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# Chloro Sulphonic Acid: A Simple and Efficient Catalyst for One-Pot Synthesis of Hantzsch 1,4-Dihydro Pyridines

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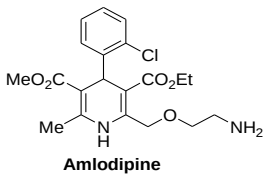
***ABSTRACT***

*An efficient methodology was developed for the synthesis Hantzsch 1,4-dihydro pyridine derivatives. All the reactions were carried out via three component coupling of aldehyde, ethyl acetoacetate and ammonium acetate in the presence of chlorosulphonic acid. All the reactions were completed with 30 minutes of reaction time, with very good yields of the corresponding products.*

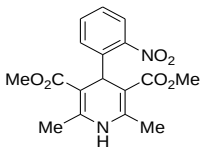
***Keywords:*** *1,4-Dihydropyridines, Aldehydes, diketoester, Ammonium Acetate, CSA.*

## 1. INTRODUCTION:

1,4-Dihydropyridines exhibit a variety of biological properties such as calcium channel modulation activities [1-3], neuroprotectants, cerebral anti-ischaemic agents and chemo sensitizers [4,5]. The tremendous biological activity of 1,4-dihydropyridines attracted many researchers and academicians. Hence, several methods have been developed for the synthesis of these compounds. The reported methods include different catalysts and reaction conditions such as microwave irradiation [6], TMSCl [7], ionic liquids [8,9], polymer supported $Yb(OTf)_3$ [10-12], $HClO_4$-$SiO_2$ [13], HY-Zeolite [14] and montmorillonite K10[15]. As part my research program, we have selected the chlorosulphonic acid (CSA) as a catalyst for one pot synthesis of Hantzsch pyridines. Chlorosulphonic acid was used for diverse types of applications such as alkylation, halogenations, cyclization, polymerization and rearrangement reactions in the literature [16].



**Amlodipine**



**Nifedipine**

## 2. EXPERIMENTAL SECTION:

IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer using KBr optics. $^1$H NMR spectra were recorded on Brucker-300 spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finning MAT 1020 mass spectrometer operating at 70 eV.

### *2.1. General Procedure*

A mixture of aldehyde (1 mmol), ethylacetoacetate (2 mmol), ammonium acetate (1.5 mmol) and chlorosulphonic acid (0.2 mmol) was grained in a mortar for a specified time (table-1). The progress of the reaction was monitored by thin layer chromatography (TLC). After completion of the reaction as indicated by TLC, the mixture was extracted with ethyl acetate (2x10 mL). The combined organic layers were washed with brine and dried over $NaHSO_4$ and concentrated under reduced pressure to afford crude products, which were purified by recrystalization from ethanol. All the products were characterized by their $^1$H NMR, IR and mass spectroscopy data.

### *2.2. Spectral Data*

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

IR (KBr): υ 3344, 3065, 2974, 2896, 1690, 1647, 1502, 1451, 1371, 1298, 1215, 1178, 1106, 1031, 842, 758, 699 cm.$^{-1}$; $^1$H NMR ($CDCl_3$). δ 1.29 (t, 6H, *J* = 6.5 Hz), 2.40 (s, 6H), 4.15 (q, 4H, *J* = 6.5 Hz), 4.88 (s, 1H), 5.50 (brs, 1H, NH), 7.05-7.20 (m, 5H).; EIMS: *m/z* (%). 328 ($M^+$ 90), 284 (100), 256 (30), 252 (40), 195 (25), 131 (10), 107 (15).

***Diethyl-4-benzyl-2,6-dimethyl-1,4-dihydro pyridine-3,5-dicarboxylate(4b):***

IR (KBr): υ 2989, 2896, 1720, 1597, 1445, 1370, 1293, 1235, 1108, 1042, 869, 764, 697 cm.$^{-1}$; $^1$H NMR ($CDCl_3$). δ 1.27 (t, 6H, *J* = 6.5 Hz), 2.18 (s, 6H), 2.55 (d, 2H, *J* = 6.5 Hz), 4.05 (q, 4H, *J* = 6.5 Hz), 4.93 (s, 1H), 5.45 (brs, 1H, NH), 6.97 (d, 2H, *J* = 7.0 Hz), 7.10-7.20 (m, 3H).; EIMS: *m/z* (%). 344 ($M^{+1}$ 20), 342 (10), 318 (30), 298 (30), 252 (100), 250 (10), 224 (15).

