# Yttrium (III) Chloride: A simple and anefficient catalyst for the synthesis of 1, 4-dihropyridines (Hantzsch pyridines)

**Racha Lenin, Rallabandi Madhusudhan Raju* and Yekkirala Venkateswarlu**

**Abstract:** A simple and an efficient procedure for the synthesis of 1,4-Dihydropyridines also known as Hantzsch pyridines has been described. The methodology described, involves a condensation reaction between an aldehyde, *β*-ketoester and ammonium acetate in the presence of Yttrium (III) Chloride as a catalyst. This protocol is simple and applicable to a wide variety of aldehydes and *β*-ketoester compounds to provide the 1,4-Dihydropyridines in good to excellent yields.

**Keywords:** Aldehydes, diketone, ammonium acetate, Yttrium (III) Chloride, 1, 4-dihydropyridines, Ethyl acetoacetate and Hantzsch pyridines

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## 1 INTRODUCTION

FUNCTIONALIZED nitrogen-heterocycles have always played a predominant role in medicinal chemistry and they have been intensively used as scaffolds for drug development. Multicomponent reactions have emerged as a powerful tool for the preparation of bioactive heterocyclic compounds. Multicomponent reactions, such as the Biginelli, passerine, Ugi, and Hantzsch, provide a wide variety of important heterocycles. [1-5]. In 1882, Arthur Rudolf Hantzsch, a German chemist reported a cyclocondensation reaction between ethyl acetoacetate, aldehyde and aqueous ammonium hydroxide to afford a heterocyclic system of 1, 4-dihydropyridine, which has become familiar as Hantzsch reaction [6, 7]. The dihydropyridine derivative exhibits a wide range of biological activities, particularly in the treatment of cardiovascular diseases, as calcium channel blockers. 1, 4-dihydropyridines have also been used as anticonvulsant, antitumor, antianxiety, vasodilator, bronchodilator, antidepressive, analgesic, hypnotic, antiinflammatory and neuroprotectants as well as platelet antiaggregatory agents [8-11]. The tremendous biological activity of Hantzsch pyridines, attracted many researchers and academicians. Hence, several attempts have been made to synthesize the 1,4-dihydropyridine derivatives using various catalysts such as ([bmim]$BF_4$), $CeCl_3.7H_2O$, $Bi(NO_3)_3$, ([BPy][$BF_4$]), $Mg_3N_2$, $P(C_6H_5)_3$, NaOH, Cyanuric chloride and $Yb(OTf)_3$ [12-21].

But many of these methods are suffering from drawbacks such as long reaction time, tedious workup procedures, low yields of the products and the use of expensive catalysts. Therefore, the development of an efficient protocol is still in demand. As part of our research program in developing new methodologies, herein we report, a simple and an efficient procedure for the synthesis of 1,4-dihydropyridine derivatives using Yttrium (III) Chloride ($YCl_3$) as an efficient catalyst in one pot condensation reaction. Yttrium (III) Chloride ($YCl_3$) is a non hygroscopic, white solid, highly soluble in water, mild Lewis acid and a well known catalyst for various organic transformations in the literature [22-23]. The polar solvent, acetonitrile was found to be the best solvent for this condensation reaction.

## 2 RESULTS AND DISCUSSION

In a typical experiment, benzaldehyde, ethyl acetoacetate and ammonium acetate were made to react in the presence of Yttrium (III) Chloride (YCl3) as a catalyst (10 mol %) and acetonitrile as a solvent under reflux conditions as shown the **Scheme 1**. The progress of the reaction was monitored by thin layer chromatography (TLC). It was observed, that one of the reactants benzaldehyde disappeared, after 3 hrs of the reaction time, indicating the completion of the reaction. The solvent from the reaction mass was then removed under reduced pressure and the residue obtained was extracted with ethyl acetate. The organic layer obtained was washed with brine,

