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A Simple and efficient protocol for the synthesis of 1,4-dihydro pyridines (Hantzsch pyridines) catalyzed by Germanium (IV) iodide

Chandramouleswararao Jillepalli, Praveen Kumar Bonkuri and Madhukar Jeripothula*

Department of Chemistry, Kakatiya University, Warangal, Telangana-506009, India

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Abstract: A simple and efficient protocol has been developed for the synthesis of Hantzsch pyridines. In the reported synthesis, a variety of aldehydes undergo smooth condensation reaction with ethyl acetoacetate and ammonium acetate in presence of Germanium (IV) iodide in acetonitrile. This method is applicable to a variety of substrates to afford the corresponding 1,4-dihydropyridines in one-pot reaction in excellent yields.

Keywords: Aldehydes; diketones; ammonium acetate; GeI_4; 1,4-Dihydropyridine. © 2014 ACG Publications. All rights reserved.

1. Introduction

Multicomponent condensation strategies offer significant advantages over conventional linear type synthesis in providing products with the diversity needed for the discovery of new lead compounds or lead optimization employing combinatorial chemistry[1-6]. In 1882, Arthur Rudolf Hantzsch, German chemist, reported a cyclocondensationbetween ethyl acetate, aldehyde and aqueous ammonium hydroxide to afford a heterocyclic system of 1,4-dihydro pyridine; since then this reaction has become familiar as the Hantzsch[7,8]. The dihydropyridine derivatives exhibit a large range of biological activities such as anticonvulsant, antitumor, antianxiety, vasodilator, bronchodilator, antidepressant, analgesic, hypnotic, anti-inflammatory and neuroprotectetive as well as platelet antiaggregatory agents[9-12]. The dihydropyridines are commercially used as calciumchannel blockers (amlodipine, felodipine, nifedipine, nitrendipine, etc.) for the treatment of cardiovascular diseases.

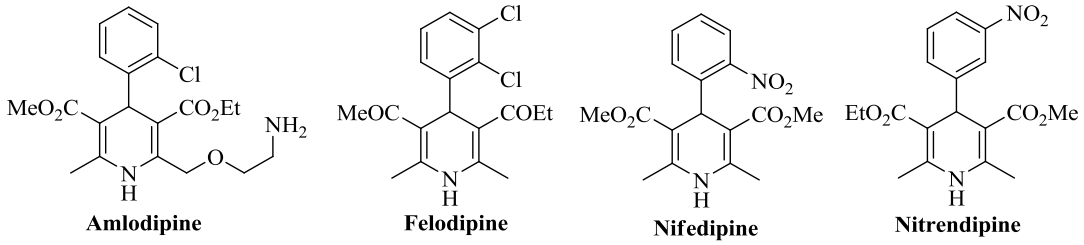

Figure 1. Some biologically active compounds of 1,4-dihydropyridines

* Corresponding author: E-mail: madhuj.biochem@gmail.com

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The tremendous biological activity of Hantzsch pyridines attracted many researchers and academicians. Hence, several attempts have been made to synthesize 1,4-dihydropyridine derivatives using various catalysts and reaction conditions such as TPP[13], CAN[14], heteropoly acids[15], Zn complex[16], phenylboronic acid[17], $Mg(ClO_4)_2$[18] cyanuricchloride[19], $Yb(OTf)_3$[20], ionic liquid[21], organo catalyst[22], L-proline[23], molecular iodine[24], tetrabutylammonium hydrogen sulfate[25], glycerin-$CeCl_3.7H_2O$[26,27], $Cd(NO_3)_2$[28], $CdCl_2$[29], PEG-400[30] and amberlite IR-120[31].But many of the methods suffer 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. As part of our research program in developing new methodologies[32,33]. Herein, we report a simple and an efficient methodology for preparation of 1,4-dihydropyridine derivatives by the condensation of aldehydes, ethyl acetoacetate and ammonium acetate in presence of Germanium (IV) iodide at acetonitrile reflux.

