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**R E S E A R C H  A R T I C L E**

# Sodium Tetrachloroaurate (III) dihydrate : A simple and Efficient Catalyst for the Synthesis of 1,4-dihydropyridine (Hantzsch Pyridines)

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**A B S T R A C T**

1,4-Dihydropyridine synthesis has been carried out using Sodium Tetrachloroaurate (III) dihydrate , as a catalyst. This protocol is applicable to a variety of aldehydes with β-ketoester and ammonium acetate to afford the corresponding Hantzsch pyridines in excellent yields. This multicomponent condensation took placevery smoothly in acetonitrile reflux.

**Keywords:** Aldehydes, Di ketones, NH4OAc, Sodium Tetrachloroaurate (III) dihydrate, 1,4-dihydropyridine

**A R T I C L E  I N F O**

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**C O N T E N T S**



## 1. Introduction

Multicomponent condensation strategies offer significant advantages over conventional linear-type synthesis in providing products with the diversity needed for the discovery of new lead compounds or lead optimization employing combinatorial chemistry [1-6]. In 1882, Arthur Rudolf Hantzsch, a German chemist, reported a cyclo condensation between ethyl acetoacetate, aldehyde and aqueous ammonium hydroxide to afford a heterocyclic system of 1,4-dihydropyridine; since then, it became familiar as the Hantzsch reaction [7,8]. The dihydro pyridine derivatives exhibit a large range of biological activities such as anticonvulsant, antitumor, antianxiety, vasodilator, bronchodilator, antidepressant, analgesic, hypnotic, anti-inflammatory and neuro protectants as well as platelet anti aggregatory agents [9-12]. Dihydropyridines are commercially used as calcium channel blockers (amlodipine, felodipine, nifedipine, nitrendipine, etc.) for the treatment of cardiovascular diseases (Figure 1). The tremendous biological activity of Hantzsch pyridines attracted many researchers and academicians. Hence, several attempts have been made to synthesize 1,4-dihydropyridine derivatives using various catalysts and

reaction conditions such as triphenyl phosphine [13], CAN [14], hetero polyacids [15], Zn complex [16], phenyl boronic acid [17], magnesium perchlorate [18], cyanuric chloride [19], Yb(OTf )3 [20], ionic liquid [21], organo catalyst [22], L-proline [23], molecular iodine [24], tetra butyl ammonium hydrogen sulfate [25] and glycerine-CeClO2.7H2O [26,27]. But many of the methods are suffering from some drawbacks such as long reaction time, low yields, tedious workup procedures and the use of expensive catalysts. Therefore, the development of efficient protocol is still in demand. As part of our research program in developing new methodologies [28-31], we report here in a simple and efficient procedure for the synthesis of 1,4-dihydropyridine derivatives using Sodium Tetrachloroaurate (III) dihydrateas a catalyst $NaAuCl_4.*2H_2O$ is a non-hygroscopic white solid that is highly soluble in water, a mild Lewis acid and a catalyst known for various organic transformations in the literature [32-34].

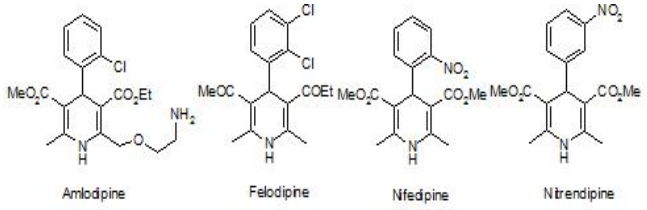


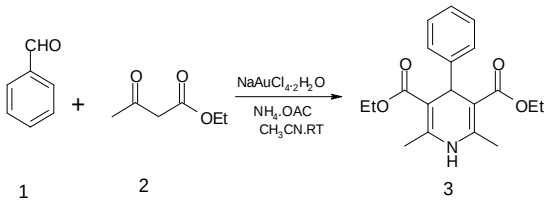

**Figure 1:** Some biologically active compounds of 1,4-dihydropyridines

Methods Results and discussions In a model reaction, benzaldehyde, β-ketoester and ammonium acetate were reacted in the presence of a catalytic amount (10 mol%) of $NaAuCl_4.*2H_2O$ at acetonitrile reflux. The reaction was completed within 3 h to afford the corresponding product, diethyl-2,6-dimethyl-4-phenyl- 1,4-dihydropyridine-3,5-dicarboxylate (compound 3a), in excellent yields as shown in Scheme 1. Encouraged by the result obtained with benzaldehyde, we had applied this methodology to a variety of aldehydes such as aromatic, hetero aromatic and aliphatic aldehydes successfully. The condensation reaction proceeded smoothly with β-ketoester and ammonium acetate in the presence of a catalytic amount of $NaAuCl_4.*2H_2O$ , at acetonitrile reflux to give the corresponding 1,4-dihydropyridine derivatives in very good yields. The acid sensitive aldehydes such as cinnamaldehyde (compound 1e), pyridine-2-aldehyde (compound 1 h) and 2-furfuraldehyde (compound 1i) worked well under these reaction conditions. The aromatic aldehydes having electron-withdrawing group react a little slower than aromatic aldehydes, and the aromatic aldehydes having electron-donating group react a little faster than aromatic aldehydes. In a similar manner, the aromatic aldehydes reacted comparatively faster than aliphatic aldehydes. This protocol is successfully applicable to both electron-rich as well as electron-deficient aldehydes. In general, all the reactions were completedwithin 3 to 5 h at 80°C to 85°C, and the products of 1,4-dihydropyridine derivatives were obtained in 75% to 93% yields. All the products were confirmed by their proton nuclear magnetic resonance (1H NMR), infrared (IR) and mass spectroscopy data.

