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Research Paper

Amberlite IR-120 catalyzed one pot four component Hantzsch reaction for the synthesis of 1,4-dihydropyrimidines

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Abstract: A convenient and practical, amberlite IR-120 catalyzed one pot four component reaction of 1,3-diketones, aromatic aldehydes, ethylacetoacetate and ammonium acetate for the synthesis of 1,4-dihydropyrimidines in good yields has been reported.

Introduction

Multicomponent reactions (MCRs) typically involve more than two reactants to combine in a sequential manner giving highly selective products while retaining majority of the atoms of the starting material. MCRs have received considerable attention because of their wide range of applications in pharmaceutical chemistry for the creation of structural diversity and combinatorial libraries for drug discovery.¹

1,4-dihydropyrimidines (**Figure 1**) are an important class of pharmaceutically important heterocycles that have attracted much attention because of their diverse therapeutic properties, such as calcium

channel blockers, vasodilator, hepatoprotective, antiatherosclerotic, bronchodilator, antitumor, geroprotective, antidiabetic activity, etc.² In addition, studies have revealed other applications such as neuroprotectant and platelet anti-aggregatory activity, cerebral anti-ischemic activity in the treatment of Alzheimer's disease, and as a chemosensitizer in tumor therapy.³

Synthesis of 1,4-dihydropyrimidine derivatives employing MCRs has been widely studied and documented in literature. Various catalysts including molecular iodine,⁴ ionic liquid,⁵ rare earth metal triflates,⁶ HClO₄-SiO₂,⁷ HY-zeolites,⁸ ZnO beta zeolite,⁹ TMSCl-NaI,¹⁰ ceric ammonium nitrate,¹¹ grinding technique,¹² ultrasound,¹³ montmorillonite K-10,¹⁴ p-

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TSA,¹⁵ polymer,¹⁶ heteropolyacid,¹⁷ organic catalyst,¹⁸ L-proline,¹⁹ Baker's yeast,²⁰ ZrCl₄,²¹ MCM-41,²² solar heat,²³ Hf(NPf₂)₄,²⁴ Yb(OTf)₃,²⁵ Cu(OTf)₂,²⁶ triphenyl phosphine,²⁷ liquid phase,²⁸ palladium nanoparticles,²⁹ In-SiO₂ composite catalyst,³⁰ microwave irradiation,³¹ and visible light irradiation³² have been reported for the synthesis of polyhydroquinoline derivatives. Some of these methods suffer from certain drawbacks, such as longer reaction time, low yields, harsh reaction conditions and environmentally toxic catalyst.

In continuation of our research work on the development of highly expedient methodologies for the synthesis of biologically important heterocyclic compounds,³³ we became interested in the development of one-pot MCR route for the synthesis of polyhydroquinolines using green catalyst. Recently, amberlite IR-120 resin has evolved as a mild and green catalyst imparting high selectivities in various organic transformations.³⁴ Compared to conventional resins, amberlite IR-120 resin in particular has advantages of low catalyst loading, moisture stability and catalyst recycling.

To the best of our knowledge, however, amberlite IR-120 resin promoted synthesis of 1,4-dihydropyrimidines has not been reported till date. In the present work, we report here a methodology for the synthesis of 1,4-dihydropyrimidines catalyzed by amberlite IR-120 resin. The overall process involves the Knoevenagel condensation of dimedone with aryl aldehydes, followed by in situ Michael addition of ethyl acetoacetate in a single operation.

Results and Discussion

As a model reaction, we selected 1 equiv of benzaldehyde **4**, 1 equiv of dimedone **5**, 1 equiv of ethylacetoacetate **7**, 1.5 equiv of ammonium acetate **8** and 10 mol% of amberlite IR-120³⁵ in ethanol to obtain 1,4-dihydropyrimidine **9a** in good yield (**Scheme 1**). As shown in **Table 1**, aromatic aldehydes carrying either electron donating or withdrawing substituent worked well, giving good yields of products.