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***Diethyl-2,6-dimethyl-4-(3-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4c):***
IR (KBr): υ 3324, 3245, 3097, 2980, 2899, 1705, 1650, 1450, 1382, 1295, 1212, 1126, 1030, 871, 752, 695 cm.$^{-1}$; $^1$H NMR ($CDCl_3$). δ 1.26 (t, 6H, *J* = 6.5 Hz), 2.37 (s, 6H), 4.12 (q, 4H, *J* = 6.5 Hz), 4.92 (s, 1H), 5.60 (brs, 1H, NH), 7.06-7.22 (m, 4H).; EIMS: *m/z* (%). 386 ($M^{+1}$ 70), 364 (50), 318 (100), 251 (25), 201 (15), 175 (20).

***Diethyl-4-(furan-2-yl)-2,6-dimethyl-1,4-dihydro pyridine-3,5-dicarboxylate (4d):***
IR (KBr): υ 3345, 2983, 1701, 1651, 1488, 1374, 1299, 1265, 1120, 1095, 1010, 812, 732, 691 cm.$^{-1}$; $^1$H NMR ($CDCl_3$). δ 1.28 (t, 6H, *J* = 6.5 Hz), 2.33 (s, 6H), 4.15 (q, 4H, *J* = 6.5 Hz), 5.10 (s, 1H), 5.62 (brs, 1H), 5.90 (s, 1H), 6.20 (s, 1H), 7.20 (s, 1H).; EIMS: *m/z* (%). 320 ($M^{+1}$ 50), 318 (30), 304 (50), 274 (15), 252 (100), 214 (20).

***(E)-Diethyl-2,6-dimethyl-4-styryl-1,4-dihydro pyridine-3,5-dicarboxylate (4e):***
IR (KBr): υ 3335, 3097, 2925, 1690, 1646, 1491, 1378, 1291, 1215, 1162, 1027, 784, 715 cm.$^{-1}$; $^1$H NMR ($CDCl_3$). δ 1.22 (t, 6H, *J* = 6.5 Hz), 2.39 (s, 6H), 3.90 (s, 3H), 4.18 (q, 4H, *J* = 6.5 Hz), 5.15 (d, 1H, *J* = 4.5 Hz), 5.60 (brs, 1H), 6.15 (dd, 1H, *J* = 4.5 & 15.0 Hz), 7.20 (d, 1H, *J* = 15.0 Hz), 7.22-7.34 (m, 5H).; EIMS: *m/z* (%). 341 ($M^{+1}$ 20), 327 (10), 297 (100), 211 (15), 183 (10), 104 (10), 76 (30), 51 (20).

***Diethyl-4-[4-(dimethylamino)-phenyl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4f):***
IR (KBr): υ 3320, 3089, 2980, 2805, 1694, 1672, 1612, 1520, 1495, 1350, 1276, 1205, 1132, 1094, 1044, 945, 820, 789, 691 cm.$^{-1}$; $^1$H NMR ($CDCl_3$). δ 1.26 (t, 6H, *J* = 6.5 Hz), 2.32 (s, 6H), 2.90 (s, 6H), 4.10 (q, 4H, *J* = 6.5 Hz), 4.80 (s, 1H), 5.50 (brs, 1H, NH), 6.60-6.70 (m, 2H), 7.10 (d, 2H, *J* = 7.0 Hz).; EIMS: *m/z* (%): 373 ($M^{+1}$ 100), 252 (25), 227 (10), 205 (10), 116 (10), 65 (10), 55 (20).