2. Results and discussion

In a typical experiment, a mixture of benzaldehyde (**1)**, ethyl acetoacetate (**2)** and ammonium acetate were reacted in presence of the catalyst GeI_4 at acetonitrile reflux as shown in the **Figure 2.** The reaction was completed within 3 h to afford the corresponding product, diethyl-2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**3a**) in excellent yields. The product was confirmed by ^{1}H NMR, ^{13}C NMR, IR and Mass spectroscopy.

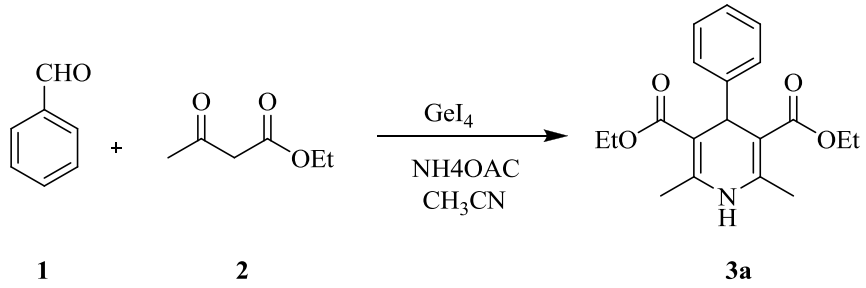
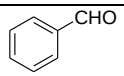
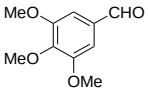
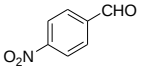
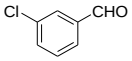
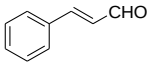
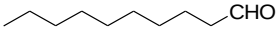
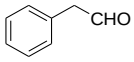
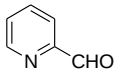
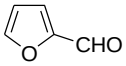
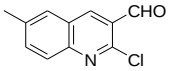
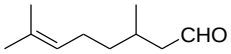
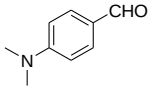
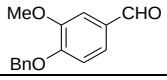


Figure 2. Diethyl-2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate

After completion of the reaction as indicated by TLC, the reaction mixture was extracted with ethyl acetate. The crude products were purified column chromatography using silica gel (60-120 mesh) by eluting with ethyl acetate-hexane (3:7)mixture. To optimize the reaction conditions, we have studied the role of catalyst Germanium (IV) iodide using in different mole ratios at room temperature as well as reflux. The observation shows that 10% mole catalyst and reflux temperature were found to be as suitable reaction conditions.

Encouraged by the above observations and the result obtained with benzaldehyde and ethyl acetoacetate, we have extended this methodology to various aldehydes such as aromatic aldehydes containing electron withdrawing and electron donating groups, hetero aromatic and aliphatic systems, which were reacted smoothly with ethylacetoacetate and ammonium acetate to give corresponding 1,4-dihydropyridines in very good to excellent yields. All the reactions were carried out in the presence of Germanium (IV) iodide using in catalytic amount (10mol%) at acetonitrile reflux. Aromatic aldehydes exhibit modest increase in reaction rate relative to aliphatic aldehydes. Electron withdrawing containing aldehydes react at a relatively slower rate than electron donating groups containing aldehydes. In general, all the reactions were completed within 3 to 5 hours of reaction time at acetonitrile reflux. The products of 1,4-dihydropyridine derivatives were obtained in 75-93% yields **(Table 1).** All the products were confirmed by their ^{1}H NMR, ^{13}C NMR, IR and Mass spectral analysis.

Table 1. GeI_4-Catalyzed synthesis of Hantzsch pyridines (**3a-m**).

