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$Cu(OTf)_2$ Catalyzed high yield synthesis of Hantzsch 1,4-dihydropyridines

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Copper(II) triflate catalyzes efficiently the three-component condensation of aldehydes, β-ketoesters and ammonium acetate in acetonitrile at 25°C to afford the corresponding Hantzsch 1,4-dihydropyridines in high yields.

Keywords: Hantzsch 1,4-dihydropyridines, calcium channel blockers, three-component condensation, cardiovascular diseases, anti-hypertensive drug

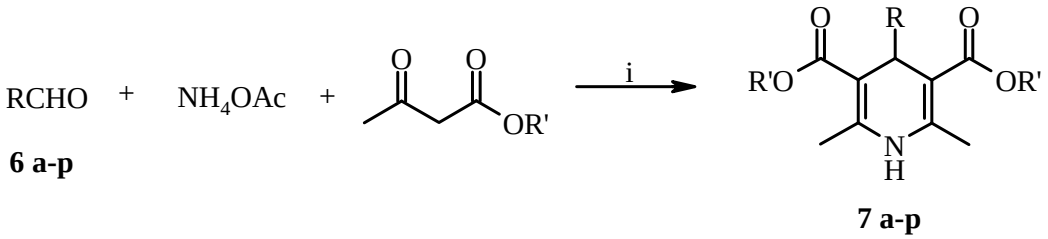
IPC: Int.Cl.[8] C07D

Hantzsch 1,4-dihydropyridines (1,4-DHPs) have emerged as one of the most important classes of drugs, particularly used as calcium channel blockers. Examples include nifedipine **1**, nitrendipine **2**, nimodipine **3**, nicardipine **4**, and amlodipine **5**, which are mainly used for the treatment of cardiovascular diseases, including hypertension[1] (**Figure 1**). Thus, the synthesis of these heterocyclic compounds is of continuing interest because of their remarkable drug action. Several synthetic strategies have been reported to improve their classical methods of preparation[2]. Hantzsch reaction[2] involves a one-pot condensation of an aldehyde with ethyl acetoacetate, and ammonia either in acetic acid or refluxing in alcohol for a longer time. However, the yields of 1,4-DHPs obtained by the Hantzsch method are generally low. Even though a number of modified methods[3] under improved conditions have been reported, many of them suffer from drawbacks such as unsatisfactory yields, requirement of high temperature conditions and long reaction times. Microwave activation stands among the alternative routes proposed during the past decade due to the drastic reduction of reaction times[4]. Thus, the development of an efficient and versatile method for the preparation of Hantzsch 1,4-DHPs is an active ongoing research area and there is scope for further improvement toward milder reaction conditions and improved yields. The versatility of $Cu(OTf)_2$ as a useful reagent in organic synthesis is well established[5]. In continuation of the studies using $Cu(OTf)_2$ (Ref. 6), herein is reported a novel and efficient synthesis of Hantzsch 1,4-dihydropyridines by the modified Hantzsch procedure using $Cu(OTf)_2$ as catalyst in CH_3CN at ambient temperature (**Scheme I**). Thus, the condensation of 2 mmole of benzaldehyde **6a** with 4 mmole of ethyl acetoacetate and 2 mmole of NH_4OAc in the presence of 1 mole % of $Cu(OTf)_2$ resulted in the formation of Hantzsch 1,4-dihydropyridine **7a** (**Scheme I**). The reaction was complete in 6 hr at RT and the product was isolated by usual work-up, in 98% yield, with excellent purity. Under similar conditions, various substituted aromatic, aliphatic and heterocyclic aldehydes with electron-donating as well as withdrawing substituents were transformed into the expected 1,4-DHPs in good to excellent yields and the results are summarized in **Table I**. All reactions were clean and the products were obtained in good yields.

In conclusion, it has been shown that $Cu(OTf)_2$ could be employed as an efficient catalyst, for the first time, to effect the three-component Hantzsch 1,4-dihydropyridine synthesis at RT. The method has successfully been applied for the synthesis of *anti-hypertensive* drug Nefidipine **1**. The catalytic system is also very effective for the aliphatic and heterocyclic aldehydes to give the corresponding dihydropyridines (DHPs) in good yields.

Experimental Section

Melting points are uncorrected. Microanalysis was performed on a Carlo ERBA EA 110B instrument. Infrared spectra were recorded on a Perkin-Elmer



6 a-p

7 a-p

Scheme I:— (i) cat. $Cu(OTf)_2$ (1 mole%), CH_3CN, 25°C, 4-24 hr, 54 - 98%

683B instrument. The ^1H and ^{13}C NMR were recorded on a 200 MHz instrument.

