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Recyclable and reusable ionic liquid catalyzed synthesis of dihydropyridines

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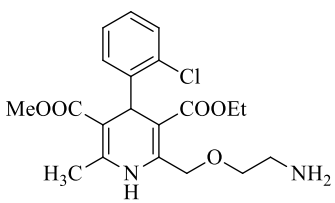
ABSTRACT

1,4-Dihydropyridine amalgamation has been completed utilizing ionic liquid as a catalyst. This convention is relevant to an assortment of aldehydes with β-ketoester and ammonium acetic acid derivation to manage the cost of the relating Hantzsch pyridines in magnificent yields. This multicomponent build up occurred easily in water reflux.

1. INTRODUCTION

Multicomponent buildup techniques offer huge points of interest over routine direct sort blend in giving items the differing qualities required for the revelation of new lead mixes or lead enhancement utilizing combinatorial science [1-3]. In 1882, Arthur Rudolf Hantzsch, a German scientist, announced a cyclocondensation among ethyl acetoacetate, aldehydes and watery ammonium hydroxide to bear the cost of a heterocyclic arrangement of 1,4-dihydropyridine; from that point forward, it got comfortable as the Hantzsch response [4-6].



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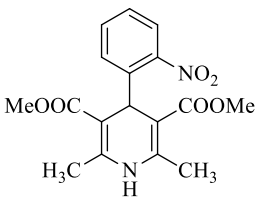
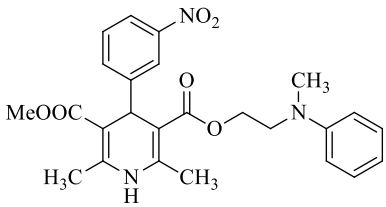


Nifedipine



Nicardipine

Figure 1. Biologically active dihydropyridine derivatives

The dihydropyridine subordinates display a substantial scope of natural exercises, for example, anticonvulsant, antitumor, antianxiety, vasodilator, bronchodilator, energizer, pain relieving, sleep inducing, calming and neuroprotectants and in addition platelet antiaggregatory specialists. Dihydropyridines are economically utilized as calcium channel blockers for the treatment of cardiovascular infections (Figure 1). The colossal natural action of Hantzsch pyridines pulled in numerous analysts and academicians. Subsequently, a few endeavors have been made to orchestrate 1,4-dihydropyridine subsidiaries utilizing different catalystes and response conditions, for example, Scandium (III) triflate [7], $NaHSO_4$-SiO_2 [8] molecular iodine [9-10], ionic liquid [11] microwaves [12], iodotrimethylsilane [13] and $Ce(SO_4)_2$-SiO_2 [14] have been used to synthesize 1,4-DHPs.

However, large portions of the strategies are experiencing a few disadvantages, for example, long response time, low yields, dreary workup techniques and the utilization of costly catalystes. In this manner, the advancement of effective convention is still sought after. As a component of our examination program in growing new strategies, we report thus a straightforward and effective strategy for the amalgamation of 1,4-dihydropyridine subordinates utilizing cadmium chloride as a catalyst. Cadmium chloride is a nonhygroscopic white strong that is exceedingly dissolvable in water, a gentle Lewis corrosive and a catalyst known for different natural changes in the writing.

2. EXPERIMENITAL

2.1 Material and methods

Reagents and chemicals were acquired from business providers and utilized without further refinement. Dissolving focuses were resolved in open vessels with an exactness computerized liquefying point Veego VMP-DS contraption and are uncorrected. IR spectra were recorded on a thermo Nicolet Nexus 670 FT-IR spectrophotometer. 1H and 13C NMR spectra were recorded on either a Bruker Avance 300 (Bruker, Germany; 300.132 MHz for 1H, 75.473 for 13C) or Varian FT-200 MHz (Gemini) spectrometer in CDCl3. The chemicals shift (δ) and coupling constants (J) cited in hertz are accounted for in parts per million in respect to tetramethylsilane (δ = 0.00 ppm) (for 1H) as an interior standard. The resonances of leftover proton and those of carbons in deuterated solvents CDCl3 (δH = 7.26 ppm, δc = 77.0 ppm) and DMSO-d6 (δH = 2.50 ppm,

δc = 39.52 ppm) were utilized as inside models. Essential investigations were performed on an Elementar Vario EL microanalyzer. Low-determination mass spectra (ESI-MS) and HRMS were recorded on Quattro LC, Micromass, and Q STAR XL, Applied Biosystems, separately. Section chromatography was performed utilizing silica gel (Acme's 60–120 mesh). Solvents for chromatography (n-hexane, acetonitrile, cyclohexane, and EtOAc) were refined preceding use. For logical thin-layer chromatography, Merck pre-covered silica gel 60 F-254 plates were utilized; the plates were pictured utilizing UV light (254 nm) or iodine vapor or by dunking the plates in phosphomolybdic corrosive ceric(IV)sulfate-sulphuric corrosive (PMA) arrangement and warming the plates at 100 °C.