***Diethyl-2,6-dimethyl-4-(3,4,5-trimethoxyphenyl) -1,4-dihydropyridine-3,5-dicarboxylate (4g):***
IR (KBr): υ 3351, 3087, 2930, 2855, 1690, 1597, 1498, 1380, 1275, 1206, 1130, 1090, 865, 749, 631 cm.$^{-1}$; $^1$H NMR ($CDCl_3$). δ 1.28 (t, 6H, *J* = 6.5 Hz), 2.35 (s, 6H), 3.78 (s, 6H), 3.80 (s,3H), 4.12 (q, 4H, *J* = 6.5 Hz), 4.95 (s, 1H), 5.50 (brs, 1H, NH), 6.45 (s, 2H).; EIMS: *m/z* (%). 420 ($M^{+1}$ 30), 374 (25), 346 (10), 328 (10), 252 (100), 227 (10), 170 (15), 121 (20).

***Diethyl-2,6-dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4h):***
IR (KBr): υ 3340, 3087, 2969, 2865, 1680, 1523, 1485, 1365, 1299, 1218, 1108, 1015, 843, 754, 701 cm.$^{-1}$; $^1$H NMR ($CDCl_3$). δ 1.25 (t, 6H, *J* = 6.5 Hz), 2.35 (s, 6H), 4.10 (q, 4H, *J* = 6.5 Hz), 5.05 (s, 1H), 5.70 (brs, 1H, NH), 7.42 (d, 2H, *J* = 7.0 Hz), 8.02 (d, 2H, *J* = 7.0 Hz).; EIMS: *m/z* (%). 375 ($M^{+1}$ 50), 348 (20), 329 (100), 301 (15), 102 (20).

***Diethyl-2,6-dimethyl-4-(4-pyridin-2-yl)-1,4-dihydropyridine-3,5-dicarboxylate (4i):***
IR (KBr): υ 3274, 3170, 3062, 2930, 1675, 1594, 1510, 1438, 1370, 1258, 1210, 1118, 1020, 851, 751, 681 cm.$^{-1}$; $^1$H NMR ($CDCl_3$). δ 1.22 (t, 6H, *J* = 6.5 Hz), 2.28 (s, 6H), 4.06 (q, 4H, *J* = 6.5 Hz), 5.15 (s, 1H), 7.10-7.15 (m, 1H), 7.30-7.40 (m, 1H), 7.50-7.60 (m, 1H), 8.05 (brs, 1H), 8.50 (d, 1H, *J* = 7.0 Hz).; EIMS: *m/z* (%). 331 ($M^{+1}$ 100), 308 (10), 286 (50), 262 (15).

***Diethyl-4-isopropyl-2,6-dimethyl-1,4-dihydro pyridine-3,5-dicarboxylate (4j):***
IR (KBr): υ 3422, 2980, 2928, 1720, 1590, 1549, 1439, 1375, 1276, 1220, 1115, 1045, 867, 770, 698 cm.$^{-1}$; $^1$H NMR ($CDCl_3$). δ 0.78 (s, 3H), 0.80 (s, 3H), 1.30 (t, 6H, *J* = 6.5 Hz), 2.22 (s, 6H), 3.88 (d, 1H, *J* = 6.5 Hz), 4.20 (q, 4H, *J* = 6.5 Hz), 5.50 (brs, 1H, NH).; EIMS: *m/z* (%). 296 ($M^{+1}$ 30), 252 (50), 250 (100), 224 (15), 204 (10), 184 (10), 102 (15), 90 (10), 87 (10), 59 (10).

## 3. RESULTS AND DISCUSSION

In a typical experiment, benzaldehyde, ethylacetoacetate, ammonium acetate and the chloro sulphonic acid were mixed in a mortar and grinned well for 20 minutes to afford the corresponding product, diethyl-2,6-dimethyl-4-phenyl-1,4-dihydro pyrimidine-3,5-dicarboxylate (**4a**) in very good yields as shown in the scheme-1. The product **4a** was confirmed by its $^1$H NMR, IR and mass spectroscopy data.

