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Synthesis and Characterization of 1,4-Dihydropyridines Catalyzed by $Zn(OTf)_2$

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ABSTRACT

A simple and efficient protocol for the synthesis of 1,4-dihydropyridines has been developed. In this one-pot multicomponent condensation methodology, all the reactants aldehydes, β-ketoester, ammonium acetate and catalyst were subjected to react at acetonitrile reflux to afford the corresponding products in very good yields. In all reactions, the catalyst $Zn(OTf)_2$ was used in catalytic amount only and all the products were characterized by their spectroscopy analysis.

Keywords: Aldehydes, diketones, NH_4OAc, $Zn(OTf)_2$, 1, 4-dihydropyridines.

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INTRODUCTION

The 1,4-dihydropyridine (DHPs) scaffold is an important pharmacophore found in a large number of biologically active and potential therapeutic compounds such as calcium channel blockers, multidrug resistant reversing agents, HIV protease inhibitors and antileishmanial.[1] The 1,4-DHPs also used for the treatment of vascular disorders,[2,3] anticancer,[4] bronchodilating,[5] antidiabetic,[6] antianginal[7] and other pharmacological activities.[8] The biological importance of Hantzsch pyridines, attracted many researchers and academicians. Hence, several attempts have been made to synthesize the 1,4-dihydropyridine derivatives using various catalysts and reaction conditions such as $CeCl_3$, Ionic liquid, Cellulose Sulphuric acid, NaOH, TPP, $Fe(NH_4)_2(SO_4)_2$, TCT, $Yb(OTf)_3$, L-proline, [9-17] Mw assisted, [18] Solar thermal energy,[19] Ultrasound irradiation,[20] Green solvents[21] Solid support[22] and Grignard reagent. [23] 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. Herein we report, a simple and efficient procedure for the synthesis of 1,4-dihydropyridine derivatives using Zinc triflate as a catalyst. Zinc triflate is a white solid, highly soluble in water, mild Lewis acid and known catalyst for various organic transformations in the literature. [24]

MATERIALS AND METHODS:

All commercial reagents were used without purification and all solvents were reagent grade. All the reaction mixtures were stirred magnetically and were monitored by TLC using 0.25 mm E-Merck silica gel $60F_{254}$ percolated glass plates, which were visualized with UV light. Melting points were recorded on a Buchi R-535 apparatus (BUCHI India Private Ltd., Mumbai, India) and were uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectro photometer (Perkin Elmer, Inc., Waltham, MA, USA) using a KBr disk. ^{1}HNMR spectra were recorded on a Gemini-200 spectrometer (HORIBA India Private Ltd., New Delhi, India) in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer (THERMO Scientific, Waltham, MA, USA) operating at 70 eV.

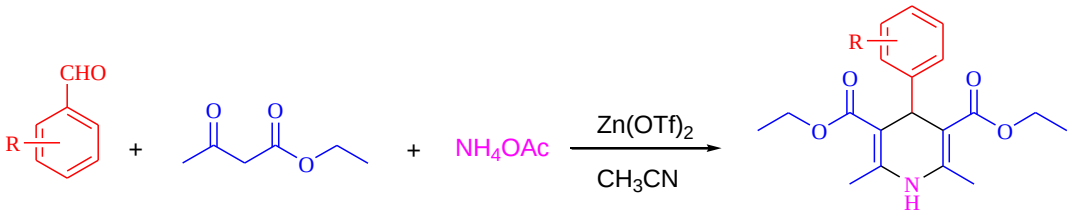
Experimental procedure:

General procedure: To a mixture of aldehyde (2 mmol), ethyl acetoacetate (4.4 mmol) in acetonitrile (10 mL) was added ammonium acetate (2.2 mmol) and zinc triflate (10 mol %). The resulting reaction mixture was stirred 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 combined organic layers were

washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to obtain the crude product, which were purified by column chromatography using silica gel 60-120 mesh and eluted with ethyl acetate-hexane mixture in 3:7 ratios. All the products were confirmed by their spectral data and compared with literature reports.

Results and Discussion:

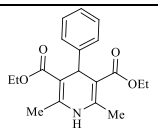
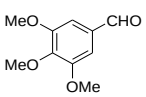
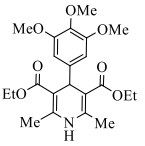
In a typical experiment, benzaldehyde, ethyl acetoacetate and ammonium acetate were reacted in the presence of $Zn(OTf)_2$ (10 mol%) at acetonitrile room temperature**.** The reaction was completed within 2 hours to afford the corresponding product, diethyl-2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**4a**) in 90% yield as shown in the **(Scheme-1)**.

