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Ammonium persulfate: A simple and efficient catalyst for the synthesis of dihydropyridines (Hantzsch reaction)

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***Abstract**: Hantzsch pyridine synthesis has been carried out using ammonium persulfate as catalyst in acetonitrile solvent at reflux conditions. A variety of aldehydes undergo smooth condensation reaction with β-ketoester and ammonium acetate to afford the corresponding 1, 4-dihydro pyridines in one-pot protocol in excellent yields.*

***Keywords**: Aldehydes, diketone, ammonium acetate, $(NH_4)S_2O_8$, 1,4-dihydropyridine.*

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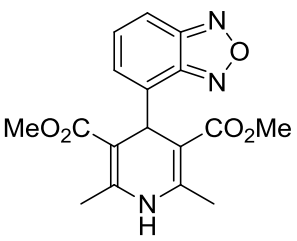
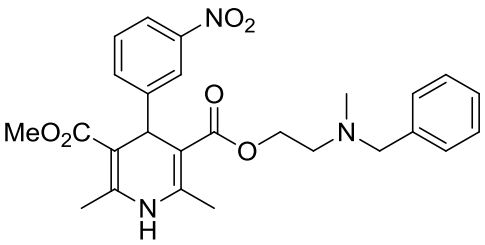
I. Introduction:

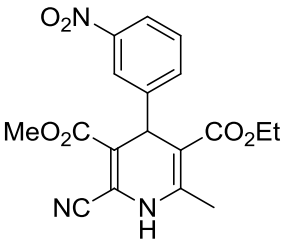
Multicomponent condensation strategies offer significant advantages over conventional linear type synthesis to provide products with the diversity needed for the discovery of new lead compounds or lead optimization employing combinatorial chemistry.[1-3] In 1882, Arthur Rudolf Hantzsch, a German chemist reported a cyclocondensation between ethyl acetoacetate, aldehyde and aqueous ammonium hydroxide to afford a heterocyclic system of 1,4-dihydropyridine, since then it became familiar as Hantzsch reaction.[4] The dihydro pyridine derivatives exhibits a large range of biological activities such as anti-convulsant, antitumor, antianxiety, vasodilator, bronchodilator, antidepressive, analgesic, hypnotic, anti-inflammatory and neuroprotectants as well as platelet anti-aggregatory agents.[5-8]



Isradipine



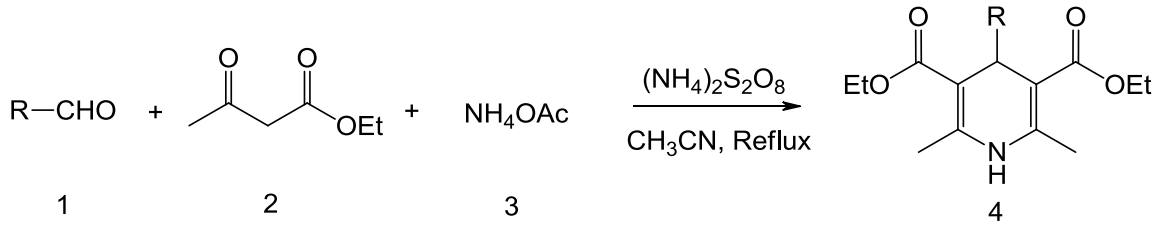
Nicardipine



Nilvadipine

The DHPs are commercially used as calcium channel blockers for the treatment of cardiovascular diseases. 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 reaction conditions.[9-17] Therefore, the development of an efficient and simple protocol is still in demand. In this respect, we have screened the catalyst ammonium perchlorate $[(NH_4)_2S_2O_8]$ for this multicomponent condensation and observed very good results. The catalyst is commercially available at low cost, highly soluble in water and can remove easily. Herein we report a highly efficient protocol for the synthesis of 1,4-dihydropyrimidine derivatives using ammonium perchlorate as a reaction medium in polar solvent acetonitrile.

In order to evaluate the practicability of the reaction, preliminary experiments were carried out by reacting the benzaldehyde, β-ketoester and ammonium acetate in presence of a catalytic amount (10 mol%) of $(NH_4)_2S_2O_8$ in acetonitrile at reflux conditions as shown in the scheme 1. The reaction was completed with in 3 h to afford the corresponding derivative of diethyl-2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-di carboxylate (**3a**) in excellent yields. The product was confirmed by ^{1}H NMR, IR and mass spectroscopy.



Scheme 1

After completion of the reaction as indicated by thin layer chromatography, the reaction mixture was extracted with ethyl acetate and the glycerine was used for further reactions up to five cycles with out any problem.