The Knoevenagel condensation followed by Michael addition reaction of dimedone with several aromatic aldehydes, ammonium acetate, and ethylacetoacetate catalysed by amberlite IR-120 was investigated using a range of different solvents. The results in **Table 2** indicate that in general, reactions proceeded to completion in most of the solvents like dichloromethane, toluene and EtOH. Reactions proceeded faster under refluxing conditions than at room temperature.

Recyclability of the amberlite IR-120 catalyst was examined. For this reason, the catalyst used was recovered from the reaction via filtration, dried and re-used for the same reaction. This procedure was repeated for three times and results are summarized in **Table 3**. It is evident that the catalyst can be recycled successfully several times without significant loss of its catalytic activity.

Conclusion

In summary, we have developed a mild and efficient strategy for the synthesis of 1,4-dihydropyrimidines from 1,3-diketones, aryl aldehydes, ethylacetoacetate and ammonium acetate via Knoevenagel condensation followed by Michael addition reaction using amberlite IR-120 catalyst. The methodology is simple, rapid, and relatively inexpensive

affording good yields with operational simplicity.

Experimental Section

General: Unless otherwise stated, all commercial reagents and solvents were used without additional purification. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F254), visualizing with ultraviolet light (254 nm) or iodine spray. Column chromatography was performed on silica gel (60-120 mesh) using a proper eluent. ^1H and ^{13}C NMR spectra were determined in CDCl_3 and DMSO solutions using Varian MR 400 and 100 MHz spectrometers respectively. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, $\delta = 0.0$) as internal standard and expressed in parts per million. Spin multiplicities are given as s (singlet), d (doublet), t (triplet), and m (multiplet) as well as b (broad). Coupling constants (J) are given in hertz. Infrared spectra were recorded on a FTIR spectrometer. Melting points were determined by using a Buchi melting point B-540 apparatus. MS spectra were recorded using an Agilent 6430 triple quadrupole mass spectrometer.

General procedure for the synthesis of compounds 9-10: In a typical experiment, a solution of aldehyde (1 mmol), 1,3-diketone (1 mmol), ethylacetoacetate (1 mmol) and ammonium acetate (1.5 mmol) in absolute ethanol (2 mL) in the presence of amberlite IR 120 (10 mol%) was stirred at rt for 3h. After the starting material disappeared (by TLC) the reaction mixture was poured into crushed ice and the separated solid product, was filtered and dried. The solid product thus obtained was dissolved in dichloromethane and amberlite IR-120 was removed by filtration. Evaporation of the solvent furnished the desired product in good yield.

Ethyl-4-(4-methoxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (9a): Pale yellow solid; **M.P:** 251-252 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.21 (d, $J = 8.8$ Hz, 2H), 6.73 (d, $J = 8.8$ Hz, 2H), 5.92 (s, 1H), 4.99 (s, 1H), 4.05 (q, $J = 14.0, 6.8$ Hz, 2H), 3.73 (s, 3H), 2.36 (s, 3H), 2.36-2.12 (m, 4H), 1.20 (t, $J = 6.8$ Hz, 3H), 1.07 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 199.5, 170.5, 160.4, 153.4, 146.9, 142.2, 131.0 (2C), 115.2 (2C), 113.5, 107.9, 61.9, 56.6, 52.5, 42.1, 38.0, 34.5, 31.8, 28.1, 19.6, 15.6; **IR** (KBr): 3276, 1700, 1606, 1217 cm^{-1} ; ESI ($\text{M}^+ - 1$): 368; Yield: 83%

ethyl 4-(4-fluorophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (9b): Pale yellow solid; **M.P:** 187-189 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.27-7.24 (m, 2H), 6.89-6.85 (t, $J = 8.8$ Hz, 2H), 5.79 (s, 1H), 5.03 (s, 1H), 4.05 (q, $J = 14.0, 6.8$ Hz, 2H), 2.38 (s, 3H), 2.36-2.17 (m, 4H), 1.18 (t, $J = 7.6, 3\text{H}$), 1.08 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 195.5, 167.3, 162.4, 160.0, 148.1, 143.4, 142.8, 129.5, 129.2, 114.6, 112.0, 106.0, 59.8, 50.6, 41.0, 36.1, 32.6, 29.4, 27.1, 19.4, 14.2; **IR** (KBr): 3566, 1705, 1605, 1281, 1219 cm^{-1} ; ESI (M^+): 357; Yield: 80%