General procedure for the Hantzsch 1, 4-dihydropyridines synthesis

A mixture of aldehydes **6a-p** (2 mmole), ethyl or methyl acetoacetate (4 mmole), ammonium acetate (2 mmole) and $Cu(OTf)_2$ as catalyst (1 mole %) in acetonitrile (5 mL) was stirred at 25°C. After stirring for a specified time (see **Table I**), the reaction mixture was diluted with water and extracted with ethyl acetate (3×20 mL). The combined organic phase was washed with aq. $NaHCO_3$ solution to remove acetic acid produced in the reaction, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude reaction mixture was then purified by column chromatography using petroleum ether and EtOAc (8:2) as eluent to afford 1,4-dihydropyridines **7a-p** in 54-98% yield.

Table I — $Cu(OTf)_2$-catalyzed synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones (DHP)[a]

No.	R	R^1	time (h)	Yield (%)[b]
a	Ph	Et	6	98
b	4-Cl-C_6H_4	Et	6	70
c	4-Me-C_6H_4	Et	6	80
d	4-MeO-C_6H_4	Et	4	85
e	4-NO_2-C_6H_4	Et	6	72
f	3- NO_2-C_6H_4	Et	6	77
g	4-NC-C_6H_4	Et	5	82
h	3,4-$(MeO)_2$-C_6H_3	Et	4	95
i	3,4-(O-CH_2-O)-C_6H_3	Et	4	90
j	2-O_2N-C_6H_4	Me	12	60
k	1-Naphthyl	Et	9	65
l	2-Naphthyl	Et	6	69
m	2-Furyl	Et	6	85
n	4-Me_2N-C_6H_4	Et	6	55
o	2-MeO-C_6H_4	Et	6	82
p	*n*-C_9H_{19}	Et	24	54

a: reaction conditions: aldehyde (2 mmole), NH_4OAc (2 mmole), ethyl or methyl acetoacetate (4 mmole), $Cu(OTf)_2$ (1 mol%), 25°C; b: isolated yield after chromatographic purification.

Diethyl 1,4-dihydro-2,6-dimethyl-4-phenylpyridine-3,5-dicarboxylate, 7a

Yield: 98%; colorless solid; m.p. 158-59°C (crystallized from EtOH), (lit.(ref. 3a) 156-57°C); IR (KBr): 460, 482, 500, 620, 1011, 1050, 1100, 1180, 1200, 1209, 1500, 1667, 1690, 2350, 2867, 3440 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.22 (t, *J* = 7.2 Hz, 6H), 2.31 (s, 6H), 4.06 (q, *J* = 7.2 Hz, 4H), 4.93 (s, 1H), 5.67 (brs, 1H), 7.08 – 7.26 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 14.28, 19.23, 39.59, 59.56, 103.92, 126.06, 127.89, 144.10, 147.61, 167.54; MS: m/z (%): 329 (M^+, 5), 300 (5), 284 (5), 272 (3), 252 (100), 224 (15), 210 (10), 196 (20), 181 (10), 150 (10), 128 (7), 105 (8), 91 (40), 77 (12), 65 (5). Anal. $C_{19}H_{23}NO_4$ requires C, 69.28; H, 7.03; N, 4.25. Found C, 69.30; H, 7.00; N, 4.20%.

Diethyl 1,4-dihydro-2,6-dimethyl-4-(4-chlorophenyl)pyridine-3,5-dicarboxylate, 7b

Yield: 70%; colorless solid; m.p. 144-45°C (crystallized from EtOH), (lit.ref. 3a) 145-46°C); IR (KBr): 500, 600, 620, 1000, 1130, 1310, 1519, 1694, 2342, 2912, 3400 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.22 (t, *J* = 7.2 Hz, 6H), 2.30 (s, 6H), 4.09 (q, *J* = 7.2 Hz, 4H), 4.91 (s, 1H), 5.86 (s, 1H), 7.16 (s, 4H); ^{13}C NMR ($CDCl_3$): δ 14.22, 19.10, 39.19, 59.57, 103.58, 127.85, 129.22, 131.69, 144.20, 146.31, 167.25. Anal. $C_{19}H_{22}ClNO_4$ requires C, 67.75; H, 6.58; N, 4.15. Found C, 67.63; H, 6.11; N, 3.89%.

