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Efficient One Pot Synthesis of 1,4-Dihydropyridines Under Solvent Free Conditions Using Carbonaceous Solid Acid Catalyst

Research Article

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Abstract

Carbonaceous solid acid catalyst was used for convenient and efficient synthesis of 1,4-dihydropyrine (DHP) derivatives under solvent free conditions. The main advantages of these protocol includes short reaction time, high yields, recyclable catalyst, selectivity towards 1,4-dihydropyridine derivatives, practical simplicity and work up free reaction conditions. Catalyst can be recovered and reused for five runs without any significant impact on yields of products.

Keywords: Carbonaceous; Dihydropyridine; Solvent free; Recovered; Reused

Introduction

1,4-Dihydropyridines (DHP's) are an important class of bioactive molecules, well-known for their role as calcium channel modulators and used extensively for the treatment of hypertension. The derivatives of DHP have shown a variety of biological activities and pharmacological activities, such as anti-tubercular, anti-convulsant, anti-tumour, anti-analgesic, anti-inflammatory, cardiovascular disease and stress protective activities [1-4]. Extensive studies have revealed that these compounds exhibit various medicinal functions such as neuroprotectant, cerebral anti-ischemic activity in the treatment of Alzheimer's disease, and chemosensitizer in tumour therapy [5].

These examples clearly indicate the remarkable potential of novel dihydropyridine derivatives as a source of valuable drug candidates. Several DHP's which are commercial products such as Diludine, Felodipine, Amlodipine, Nimodipin etc. are manufactured and used worldwide (Figure 1) [6,7]. Synthesis of 1,4-dihydropyridine was for the first time developed by Arthur Hantzsch in 1882 [8]. Realizing the biological importance of DHP derivatives, several synthetic methods have been reported till date such as Lewis acid catalyst [9-12], ionic liquids [13-17], organocatalysis [18], microwave assisted [19-23], heteropolyacids [24], nanoparticles [25], solar thermal energy [26], ultrasound irradiation [27], visible light [28], solid support [29-31], salts [32,33] and Grignard reagents [34]. However, a number of methods have been reported for the synthesis of DHPs, which suffer from drawbacks like longer reaction times, low to moderate yields, and require highly acidic reaction conditions. It is noteworthy to observe that disposal of toxic solvents often pose environmental and health problems. Therefore, the search for a better catalyst for the

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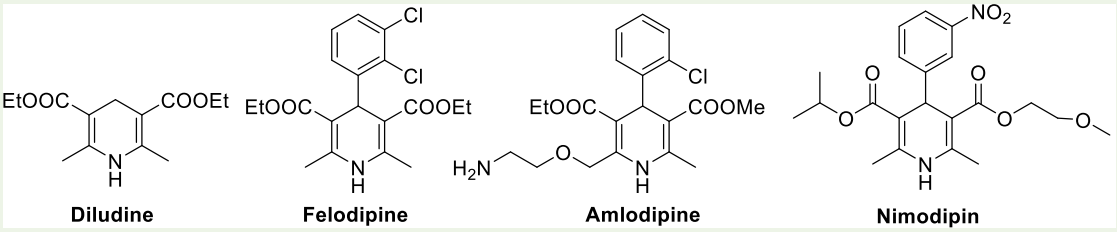

Figure 1: Biological important drugs.

synthesis of DHP derivatives using less hazardous solvents or solvent free conditions is of prime importance.

Materials and Methods

All reagents were purchased from Aldrich, Fluka, MERCK, TCI and were used without further purification. IR was measured on Bruker Alpha instrument. NMR spectra were recorded in $CDCl_3$ at 25 °C on Bruker 500 (500 MHz). For ^1H NMR spectra, proton chemical shifts (δ) are given in ppm relative to tetramethylsilane (0.00 ppm) in $CDCl_3$. Multiplicities are indicated by s (singlet), d (doublet), t (triplet), m (multiplet), and br (broad). Confirmations of products were analyzed by GCMS.