Ethyl-4-(3-cyanophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (9c): Pale yellow solid; **M.P:** 176-178 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.60 (d, $J = 8.0$ Hz, 1H), 7.55 (s, 1H), 7.40-7.38 (m, 1H), 7.32-7.25 (m, 1H), 6.46 (s, 1H), 5.06 (s, 1H), 4.04 (q, $J = 14.0, 6.8$ Hz, 2H), 2.38 (s, 3H), 2.37-2.11 (m, 4H), 1.17 (t, $J = 7.6$ Hz, 3H), 1.07 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 195.6, 167.0, 149.4, 148.6, 144.8, 133.2, 131.8, 129.9, 128.7, 119.4, 111.6, 110.9, 104.8, 59.9, 50.6, 40.6, 37.0, 32.6, 29.4, 27.2, 19.3, 14.2; **IR** (KBr): 3278, 2229,

1699, 1618 cm^{-1} ; ESI (M^+): 364.9; Yield: 84%

Ethyl-4-(4-bromophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (9d): Pale yellow solid; **M.P:** 252-254 $^{\circ}\text{C}$, ^1H NMR (400 MHz, CDCl_3): δ 7.31 (d, $J = 8$ Hz, 2H), 7.18 (d, $J = 8$ Hz, 2H), 5.87 (s, 1H), 5.01 (s, 1H), 4.04 (q, $J = 14.4$, 7.2 Hz, 2H), 2.38 (s, 3H), 2.35-2.12 (m, 4H), 1.18 (t, $J = 7.2$, 3H), 1.07 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 195.5, 167.2, 148.4, 146.1, 143.7, 131.1, 130.6, 130.0, 129.6, 119.7, 111.6, 105.6, 59.9, 50.6, 40.9, 36.5, 32.6, 29.5, 27.2, 19.5, 14.3; **IR** (KBr): 3275, 1701, 1605, 1281, 1216 cm^{-1} ; ESI (M^+): 417.8; Yield: 78%

Ethyl-4-(3-fluoro-4-methoxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (9e): Off white solid; **M.P:** 234-235 $^{\circ}\text{C}$, ^1H NMR (400 MHz, CDCl_3): δ 7.05-7.00 (m, 2H), 6.79 (t, $J = 8.8$ Hz, 1H), 5.72 (brs, 1H), 4.99 (s, 1H), 4.06 (q, $J = 14.0$, 6.8 Hz, 2H), 3.82 (s, 3H), 2.38 (s, 3H), 2.35-2.12 (m, 4H), 1.20 (t, $J = 8.8$ Hz, 3H), 1.08 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 195.5, 167.3, 153.3, 150.9, 148.1, 143.4, 140.4, 112.6, 111.8, 105.7, 59.8, 56.2, 50.6, 41.0, 36.0, 35.5, 32.6, 29.5, 22.7, 19.5, 19.2, 14.3; **IR** (KBr): 3275, 1704, 1214, 1159 cm^{-1} ; ESI (M^+): 387.9; Yield: 80 %

Ethyl-2,7,7-trimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (9f): Light yellow solid; **M.P:** 220-221 $^{\circ}\text{C}$, ^1H NMR (400 MHz, CDCl_3): δ 7.30 (d, $J = 7.2$ Hz, 2H), 7.19 (t, $J = 7.6$ Hz, 2H), 7.11-7.07 (m, 1H), 5.79 (brs, 1H), 5.05 (s, 1H), 4.05 (q, $J = 14.4$, 7.2 Hz, 2H), 2.38 (s, 3H), 2.35-2.13 (m, 4H), 1.19 (t, $J = 6.8$ Hz, 3H), 1.07 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 195.7, 167.5, 148.7, 147.1, 143.7, 128.2, 127.6, 126.2, 111.9, 105.9, 59.8, 50.7, 41.1, 36.8, 36.3,