Diethyl 1,4-dihydro-2,6-dimethyl-4-(4-methylphenyl)pyridine-3,5-dicarboxylate, 7c

Yield: 80%; colorless solid; m.p. 160-61°C (crystallized from EtOH); IR (KBr): 500, 1040, 1150, 1200, 1300, 1390, 1450, 1700, 2400, 2460, 3300 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.23 (t, *J* = 7.2 Hz, 6H), 2.27 (s,

3H), 2.30 (s, 6H), 4.09 (q, *J* = 7.2 Hz, 4H), 4.86 (s, 1H), 5.77 (brs, 1H), 6.95 (d, *J* = 8.1 Hz, 2H), 7.09 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 14.25, 19.08, 20.98, 39.03, 59.46, 103.82, 127.68, 128.44, 135.17, 144.10, 144.95, 167.59. Anal. $C_{20}H_{25}NO_4$ requires C, 69.94; H, 7.33; N, 4.07. Found C, 69.88; H, 7.21; N, 3.89%.

Diethyl 1,4-dihydro-2,6-dimethyl-4-(4-methoxyphenyl)pyridine-3,5-dicarboxylate, 7d

Yield: 85%; colorless solid; m.p. 193-94°C (crystallized from EtOH); IR (KBr): 500, 700, 1000, 1050, 1200, 1250, 1300, 1500, 1700, 2400, 3300 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.23 (t, *J* = 7.1 Hz, 6H), 2.30 (s, 6H), 3.74 (s, 3H), 4.05 (q, *J* = 7.1 Hz, 4H), 4.87 (s, 1H), 5.92 (s, 1H), 6.68 (d, *J* = 8.7 Hz, 2H), 7.11 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 14.68, 19.55, 39.13, 55.30, 59.85, 104.53, 113.62, 129.19, 140.79, 144.17, 158.30, 167.98. Anal. $C_{20}H_{25}NO_5$ requires C, 66.83; H, 7.01; N, 3.89. Found C, 66.63; H, 7.11; N, 3.77%.

Diethyl 1,4-dihydro-2,6-dimethyl-4-(4-nitrophenyl)pyridine-3,5-dicarboxylate, 7e

Yield: 72%; colorless solid; m.p. 128-29°C (crystallized from EtOH), (lit. ref. 3a) 129-30°C); IR (KBr): 600, 620, 800, 850, 170, 1200, 1310, 1500, 1300, 1700, 2953, 3370 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.22 (t, *J* = 7.3 Hz, 6H), 2.34 (s, 6H), 4.09 (q, *J* = 7.3 Hz, 4H), 5.05 (s, 1H), 5.80 (s, 1H), 7.40 (d, *J* = 8.8 Hz, 2H), 8.06 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 14.17, 20.07, 40.94, 59.75, 102.52, 124.28, 145.16, 146.09, 155.16, 166.88. Anal. $C_{19}H_{22}NO_6$ requires C, 60.95; H, 5.92; N, 7.48. Found C, 60.63; H, 5.91; N, 7.50%.

Diethyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarboxylate, 7f

Yield: 77%; ^{1}H NMR ($CDCl_3$): δ 1.22 (t, *J* = 7.3 Hz, 6H), 2.32 (s, 6H), 4.14 (q, *J* = 7.8 Hz, 4H), 4.98 (s, 1H), 5.97 (s, 1H), 7.32 – 8.11 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 14.12, 19.28, 40.17, 59.62, 102.88, 123.52, 126.78, 131.63, 132.86, 143.14, 146.27, 148.55, 168.40. Anal. $C_{19}H_{22}NO_6$ requires C, 60.95; H, 5.92; N, 7.48. Found C, 60.89; H, 5.80; N, 7.43%.

Diethyl 1,4-dihydro-2,6-dimethyl-4-(4-cyanophenyl)pyridine-3,5-dicarboxylate, 7g

Yield: 82%; colorless solid; m.p. 200-02°C (crystallized from EtOH); IR (KBr): 500, 1000, 1040, 1200, 1400, 1400, 1685, 2200, 2930, 3300 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.21 (t, *J* = 7.1 Hz, 6H), 2.33 (s, 6H), 4.10 (q, *J* = 7.2 Hz, 4H), 5.99 (s, 1H), 5.91 (s, 1H), 7.34 (d, *J* = 8.5 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 14.19, 19.05, 40.08, 59.66, 102.71, 109.53 118.97, 128.74, 131.61, 144.98, 153.19, 166.91. Anal. $C_{20}H_{22}N_2O_4$ requires C, 73.37; H, 6.77; N, 8.55. Found C, 73.33; H, 6.70; N, 8.60%.

