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Samarium Chloride: An efficient catalyst synthesis of 1,4-dihydropyridines (Hantzsch pyridines)

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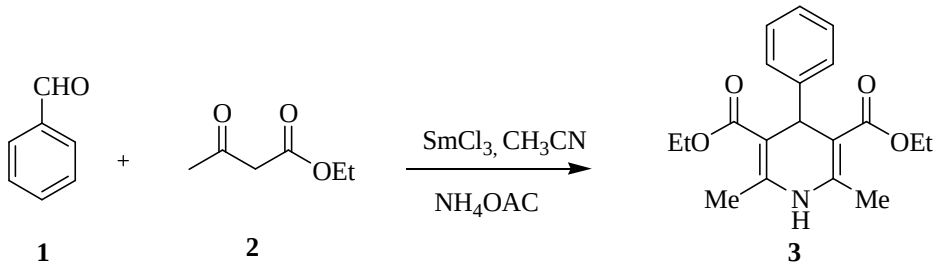
ABSTRACT

Samarium trichloride catalyzed one-pot synthesis of dihydropyrines has been developed. The methodology was successfully applied to various aldehydes. All the reactions were carried out at acetonitrile reflux.

Keywords: Aldehydes, ethylacetoacetate, samarium trichloride, dihydropyridines.

INTRODUCTION

Functionalized nitrogen heterocycles play a predominant role in medicinal chemistry and they have been intensively used as scaffolds for drug development. The dihydropyridine derivatives are among one and exhibits a large range of biological activities such as anti-convulsant, antitumor, antianxiety, vasodilator, bronchodilator, antidepressive, analgesic, hypnotic, antiinflammatory and neuroprotectants as well as platelet antiaggregatory agents [1-3]. The biological importance of dihydropyridine attracted many researchers and led to their synthesis using different catalysts [4] and conditions [5] but many of reported have some drawbacks like high temperature conditions, prolonged reaction times and low yields. As part of our research program, we have developed a simple and efficient methodology for one-pot synthesis of dihydropyridine derivatives using samarium trichloride as catalyst as shown in the scheme-1.



1 **2** **3**

Scheme-1

MATERIALS AND METHODS

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 samarium trichloride (0.2 mmole). 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 (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 ratio. All the products were confirmed by their spectral data and compared with literature reports.

Spectral data:

Diethyl-2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (3a): Solid, Mp, 153-154 ^oC. IR (KBr): υ 3342, 3061, 2978, 2931, 1690, 1651, 1481, 1453, 1375, 1300, 1248, 1212, 1121, 1091, 1024, 825, 767 $cm.^{-1}$; ^1H 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 (s, 1H, NH), 7.08-7.25 (m, 5H).; ESI-MS m/z (%): 330 ($[M+H]^+$, 95), 284 (100), 256 (25), 252 (15), 173 (20), 131 (15), 107 (20).

Diethyl-2,6-dimethyl-4-(3,4,5-trimethoxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (**3b**): Solid, Mp, 157-158 ^oC. IR (KBr): υ 3357, 2928, 2853, 1696, 1636, 1593, 1497, 1460, 1378, 1205, 1127, 1092, 864, 748 $cm.^{-1}$; ^1H 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).; ESI-MS *m/z* (%): 420 ($[M+H]^+$, 30), 374 (25), 346 (20), 328 (5), 252 (100).

Diethyl-4-[4(dimethylamino)phenyl]2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**3c**): IR (KBr): υ 3319, 3095, 2979, 2923, 2804, 1697,1674, 1519, 1492, 1446, 1352, 1302, 1276, 1203, 1128, 1096, 1021, 945, 785 $cm.^{-1}$; ^1H 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, *J* = 7.0 Hz), 7.10 (d, 2H, *J* = 7.0 Hz).; ESI-MS *m/z* (%): 373 ($[M+H]^+$, 100), 252 (20), 55 (20).