32.6, 29.5, 27.2, 19.4, 19.1, 14.0; **IR** (KBr): 3273, 1698, 1284, 1213 cm^{-1} ; ESI (M^+): 339.9; Yield: 81%

ethyl 2,7,7-trimethyl-4-(4-nitrophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (9g): Bright yellow solid; **M.P:** 103-105 $^{\circ}\text{C}$, ^1H NMR (400 MHz, CDCl_3): δ 8.07 (d, $J = 8.8$ Hz, 2H), 7.47 (d, $J = 8.8$ Hz, 2H), 5.82 (s, 1H), 5.15 (s, 1H), 4.04 (q, $J = 14.4$, 7.2 Hz, 2H), 2.42 (s, 3H), 2.40-2.12 (m, 4H), 1.17 (t, $J = 7.2$ Hz, 3H), 1.09 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 195.4, 166.8, 154.4, 148.6, 146.2, 144.4, 129.2, 128.6, 123.2, 111.1, 104.8, 60.1, 50.5, 41.0, 37.4, 36.9, 32.7, 29.4, 27.1, 19.6, 14.3; **IR** (KBr): 3292, 1692, 1487, 1345, 1219 cm^{-1} ; ESI (M^+): 384.9; Yield: 91%

Ethyl-4-(3-chlorophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (9h): Bright yellow solid; **M.P:** 200-202 $^{\circ}\text{C}$, ^1H NMR (400 MHz, CDCl_3): δ 7.24-7.20 (m, 2H), 7.14-7.06 (m, 2H), 6.40-6.18 (brs, 1H), 5.02 (s, 1H), 4.08-4.03 (m, 2H), 2.38 (s, 3H), 2.33-2.18 (m, 4H), 1.19 (t, $J = 7.2$ Hz, 3H), 1.08 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 195.5, 167.2, 148.9, 143.9, 133.7, 129.5, 128.6, 127.5, 126.9, 126.6, 125.9, 111.4, 105.5, 59.9, 50.5, 37.0, 36.2, 32.7, 29.4, 27.1, 14.2; **IR** (KBr): 3273, 1701, 1604, 1282, 1213 cm^{-1} ; ESI (M^+): 373.9; Yield: 85%

Ethyl-2,7,7-trimethyl-5-oxo-4-(thiophen-2-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (9i): Off white solid; **M.P:** 237-239 $^{\circ}\text{C}$, ^1H NMR (400 MHz, CDCl_3): δ 7.01 (d, $J = 4.4$ Hz, 1H), 6.82-6.81 (m, 2H), 6.24 (brs, 1H), 5.40 (s, 1H), 4.14 (q, $J = 14.0$, 7.2 Hz, 2H), 2.37 (s, 3H), 2.33-2.22 (m, 4H), 1.24 (t, $J = 7.2$ Hz, 3H), 1.08 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 195.4, 167.2, 150.9, 148.7, 143.9, 125.7, 123.9, 123.4, 122.2, 111.5, 105.6, 59.9, 50.6,

32.7, 31.8, 30.5, 29.5, 27.2, 14.4; **IR** (KBr): 3282, 1674, 1218.8, cm^{-1} ; **ESI** (M^{+1}): 344; Yield: 85%

Ethyl-4-(4-hydroxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (9j):

Off white solid, **M.P.**: 233-235 °C, ^1H **NMR** (400 MHz, CDCl_3): δ 7.16 (d, $J = 8$ Hz, 2H), 6.65 (d, $J = 8$ Hz, 2H), 5.58 (brs, 1H), 5.98 (s, 1H), 4.62 (s, 1H), 4.05 (q, $J = 14.4$, 7.2 Hz, 2H), 2.40 (s, 3H), 2.37-2.17 (m, 4H), 1.19 (t, $J = 7.2$ Hz, 3H), 1.08 (s, 3H), 0.94 (s, 3H); ^{13}C **NMR** (100 MHz, CDCl_3): δ 196.6, 168.1, 154.4, 149.8, 144.0, 138.6, 128.6 (2C), 114.2 (2C), 111.4, 105.6, 59.5, 50.2, 40.0, 35.3, 32.2, 28.9, 26.5, 18.1, 13.7; **IR** (KBr): 3439, 3278, 1676, 1285, 1218 cm^{-1} ; **ESI** (M^{+}): 355.9; Yield: 79%