Diethyl 1,4-dihydro-2,6-dimethyl-4-(3,4-dimethoxyphenyl)pyridine-3,5-dicarboxylate, 7h

Yield: 95%; colorless solid; m.p. 163-65°C (crystallized from EtOH); IR (KBr): 450, 1050, 1200, 1250, 1300, 1500, 1689, 2390, 2900, 3320 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.24 (t, *J* = 7.1 Hz, 6H), 2.32 (s, 6H), 3.81 (s, 3H), 3.82 (s, 3H), 4.11 (q, *J* = 7.1 Hz, 4H), 4.89 (s, 1H), 5.72 (s, 1H), 6.70 (m, 1H), 6.83 (m, 1H), 7.14 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 14.26, 19.98, 38.80, 55.50, 59.37, 103.7, 110.94, 111.77, 119.68, 140.81, 143.92, 147.21, 148.06, 167.45. Anal. $C_{21}H_{27}NO_6$ requires C, 64.76; H, 6.98; N, 3.59. Found C, 64.63; H, 6.81; N, 3.45%.

Diethyl 4-(benzo[*d*][1,3]dioxol-6-yl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate, 7i

Yield: 90%; colorless solid; m.p. 200-02°C (crystallized from EtOH), (lit. ref. 3a) 202-03°C); IR (KBr): 858, 1108, 1530, 1595, 1630, 1670, 3325, 3406 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.24 (t, *J* = 7.2 Hz, 6H), 2.30 (s, 6H), 4.12 (q, *J* = 7.2 Hz, 4H), 4.84 (s, 1H), 5.86 (s, 1H), 6.00 (s, 2H), 6.72 (m, 3H); ^{13}C NMR (DMSO-d_6): δ 14.25, 19.97, 38.80, 59.37, 91.3, 103.7, 110.94, 111.77, 119.68, 140.81, 143.92, 147.21, 148.06, 167.45. Anal. $C_{20}H_{23}NO_6$ requires C, 64.33; H, 6.20; N, 3.75. Found C, 64.16; H, 6.14; N, 3.66%.

Dimethyl 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)pyridine-3,5-dicarboxylate, 7j (Nefidipine)

Yield: 60%; colorless solid; m.p. 173-74°C (crystallized from EtOH), (lit. ref. 3a) 172-74°C); IR (KBr): 462, 667, 757, 831, 858, 1020, 1103, 1118, 1190, 1217, 1284, 1309, 1352, 1434, 1492, 1529, 1618, 1649, 1689, 3020, 3442 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.34 (s, 6H), 3.59 (s, 6H), 5.73 (s, 1H), 5.87 (s, 1H), 7.21 – 7.30 (m, 1H), 7.41 – 7.54 (m, 2H), 7.66 – 7.70 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 19.0, 34.29, 50.84, 103.0, 123.65, 126.88, 130.88, 132.70, 142.10, 145.42, 147.54, 167.62. Anal. $C_{17}H_{18}N_2O_6$ requires C, 58.95; H, 5.23; N, 8.08. Found C, 58.88; H, 5.20; N, 8.00%.

Diethyl 1,4-dihydro-2,6-dimethyl-4-(1-naphthyl)-pyridine-3,5-dicarboxylate, 7k

Yield: 65%; colorless solid; m.p. 202-05°C (crystallized from EtOH), (lit. ref. 3a) 202-03°C); ^{1}H NMR ($CDCl_3$): δ 0.95 (t, *J* = 8.2 Hz, 6H), 2.29 (s, 6H), 3.92 (q, *J* = 8.2 Hz, 4H), 5.55 (brs, 1H), 5.76 (s, 1H), 7.30–7.55 (m, 4H), 7.60 (d, *J* = 8.7 Hz, 1H), 7.72 (d, *J* = 8.6 Hz, 1H), 8.55 (d, *J* = 8.6 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 13.7, 18.6, 28.3, 59.9, 100.6, 123.9, 125.2, 125.4, 126.2, 126.4, 126.5, 128.3, 132.5, 133.4, 134.0, 142.7, 165.0. Anal. $C_{23}H_{25}NO_4$ requires C, 72.80; H, 6.64; N, 3.69. Found C, 72.75; H, 6.49; N, 3.58%.

