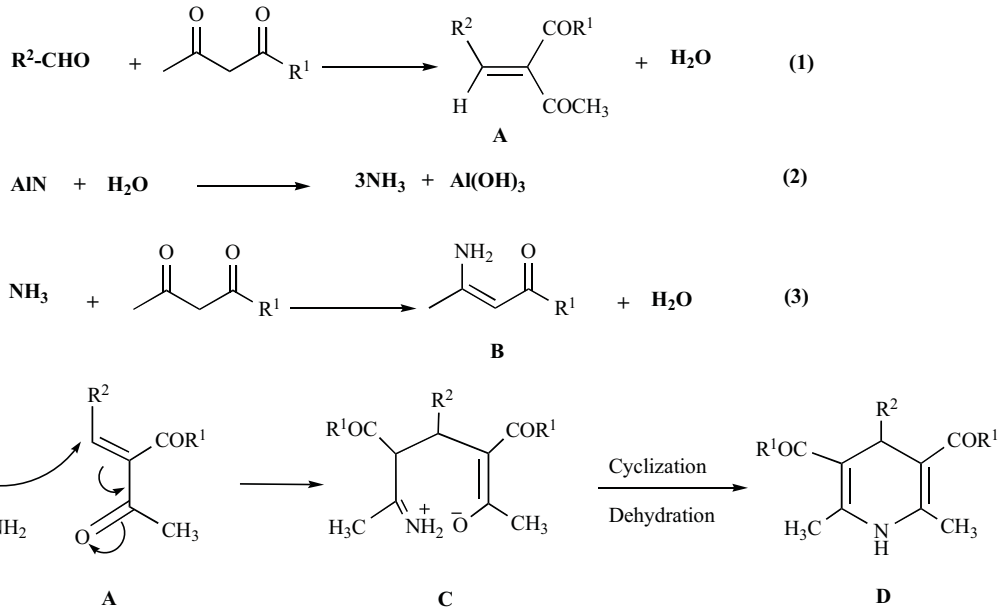
Entry	Compound	R^1	R^2	Product	Yield A[b] (B)[c] %
1	**4a**	OCH_2Ph	4-MeO-C_6H_4		96(45)
2	**4b**	OCH_2Ph	4-Br-C_6H_4		88(60)
3	**4c**	OCH_2Ph	4-Cl-C_6H_4		95(56)
4	**4d**	OCH_2Ph	4-Me-C_6H_4		93(41)
5	**4e**	$OC_2H_4OCH_3$	4-Cl-C_6H_4		87(56)
6	**4f**	$OC_2H_4OCH_3$	4-MeO-C_6H_4		75(45)

Table 1. Contd…..

Entry	Compound	R^1	R^2	Product	Yield A[b] (B)[c] %
7	**4g**	$OC_2H_4OCH_3$	4-F-C_6H_4		72(50)
8	**4h**	$OC_2H_4OCH_3$	4-Me-C_6H_4		76(41)

[a]Molar ration of the reagents: *β*-dicarbonylcompound/ aldehyde/ aluminum nitride= (2.2 mmol/ 1 mmol/ 3 mmol); [b] Crude isolated yield. [c] Yield of pure product (Purified by P-TLC).



Scheme 2. Possible mechanism.

As can be seen from (Table **1**), the experimental procedure is simple and mild and has the ability to tolerate a variety of functional groups such as methoxy, methyl, and halides under the reaction conditions.

According to the results, the reaction can be mechanistically considered to proceed via the initial formation of the intermediates **A** (equation 1) through a Knoevenagel condensation of an aldehyde with *β*-dicarbonyl compound.

Aluminum nitride contributes to generate a solution of ammonia *via* hydrolysis, which is known reaction (equation 2) [24-26].

A second key intermediate **B** is an enamine, which is produced by condensation of the of *β*-dicarbonylcompound with NH_3. Then, Michael addition between these two fragments (**A** and **B**) gives the 1,4-dihydropyridine derivative **D** (Scheme **2**).

In conclusion, we have described a successful strategy, an efficient and convenient green synthesis for the preparation of Hantzch 1,4-dihydropyridines 4a-h in three-component cyclocondensation reaction of different aldehydes, benzyl-3-oxobutanoate 2 or 2-methoxyethyl-3-oxobutanoate 3 and nano aluminium nitride in water. Hantzsch 1,4-dihydropyridine derivatives were synthesized

in a simple pathway without the use of metal as a catalyst or an organic solvent. Thus, this is an ecofriendly and environmentally friendly procedure for the synthesis of 1,4-dihydropyridine derivatives.

EXPERIMENTAL

General Methods

Chemicals were purchased from Sigma-Aldrich, Fisher, and Merck. The1,4-dihydropyridine derivatives were characterized by ^{1}H and ^{13}C NMR spectra (^{1}H NMR, 400 MHz; ^{13}C NMR, 100 MHz) and IR. Scanning electron microscopy (SEM) studies were conducted on a JSM 740 scanning electron microscope. TLC plates are prepared by mixing the adsorbent, such as silica gel type 60 (Merck) in water. This mixture is spread as thick slurry on an unreactive carrier sheet, usually glass. The resultant plate is dried and activated by heating in an oven for thirty minutes at 110 °C. The thickness of the absorbent layer is typically around 0.1 – 0.25 mm for analytical purposes and around 0.5 – 2.0 mm for preparative TLC.

General Procedure for Preparation of Dibenzyl 1,4-dihydro-4-(4-methoxyphenyl)-2,6-dimethylpyridine-3,5-dicarboxylate (4a):

To the mixture of aluminum nitride (0.123 g, 3 mmol) and 4-methoxybenzaldehyde (**1a**) (0.185 g, 1 mmol) in water (5 mL), benzyl-3-oxobutanoate (**2**) (0.423 g, 2.2 mmol) was added at room temperature. The reaction vessel was sealed and allowed to warm to 80°C over 6 h with constant stirring. Then the reaction mixture was cooled down to room temperature and the crude product was extracted by dichloromethane. Dichloromethane was removed by simple evaporation. Finally crude product (0.467 g, 88%) was purified using preparative TLC plate 0.207 g (60%); mp: 122-123°C; ir: NH 3328, CO 16998, 1611, 1507, 1439, 1237, 1198, 1073, 1029, 746 cm^{-1}; ^{1}H NMR: δ 2.34 (s, 6H), 3.79 (s, 3H), 5.06 (s, 1H), 5.13 (m, 4H), 5.99 (br, 1H), 6.73(d, 2H, J=8.8 Hz), 7.16 (d, 2H, J=8.4 Hz), 7.24-7.40 (m, 10H); ^{13}C NMR: δ 19.6, 38.6, 55.2, 65.6, 104.1, 113.3, 127.8, 127.9, 128.4, 129.1, 136.6, 140.1, 144.3, 157.9, 167.4. *Anal.* Calcd. for $C_{30}H_{29}NO_5$: C, 74.52; H, 6.04; N, 2.9. Found: C, 74.11; H, 5.66; N, 2.52.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

The authors acknowledge Ilam University, Ilam, Iran for financial support of this work.

SUPPLEMENTARY MATERIAL

Supplementary material is available on the publishers Web site along with the published article.

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