We have examined the effect of temperature, amount of the catalyst $(NH_4)_2S_2O_8$ and solvents role on the condensation reaction and the results shows that the use of catalyst in 10% mol and acetonitrile as solvent at 85-90 ^{0}C reaction temperature were found to be ideal.

Encouraged by the result obtained with the above typical experiment, this methodology was extended to a variety of aldehydes such as aromatic (a, b, c, d, l), heteroaromatic (h, i) and aliphatic (f, j), the different aldehydes were reacted smoothly with β-ketoester and ammonium acetate to give the corresponding 1,4-dihydropyridines in excellent yields. The reactions proceeded efficiently at 85-90 ^{0}C with high yields. The acid sensitive aldehydes worked well under these reaction conditions. This protocol is successfully applicable to both electron rich as well as electron deficient aldehydes.

In general, this reaction mechanistically proceeds in three stages. The first stage is the reaction of β-keto ester with ammonium acetate to form an enamine. The second step involves the reaction of aldehyde and β-ketoester by Knoevenagel condensation to form an olefin compound. The third stage involves the condensation of inamine and olefin compound to form a 1,4-dihydropyridine derivatives. All the reactions were completed within 3 to 5 hours of reaction time at 85-90 ^{o}C in acetonitrile solvent. The products of 1,4-dihydropyridine derivatives were obtained in 80-95% yields. All the products were confirmed by their ^{1}H NMR, IR and mass spectroscopy data.

In conclusion, we have demonstrated a simple and efficient one-pot three-component process for the synthesis of 1,4-dihydropyridines by the condensation of aldehyde, β-ketoester and ammonium acetate using ammonium persulfate as novel protocol in presence of a catalytic amount of $(NH_4)S_2O_8$. The notable features of this protocol are mild reaction conditions, simplicity in operation, improved yields, cleaner reaction profiles and economic and eco-friendly process for the synthesis of 1,4-dihydropyridines.

Experimental Section:

General Methods. Melting points were recorded on Buchi R-535 apparatus. IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer. ^{1}H NMR spectra were recorded on Gemini-200 spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV.

General Procedure for the synthesis of 1, 5-benzodiazepines: To a stirred solution of aldehyde (1 mmol), in acetonitrile (5 mL) were added ethylacetoacetate (2.2 mmol), ammonium acetate (1.1 mmol) and ammonium persulfate (0.1 mmol). The resulting reaction mixture stirred at reflux for a specified period (as shown in table 1). The progress of the reaction was monitored by thin layer chromatography (TLC). After completion of the reaction as indicated by TLC, the solvent was removed and the residue was extracted with ethyl acetate (2x10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to obtain the crude products, which were purified by column chromatography using 60-120 mesh. All the products were confirmed by their spectral data and compared with literature reports.

Spectral data for compounds:

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Diethyl-2,6-dimethyl-4-phenyl-1, 4-dihydropyrimidine-3, 5-dicarboxylate (**3a**): Solid, mp, 155-156 ^{o}C. IR (KBr): υ 3342, 3061, 2978, 2931, 1690, 1651, 1489, 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), 2.35 (s, 6H), 4.10 (q, 4H, *J* = 6.0 Hz), 4.90 (s, 1H), 5.52 (brs, 1H, NH), 7.08-7.25 (m, 5H).; ^{13}C NMR (75, MHz, $CDCl_3$): δ 168.3, 146.1, 143.9, 136.1, 129.2, 126.8, 103.9, 60.1, 40.0, 20.5, 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), 107 (20).

Diethyl-2,6-dimethyl-4-(3,4,5-trimethoxyphenyl)-1,4-dihydropyrimidine-3,5-dicarbo xylate (**3b**): IR (KBr): υ 3357, 2928, 2853, 1696, 1636, 1593, 1497, 1460, 1378, 1317, 1273, 1205, 1127, 1092, 1001, 864, 803, 748, 627 cm.$^{-1}$; ^{1}H NMR ($CDCl_3$): δ 1.28 (t, 6H, *J* = 6.0 Hz), 2.35 (s, 6H), 3.78 (s, 6H), 3.80 (s, 3H), 4.12 (q, 4H, *J* = 6.0 Hz), 4.90 (s, 1H), 5.52 (brs, 1H, NH), 6.45 (s, 2H).; EIMS *m/z* (%): 420 (m^{+1} 30), 374 (25), 346 (20), 328 (10), 252 (100), 227 (10), 170 (10), 121 (10).