Entry	Aldehyde	Product	Time (h)	Yield[b](%)
1		3a	3.0	91
2		3b	3.0	93
3		3c	5.0	82
4		3d	4.0	90
5		3e	4.0	75
6		3f	5.0	82
7		3g	4.0	89
8		3h	4.0	82
9		3i	3.0	92
10		3j	4.0	80
11		3k	5.0	80
12		3l	4.0	87
13		3m	3.0	89

3. Experimental Section

Melting points were recorded on Buchi R-535 apparatus. IR spectra were recorded on a Perkin-Elmar FT-IR 240-c spectrophotometer using KBr disk. ^{1}H NMR-Spectra were recorded on Gemini spectrometer (300 MHz) in $CDCl_3$ using TMS as internal standard and chemical shifts were given as δ. Mass spectra were recorded on a Finnegan MAT 1020 mass spectrometer operating at 70 eV.

3.1.General procedure for the preparation of diethyl-2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate: A stirred mixture of aldehyde (1mmol), ethyl acetoacetate (2.2mmol) and ammonium acetate (1.1mmol) were stirred in acetonitrile (5 mL) in the presence of GeI_4 (0.1mmol) at 80-85 °C for a period of appropriate time (3-5 hours) mentioned in the **Table 1**. The progress of the reaction was monitored by thin layer chromatography (TLC). After completion of reaction, as indicated by TLC, the solvent was removed under reduced pressure and the residue was extracted with ethyl acetate (2x10mL). The combined organic layer 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 silica-gel (60-120mesh) by eluting with ethyl acetate-hexane (3:7) mixture. All the pure products were confirmed by their spectral data.

3.1. Spectral data for compounds

3.1.1.Diethyl-2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (3a): Solid; Mp. 155-156 °C; IR (KBr):υ_{max}3342, 3061, 2978, 2931, 1690, 1651, 1489, 1453, 1375, 1300, 1248, 1212, 1121,

1091, 1024, 825, 767cm^{-1}.; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (t, *J*=6.0 Hz, 6H), 2.35 (s, 6H), 4.10 (q, *J*=6.0 Hz, 4H), 4.90 (s, 1H), 5.52 (brs, 1H, NH), 7.08-7.25 (m, 5H).;^{13}C NMR (75 MHz, $CDCl_3$): δ 14.3, 20.5, 40.0, 60.1, 103.9, 126.8, 129.2, 136.1, 143.9, 146.1, 168.3.; MS (ESI)*m/z* (%): 328 (M+1, 95), 284 (100), 256 (25), 252 (35), 225 (15), 219 (10), 195 (10), 181 (12), 173 (25), 131 (15), 107 (20).

3.1.2.Diethyl-2,6-dimethyl-4-(3,4,5-trimethoxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (3b): IR (KBr):υ_{max}3357, 2928, 2853, 1696, 1636, 1593, 1497, 1460, 1378, 1317, 1273, 1205, 1127, 1092, 1001, 864, 803, 748cm^{-1}.;^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28 (t,*J* = 6.0 Hz, 6H), 2.35 (s, 6H), 3.78 (s, 6H), 3.80 (s, 3H), 4.12 (q,*J*=6.0 Hz, 4H), 4.90 (s, 1H), 5.52 (brs, 1H, NH) 6.45 (s, 2H).; MS (ESI) *m/z* (%): 420 (M+1, 30), 374 (25), 346 (20), 328 (10), 252 (100), 227 (10), 170 (10), 121 (10).

3.1.3.Diethyl-2,6-dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (3c): Solid; Mp. 130-131 ^{0}C;IR (KBr):υ_{max}3341, 3084, 2979, 2927, 2855, 1683, 1518, 1484, 1344, 1301, 1213, 1101, 1020, 828, 754cm^{-1}.; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (t, *J*=6.0 Hz ,6H), 2.35 (s, 6H), 4.10 (q,*J*=6.0 Hz, 4H), 5.05 (s, 1H), 5.70 (brs, 1H, NH), 7.41 (d, *J*=6.5 Hz, 2H), 8.06 (d, *J*=6.5 Hz, 2H).;^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 20.3, 40.2, 60.1, 103.4, 123.5, 128.3, 144.7, 145.9, 156.0, 166.9.;MS (ESI) *m/z*(%): 375 (M+1, 45), 348 (10), 329 (100), 320 (10), 301 (25), 102 (10).