## 2. Materials and Methods

**All Commercial grecgent were used without purification and all solvents were regenerated**

All the reaction mixtures were stirred megnetically and were monitored by TLC using 0.25mm. E-Mercu Silica gel 60f254 percolated glass plates, which were visualixed with UV light Metting points were recorded on a BuchieR-535 apparatus (BUCHI india private Ltd., Mumbai, India) and were uncorrected. IR speetro were recorded on a perkin-Elmer FT-IR 240-c Spectrophotometer (perkin Elmer Inc., Walthans, MA,USA) (IdORZBA) India private Ltd., New Delhi, india) in coely using TMS as internal standard Mass Spectro were recorded on a Finnigan MAT 1020 mass Spectrometer Thermo Scientific, Walthon, MA, USA) operating at 70er. General procedure for the synthesis of 1,4-dihydropyridines To a stirred mixture of aldehyde (212 mg, 2 mmol) and ethyl acetoacetate (572 mg, 4.4 mmol) in acetonitrile (10 mL) was added ammonium acetate (170 mg, 2.2 mmol) and ,$NaAuCl_4.*2H_2O$ (36.6 mg, 0.2 mmol).




**Scheme-1**

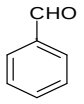
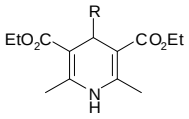
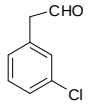
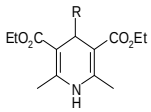
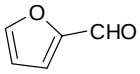
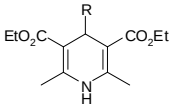
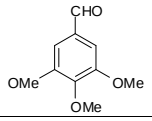
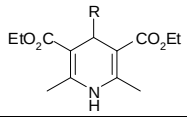
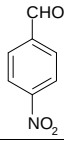
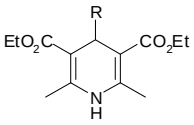
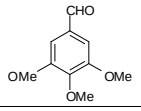
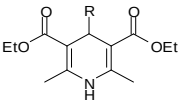
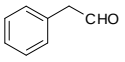
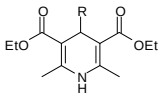
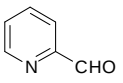
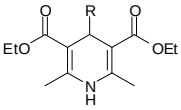
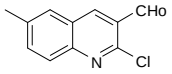
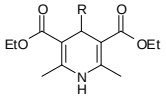
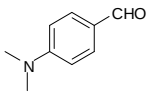
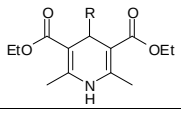
The resulting reaction mixture was refluxed for a specified period (Table 1). After completion of the reaction, as indicated by TLC, the solvent was removed under reduced pressure, and the residue was extracted with ethyl acetate (2 × 15 mL). The combined organic layers were washed with brine, dried over Na2SO4 and concentrated under reduced pressure to obtain the crude products, which were purified by column chromatography using silica gel 60 to 120 mesh and eluted with ethyl acetate-hexane mixture in 3:7 ratio. All the products were confirmed by their spectral data and compared with literature reports.

## 3. Results and Discussion

**Spectral data for all the compounds**

**Diethyl-2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (3a)**: Solid, Melting point (Mp) 155°C to 156°C. IR (KBr): υ 3,342, 3,061, 2,978, 2,931, 1,690, 1,651, 1,489, 1,453, 1,375, 1,300, 1,248, 1,212, 1,121, 1,091, 1,024, 825, 767 and 701 cm−1 ; 1H NMR (300 MHz, CDCl3): δ 1.25 (t, 6 H, J = 6.0 Hz), 2.35 (s, 6 H), 4.10 (q, 4 H, J = 6.0 Hz), 4.90 (s, 1 H), 5.52 (brs, 1 H, NH) and 7.08 to 7.25 (m, 5 H); 13C NMR (75 MHz, CDCl3): δ 168.3, 146.1, 143.9, 136.1, 129.2, 126.8, 103.9, 60.1, 40.0, 20.5 and 14.3; EIMS m/z (%): 328 (m+ 95), 284 (100), 256 (25), 252 (35), 225 (15), 219 (10), 195 (10), 181 (12), 173 (25), 131 (15) and 107 (20).

**Table 1:** NaAuCl4.*2H2OCatalyzed synthesis of Hantzsch pyridines (3a-j)

| S.No | Aldehyde (R) | Products | Time(min) | Yield (%) |
|---|---|---|---|---|
| 3 |  |  | 20 | 84 |
| b. |  |  | 25 | 83 |
| c. |  |  | 25 | 83 |
| d. |  |  | 20 | 88 |
| e. |  |  | 30 | 76 |
| f. |  |  | 3.0 | 93 |
| g. |  |  | 4.0 | 89 |
| h. |  |  | 4.0 | 82 |
| i. |  |  | 4.0 | 80 |
| j. |  |  | 4.0 | 80 |

## 4. Conclusion

In conclusion, we have demonstrated a simple and efficient three-component process for the synthesis of 1, 4-dihydropyridines by condensation of aldehyde, β-ketoester and ammonium acetate using $NaAuCl_4.*2H_2O$as the catalyst. The notable features of this protocol are mild reaction conditions, simplicity in operation, improved yields, and cleaner reaction profiles.

## 5. Acknowledgements

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