Diethyl-2,6-dimethyl-4-(4-nitrophenyl)-1,4-dihydropyrimidine-3,5-dicarboxylate(**3c**) :Solid, mp, 130-131 ^{0}C. IR (KBr): υ 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), 5.70 (brs, 1H, NH), 7.41 (d, 2H, *J* = 6.5 Hz), 8.06 (d, 2H, *J* = 6.5 Hz).; ^{13}C NMR (75, MHz, $CDCl_3$): δ 166.9, 156.0, 145.9, 144.7, 128.3, 123.5, 103.4, 60.1, 40.2, 20.3, 14.2.; EIMS *m/z* (%): 375 (m^{+1} 45), 348 (10), 329 (100), 320 (10), 301 (25), 102 (10).

Diethyl-2,6-dimethyl-4-(3-chlorophenyl)-1,4-dihydropyrimidine-3,5-dicarboxylate (**3d**): Solid, mp, 130-131 ^{o}C. IR (KBr): υ 3323, 3246, 3098, 2979, 2925, 1705, 1649, 1488, 1375, 1333, 1299, 1214, 1119, 1022, 869, 788, 751, 694 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), 5.58 (brs, 1H, NH), 7.05-7.20 (m, 4H).; ^{13}C NMR (75, MHz, $CDCl_3$): δ 167.9, 150.1, 144.1, 143.5, 132.6, 128.0, 127.6, 126.0, 103.6, 60.1, 40.2, 19.3, 14.8.; EIMS *m/z* (%): 386 (m^{+1} 65), 364 (40), 318 (100), 292 (10), 251 (20), 201 (10), 171 (25).

(*E*)-Diethyl-2,6-dimethyl-4-styryl-1,4-dihydropyridine-3,5-dicarboxylate (**3e**): Solid, mp, 148-150 ^{o}C. IR (KBr): υ 3334, 3095, 2924, 1690, 1644, 1490, 1375, 1326, 1296, 1219, 1161, 1116, 1025, 783, 755, 715 cm.$^{-1}$; ^{1}H NMR ($CDCl_3$): δ 1.22 (t, 3H, *J* = 6.0 Hz), 2.38 (s, 6H), 3.92 (s, 3H), 4.18 (q, 2H, *J* = 6.0 Hz), 5.14 (d, 1H, *J* = 4.5 Hz), 5.6.0 (brs, 1H), 6.15 (dd, 1H, *J* = 4.5 & 14.8 Hz), 7.18 (d, 1H, *J* = 14.8 Hz), 7.22-7.34 (m, 5H).; EIMS *m/z* (%): 341 (m^{+1} 20), 327 (10), 297 (100), 269 (10), 211 (15), 183 (20), 104 (18), 81 (25), 76 (35), 51 (22).

Diethyl-4-decyl-2,6-dimethyl-1,4-dihydropyrimidine-3,5-dicarboxylate(**3f**): IR (neat): υ 3377, 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), 4.20 (q, 4H, *J* = 6.0 Hz), 5.48 (brs, 1H, NH).; EIMS *m/z* (%): 393 (m^{-1} 100), 335 (10), 320 (10).

Diethyl-4-benzyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (**3g**): IR (neat): υ 2978, 2927, 1719, 1592, 1443, 1369, 1289, 1252, 1222, 1105, 1043, 863, 769, 699 cm.$^{-1}$; ^{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), 4.05 (q, 4H, *J* = 6.0 Hz), 4.97 (s, 1H), 5.45 (brs, 1H, NH), 6.98 (d, 2H, *J* = 7.0 Hz), 7.10-7.20 (m, 3H).; EIMS *m/z* (%): 344 (m^{+1} 20), 342 (10), 318 (10), 250 (10), 298 (25), 252 (100), 224 (10).

Diethyl-4-(furan-2-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate(**3h**):Solid, mp, 158-160 ^{0}C. IR (KBr): υ 3346, 2981, 1702, 1650, 1487, 1373, 1331, 1298, 1262, 1209, 1119, 1095, 1047, 1013, 807, 731, 687 cm.$^{-1}$; ^{1}H NMR ($CDCl_3$): δ 1.28 (t, 6H, *J* = 6.0 Hz), 2.32 (s, 6H), 4.10-4.22 (m, 4H), 5.12 (s, 1H), 5.61 (brs, 1H), 5.90 (s, 1H), 6.20 (s, 1H), 7.18 (s, 1H).; ^{13}C NMR (75, MHz, $CDCl_3$): δ 168.1, 159.0, 145.5, 141.2, 109.8, 104.9, 99.8, 60.2, 33.5, 20.1, 14.5.; EIMS *m/z* (%): 320 (m^{+1} 45), 318 (25), 304 (40), 274 (10), 261 (10), 252 (100), 214 (15).