Ethyl-4-(3-(benzyloxy)-4-methoxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (9k):

Off white solid, **M.P.**: 76-78 °C, ^1H **NMR** (400 MHz, CDCl_3): δ 7.41-7.39 (m, 2H), 7.34 (t, $J = 7.2$ Hz, 2H), 7.29 (d, $J = 4$ Hz, 1H), 6.86-6.82 (m, 2H), 6.72 (d, $J = 8.0$ Hz, 1H), 5.52 (brs, 1H), 5.11 (s, 2H), 4.94 (s, 1H), 4.03-4.00 (m, 2H), 3.80 (s, 3H), 2.30 (s, 3H), 2.28-2.06 (m, 4H), 1.16 (t, $J = 7.2$ Hz, 3H), 1.05 (s, 3H), 0.90 (s, 3H); ^{13}C **NMR** (100 MHz, CDCl_3): δ 195.5, 167.4, 147.8, 147.7, 147.6, 143.1, 139.8, 137.7, 128.4 (2C), 127.5, 127.2 (2C), 120.6, 114.2, 112.1, 11.2, 105.9, 71.0, 59.7, 55.8, 50.6, 40.9, 35.6, 32.5, 29.3, 27.1, 19.3, 14.2; **IR** (KBr): 3289, 1691.3, 1609, 1494, 1219 cm^{-1} ; **ESI** (M^{+1}): 474.1; Yield: 76%

ethyl-4-(4-chlorophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (9l): pale yellow solid, **M.P.**: 231-232 °C; ^1H **NMR** (400 MHz, CDCl_3): δ 7.24-7.22 (m, 2H), 7.16-7.14 (m, 2H), 5.83 (s, 1H), 5.02 (s, 1H), 4.05 (q, $J = 14.8$, 7.6 Hz, 2H), 2.38 (s, 3H), 2.35-2.12 (m, 4H),

1.18 (t, $J = 7.2$ Hz, 3H), 1.07 (s, 3H), 0.92 (s, 3H); ^{13}C **NMR** (100 MHz, CDCl_3): δ 195.3, 167.1, 147.8, 145.4, 143.4, 131.5, 129.3 (2C), 127.9 (2C), 111.8, 105.7, 59.8, 50.5, 41.0, 36.1, 32.6, 29.3, 27.0, 19.3, 14.1; **IR** (KBr): 3276, 1702, 1216 cm^{-1} ; **ESI** (M^{+1}): 372; Yield: 78%

Ethyl-4-(4-bromophenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (10a):

Off white solid, **M.P.**: 242-244 °C, ^1H **NMR** (400 MHz, CDCl_3): δ 7.31 (brs, 2H), 7.18 (brs, 2H), 5.80-5.90 (brs, 1H), 5.04 (s, 1H), 4.05-4.03 (m, 2H), 2.40 (s, 3H), 2.30-1.85 (m, 6H), 1.17 (t, $J = 8$ Hz, 3H); ^{13}C **NMR** (100 MHz, CDCl_3): δ 195.6, 167.3, 150.8, 146.6, 144.6, 131.2 (2C), 130.3 (2C), 129.4, 112.4, 104.8, 59.6, 40.5, 39.7, 36.5, 29.6, 21.0, 14.2; **IR** (KBr): 3287, 1694, 1287, 1183 cm^{-1} ; **ESI** (M^{+}): 389.8; Yield: 80%

Ethyl-2-methyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (10b):