Diethyl-2,6-dimethyl-4-(3-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (3d): Solid, Mp, 130-131 ^oC. IR (KBr): υ 3323, 3246, 3098, 2979, 2925, 1705, 1649, 1488, 1375, 1214, 1119, 1022, 869, 751 $cm.^{-1}$; ^1H 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 (brs, 1H, NH), 7.05-7.20 (m, 4H).; 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 (**3e**): Solid, Mp, 147-148 ^oC. IR (KBr): υ 3335, 3242, 3098, 3023, 2981, 1690, 1645, 1491,1447. 1373, 1327, 1297, 1259, 1220, 1160, 1120, 1097, 1025, 968, 783, 757 $cm.^{-1}$; ^1H 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 (brs, 1H), 6.15 (dd, 2H, *J* = 4.5, 14.8 Hz), 7.10-7.34 (m, 5H).; 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 (3f): Solid, Mp, 120-121 ^oC. IR (neat): υ 3377, 2926, 2855, 1728, 1567, 1461, 1376, 1282, 1041, 860, 772 $cm.^{-1}$; ^1H 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).; ESI-MS *m/z* (%): 393 ($[M]^+$, 100), 335 (10), 320 (10).

Diethyl-4-benzyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**3g**): Solid Mp, 117-118 ^oC. IR (KBr): υ 2978, 2927, 1719, 1592, 1443, 1369, 1289, 1252, 1222, 1105, 1043, 863, 769, 699 $cm.^{-1}$; ^1H 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 (brs, 1H, NH), 7.10-7.30 (m, 5H).; ESI-MS *m/z* (%): 344 ($[M+H]^+$, 05), 298 (10), 252 (100), 242 (05).

Diethyl-4-(2,6-dimethylhept-5-enyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**3h**): IR (KBr): υ 3373, 2967, 2927, 1728, 1565, 1449, 1377, 1283, 1236, 1106, 1040, 859, 775 $cm.^{-1}$; ^1H 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 (brs, 1H, NH).; ESI-MS *m/z* (%): 378 ($[M+H]^+$, 40), 376 (50), 332 (10), 306 (05), 274 (05), 252 (80), 116 (10), 65 (05).

Diethyl-4-(furan-2-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**3i**): Solid, Mp, 158-159 ^oC. IR (KBr): υ 3346, 2923, 2852, 1701, 1650, 1488, 1372, 1332, 1300, 1263, 1210, 1121, 1095 1048, 1013, 921, 807, 730, 687 $cm.^{-1}$; ^1H 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 (brs, 1H), 5.90 (d, 1H), 6.20 (d,1H), 7.18 (dd, 1H).; ESI-MS *m/z* (%): 320 ($[M+H]^+$, 45), 318 (20), 304 (40), 252 (100), 214 (05).

Diethyl-2,6-dimethyl-4-(pyridin-2-yl)-1,4-dihydropyridine-3,5-dicarboxylate (**3j**): Solid, Mp, 165-166 ^oC. IR (KBr): υ 3273, 3171, 3053, 2925, 1670, 1638, 1592, 1509, 1478, 1434, 1366, 1304, 1256, 1212, 1116, 1090, 1018, 776, 751, 677 $cm.^{-1}$; ^1H 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 (brs, 1H), 8.48 (d, 1H, *J* = 6.0 Hz).; ESI-MS *m/z* (%): 331 ($[M+H]^+$, 100), 308 (10), 285 (08).

Diethyl-2,6-dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate(3k): Solid, Mp, 132-133 ^{o}C. IR (KBr): υ 3341, 3084, 2979, 2927, 2855, 1683, 518, 1484, 1344, 1301, 1213, 1101, 1020, 828, 754 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), 348 (10), 329 (100), 301 (20), 102 (10).

