



THREE – COMPONENT REACTION OF 3 – NITRO BENZALDEHYDE, ISOPROPYL ACETOACETATE AND 1-BENZHYDRYLAZETIDIN – 3- YL - 2 AMINO – 2- IMMINOACETATE IN PRESENCE OF POTASSIUM CARBONATE: AN EFFICIENT ONE-POT SYNTHESIS OF 1, 4-DIHYDROPYRIDINE DERIVATIVE

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ABSTRACT

A new and efficient one-pot synthesis of 1, 4 – dihydropyridine derivative by three component reaction 3 - Nitro benzaldehyde, isopropyl acetoacetate and 1-benzhydrylazetididin -3 - yl - 2 amino - 2 - imminoacetate in presence of dimethylformamide is described. The reaction was performed in dimethylformamide at 90°C and mild basic condition.

Key words: 3 - Nitro benzaldehyde, isopropyl acetoacetate, 1-benzhydrylazetididin - 3- yl - 2 amino - 2- imminoacetate, dimethylformamide, Multicomponent, 1, 4-dihydropyridine derivative

INTRODUCTION

As green chemistry has become a major concern to organic chemists in present years, reactions under solvent-free conditions have received much attention. These reactions offer several advantages in preparative procedures such as environmentally friendly, simplifying work-up, formation of cleaner products, enhanced selectivity and much improved reaction rates¹.

Hantzsch 1, 4-dihydropyridines (1, 4-DHPS) are biologically active compounds which including various vasodilator, antihypertensive, branchodilator, antiatherodclerotic, hepatoprotective, antitumor, antimutagenic, geroprotective and antidiabetic agents². DHPs have found commercial utility as calcium channel blockers^{3,4} such as Azelnidipine, Nifedipine, Nitrendipine and Nimodipine. A number of DHP calcium antagonists have been introduced as potential drugs for the treatment of congestive heart failure^{5,6}. Among DHPs with other types of bioactivity, cerebrocrast has been introduced as a neuroprotectant and cognition enhancer. In addition, a number of DHPs with platelet antiaggregatory activity have also been discovered⁷.

1, 4-dihydropyridines have been synthesized by the Hantzsch reaction⁸, which involves cyclocondensation of an aldehyde, b-ketoester, and ammonia either in refluxing acetic acid or in refluxing ethanol. 1, 4-dihydropyridines have also been synthesized on a solid phase for making combinatorial libraries⁹. Recently, Hantzsch's reaction for the synthesis of dihydropyridines has received renewed interest and several improved procedures have been reported¹⁰⁻¹³. However, there are several disadvantages associated with these methodologies including unsatisfactory yields, long conversion times, difficult handling of reagents, toxic organic solvents. Recently, the microwave -promoting Hantzsch's reaction has also been reported¹⁴⁻¹⁷. Thus, development of facile and environmental friendly synthetic methods to the Hantzsch's reaction is demanded.

In this article, we wish to report a mild and efficient version of the Hantzsch's reaction for synthesis of 1,4-dihydropyridines by three component reaction 3 - Nitro benzaldehyde, isopropyl acetoacetate and 1-benzhydrylazetididin -3 - yl - 2 amino - 2 - imminoacetate in presence of dimethylformamide is described. The reaction

was performed in dimethylformamide at 90°C and mild basic condition.

CHEMISTRY

In scheme-1, preparation of 3-(1-benzhydrylazetididin-3-yl) 5-isopropyl 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4) from the condensation of 3- Nitro benzaldehyde (1) and isopropyl acetoacetate (2) by using of piperidine and acidic acetic acid to form (Z)-isopropyl 3-methyl-2-(3-nitrobenzylidene)but-3-enoate (3) a white solid obtained 1.0 w/w yield. In second conversion 1-benzhydrylazetididin-3-yl 2-amino-2-iminoacetate and (Z)-isopropyl 3-methyl-2-(3-nitrobenzylidene) but-3-enoate (3) in presence of sodium hydroxide and isopropyl alcohol a light yellow solid obtained. In **scheme 2** a mixture of components are 3- Nitro benzaldehyde (5), isopropyl acetoacetate (6) and 1-benzhydrylazetididin-3-yl 2-amino-2-iminoacetate (7) in the presence of potassium carbonate and dimethylformamide to obtained 3-(1-benzhydrylazetididin-3-yl)5-isopropyl2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4). In conclusion, a synthesis was developed which fulfilled our initial requirements of readily available starting materials no purifications and good yield. The basic premise of objective was too tried different a number of bases and solvents were studied given table 1. As shown below, but comparison this conversion of the reagent was more effective yield and purity.

EXPERIMENTAL SECTION

All reactions were run under a nitrogen atmosphere unless otherwise noted. All of the final compounds synthesized were characterized by ¹H and ¹³C NMR and melting point for solids.