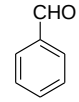
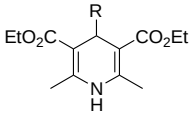
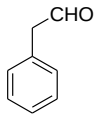
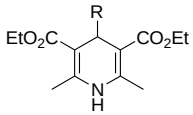
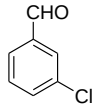
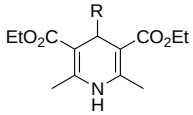
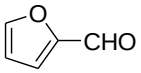
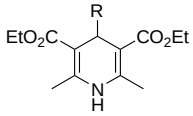
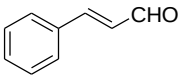
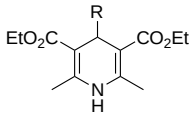
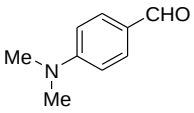
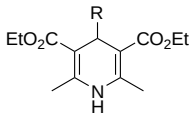
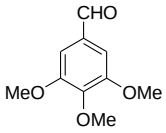
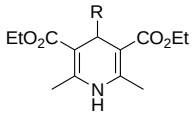
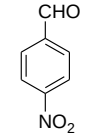
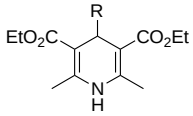
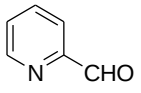
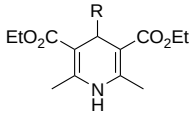
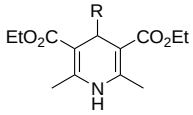

**Scheme-1**

Encouraged by the result obtained with benzaldehyde, we have applied this methodology to a variety of aldehydes containing electron withdrawing and electron donating groups in ring system and the results were mentioned in the table-1. In general, all the reactions were completed with 30 minutes of reaction time. Electron withdrawing group containing aldehydes reacted comparatively slowly than other aldehydes. Acid sensitive aldehydes such as furfuraldehyde and cinnamaldehyde were reacted very smoothly to afford the corresponding products under these conditions without forming any side products. In a similar manner, the aliphatic system of Isobutyral--

dehyde also reacted smoothly to obtain the Hantzsch pyridine derivative in very good yield.

We have examined the role of catalyst chlorosulphonic acid, while using in different quantities. In the first experiment, benzaldehyde (1mmol), ethyl acetoacetate (2mmol), ammonium acetate (1.5mmol) and the catalyst chlorosulphonic acid (1mmol) were grinned well in a mortar for 20 minutes and the TLC observation shows that the reaction was completed. In second experiment, the same quantity of reactants was treated with 0.5 mmol quantity of catalyst and after 20 minutes grinding, the TLC observation shows that the reaction was completed. In third experiment, the same quantity of reactants was treated with 0.2 mmol quantity of catalyst and after 20 minutes grinding, the TLC observation shows that the reaction was completed. In fourth experiment, the same quantity of reactants was treated with 0.1 mmol quantity of catalyst and after 20 minutes grinding, the TLC observation shows that the reaction 50% was completed. From these experiments, we concluded that the use of catalyst 20% is enough for the completion of reaction and all the reactions were carried out using the catalyst in 20%.

**Table-1:** Synthesis of 1,4-dihydropiridines by using CSA as catalyst:

| S.No. | Aldehyde (R) | Product (4a-4i) | Time (min) | Yield (%) | Melting Points ($^oC$) |
|---|---|---|---|---|---|
| **a** |  |  | 20 | 84 | 157-158 |
| **b** |  |  | 25 | 81 | 132-133 |
| **c** |  |  | 25 | 83 | 140-141 |
| **d** |  |  | 20 | 88 | 160-161 |
| **e** |  |  | 20 | 75 | 147-148 |
| **f** |  |  | 30 | 78 | 150-151 |
| **g** |  |  | 20 | 88 | 134-135 |
| **h** |  |  | 30 | 76 | 127-128 |
| **i** |  |  | 20 | 77 | 117-118 |
| **j** |  |  | 30 | 76 | 97-98 |

## 4. CONCLUSIONS

In summary, we have demonstrated, a simple and efficient methodology for the synthesis of 1,4-dihydropiridines derivatives using chlorosulphonic acid as catalyst. In this protocol, the catalyst chlorosulphonic acid was used in 20%. All the reactions were completed with 30 minutes of reaction time and the yields were very good.

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