General procedure for 1,4-dihydropyridine synthesis

A mixture of aldehyde (1 mmol), ethyl acetoacetate (2 mmol), ammonium acetate (1 mmol) and catalyst (10 wt %) were stirred in round bottle flask (10 mL) under solvent free conditions at 80 °C for required time. After completion of the reaction, EtOAc (25 mL) was added and the catalyst was removed by filtration. The filtrate was concentrated under reduced pressure, to afford crude DHP derivatives which were then column purified to obtain pure 1,4-DHP products.

Characterization

(Table 3, Entry 1): Yield-92%, m.p. 160-162 °C; R_f: 0.52 (Ethyl Acetate: Pet ether = 3:7); IR ($CHCl_3$) υ = 3342, 2982, 1652, 1488, 703 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.21 (t, *J* = 7.2 Hz, 6H), 2.31 (s, 6H), 4.01-4.16 (m, 4H), 4.99 (s, 1H), 5.78 (s, 1H), 7.07-7.30 (m, 5H); MS (EI) m/z 329.

(Table 3, Entry 2): Yield-85%, mp 115-118 °C; R_f: 0.56 (Ethyl Acetate: Pet ether = 3:7); IR ($CHCl_3$) υ = 3343, 2920, 2538, 2252, 1682, 1492, 732 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.20 (t, *J* = 7.1Hz, 6H), 2.27 (s, 6H), 3.72 (s, 3H), 3.74 (s, 3H), 4.01-4.12 (m, 4H), 5.26 (s, 1H), 5.79 (s, 1H), 6.65 (d, *J* = 8.8 Hz, 1H), 6.70 (s, 1H), 6.80 (d, 1H, *J* = 8.9Hz); MS (EI) m/z 389.

(Table 3, Entry 3): Yield-88%, m.p. 158-160 °C; R_f: 0.56 (Ethyl Acetate: Pet ether = 3:7); IR ($CHCl_3$) υ = 3338, 2984, 2054, 1644, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.22 (t, *J* = 7.2 Hz, 6H,), 2.32 (s, 6H), 3.75 (s, 3H), 4.03-4.15 (m, 4H), 4.93 (s, 1H), 5.60 (s, 1H), 6.75 (d, *J* = 8.7 Hz, 2H), 7.19 (d, *J* = 8.7 Hz, 2H); MS (EI) m/z 359.

(Table 3, Entry 4): Yield-97%, m.p. 163-165 °C; R_f: 0.46 (Ethyl Acetate: Pet ether = 4:6); IR ($CHCl_3$) υ = 3321, 2980, 2355, 1651, 1348, 708 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.22 (t, *J* = 7.0 Hz, 6H), 2.37 (s, 6H), 4.04-4.15 (m, 4H), 5.10 (s, 1H), 5.75 (s, 1H), 7.30 (t, *J* = 7.8 Hz, 1H,), 7.65 (d, *J* = 7.7 Hz, 1H,), 8.0 (t, *J* = 2.1 Hz, 1H), 8.13 (t, *J* = 1.9 Hz, 1H); MS (EI) m/z 374.

(Table 3, Entry 5): Yield- 95%, m.p. 133-135 °C; R_f: 0.5 (Ethyl Acetate: Pet ether = 3:7); IR ($CHCl_3$) υ = 3345, 2991, 1646, 1348, 705 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.22 (t, *J* = 7.2 Hz, 6H), 2.32 (s, 6H), 4.05-4.15 (m, 4H), 5.10 (s, 1H), 5.64 (s, 1H), 7.46 (d, *J* = 8.8 Hz, 2H), 8.09 (d, *J* = 8.8 Hz, 2H); MS (EI) m/z 374.