3.1.4.Diethyl-2,6-dimethyl-4-(3-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (3d): Solid; Mp. 130-131°C;IR (KBr):υ_{max}3323, 3246, 3098, 2979, 2925, 1705, 1649, 1488, 1375, 1333, 1299, 1214, 1119, 1022, 869, 788, 751cm^{-1}.; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.23 (t, *J*=6.0 Hz, 6H), 2.36 (s, 6H), 4.10 (q,*J*=6.0 Hz, 4H), 4.90 (s, 1H), 5.58 (brs, 1H, NH), 7.05-7.20 (m, 4H).;^{13}C NMR (75 MHz, $CDCl_3$): δ 14.8, 19.3, 40.2, 60.1, 103.6, 126.0, 127.6, 128.0, 132.6, 143.5, 144.1, 150.1, 167.9.; MS (ESI) *m/z*(%): 386 (M+1, 65), 364 (40), 318 (100), 292 (10), 251 (20), 201 (10),171 (25).

3.1.5. (E)-Diethyl-2,6-dimethyl-4-styryl-1,4-dihydropyridine-3,5-dicarboxylate (3e): Solid; Mp. 148-150°C; IR (KBr):υ_{max}3334, 3095, 2924, 1690, 1644, 1490, 1375, 1326, 1296, 1219, 1161, 1116, 1025, 783, 755cm^{-1}.; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (t, *J*=6.0 Hz, 3H), 2.38 (s, 6H), 3.92 (s, 3H), 4.18 (q, *J*=6.0 Hz, 2H), 5.14 (d, *J*=4.5 Hz, 1H), 5.6.0 (brs, 1H), 6.15 (dd, *J*=4.5 & 14.8 Hz, 1H), 7.18 (d, *J*=14.8 Hz, 1H), 7.22-7.34 (m, 5H); MS (ESI) *m/z*(%): 341 (M+1, 20), 327 (10), 297 (100), 269 (10), 211 (15), 183 (20), 104 (18), 81 (25), 76 (35), 51 (22).

3.1.6.Diethyl-4-decyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (3f): IR (KBr):υ_{max}3377, 2926, 2855, 1728, 1567, 1461, 1376, 1282, 1233, 1104, 1041, 860, 772cm^{-1}.; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90 (t, *J*=6.0 Hz , 3H), 1.20-1.36 (m, 24 H), 2.29 (s, 6H), 3.85 (t, *J*=6.0 Hz , 1H), 4.20 (q, *J*=6.0 Hz , 4H), 5.48 (brs, 1H, NH); MS (ESI) *m/z*(%): 393 (M-1, 100), 335 (10).

3.1.7.Diethyl-4-benzyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (3g): IR (KBr):υ_{max}2978, 2927, 1719, 1592, 1443, 1369, 1289, 1252, 1222, 1105, 1043, 863, 769cm^{-1}.; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 (t, *J*=6.0 Hz, 6H), 2.15 (s, 6H), 2.55 (d, *J*=5.0 Hz , 2H), 4.05 (q, *J*=6.0 Hz, 4H), 4.97 (s, 1H), 5.45 (brs, 1H, NH), 6.98 (d, *J*=7.0 Hz, 2H), 7.10-7.20 (m, 3H).; MS (ESI) *m/z*(%): 344 (M+1, 20), 342 (10), 318 (10), 250 (10), 298 (25), 252 (100), 224 (10).

3.1.8.Diethyl-2,6-dimethyl-4-(pyridin-2-yl)-1,4-dihydropyridine-3,5-dicarboxylate (3h): IR (KBr):υ_{max}3273, 3172, 3054, 2925, 1676, 1593, 1508, 1437, 1371, 1304, 1256, 1212, 1116, 1018, 751cm^{-1}.;^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20 (t, *J* =6.0 Hz , 6H), 2.25 (s, 6H), 4.05 (q, *J*=6.0 Hz, 4H), 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, *J*=6.0 Hz, 1H).; MS (ESI) *m/z*(%): 331 (M+1, 100), 308 (10), 286 (55), 292 (10), 262 (10).