RESULTS AND DISCUSSION

In a typical experiment, benzaldehyde, ethyl acetoacetate and ammonium acetate were reacted in the presence of $SmCl_3$ at acetonitrile reflux. The progress of reaction was monitored by thin layer chromatography. The observation showed that after 3 hours of reaction time, one of the reactant benzaldehyde was disappeared in the reaction mixture. Then, the solvent was removed under reduced pressure and residue was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to obtain the crude product, which was purified by column chromatography to afford pure product, diethyl-2,6-dimethyl-4-phenyl-1,4-dihydro pyridine-3,5-dicarboxylate (**3a**) in 85% yield. The pure product was confirmed by its ^{1}H NMR, IR and mass spectroscopy analysis. In this reaction the catalyst samarium trichloride acts as Lewis acid to facilitate the formation of the corresponding, α,β-unsaturated carbonyl compound through the condensation of ethyl acetate and aldehyde. The second step involves the reaction of ethyl acetoacetate with ammonium acetate to form an enamine. Following a Michael addition of the enamine to the α,β-unsaturated carbonyl, there is a ring closure step and subsequent loss of water to afford the 1,4-dihydropyridine. The role of catalyst was studied while using in different quantities and found that the best condition was with 10% mole of catalyst in acetonitrile at reflux conditions. Encouraged by the result obtained with benzaldehyde, we have extended to various aldehydes.

In general, aromatic aldehydes having electron donating groups reacts faster comparatively electron withdrawing groups. In a similar manner, aromatic aldehydes react faster than aliphatic aldehydes. The sensitive aldehydes such as cinnamaldehyde, furfural and pyridine aldehydes react smoothly without forming any side products. All the reactions were very clean, carried out at acetonitrile reflux and completed within 2 to 5 hours of reaction time. All the products were purified by column chromatography, using silica gel (60-120 mesh) as stationary phase and ethyl acetate-hexane mixture as mobile phase and the products obtained in 74 to 90%. All the products were confirmed by their ^{1}HNMR, IR and mass spectroscopy analysis.

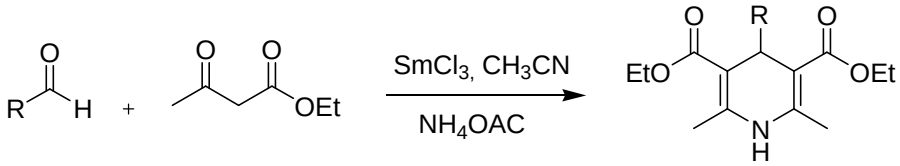
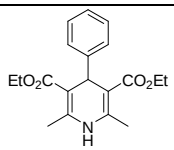
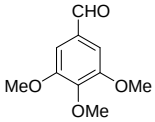
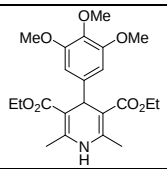
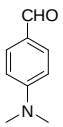
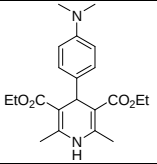
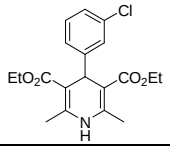
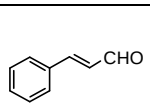
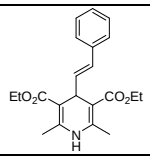
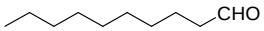
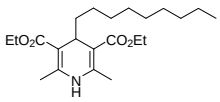
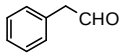
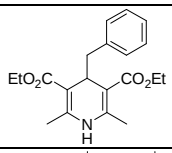
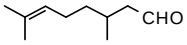
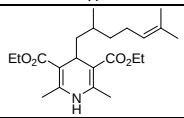
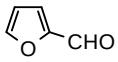
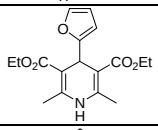
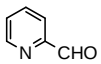
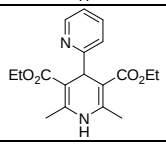
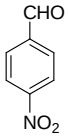
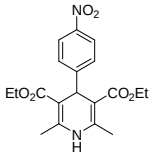