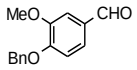
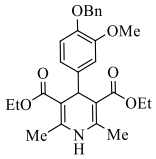
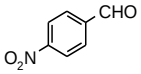
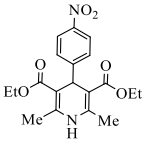
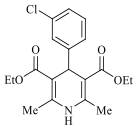
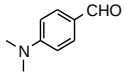
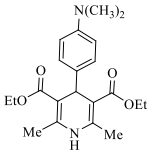
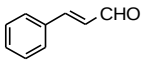
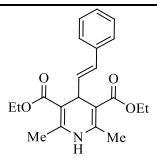
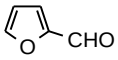
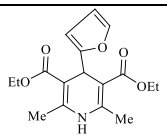
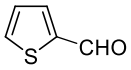
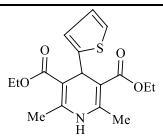
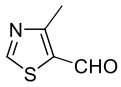
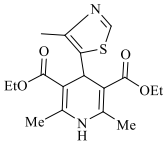
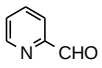
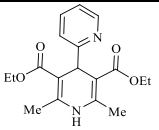
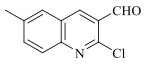
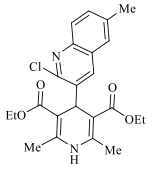
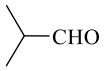
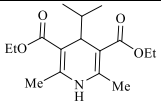


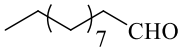
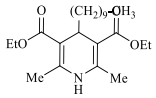
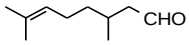
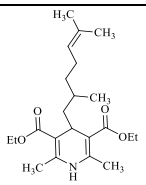
Scheme-1

This methodology is applied to a variety of aldehydes such as aromatic, heteroaromatic and aliphatic successfully. The aromatic aldehydes having different substitution on ring system (electron withdrawing and electron donating groups) were used for the condensation without any difficulty. Where as in the ease of aliphatic aldehyde such as undecanal and citronella requires little longer time (4 h) to form the corresponding dihydropyridine derivatives, *α, β*-unsaturated aldehyde like (cinnamaldehyde) also forms the condensation product in very good yield. Further the heteroaromatic aldehydes, which were sensitive towards acidic medium, also reacted very well to afford the dihydropyridine derivatives.

Table.1: Zinc triflate: Catalyzed synthesis of Hantzsch pyridines:

Entry	Aldehyde	Product (4a-o)	Time (h)	Yield (%)
a			2.0	90
b			2.0	93

c			3.0	87
d			4.0	84
e			2.0	86
f			3.5	82
g			2.0	82
h			2.0	94
i			3.0	85
j			3.5	83
k			2.5	84
l			4.0	82
m			3.5	83

n			4.0	85
o			4.0	86

From the above observation; it is very clear that this methodology is applicable 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. All the reactions were carried out using the catalyst $Zn(OTf)_2$ (10 mol%). All the reactions were completed within 2.0 to 4.0 h of reaction time and the yields were 82-94%. The experimental procedure was very simple and the isolation of products also very easy.

Analytical data:

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

Solid, Mp: 154-156 ^{o}C.

IR (KBr): ῡ 3342, 3061, 2978, 2930, 1689, 1651, 1488, 1453, 1375, 1300, 1248, 1212, 1121, 1091, 1024, 825, 767, 701 cm.$^{-1}$

^{1}H NMR ($CDCl_3$): 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 (brs, 1H, NH), 7.08-7.25 (m, 5H).

ESI-MS: *m/z* 329 ([M-H],$^{+}$ 90), 284 (95), 256 (20), 252 (25), 173 (10), 131 (06), 107 (10).

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

Solid, Mp: 180-181 ^{o}C.

IR (KBr): ῡ 3357, 2928, 2853, 1696, 1636, 1593, 1497,1460, 1378, 1317, 1273, 1205, 1127, 1092, 1001, 864, 803, 748 cm.$^{-1}$

^{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 (brs, 1H, NH), 6.45 (s, 2H).

ESI-MS: *m/z* (%): 420 ([M+H]$^{+}$, (30), 374 (25), 346 (20), 328 (10), 252 (100), 227 (10), 170 (10), 121 (10)

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

Low melting solid. IR (KBr): ῡ 3365, 3063, 2926, 2853, 1693, 1642, 1621, 1511, 1484, 1422, 1380, 1270, 1201,

1161, 1093, 1049, 1007, 862, 812, 748, 703 cm.$^{-1}$

^{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, *J* = 6.0 Hz), 4.85 (s, 1H), 5.05 (s, 2H), 5.42 (brs, 1H, NH), 6.62-6.70 (m, 2H), 6.82 (s, 1H), 7.28-7.42 (m, 5H).