3.1.9.Diethyl-4-(furan-2-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (3i): Solid; Mp. 158-160°C.IR (KBr):υ_{max}3346, 2981, 1702, 1650, 1487, 1373, 1331, 1298, 1262, 1209, 1119, 1095, 1047, 1013, 807, 731cm^{-1}.; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28 (t, *J*=6.0 Hz, 6H), 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, $CDCl_3$): δ14.5, 20.1, 33.5, 60.2, 99.8, 104.9, 109.8, 141.2, 145.5, 159.0, 168.1.; MS (ESI) *m/z*(%): 320 (M+1, 45), 318 (25), 304 (40), 274 (10), 261 (10), 252 (100), 214 (15).

3.1.10.Diethyl-4-(2-chloro-6-methylquinolin-3-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (3j): IR (KBr):υ_{max}3338, 2981, 1725, 1695, 1560, 1495, 1448, 1375, 1301, 1275, 1213, 1171, 1104, 1043, 925, 824, 755cm^{-1}.;^{1}H NMR (300 MHz, CDCl3): δ 1.19 (t, *J*=6.0 Hz, 6H), 2.32 (s, 6H), 2.50 (s, 3H), 4.01-4.12 (m, 4H), 5.42 (s, 1H), 5.65 (brs, 1H), 7.40-7.50 (m, 2H), 7.82 (d, *J*=7.0 Hz , 1H), 7.99 (s, 1H).;MS (ESI) *m/z*(%): 429 (M+1, 100), 393 (35), 251 (10), 178 (20).

3.1.11.Diethyl-4-(2,6-dimethylhept-5-enyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (3k): IR (KBr):υ_{max}3373, 2967, 2927, 1728, 1565, 1449, 1377, 1283, 1236, 1106, 1040, 859, 775 cm^{-1}.; ^{1}H NMR (300 MHz, $CDCl_3$): 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, 2 H), 2.30 (s, 6H), 4.20 (q, *J*=6.0 Hz, 4H), 5.48 (brs, 1H, NH).; MS (ESI) *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).

3.1.12.Diethyl-4-[4-(dimethylamino)phenyl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxyl-ate (3l): IR (KBr):υ_{max}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 (300 MHz, $CDCl_3$): δ 1.26 (t, *J*=6.0 Hz, 6H), 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, *J*=7.0 Hz, 2H).; MS (ESI) *m/z*(%): 373 (M+1, 100), 252 (25), 227 (10), 205 (10), 116 (10), 65 (10), 55 (10).

3.1.13.Diethyl-4-[4-(benzyloxy)-3-methoxyphenyl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (3m): IR (KBr):υ_{max}3365, 3063, 2926, 2853, 1693, 1642, 1621, 1511, 1484, 1422, 1380, 1270, 1201, 1161, 1093, 1049, 1007, 862, 812, 748cm^{-1}.; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (t, *J*=6.0 Hz, 6H), 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).; MS (ESI) *m/z*(%): 465 (M+1, 35), 464 (65), 420 (15), 392 (20), 367 (10), 322 (10), 252 (100), 152 (10), 115 (10), 102 (15), 75 (10).

4. Conclusion

In summary, we have described a simple and efficient methodology for the synthesis of 1,4-dihydropyridines using GeI_4 as a catalyst at acetonitrile reflux, *via* smooth cyclo condensation of aldehydes, ethyl acetoacetate and ammonium acetate successfully. Our method is very simple, with short reaction times and cleaner reactions with improved yields, which make it a useful process for the synthesis of 1, 4-dihydropyridine derivatives.

Acknowledgments

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