Table-1: Samarium trichloride catalyzed synthesis of Hantzsch pyridines:

Entry	Aldehyde	Product (3a-3k)	Time (h)	Yield (%)
a			3.0	85
b			2.0	90
c			4.0	79
d			3.0	83

e			3.0	74
f			5.0	76
g			4.0	80
h			4.0	76
i			2.0	90
j			3.0	78
k			5.0	79

CONCLUSION

In conclusion, we have demonstrated, a simple and efficient methodology, for the synthesis of 1,4-dihydropyridines using samarium trichloride as catalyst. In this method, catalyst was used in 10% mole and carried out at acetonitrile reflux. This methodology offers advantages like mild reaction conditions, easy isolation of products and operational simplicity. The scope and generality of this protocol was illustrated with respect to various aldehydes.

REFERENCES

[1] (a) S. Cosconati, L. Marinelli, A. Lavecchia, E. Novellino, *J. Med. Chem*., **2007**, 50, 1504. (b) J. J. V. Eynde, A. Mayence, *Molecules.*, **2003**, 8, 381. (c) A. Hantzsch, *Ber*., **1881**, 14, 1637. (d) B. L. Nilsson, L. E. Overman., *J. Org. Chem.* **2006**, 71, 7706.
[2] (a) R. Mannhold, B. Jablonka, W. Voigdt, K. Schoenafinger, K. Schravan, *Eur. J. Med. Chem*., **1992**, 229. (b) M. Syamala, *Org. Prep. Proc. Int.*, **2009**, 41, 1. (c) R. A. De Silva, S. Santra, P. R. Andreana., *Org. Lett*. **2008**, 10, 4541.
[3] (a) R. Miri, K. Javidnia, H. Sarkarzadeh, B. Hemmateenejad, *Bioorg. Med. Chem. Lett*., **2006**, 14, 4842. (b) A. Domling, I. Ugi, *Angew. Chem. Int. Ed*., **2000**, 39, 3168. (c) R. Boer, V. Gekeler, *Drugs Future*., **1995**, 20, 499. (d) A. Hantzsch, *Jusfus Liebigs Ann. Chem*., **1882**, 215, 1. (e) A. Saini, S. Kumar, J. S. Sandhu. *J. Sci. Ind. Res*., **2008**, 67, 95.
[4] (a) D.Bandyopadhyay, S. Maldonado, B. K. Banik., *Molecules* **2012**, 17, 264. (b) K. L. Brigwood, E. G. Veitch, S. V. Ley. *Org. Lett.*, **2008**, 10, 3627. (c) A. Debache, L. Chouguiat, R. Boulcina, B. Carbonib. *Open Org. Chem. J*., **2012,** 6, 12. (d) X. Y. Wu. *Synth. Commun.*, **2012**, 42, 454. (e) S. B. Sapkal, K. F. Shelke, B. B. Shingate, M. S.Shingare. *Tetrahedron Lett*., **2009**, 50, 1754. (f) K. L. Brigwood, E. G. Veitch, S. V. Ley. *Org. Lett.*, **2008**, 10, 3627.
[5] (a) J. S. Yadav, B. V. S. Reddy, A. K. Basak, A. V. Narsaiah, A. V. *Green Chem.* **2003**, 5, 60. (b) A. V. Narsaiah, B. Nagaiah., *Asian J. Chem*. **2010**, 22, 8099. (c) R, He, P. H. Toy, Y. Lam. *Adv. Synth. Catal*., **2008**, 350, 54. (d) J. Yang, Ch. Jiang, J. Yang, C. Qian, D. Fang. *Green Chem. Letters Rev*., **2013**, 6, 262. (e) S. Pal, M. L. H. Choudhury, T. Parvin, *Synth. Commun*., **2013**, *43*, 986.