Diethyl 1,4-dihydro-2,6-dimethyl-4-(2-naphthyl)-pyridine-3,5-dicarboxylate, 7l

Yield: 69%; colorless solid; m.p. 196-98°C (crystallized from EtOH), (lit. ref. 3a) 195-98°C); ^{1}H NMR ($CDCl_3$): δ 0.95 (t, *J* = 8.2 Hz, 6H), 2.30 (s, 6H), 3.95 (q, *J* = 8.2 Hz, 4H), 5.55 (brs, 1H), 5.75 (s, 1H), 7.25 - 7.45 (m, 4H), 7.60 (d, *J* = 8.6 Hz, 1H), 7.70 (d, *J* = 8.6 Hz, 1H), 8.55 (s, 1H); ^{13}C-NMR ($CDCl_3$): δ 13.7, 18.6, 30.4, 59.9, 100.5, 124.8, 125.7, 126.7, 127.2, 127.4, 127.5, 127.9, 131.6, 133.5, 135.2, 142.7, 165.0. Anal. $C_{23}H_{25}NO_4$ requires C, 72.80; H, 6.64; N, 3.69. Found C, 72.43; H, 6.41; N, 3.55%.

Diethyl 1,4-dihydro-2,6-dimethyl-4-(2-furyl)-pyridine-3,5-dicarboxylate, 7m

Yield: 85%; colorless solid; m.p. 163-65°C (crystallized from EtOH), (lit. ref. 3a) 164°C); ^{1}H NMR ($CDCl_3$): δ 1.30 (t, *J* = 8.2 Hz, 6H), 2.40 (s, 6H), 4.20 (q, *J* = 8.2 Hz, 4H), 5.30 (s, 1H), 5.80 (brs, 1H), 6.80 – 7.05 (m, 3H); ^{13}C NMR ($CDCl_3$): δ 13.7, 18.0, 31.2, 59.9, 100.6, 105.7, 110.6, 141.2, 142.7, 152.5, 165.0. Anal. $C_{17}H_{21}NO_5$ requires C, 63.94; H, 6.63; N, 4.39. Found C, 63.70; H, 6.45; N, 4.18%.

Diethyl 1,4-dihydro-2,6-dimethyl-4-(4-*N*,*N*-dimethylaminophenyl)pyridine-3,5-dicarboxylate, 7n

Yield: 55%; colorless solid; m.p. 200-02°C (crystallized from EtOH), (lit. ref. 3a) 203°C); ^{1}H NMR ($CDCl_3$): δ 1.25 (t, *J* = 8.2 Hz, 6H), 2.35 (s, 6H), 3.10 (s, 6H), 4.15 (q, *J* = 8.2 Hz, 4H), 5.10 (s, 1H), 5.6 (brs, 1H), 7.15 – 7.75 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 13.7, 18.6, 30.0, 43.6, 59.9, 100.5, 113.0, 113.7, 120.1, 127.2, 130.1, 141.5, 142.7, 165.0. Anal. $C_{21}H_{28}N_2O_4$ requires C, 67.72; H, 7.58; N, 7.52. Found C, 67.68; H, 7.51; N, 7.26%.

Diethyl 1,4-dihydro-2,6-dimethyl-4-(2-methoxy-phenyl)pyridine-3,5-dicarboxylate, 7o

Yield: 82%; colorless solid; m.p. 142-43°C (crystallized from EtOH), (lit. ref. 3a) 138-43°C); ^{1}H NMR ($CDCl_3$): δ 1.25 (t, *J* = 8.2 Hz, 6H), 2.30 (s, 6H), 3.90 (s, 3H), 4.10 (q, *J* = 8.2 Hz, 4H), 5.10 (s, 1H), 5.80 (brs, 1H), 6.80 (d, *J* = 8.7 Hz, 2H), 7.4 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 14.55, 19.45, 39.33, 55.32, 59.80, 104.56, 113.61, 129.20, 141.21, 144.23, 158.34, 167.77. Anal. $C_{20}H_{25}NO_5$ requires C, 66.84; H, 7.01; N, 3.90. Found C, 66.42; H, 6.89; N, 3.55%.

Diethyl 1,4-dihydro-2,6-dimethyl-4-nonylpyridine-3,5-dicarboxylate, 7p

Yield: 54%; gum; ^{1}H NMR ($CDCl_3$): δ 0.90 (t, *J* = 8.4 Hz, 3H), 1.15 (m, 16H), 1.25 (t, *J* = 8.4 Hz, 6H), 1.45 (m, 2H), 2.30 (s, 6H), 3.85 (m, 1H), 4.15 (q, *J* = 8.6 Hz, 4H), 5.65 (brs, 1H); ^{13}C NMR ($CDCl_3$): δ 13.7, 14.0, 18.5, 23.1, 26.8, 28.3, 29.4, 30.0, 30.3, 30.8, 32.5, 59.9, 108.5, 141.2, 165.1. Anal. $C_{23}H_{39}NO_4$ requires C, 72.04; H, 7.42; N, 3.65. Found C, 71.86; H, 7.39; N, 3.42%.

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