ESI-MS *m/z* (%): 465 ([M+H],$^+$ 35), 464 (65), 420 (15), 392 (20), 252 (100), 102 (15), 75 (10).

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

Solid, Mp. 134-136 ^{o}C.

IR (KBr): ῡ 3341, 3084, 2979, 2927, 2855, 1683, 1518, 1484, 1344, 1301, 1213, 1101, 1020, 828, 754, 706 cm.$^{-1}$

^{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).

ESI-MS *m/z* (%): 375 ([M+H]$^+$, 45), 329 (100), 301 (25), 102 (10).

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

Solid, Mp.133-135 ^{o}C.

IR (KBr): ῡ 3323, 3246, 3098, 2979, 2925, 1705, 1649, 1488, 1375, 1333, 1299, 1214, 1119, 1022, 869, 788, 751 cm.$^{-1}$

^{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), 5.60 (brs, 1H, NH), 7.05-7.20 (m, 4H).

ESI(+)-MS *m/z* (%): 386 ([M+H]$^+$, 65), 364 (40), 318 (100), 171 (25).

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

Solid, Mp: 125-127 ^{o}C.

IR (KBr): ῡ 3319, 3095, 2979, 2923, 2804, 1697, 1674, 1613, 1519, 1492, 1446, 1352, 1302, 1276, 1203, 1128, 1096, 1050, 1021, 945, 818, 785, 747 cm.$^{-1}$

^{1}H NMR ($CDCl_3$): δ 1.26 (t, 6H, *J* = 6.0 Hz), 2.32 (s, 6H), 2.90 (s, 6H), 4.10 (q, 4H, *J* = 6.0 Hz), 4.81 (s, 1H), 5.50 (brs, 1H, NH), 7.05 (d, 2H, *J* = 7.0 Hz), 7.20 (d, 2H, *J* = 7.0 Hz).

ESI-MS *m/z* (%): 373 ([M+H]$^+$,100), 252 (10), 55 (10):

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

Solid, Mp:148-149 ^{o}C.

IR (KBr): ῡ 3335, 3241, 3098, 3023, 2981, 1689, 1644, 1490, 1447, 1372, 1326, 1297, 1219, 1159, 1120, 1096, 1051, 1025, 783, 755, 718 cm.$^{-1}$

^{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), 4.55 (d, 1H, *J* = 4.5 Hz), 5.60 (brs, 1H), 6.15 (dd, 2H, *J* = 4.5, 14.8 Hz), 7.18 (d, 2H, *J* = 14.8 Hz), 7.22-7.34 (m, 3H).

ESI-MS *m/z* (%): 355 ($[M+H]^+$, 30), 253 (30), 252 (100), 244 (10).

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

Solidl, Mp: 158-159 ^oC.

IR (KBr): ῡ 3346, 3061, 2981, 1702, 1650, 1487, 1373, 1331, 1298, 1262, 1209, 1119, 1095, 1047, 1013, 807, 731 $cm.^{-1}$

^{1}H NMR ($CDCl_3$): δ 1.28 (t, 6H, *J* = 6.0 Hz), 2.32 (s, 6H), 4.10-4.25 (m, 4H), 5.12 (s, 1H), 5.61 (brs, 1H, NH), 5.90 (d, 1H, *J* = 6.5 Hz), 6.20 (t, 1H, *J* = 6.5 Hz), 7.18 (d, 1H, *J* = 6.5 Hz).

ESI-MS *m/z* (%): 320 ($[M+H],^+$ 45), 318 (25), 304 (40), 252 (100), 214 (05)

Diethyl-2,6-dimethyl-4-(thiophen-2-yl)-1,4-dihydropyridine-3,5-dicarboxylate (4i)

Pale yellow solid, Mp: 191-192 ^oC.

IR (KBr): ῡ 3343, 3240, 3109, 2982, 1726, 1691, 1652, 1484, 1449, 1370, 1326, 1298, 1258, 1207, 1162, 1123, 1093, 1042, 1019, 845, 814, 789, 748, 719 $cm.^{-1}$

^{1}H NMR ($CDCl_3$): δ 1.25 (t, 6H, *J* = 6.0 Hz), 2.37 (s, 6H), 4.20 (q, 4H, *J* = 6.0 Hz), 5.37 (s, 1H), 5.76 (brs, 1H, NH), 6.80-6.90 (m, 2H), 7.20 (d, 1H, *J* = 6.5 Hz).