Diethyl-2,6-dimethyl-4-(pyridin-2-yl)-1,4-dihydropyridine-3,5-dicarboxylate (**3i**): IR (KBr): υ 3273, 3172, 3054, 2925, 1676, 1593, 1508, 1437, 1371, 1304, 1256, 1212, 1116, 1018, 751, 677 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), 7.08-7.12 (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).; EIMS *m/z* (%): 331 (m^{+1} 100), 308 (10), 286 (55), 292 (10), 262 (10).

Diethyl-4-(2, 6-dimethylhept-5-enyl)-2, 6-dimethyl-1, 4-dihydropyridine-3, 5-dicarbo xylate (**3j**): IR (neat): υ 3373, 2967, 2927, 1728, 1565, 1449, 1377, 1283, 1236, 1106, 1040, 859, 775 cm.$^{-1}$; ^{1}H NMR ($CDCl_3$): δ 0.88 (s, 3H), 0.90 (s, 3H), 0.98-1.10 (m, 1H), 1.20-1.35 (m, 10H), 1.58 (s, 3H), 1.68 (s, 3H), 1.80-1.95 (m, 2H), 2.30 (s, 6H), 4.20 (q, 4H, *J* = 6.0 Hz), 5.48 (brs, 1H, NH).; EIMS *m/z* (%): 378 (m^{+1} 40), 376 (50), 332 (20), 306 (10), 274 (15), 252 (100), 197 (10), 161 (10), 116 (10), 81 (10), 65 (18).

Diethyl-4-[4-(dimethylamino) phenyl] -2, 6-dimethyl-1, 4-dihydropyridine-3, 5-dicar boxylate (**3k**): IR (KBr): υ 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.$^{-1}$; ^{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 (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 (10).

Diethyl-4-[4-(benzyloxy)-3-methoxyphenyl]-2,6-dimethyl-1,4-dihydropyridine-3,5-di carboxylate (**3l**): IR (KBr): υ 3365, 3063, 2926, 2853, 1693, 1642, 1621, 1511, 1484, 1422, 1380, 1270, 1201, 1161, 1093, 1049, 1007, 862, 812, 748, 703, 658 cm.$^{-1}$;^{1}H NMR ($CDCl_3$): δ 1.25 (t, 6H, *J* = 6.0 Hz), 2.32 (s, 6H), 3.82 (s, 3H), 4.06-4.15 (m, 4H), 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).; EIMS *m/z* (%): 465 (m^{+} 35), 464 (65), 420 (15), 392 (20), 367 (10), 322 (10), 252 (100), 152 (10), 115 (10), 102 (15), 75 (10).

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Table-1: $(NH_4)_2S_2O_8$: Catalyzed Synthesis of Hantzsch Pyridines:

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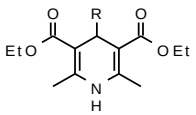
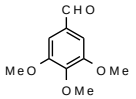
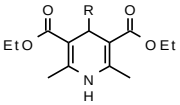
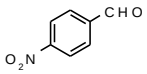
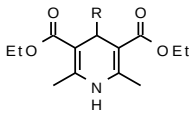
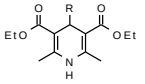
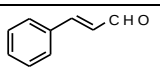
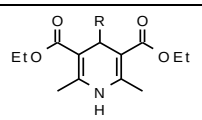
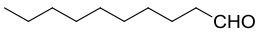
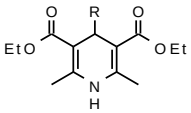
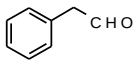
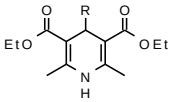
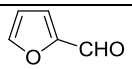
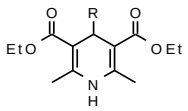
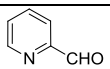
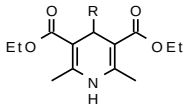
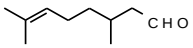
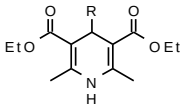
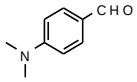
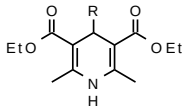
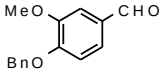
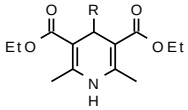
a			3.0	93
b			3.0	95
c			5.0	87
d			4.0	90
e			4.0	80

f			5.0	86
g			4.0	90
h			3.0	93
i			4.0	85
j			5.0	87
k			4.0	90
l			3.0	91

[a]Products were confirmed by their ^{1}H NMR, IR and mass spectroscopy.
[b]Yields were isolated by column chromatography and unoptimized.

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