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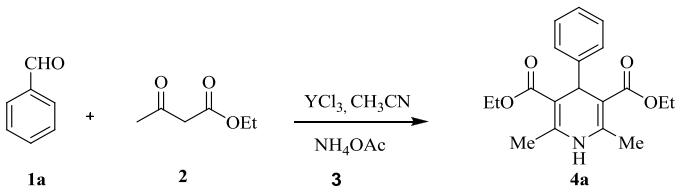
dried over anhydrous Sodium sulphate and concentrated under reduced pressure to obtain the crude product. The crude product obtained was purified by column chromatography using 60-120 silica mesh and eluted using 20% ethyl acetate in hexane to get the pure product, diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**4a**) in 88% yield.

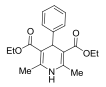
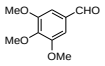
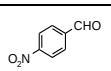
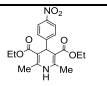
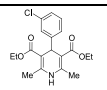
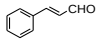
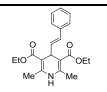
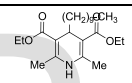
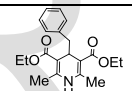
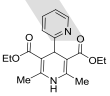
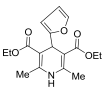
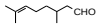
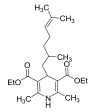
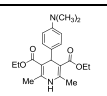
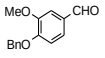
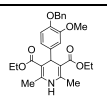



**Scheme 1**

This methodology is successfully applied to a variety of aldehydes such as aromatic, heteroaromatic and aliphatic aldehydes. The aromatic aldehydes having different substitution on ring system (electron withdrawing and donating groups) were used for the condensation reaction without any difficulty. The aliphatic aldehyde such as undecanal and citronella aldehyde required little longer time (5 hours) to form the corresponding dihydropyridine derivatives. The *a β*-unsaturated aldehyde like cinnamaldehyde, also used in the condensation reaction, resulted in the good yield of the DHP derivatives. Further the heteroaromatic aldehydes, which were sensitive towards acidic medium, also reacted very well to afford the dihydropyridine derivatives. From the above observation, it is very clear that this methodology can be extended to a wide range of reactants having different functional groups. Many of the pharmacologically relevant substitution patterns on the aryl ring can thus be introduced with high efficiency. In general, all the reactions were carried out in acetonitrile at 75-80°C, in the presence of $YCl_3$ as a catalyst using (10 mol%), the reaction was completed within 3 to 5 hours and the yields obtained varied from 75-90%. All the products were confirmed by their proton nuclear magnetic resonance ($^1$H-NMR), infrared (IR) and Elecron Impact ionization mass spectroscopy (EIMS) data.

**TABLE 1**
YTTRIUM (III) CHLORIDE ($YCl_3$) CATALYZED SYNTHESIS OF HANTZSCH PYRIDINES (**4A-L**)

**REACTANTS**: ALDEHYDES (**1A-L**), ETHYL ACETOACETATE (**2**), AND AMMONIUM ACETATE (**3**)

| ENTRY | ALDEHYDE (*1A-L*) | PRODUCT (*4A-L*) | TIME (H) | YIELD (%) |
|---|---|---|---|---|
| A |  |  | 3.0 | 88 |
| B |  |  | 3.0 | 90 |
| C |  |  | 5.0 | 80 |
| D |  |  | 4.0 | 89 |
| E |  |  | 4.0 | 75 |
| F |  |  | 5.0 | 78 |
| G |  |  | 4.0 | 82 |
| H |  |  | 3.0 | 80 |
| I |  |  | 3.0 | 90 |
| J |  |  | 5.0 | 79 |
| K |  |  | 4.0 | 81 |
| L |  |  | 3.0 | 86 |

## 3 EXPERIMENTAL SECTIONS

**General Methods:**

Melting points were recorded on Büchi R-535 apparatus Nuclear Magnetic Resonance ($^1$H NMR) spectra were recorded with a Bruker AM 300 MHz, NMR spectrometer. Infrared spectra were recorded using neat liquids or KBr pellets on perkin- Elmer 683 or Thermo Nicolet Nexus 670 spectrometer. Mass spectra were recorded using API 2000 Perkin-Elmer (PE-SCIEX) mass spectrometer in the electrospray ionization mode.