^{13}CNMR ($CDCl_3$): δ 15.0, 20.0, 35.0, 60.0, 104.0, 123.0, 127.0, 145.0, 153.0, 167.0.

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

Yellow solid, Mp: 199-200 ^oC.

IR (KBr): ῡ 3166, 3048, 2973, 2819, 1691, 1633, 1540, 1501, 1443, 1378, 1300, 1265, 1201, 1168, 1116, 1089, 1045, 1017, 941, 852, 782, 712 $cm.^{-1}$

^{1}H NMR ($CDCl_3$): δ 1.29 (t, 6H, *J* = 6.0 Hz), 2.65 (s, 6H), 2.55 (s, 3H), 4.15 (q, 4H, *J* = 6.0 Hz), 5.38 (s, 1H), 5.85 (brs, 1H, NH), 8.49 (s, 1H).

^{13}C NMR ($CDCl_3$): δ 14.0, 15.0, 20.0, 32.0, 50.0, 104.0, 140.0, 145.0, 147.0, 150.0, 167.00;

ESI-MS *m/z* (%): 351 ($[M+H]^+$).

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

Thick syrup.

IR (KBr): ῡ 3273, 3172, 3054, 2925, 1676, 1593, 1508, 1437, 1371, 1304, 1256, 1212, 1116, 1018, 751 $cm.^{-1}$

^{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), 7.10 (t, 1H, *J* = 6.0 Hz), 7.35 (t, 1H, *J* = 6.0 Hz), 7.55 (t, 1H, *J* = 6.0 Hz), 8.05 (brs, 1H, NH), 8.48 (d, 1H, *J* = 6.0 Hz).

ESI-MS *m/z* (%): 331 ($[M+H]^+$,100), 308 (10), 285 (55).

Diethyl-4-(2-chloro-6-methylquinolin-3-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-di carboxylate (**4l**):

IR (KBr): ῡ 3338, 2981, 1725, 1695, 1560, 1495, 1448, 1375, 1301, 1275, 1213, 1171, 1104, 1043, 925, 824, 755 $cm.^{-1}$

^{1}H NMR ($CDCl_3$): δ 1.19 (t, 6H, *J* = 6.0 Hz), 2.32 (s, 6H), 2.50 (s, 3H), 4.01-4.12 (m, 4H), 5.42 (s, 1H), 5.65 (brs, 1H, NH), 7.40-7.50 (m, 2H), 7.82 (d, 1H, *J* = 7.0 Hz), 8.01 (s, 1H).

ESI-MS *m/z* (%): 429 ($[M+H]^+$ 100), 393 (40), 178 (20).

Diethyl-4-isopropyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4m):

Syrupy liquid.

IR (KBr): ῡ 3421, 2981, 2930, 1722, 1592, 1553, 1442, 1372, 1295, 1255, 1223, 1117, 1043, 865, 771 $cm.^{-1}$

^{1}H NMR ($CDCl_3$): δ 0.72 (d, 6H, *J* = 4.5 Hz), 1.31 (t, 6H, *J* = 6.0 Hz), 2.21 (s, 6H), 3.88 (d, 1H, *J* = 6.0 Hz), 4.09-4.30 (m, 4H), 5.48 (brs, 1H, NH).

ESI-MS *m/z* (%): 296 ($[M+H]^+$ 30), 252 (55), 250 (100), 102 (12), 59 (15).

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

IR (KBr): ῡ 3376, 2926, 2855, 1728, 1567, 1461, 1376, 1282, 1233, 1104, 1041, 860, 772 $cm.^{-1}$

^{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), 4.10-4.30 (m, 4H), 5.48 (brs, 1H, NH).

ESI-MS *m/z* (%): 393 ($[M+H]^+$ 100).

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

Thick syrup.

IR (KBr): ῡ 3373, 2967, 2927, 1728, 1565, 1449, 1377, 1283, 1236, 1106, 1040, 859, 774 $cm.^{-1}$

^{1}H NMR ($CDCl_3$): δ 0.88 (d, 3H, *J* = 6.0 Hz), 1.20-1.35 (m, 10H), 1.55 (s, 3H), 1.65 (s, 3H), 1.80-1.95 (m, 3H), 2.30 (s, 6H), 3.91 (t, 1H, *J* = 6.0 Hz), 4.10-4.25 (m, 4H), 5.10 (t, 1H, *J* = 6.0 Hz), 5.85 (brs, 1H, NH).

ESI-MS *m/z* (%): 378 ($[M+H]^+$ 40), 376 (50), 332 (20), 306 (10), 274 (15), 252 (65), 116 (10), 65 (10).

CONCLUSION:

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

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