(Table 3, Entry 6): Yield- 86%, m.p. 138-141 °C; R_f: 0.5 (Ethyl Acetate: Pet ether = 3:7); IR ($CHCl_3$) υ = 3355, 2926, 2856, 1702, 1682, 1484, 856, 681 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.21 (t, *J* = 7.0 Hz, 6H), 2.32 (s, 6H), 4.03-4.15 (m, 4H), 4.97 (s, 1H), 5.76 (s, 1H), 6.88 (d, *J* = 7.8 Hz, 2H), 7.22 (d, *J* = 7.8 Hz, 2H); MS (EI) m/z 347.

(Table 3, Entry 7): Yield- 82%, m.p. 120-122 °C; R_f: 0.5 (Ethyl Acetate: Pet ether = 3:7); IR ($CHCl_3$) υ =3359, 2988, 2362, 1652, 831 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.20 (t, *J* = 7.0 Hz, 6H), 2.29 (s, 6H), 4.02-4.13 (m, 4H), 5.40 (s, 1H), 5.84 (s, 1H), 6.99-7.16 (m, 2H), 7.22 (dd, *J* = 7.7 and 1.7 Hz, 1H), 7.38 (dd, *J* = 7.5 and 1.9 Hz, 1H); MS (EI) m/z 363.

(Table 3, Entry 8): Yield-83%, m.p. 115-117 °C; R_f: 0.5 (Ethyl Acetate: Pet ether = 3:7); IR ($CHCl_3$) υ = 3350, 2977, 2351, 1650, 1596, 1433, 1290, 1112, 730 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.21 (t, *J* = 7.0 Hz, 6H,), 2.36 (s, 6H), 4.0-4.17 (m, 4H), 5.04 (s, 1H), 5.66 (s, 1H), 7.32-7.58 (m, 4H); MS (EI) m/z 397.

(Table 3, Entry 9): Yield-88%, m.p. 100-102 °C; R_f: 0.5 (Ethyl Acetate: Pet ether = 3:7); IR (CHCl3) υ = 3355, 2980, 2349, 1655, 1596,1430,1285, 1112, 773 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.21 (t, J = 7.0 Hz, 6H), 2.37 (s, 6H), 4.0-4.2 (m, 4H), 5.09 (s, 1H), 5.82 (s, 1H), 7.65-7.71 (m, 3H); MS (EI) m/z 465.

(Table 3, Entry 10): Yield-87%, m.p. 118-120 °C; R_f: 0.5 (Ethyl Acetate: Pet ether = 3:7); IR ($CHCl_3$) υ = 3382, 1712, 1291 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.23 (t, *J* = 7.2 Hz, 6H), 2.34 (s, 6H), 4.1-4.18 (m, 4H), 4.95 (s, 1H), 5.69 (s, 1H), 7.08 (t, *J* = 7.7 Hz, 1H), 7.24 (d, *J* = 7.9 Hz, 2H), 7.39-7.41 (m, 1H); MS (EI) m/z 407.

(Table 3, Entry 11): Yield-94%, m.p. 165-167 °C; R_f: 0.5 (Ethyl Acetate: Pet ether = 3:7); IR ($CHCl_3$) υ = 3347, 2984, 1651, 1489, 1210, 1122, 1008, 731 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.26 (t, *J* = 7.0 Hz, 6H), 2.33 (s, 6H), 4.09-4.25 (m, 4H), 5.20 (s, 1H), 5.86 (s, 1H), 5.94 (d, *J* = 3.1 Hz, 1H), 6.21 (dd, *J* = 3.1 and 1.7 Hz, 1H), 7.21-7.22 (m, 1H); MS (EI) m/z 319.

(Table 3, Entry 12): Yield-82%, m.p. 132-134 °C; R_f: 0.5 (Ethyl Acetate: Pet ether = 3:7); IR ($CHCl_3$) υ =3362, 1698, 1487 cm^{-1} ; ^1H

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NMR ($CDC1_3$, 500 MHz): δ 1.23 (t, *J* = 7.2 Hz, 6H), 2.28 (s, 3H), 2.33 (s, 6H), 4.04-4.15 (m, 4H), 4.96 (s, 1H), 5.64 (s, 1H), 7.02 (d, *J* = 7.8Hz, 2H), 7.18 (d, *J* = 8Hz, 2H); MS (EI) m/z 343.