2.2 General procedure

A mixture of benzaldehyde (1 mmol, 106 mg), ethyl acetoacetate (2 mmol, 260 mg), ammonia derivation (4 mmol, 308 mg), and the ionic liquid (200 mg) will be combined in a round flask in water (10 mL) at Room Temperature (RT) for 2h. The advance of the response will be checked by TLC. After culmination of the response, the catalyst is isolated by utilizing a magnet and reused for further utilize. The reaction mixture will be diluted with EtOAc (10mL) and washed with brine water (2x10 mL), dried over anhydrous Na_2SO_4, and dissipated *in vacuo*, and the subsequent item will be subjected to column chromatography on silica gel with 5% EtOAc in hexane to isolate pure dihydropyridine.

Synthesis of ionic liquid:

1-Methylimidazole (15.8 ml, 0.2mol) and 1,4-butane sultone (22 ml, 0.2mol) were charged into a 100 ml round-bottom flask. Then, the mixture was stirred at 40ºC for 10h. The white solid zwitterion was washed repeatedly with ether (80x5 ml) to remove non-ionic residues and dried in vacuum. Then, a stoichiometric amount of concentrated sulfuricacid (98%, 10.9 ml) was added by dropwise and the mixture stirred for 6 h at 80oC to form the IL. 1H NMR (400 MHz, D_2O): δ = 1.28-1.32 (m, 2H, -CH_2), 1.56-1.60 (m, 2H, -CH_2),2.48-2.52 (t, J = 7.7 Hz, 2H, -CH_2), 3.45 (s, 3H, -CH_3), 3.78-3.82 (t, J = 7.1 Hz, 2H, -CH_2), 7.00 (s, 1H, imidazole), 7.05 (s, 1H, imidazole), 8.27 (s, 1H, imidazole);^{13}C NMR (100 MHz, D_2O): δ = 20.75, 27.90 (-CH_2), 35.63 (-CH_3, imidazole), 48.75, 49.94 (-CH_2), 121.90, 123.62 and 135.77 (-CH, imidazole).

Selected Spectroscopic Data

(3a) Diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate

Yellow crystalline solid: mp 154-156 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)7.27 (d, *J* = 7.5 Hz, 2 H), 7.19 (t, *J* = 7.3 Hz, 2H), 7.10 (t, *J* = 7.3 Hz, 1 H), 6.21 (br s, 1 H), 4.99 (s, 1 H), 4.08 (q, *J* =7.2 Hz, 4 H), 2.28 (s, 6 H), 1.21 (t, *J* = 7.2 Hz, 6 H); ^{13}C NMR (75 MHz, CDCl3) δ (ppm) 167.8, 147.9, 144.3, 127.9, 127.8, 126.1, 103.9, 59.7, 39.6, 19.3, 14.2; MS (ESI) m/z 330$(M+H)^+$; HRMS (ESI) Calcd for $C_{19}H_{24}NO_4$ $(M+H)^+$ 330.1705., found 330.1693.

(3b) Diethyl 4-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate

Yellow crystalline solid: mp 150-152 °C; ^{1}H NMR(300 MHz, $CDCl_3$) δ (ppm) 1.20(t, 6H, *J*=7.18), 2.26(s, 6H), 3.71(s, 3H), 3.93-4.09(m, 4H), 4.78(s, 1H), 6.66(d, 2H, *J*=8.50), 7.07(d, 2H, *J*=8.50), 8.29(s, 1H); ^{13}C NMR(75 MHz, d_6-DMSO) δ (ppm) 14.10, 18.16, 37.94, 54.75, 58.89, 102.13, 113.09, 128.29, 140.52, 144.94, 157.41, 166.98; MS (ESI) m/z 382$(M+Na)^+$; HRMS (ESI) Calcd for $C_{20}H_{25}NO_5Na$ $(M+Na)^+$ 382.1630., found 382.1635.

(3c) Diethyl 2,6-dimethyl-4-(naphthalen-2-yl)-1,4-dihydropyridine-3,5-dicarboxylate

Yellow crystalline solid: mp 137-139 °C; ^{1}H NMR (300 MHz, CDCl3) δ(ppm) 7.75 (dd, *J* = 7.3 and 4.6 Hz, 2 H), 7.69 (d, *J* = 8.5 Hz, 1 H), 7.67 (s, 1 H), 7.48 (dd, *J* = 8.5 and 1.5 Hz, 1 H), 7.39 (app qu, *J* = 8.8 Hz, 2 H), 5.64 (br s, 1 H), 5.17 (s, 1 H), 4.08 (m, 4 H), 2.36 (s, 6 H), 1.22 (t, *J* =7.1 Hz, 6 H); 13C NMR (75 MHz, CDCl3) δ (ppm) 167.6, 145.2, 143.8, 133.3, 132.3, 127.8, 127.4, 127.4, 127.1, 126.3, 125.5, 125.0, 104.1, 59.7, 39.9, 19.6, 14.2; MS (ESI) m/z 402$(M+Na)^+$; HRMS (ESI) Calcd for $C_{23}H_{25}NO_4Na(M+Na)^+$ 402.1681., found 402.1668.