**General procedure:**

To a stirred mixture of aldehyde (2 mmole), ethyl acetoacetate (4.4 mmole) in acetonitrile (10 ml) was added ammonium acetate (2.2 mmole) and yttrium chloride (0.2 mmole). The resulting reaction mixture was refluxed for a specified period given in (**Table 1**). After the completion of the reaction as indicated by TLC, the solvent was removed under reduced pressure and the residue was extracted with ethyl acetate (2x15 ml). The organic layer was washed with brine, dried over $Na_2SO_4$ and concentrated under reduced pressure to obtain the crude product, which was purified by column chromatography using silica gel 60-120 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.



## 4 SPECTRAL DATA FOR 4A-L

**Diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (4A)**:

Solid, mp: 155-156°C. $^1$H-NMR (300 MHz, $CDCl_3$)δ: 1.25 (t. 6H, J = 6.0 Hz), 2.30 (s, 6H), 4.10 (q, 4H, J = 6.0 Hz), 4.90 (s, 1H), 5.51 (br, 1H, NH), 7.08-7.25 (m, 5H). IR (KBr) ($cm^{-1}$): 3342, 3061, 2978, 2931, 1690, 1651, 1481, 1453, 1375, 1300, 1248, 1212, 1121, 1091, 1024, 825, 767, 701. Mass: m/z =330 ([M+H] $^+$, 95), 284 (100), 256 (25), 252 (15), 173 (20), 131 (15), 107 (20).

**Diethyl2,6-dimethyl-4-(3,4,5-trimethoxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4B)**:

Solid, mp: 160-162°C. $^1$H NMR ($CDCl_3$) δ: 1.23 (t, 6H, *J* = 6.0 Hz), 2.35 (s, 6H), 3.80 (s, 9H), 4.12 (q, 4H, *J* = 6.0 Hz), 4.90 (s, 1H), 5.52 (s, 1H, NH), 6.45 (s, 2H). IR (KBr): 3357, 2928, 2853, 1696, 1636, 1593, 1497, 1460, 1378, 1317, 1273, 1205, 1127, 1092, 1001, 864, 803, 748, 627, 576 cm.$^{-1}$ ESI-MS: *m/z* = 420 ([M+H]$^+$, 30), 374 (25), 346 (20), 328 (5), 252 (100).

**Diethyl 2,6-dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine -3,5-dicarboxylate (4C)**:

Solid, mp: 133-134°C. $^1$H NMR ($CDCl_3$) δ: 1.25 (t, 6H, *J* = 6.0 Hz), 2.35 (s, 6H), 4.10 (q, 4H, *J* = 6.0 Hz), 5.05 (s, 1H), 7.41 (d, 2H, *J* = 6.5 Hz), 8.06 (d, 2H, *J* = 6.5 Hz). IR (KBr): 3341, 3084, 2979, 2927, 2855, 1683, 518, 1484, 1344, 1301, 1213, 1101,1020, 828, 754, 706, 627 cm.$^{-1}$ ESI-MS: *m/z* = 375 ([M+H]$^+$, 45), 348 (10), 329 (100), 301 (20), 102 (10).

**Diethyl 2,6-dimethyl-4-(3-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4D)**:

Solid, mp: 130-131°C. $^1$H NMR ($CDCl_3$) δ: 1.23 (t, 6H, *J* = 6.0 Hz), 2.36 (s, 6H), 4.10 (q, 4H, *J* = 6.0 Hz), 4.90 (s, 1H), 5.58 (br, 1H, NH), 7.05-7.20 (m, 4H). IR (KBr): 3323, 3246, 3098, 2979, 2925, 1705, 1649, 1488, 1375, 1333, 1299, 1214, 1119, 1022, 869, 788, 751, 694 cm.$^{-1}$ ESI-MS: *m/z* = 364 ([M+H]$^+$, 65), 318 (100), 171 (25).