(Table 3, Entry 13): Yield-82%, m.p. 181-163 °C; R_f: 0.5 (Ethyl Acetate: Pet ether = 3:7); IR ($CHCl_3$) υ = 3338, 2984, 2054, 1644, 1630 750 cm^{-1}; ^1H NMR ($CDC1_3$, 500 MHz): δ 1.21 (t, *J* = 7.2 Hz, 6H,), 2.35 (s, 6H), 3.88 (s, 3H), 4.03-4.18 (m, 4H), 5.05 (s, 1H), 5.73 (s, 1H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.90 (d, *J* = 8.4 Hz, 2H); MS (EI) m/z 387.

(Table 3, Entry 14): Yield-86%, m.p. 134-137 °C; R_f: 0.5 (Ethyl Acetate: Pet ether = 3:7); IR ($CHCl_3$) υ = 3337, 2979, 1647, 1493, 1221, 1122, 1028, 720 cm^{-1}; ^1H NMR ($CDC1_3$, 500 MHz): δ 1.24 (t, *J* = 7.2 Hz, 6H), 2.32 (s, 6H), 4.05-4.17 (m, 4H), 4.92 (s, 1H), 5.65 (s, 1H), 5.88 (s, 2H), 6.64 (d, *J* = 7.7 Hz, 1H), 6.74 (d, *J* = 7.8 Hz, 1H), 6.78 (s, 1H); MS (EI) m/z 373.

(Table 3, Entry 15): Yield-91%, m.p. 119-121 °C; R_f: 0.5 (Ethyl Acetate: Pet ether = 3:7); IR ($CHCl_3$) υ = 3332, 1753, 1445 cm^{-1}; ^1H NMR ($CDC1_3$, 500 MHz): δ 1.28 (t, *J* = 7.2 Hz, 6H), 2.31 (s, 6H), 4.10-4.26 (m, 4H), 4.62 (d, *J* = 5.8 Hz, 1H,), 6.12 (s, 1H), 6.1-6.2 (m, 2H), 7.14-7.33 (m, 5H); MS (EI) m/z 355.

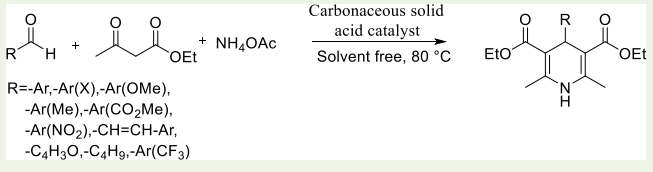
(Table 3, Entry 16): Yield-89%, m.p. 80-84 °C; R_f: 0.5 (Ethyl Acetate: Pet ether = 3:7); IR ($CHCl_3$) υ = 3370, 1724, 1440 cm^{-1}; ^1H NMR ($CDC1_3$, 500 MHz): δ 0.86 (s, 3H), 0.89 (s, 3H), 1.12 (t, *J* = 6.7 Hz, 2H) 1.30 (t, *J* = 7.0 Hz, 6H), 1.39-1.56 (m, 1H), 2.29 (s, 6H), 3.95 (t, *J* = 6.7 Hz, 1H), 4.09-4.26 (m, 4H), 5.87 (s, 1H); MS (EI) m/z 309.

(Table 3, Entry 17): Yield-90%, m.p. 179-182 °C; R_f: 0.5 (Ethyl Acetate: Pet ether = 3:7); IR ($CHCl_3$) υ = 3385, 1731, 1424 cm^{-1}; ^1H NMR ($CDC1_3$, 500 MHz): δ 1.29 (t, *J* = 7.0 Hz, 6H), 2.19 (s, 6H), 3.26 (s, 2H), 4.11-4.22 (m, 4H), 5.26 (s, 1H); MS (EI) m/z 253.