Dark yellow solid, **M.P.**: 233-235 °C, ^1H **NMR** (400 MHz, CDCl_3): δ 7.29 (d, $J = 7.6$ Hz, 2H), 7.19 (t, $J = 7.6$ Hz, 2H), 7.10 (t, $J = 7.2$ Hz, 1H), 5.92 (s, 1H), 5.09 (s, 1H), 4.05 (q, $J = 14.4$, 7.2 Hz, 2H), 2.41 (s, 3H), 2.25-2.45 (m, 6H), 1.18 (t, $J = 7.2$ Hz, 3H); ^{13}C **NMR** (100 MHz, $\text{CDCl}_3 + \text{CD}_3\text{OD}$): δ 191.0, 162.2, 141.5, 122.0, 121.9, 120.1 (2C), 53.9, 43.4, 43.2, 43.1, 42.9, 42.7, 31.0, 30.5, 20.9, 15.1, 12.6, 8.2; **IR** (KBr): 3282, 1692, 1287, 1225 cm^{-1} ; **ESI** (M^{+}): 311.9; Yield: 94%

ethyl 4-(4-fluorophenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (10c):

Yellow solid, **M.P.**: 208-210 °C, ^1H **NMR** (400 MHz, CDCl_3): δ 7.27-7.23 (m, 2H), 6.87 (t, $J = 8.0$ Hz, 2H), 5.92 (s, 1H), 5.06 (s, 1H), 4.04 (q, $J = 14.0$, 8.0 Hz, 2H), 2.39 (s, 3H), 1.91-2.45 (m, 6H), 1.17 (t, $J = 6.8$ Hz, 3H); ^{13}C **NMR** (100 MHz, CDCl_3): δ 196.6, 167.7, 162.2, 159.8,

151.2, 144.2, 143.1, 129.2, 114.4, 112.5, 105.2, 59.7, 49.0, 36.7, 35.6, 26.7, 20.8, 18.4, 14.0; **IR** (KBr): 3293, 1697, 1222 cm^{-1} ; **ESI** (M^+): 329.9; Yield: 81%

ethyl 2-methyl-5-oxo-4-(thiophen-2-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (10d): Orange solid, **M.P.**: 224-226 °C, ^1H **NMR** (400 MHz, CDCl_3): δ 7.03-7.02 (d, J = 4.0 Hz, 1H), 6.84-6.81 (m, 2H), 6.11 (s, 1H), 5.43 (s, 1H), 4.17-4.11 (m, 2H), 2.47-1.99 (m, 6H), 2.37 (s, 3H), 1.24 (t, J = 7.6 Hz, 3H); ^{13}C **NMR** (100 MHz, CDCl_3): δ 195.7, 167.2, 151.2, 150.2, 143.9, 126.4, 123.3, 123.1, 112.6, 105.4, 59.9, 36.9, 31.1, 27.3, 21.1, 19.2, 14.2; **IR** (KBr): 3291, 1694, 1288 cm^{-1} ; **ESI** (M^+ -1): 315.9; Yield: 94 %

ethyl 4-(4-hydroxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (10e): Light yellow solid, **M.P.**: 247-249 °C; ^1H **NMR** (400 MHz, CDCl_3): δ 7.17 (d, J = 8.0 Hz, 2H), 6.67 (d, J = 8.0 Hz, 2H), 5.67 (s, 1H), 5.04 (s, 1H), 4.70 (s, 1H), 4.07 (q, J = 14.4, 7.6 Hz, 2H), 2.40 (s, 3H), 2.44-2.01 (m, 6H), 1.20 (t, J = 6.8 Hz, 3H); ^{13}C **NMR** (100 MHz, CDCl_3): δ 200.2, 170.9, 157.5, 155.2, 146.9, 141.5, 131.2 (2C), 116.8, 115.0 (2C), 108.2, 62.1, 39.1, 37.9, 28.9, 23.4, 19.9, 15.9; **IR** (KBr): 3447, 3289, 1678, 1225 cm^{-1} ; **ESI** (M^+ -1): 325.9; Yield: 78 %

ethyl 4-(3-cyanophenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (10f): Light green solid, **M.P.**: 209-210 °C; ^1H **NMR** (400 MHz, CDCl_3): δ 7.62 (d, J = 7.6 Hz, 1H), 7.54 (s, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.32-7.28 (m, 1H), 5.89 (brs, 1H), 5.10 (s, 1H), 4.04 (q, J = 14.4, 7.2 Hz, 2H), 2.41 (s, 3H), 2.47-1.88 (m, 6H), 1.17 (t, J = 7.2 Hz, 3H); ^{13}C **NMR** (100 MHz, CDCl_3): δ 195.6, 166.9, 150.1, 148.6, 144.2, 133.6, 132.5, 131.1, 129.0, 128.0, 119.4, 112.6, 111.9, 105.1, 60.0, 36.2, 27.3,