**Diethyl 2,6-dimethyl-4-(E-styryl)-1,4-dihydropyridine-3,5-dicarboxylate (4E)**:

Solid, Mp:148 150°C. $^1$H NMR ($CDCl_3$) δ: 1.25 (t, 6H, *J* = 6.0 Hz), 2.40 (s, 6H), 4.18 (q, 4H, *J* = 6.0 Hz), 4.60 (d, 1H, *J* = 4.5 Hz), 5.60 (br, 1H), 6.15 (dd, 2H, *J* = 4.5 & 14.8 Hz), 7.10-7.34 (m, 5H). IR (KBr): 3335, 3242, 3098, 3023, 2981, 1690, 1645, 1491,1447. 1373, 1327, 1297, 1259, 1220, 1160, 1120, 1097, 1052, 1025, 968, 783, 757, 718, 697 cm.$^{-1}$ ESI-MS: *m/z* = 356 ([M+H]$^+$, 30), 253 (30), 252 (100), 244 (10).

**Diethyl 4-n-decyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4F)**:

Solid, mp: 120-125°C. $^1$H NMR ($CDCl_3$): δ 0.90 (t, 3H, *J* = 6.0 Hz), 1.20-1.36 (m, 24H), 2.29 (s, 6H), 3.85 (t, 1H, *J* = 6.0 Hz), 4.20 (q, 4H, *J* = 6.0 Hz), 5.48 (s, 1H, NH). IR (neat): 3377, 2926, 2855, 1728, 1567, 1461, 1376, 1282, 1233, 1104, 1041, 860, 772, 640 cm.$^{-1}$ ESI-MS: *m/z* = 393 ([M]$^+$, 100), 335 (10), 320 (10).

**Diethyl 4-benzyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4G)**:

Solid. Mp:118-119°C. $^1$H NMR ($CDCl_3$) δ: 1.26 (t, 6H, *J* = 6.0 Hz), 2.15 (s, 6H), 2.55 (d, 2H, *J* = 5.0 Hz), 3.55 (t, 1H), 4.05 (q, 4H, *J* = 6.0 Hz), 5.45 (br, 1H, NH), 7.10-7.30 (m, 5H). IR (KBr): 2978, 2927, 1719, 1592, 1443, 1369, 1289, 1252, 1222, 1105, 1043, 863, 769, 699 cm.$^{-1}$ ESI-MS: *m/z* (%) = 344 ([M+H]$^+$, 05), 298 (10), 252 (100), 242 (05).

**Diethyl 2,6-dimethyl-4-(pyridin-2-yl)-1,4-dihydropyridine-3,5-dicarboxylate (4H)**:

Solid, mp: 166-168°C. $^1$H NMR ($CDCl_3$): δ 1.20 (t, 6H, *J* = 6.0 Hz), 2.25 (s, 6H), 4.05 (q, 4H, *J* = 6.0 Hz), 5.12 (s, 1H), 7.08-7.12 (m, 1H), 7.32-7.38 (m, 1H), 7.51-7.58 (m, 1H), 8.05 (br, 1H), 8.48 (d, 1H, *J* = 6.0 Hz). IR (KBr): 3273, 3171, 3053, 2925, 1670, 1638, 1592, 1509, 1478, 1434, 1366, 1304, 1256, 1212, 1116, 1090, 1018, 776,

751, 677 cm.$^{-1}$ ESI-MS: *m/z* = 331 ([M+H]$^+$, 100), 308 (10), 285 (08).