Results and Discussion

Organic reactions on carbonaceous catalyst especially under solvent-free conditions have attracted much attention from chemists particularly from green chemistry point of view. The advantage of these methods over conventional reactions is that they provide greater selectivity, enhanced reaction rates, cleaner reaction products, and operational simplicity, and are eco-friendly. Herein, we wish to report the carbonaceous solid acid catalyst synthesized in our laboratory [35] from β-cyclodextrin as a renewable and recoverable heterogeneous catalyst for one pot three component Hantzsch reaction of aldehydes, ethyl acetoacetate and ammonium acetate under solvent free conditions at 80 °C (Scheme 1).

The DHP's were synthesized by stirring a mixture of benzaldehyde (1 mmol), ethylacetoacetate (2 mmol), ammonium acetate (1 mmol), and catalyst (10 wt %) at 80 °C under solvent free conditions. To select



Scheme 1: Synthesis of 1, 4-dihydropyridine derivatives using carbonaceous catalyst.

an appropriate amount of catalyst, different percentage of catalyst loading was studied under solvent free conditions (Table 1). 1 wt% of catalyst when used, only 10% DHP product formation was seen. 5 wt% of catalyst when used gave good yield of DHP, while 10 wt% of catalyst gave excellent yields of the DHP's.

Different temperatures under solvent free conditions with 10% catalyst loading were also studied. At room temperature, the reaction was found to proceed slowly. Reaction proceeded slowly at 40 °C and 60 °C with lower yields and less selectivity. At 80 °C, reaction proceeded smoothly giving higher yields of DHP's in lesser time with higher selectivity. Furthermore, to select a solvent for the reaction, a green approach was chosen and this was optimized using different solvents like CH_3CN, THF, EtOH, H_2O and a solvent free condition. The results are summarized in Table 2 and the best condition identified was the solvent free condition.

After setting the optimum reaction conditions, we further tried to explore the carbonaceous catalyst on various substituted aldehydes possessing either electron donating or electron withdrawing substituents with ethyl acetoacetate and ammonium acetate using 10 wt% of the catalyst. All the reactions were carried out under solvent-free conditions and were rapid, clean, and high-yielding and the results are summarized in Table 3. In all cases the crude products were obtained by filtering the catalyst and were purified by column chromatography. The products were characterized by IR, ^1H NMR and GC Mass.

Green chemistry requires not only the utilization of environmentally friendly reagents, but also the recovery and reuse of the catalysts. Hence, the reusability of the carbonaceous catalyst for the Hantzsch reaction was studied. The carbonaceous catalyst was separated after each reaction by filtration, washed 3-4 times with water and methanol and used without any further activation. No significant impacts on yields of products were obtained even after subsequent five runs (Figure 2).

Table 1: Catalyst loading study in the synthesis of 1,4-dihydropyridines[a].

Entry	Catalyst (wt %)	Yield[b] (%)
1	1	10
2	5	65
3	10	90

[a]Reaction conditions: benzaldehyde (1 mmol), ethylacetoacetate (2 mmol), ammonium acetate (1 mmol) and catalyst (10 wt %) at 80 °C for 20 min. [b] Isolated yields

Table 2: Comparision of solvents in the synthesis of 1,4-dihydropyridines using carbonaceous catalyst[a].