(Z)-Isopropyl 3-methyl-2-(3-nitrobenzylidene) but-3-enoate (3): To stirred solution of isopropyl alcohol (25 mL), 3- Nitrobenzaldehyde (5 gm) and isopropyl acetoacetate (5.2 g) was added acetic and piperidine at cool to 5°C then maintained reaction mass at ambient temperature for 6 hrs resulting filtered the title compound (3).

¹HNMR (CDCl₃) δ ppm: 1.08, 1.26 (6H, 2d), 2.35 (3H, s), 2.63, 3.06, 3.50, 3.62 (1H, s), 7.1-8.2 (14H, m).

IR (Kbr): 3450, 3310, 1675

Mass spectra (m/z): 583 (M⁺ + H)

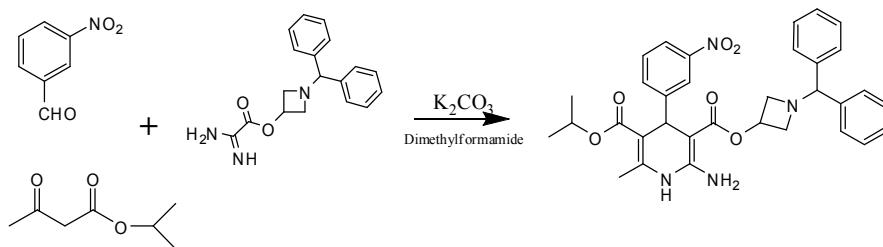
3-(1-benzhydrylazetid-3-yl) 5-isopropyl 2-amino-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4)

To stirred solution of isopropyl alcohol (25 mL), 3-Nitrobenzaldehyde (5 gm) and isopropyl acetoacetate (5.2 g) acetic and piperidine at cool to 5°C then maintained reaction

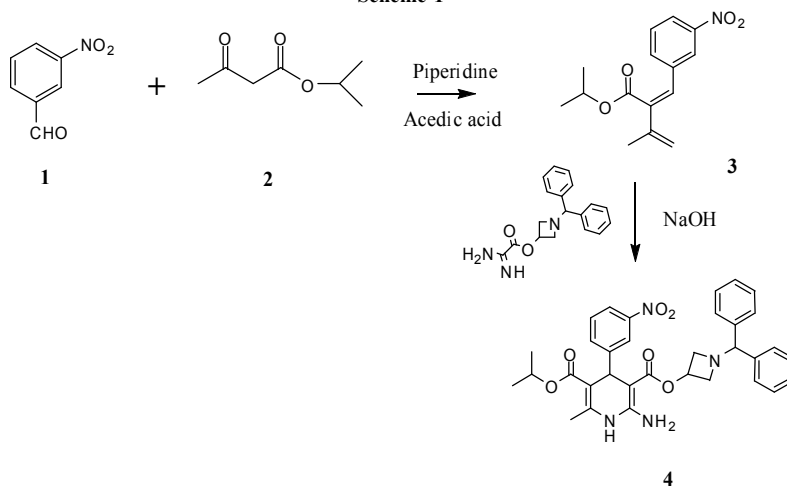
mass 2 hours and added 1-benzhydrylazetid-3-yl 2-amino-2-iminoacetate (6.4 g) then heated to 85°C for 10 hours resulting obtained title compound (2).

¹HNMR (CDCl₃) δ ppm: 7.2-8.1 (4H, m), 4.43 (1H, s), 3.76, 3.62 (2H, s), 1.7-1.69 (2H, s).

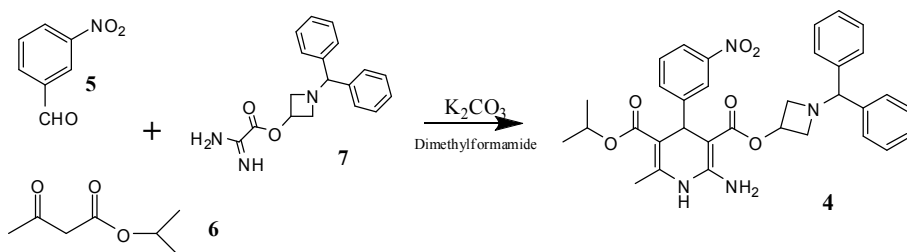
Mass spectra (m/z): 347 (M⁺ + H).



Scheme-1



Scheme 2

**CONCLUSION**

An efficient one-pot synthesis of 1, 4 – dihydropyridine derivative by three component reaction 3 - Nitro benzaldehyde, isopropyl acetoacetate and 1-benzhydrylazetid-3-yl - 2 amino - 2 - iminoacetate in presence of dimethylformamide is described.

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