**Diethyl 4-(furan-2-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4I)**:

Solid, mp: 158-160°C. $^1$H NMR ($CDCl_3$) δ: 1.28 (t, 6H, *J* = 6.0 Hz), 2.32 (s, 6H), 4.20 (q, 4H), 5.12 (s, 1H), 5.61 (br, 1H), 5.90 (d, 1H), 6.20 (d,1H), 7.18 (dd, 1H). IR (KBr): 3346, 2923, 2852, 1701, 1650, 1488, 1372, 1332, 1300, 1263, 1210, 1121, 1095 1048, 1013, 921, 807, 730, 687 cm.$^{-1}$ ESI-MS *m/z* =: 320 ([M+H]$^+$, 45), 318 (20), 304 (40), 252 (100), 214 (05).

**Diethyl4-(2,6-dimethylhept-5-enyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate(4J)**:

$^1$H NMR ($CDCl_3$) δ: 0.88 (d, 3H), 1.20-1.35 (m, 8H), 1.58 (s, 3H), 1.68 (s, 3H), 1.80-1.95 (m, 5H), 2.30 (s, 6H), 3.90 (t, 1H), 4.20 (q, 4H, *J* = 6.0 Hz), 5.20-5.40 (m, 1H), 5.48 (br, 1H, NH). IR (KBr): 3373, 2967, 2927, 1728, 1565, 1449, 1377, 1283, 1236, 1106, 1040, 859, 775 cm.$^{-1}$ ESI-MS: *m/z* = 378 ([M+H]$^+$, 40), 376 (50), 332 (10), 306 (05), 274 (05), 252 (80), 116 (10), 65 (05).

**Diethyl4-[4-(dimethylamino)phenyl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4K):**

$^1$H NMR ($CDCl_3$): δ 1.26 (t, 6H, *J* = 6.0 Hz), 2.32 (s, 6H), 2.90 (s, 6H), 4.02-4.15 (m, 4H), 4.81 (s, 1H), 5.50 (s, 1H, NH), 6.70 (d, 2H), 7.10 (d, 2H, *J* = 7.0 Hz). IR (KBr): 3319, 3095, 2979, 2923, 2804, 1697,1674, 1613, 1519, 1492, 1446, 1352, 1302, 1276, 1203, 1128, 1096, 1050, 1021, 945, 818, 785, 747, 683 cm.$^{-1}$ ESI-MS: *m/z* (%) = 373 ([M+H]$^+$, 100), 252 (20), 55 (20).

**Diethyl4-[4-(benzyloxy)-3-methoxyphenyl]-2,6-dimethyl-1,4-dihydropyridine-3,5-di carboxylate (4L)**:

Solid, mp: 307-308°C. $^1$H NMR ($CDCl_3$) δ: 1.25 (t, 6H, *J* = 6.0 Hz), 2.32 (s, 6H), 3.82 (s, 3H), 4.10 (q, 4H), 4.85 (s, 1H), 5.05 (s, 2H), 5.42 (s, 1H, NH), 6.62-6.70 (m, 2H), 6.82 (d, 1H), 7.28-7.42 (m, 5H). IR (KBr): 3365, 3063, 2926, 2853, 1693, 1642, 1621, 1511, 1484, 1422, 1380, 1270, 1201,1161, 1093, 1049, 1007, 862, 812, 748, 703, 658 cm. $^1$ESI-MS: *m/z* = 465 ([M], 35), 464 (65), 420 (15), 392 (20), 367 (10), 322 (10), 252 (100), 102 (10), 75 (10).

## 4 Conclusion

In conclusion, yttrium trichloride was found to be an efficient catalyst for the synthesis of 1,4-dihydropyridines in very good to excellent yields. This methodology offers several advantages e.g. mild reaction conditions, enhanced reaction rates, easy isolation of products and operational simplicity. The scope and generality of this protocol was illustrated with respect to various aldehydes and ethyl acetoacetate compounds.

## 5 Acknowledgment

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