Entry	Solvent	Catalyst (wt %)	Yield[b] (%)
1	CH_3CN	10	45
2	THF	10	55
3	EtOH	10	74
4	H_2O	10	64

[a]Reaction conditions: benzaldehyde (1 mmol), ethylacetoacetate (2 mmol), ammonium acetate (1 mmol) and catalyst (10 wt %) at 80 °C. [b] Isolated yields

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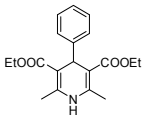
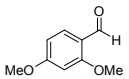
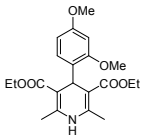
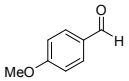
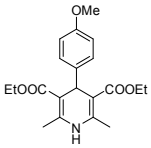
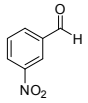
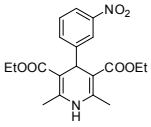
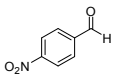
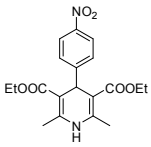
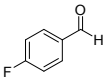
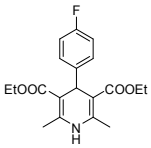
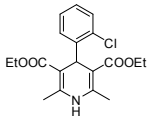
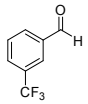
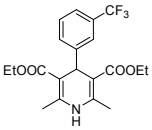
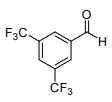
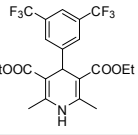
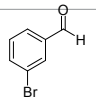
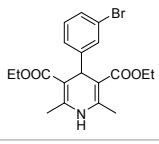
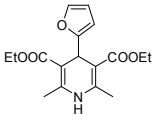
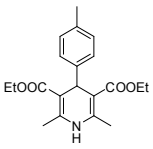
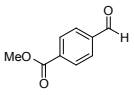
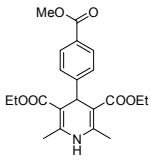
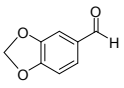
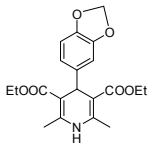
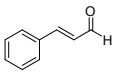
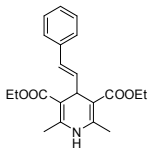
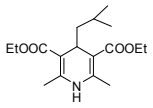
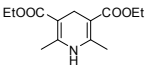
Table 3: Carbonaceous catalyst in one pot synthesis of 1, 4-Dihydropyridines.[a]

No.	Aldehyde	Product	Time (min)	Yield[b] (%)
1			20	92
2			45	85
3			40	88
4			30	97
5			35	95
6			25	86
7			22	82
8			15	83
9			20	88
10			30	87
11			10	94
12			35	82
13			35	82
14			25	86
15			20	91
16			45	89
17			10	90

[a]Reaction conditions: aldehyde (1 mmol), ethylacetoacetate (2 mmol), ammonium acetate (1 mmol) and catalyst (10 wt %) at 80 °C. [b] Isolated yields

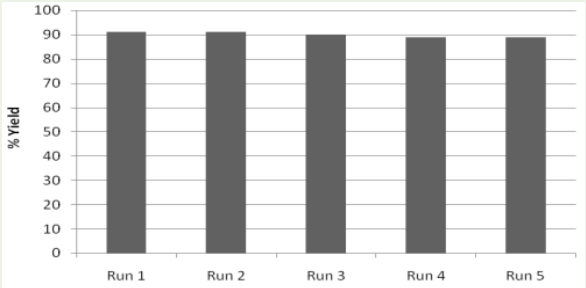


Figure 2: Catalyst reusability[a].

[a]Reaction conditions: benzaldehyde (1 mmol), ethylacetoacetate (2 mmol), ammonium acetate (1 mmol) and reused catalyst (10 wt %) at 80 °C for 20 min under solvent free conditions.

Conclusion

In summary, a carbonaceous catalyst was efficiently used in one pot reaction of various aldehydes with ethyl acetoacetate in presence of ammonium acetate under solvent free conditions. The new procedure is simple, inexpensive, solvent-free conditions, eco-friendly, short reaction times, high yields, high selectivity and high reusability, making it a useful alternative to the existing methods.

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Supporting Information

^{1}H NMR spectra for all the compounds. This material can be found online on articles webpage.

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