(3d) Diethyl 4-(2-fluorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate

Yellow crystalline solid: mp 148-152 °C; ^{1}H NMR (300 MHz, CDCl3) δ (ppm) 7.28 (t, *J* = 7.5 Hz, 1 H), 7.05 (d, *J* = 6.2 Hz, 1 H), 6.95 (t, *J* = 7.4 Hz, 1 H), 6.86 (t, *J* = 8.9 Hz, 1 H), 6.64 (s, 1 H), 5.24 (s, 1 H), 4.02 (q, *J* = 7.2 Hz, 4 H), 2.22 (s, 6 H), 1.16 (t, *J* = 7.3 Hz, 6 H); ^{13}C NMR (75 MHz, CDCl3) δ (ppm) 167.8, 159.6, 145.0, 135.2, 131.0, 127.6, 123.6, 114.8, 102.6, 59.7, 34.1, 19.0, 14.0; MS (ESI) m/z 370$(M+Na)^+$; HRMS (ESI) Calcd for $C_{19}H_{22}NO_4FNa(M+Na)^+$ 370.1431., found 370.1428.

(3e) Diethyl 4-(furan-2-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate

Orange crystalline solid: mp 153-155 °C; ^{1}H NMR (300 MHz, CDCl3) δ (ppm) 7.18 (s, 1 H), 6.18 (br s, 2 H), 5.91 (d, *J* = 4.8 Hz, 1 H), 5.18 (s, 1 H), 4.17 (q, *J* = 7.1 Hz, 2 H), 4.12 (q, *J* = 7.1 Hz, 2 H), 2.29 (s, 6 H), 1.24 (t, *J* = 7.1 Hz, 6 H); ^{13}C NMR (75 MHz, CDCl3) δ (ppm) 167.5, 158.7, 145.3, 140.8, 110.0, 104.4, 100.5, 59.8, 33.4, 19.3, 14.3; MS (ESI) m/z 320$(M+H)^+$; HRMS (ESI) Calcd for $C_{17}H_{22}NO_5$ $(M+H)^+$ 320.1498., found 320.1493.

(3f) Diethyl 4-(3,4-dihydroxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate

^{1}H NMR(500 MHz, $CDCl_3$) δ (ppm) 1.21(t, 6H, *J*=6.98), 2.24(s, 6H), 3.97-4.08(m, 4H), 4.71(s, 1H), 6.43-6.61(m, 3H), 8.22(s, 1H); ^{13}C NMR(75 MHz, d_6-DMSO) δ (ppm) 14.19, 18.20, 40.94, 55.76, 61.24, 102.13, 116.09, 117.29, 120.76, 128.29, 140.52, 144.94, 147.45, 157.41, 167.58;MS (ESI) m/z 362$(M+H)^+$; HRMS (ESI) Calcd for $C_{20}H_{26}NO_6(M+H)^+$ 362.1604., found 362.1600.

(3g) Diethyl 4-(3-hydroxy-4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate

^{1}H NMR(300 MHz, $CDCl_3$) δ (ppm) 1.23(t, 6H, *J*=7.18), 2.25(s, 6H), 3.77(s, 3H), 3.96-4.10(m, 4H), 4.75(s, 1H), 6.51-6.61(m, 2H), 6.71(s, 1H), 8.21-8.32 (bs, 1H); ^{13}C NMR(75 MHz, $CDCl_3$) δ (ppm) 14.25, 19.35, 39.01, 55.65, 59.60, 103.97, 110.90, 113.85, 120.34, 140.09, 143.81, 145.77, 167.76; MS (ESI) m/z 376$(M+H)^+$; HRMS (ESI) Calcd for $C_{20}H_{26}NO_6(M+H)^+$ 376.1755., found 376.1760.

(3h) Diethyl 4-(4-(3-fluoro-4-nitrophenoxy)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-di carboxylate

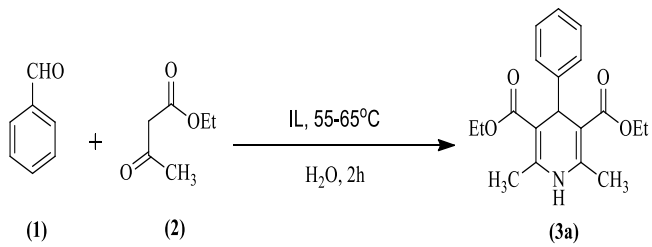
^{1}H NMR(300 MHz, $CDCl_3$) δ (ppm) 1.23(t, 6H, *J*=6.80), 2.33(s, 6H), 4.00-4.21(m, 4H), 4.95(s, 1H), 6.60(dd, 1H, $J_{(1,2)}$=2.27, $J_{(1,3)}$=9.82), 6.75-6.83(m, 1H), 6.92(d, 2H, *J*=8.31), 7.24-7.34(m, 3H); ^{13}C NMR (75 MHz, CDCl3) δ (ppm) 14.22, 19.3, 39.6, 59.7, 102.77, 106.92, 115.08, 117.45, 126.1, 127.9, 130.33, 135.67, 144.3, 147.92, 154.08, 155.65, 164.09, 167.8; MS (ESI) m/z 485$(M+H)^+$;

(3i) Diethyl 2,6-bis((2-(1,3-dioxoisoindolin-2-yl)ethoxy)methyl)-4-(4-methoxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate

^{1}H NMR(500 MHz, d_6-DMSO) δ (ppm) 1.14(t, 3H, *J*=6.64), 1.25(t, 3H, *J*=7.47), 2.55(s, 1H), 3.56-3.79(m, 7H), 3.86-4.05(m, 4H), 4.07-4.16(m, 1H), 4.28(d, 1H, J=16.60), 4.56-4.60(bs, 1H), 4.68(d, 1H, *J*=16.60), 5.88(s, 1H), 6.11(s, 1H), 6.74(d, 2H, *J*=8.30), 7.03(d, 2H, *J*=9.13), 7.68-7.88(m, 8H); ^{13}C NMR(75 MHz, $CDCl_3$) δ (ppm) 14.25, 39.22, 43.82, 55.22; 62.02, 68.09, 70.84, 99.92, 114.56, 127.82, 131.06, 132.87, 133.67, 145.36, 158.22, 166.92, 168.02; MS (ESI) m/z 738$(M+H)^+$.

3. RESULTS AND DISCUSSION

To optimize the reactions conditions, we checked the four-part buildup response of benzaldehyde (1 mmol), ethyl acetoacetate (1 mmol), and ammonia (4 mmol) in the nearness of various reactant measures of ionic liquid at room temperature in 5 mL of EtOH, as a model response. It was found that 0.03 g of catalyst was sufficient to catalyze the response to deliver exceptional returns of dihydropyridines subsidiaries. As appeared in Table 1 (Entries 1–4), utilizing 0.03 g of the catalyst was sufficient to advance the response what's more, an augmentation of the catalyst sum did not make strides the yields. In the second stage the impact of dissolvable was examined. As can be seen from Table 1 (Entries 5–9), it was found that EtOH is the best dissolvable for this response to create exceptional returns in short response time in examination with other polar, non-polar, protic and aprotic solvents. To concentrate the sweeping statement of this technique, diverse sorts of beginning material were responded in the union of 1,4-dihydropyridines. As represented in Table 1, sweet-smelling aldehyde with both electron pulling back gatherings and electron giving gatherings respond well to give the items in great to phenomenal yields. As it anticipated beginning from aldehyde with electron withdrawing reduce the yields, the electron donating response happens in the lower time in examination with electron giving good yields, (for example, alkoxy).



Synthesis of dihydropyridines

4. CONCLUSION

In conclusion, nano catalyzed synthesis of dihydropyridine derivatives has been produced. Different aromatic aldehydes, ethylaceto acetate and ammonia can be endured in this response to manage the cost of the coveted items in great yields. Response time perceptibly diminishes from days or hours in presence of nano catalyst. Additionally studies to extend the substrate extension and detail response component are as of now in progress in our lab.

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Table 1. Catalyzed synthesis of dihydropyridine

S.No.	Aldehyde	Keto Ester	Product[a]	Time(h)	Yield(%)[b]
(1)	(1a)	(2a)	(3a)	2.0	95
(2)	(1b)	(2a)	(3b)	1.9	96
(3)	(1c)	(2a)	(3c)	2.1	90
(4)	(1d)	(2a)	(3d)	2.2	88
(5)	(1e)	(2a)	(3e)	2.3	89
(6)	(1f)	(2a)	(3f)	2.2	89
(7)	(1g)	(2a)	(3g)	2.2	90
(7)	(1g)	(2a)	(3g)	2.2	90
(8)	(1h)	(2a)	(3h)	2.2	88
(9)		(2b)	(3i)	2.3	85

[a]All products were characterized by IR, 1H NMR and mass spectroscopy.
[b]Yield refers to pure products after column chromatography.

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