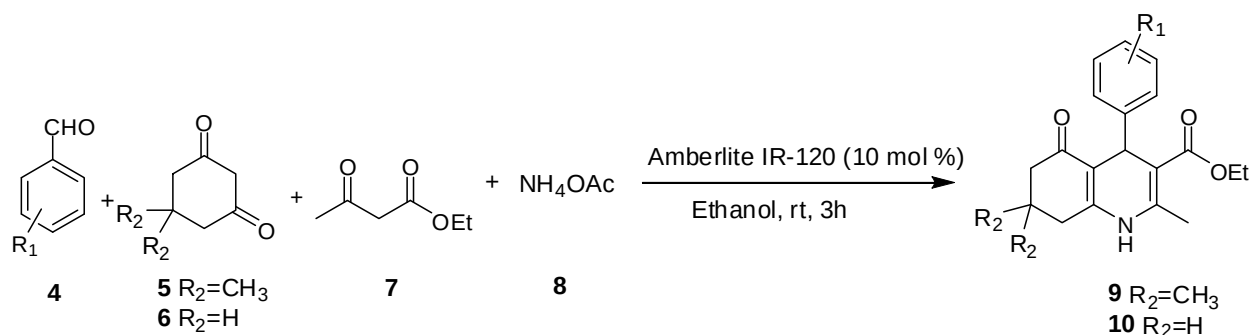
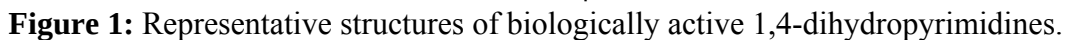
21.1, 18.9, 14.2; **IR** (KBr): 3293, 2228, 1696, 1608, 1226 cm^{-1} ; **ESI** (M^+ +1): 337; Yield: 76 %

ethyl 4-(4-chlorophenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (10g): Off-white solid, **M.P.**: 248-249 °C; ^1H **NMR** (400 MHz, CDCl_3): δ 7.24 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 8.0 Hz, 2H), 5.73 (s, 1H), 5.06 (s, 1H), 4.05 (q, J = 14.4, 7.2 Hz, 2H), 2.46-1.92 (m, 6H), 2.41 (s, 3H), 1.18 (t, J = 14.0 Hz, 3H); ^{13}C **NMR** (100 MHz, CDCl_3): δ 195.6, 167.1, 149.5, 45.6, 143.4, 131.5, 129.3 (2C), 127.9 (2C), 113.1, 105.6, 59.5, 36.8, 35.9, 27.3, 20.9, 19.3, 14.1; **IR** (KBr): 3285, 1698, 1286, 1182 cm^{-1} ; **ESI** (M^+): 345.9; Yield: 75 %

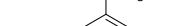
ethyl 4-(3-(benzyloxy)-4-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (10h): Light yellow solid, **M.P.**: 172-174 °C, ^1H **NMR** (400 MHz, CDCl_3): δ 7.41-7.39 (m, 2H), 7.34 (t, J = 7.2 Hz, 2H), 7.29-7.27 (m, 1H), 6.84-6.81 (m, 2H), 6.73 (d, J = 8.0 Hz, 1H), 5.55 (s, 1H), 5.18-5.08 (m, 2H), 4.98 (s, 1H), 4.02 (q, J = 14.0, 6.8 Hz, 2H), 3.82 (s, 3H), 2.35 (s, 3H), 2.41-1.81 (m, 6H), 1.15 (t, J = 7.2 Hz, 3H); ^{13}C **NMR** (100 MHz, CDCl_3): δ 195.8, 167.4, 149.6, 147.8, 147.5, 143.2, 140.0, 137.7, 128.4 (2C), 127.5, 127.2 (2C), 120.4, 114.3, 113.2, 111.2, 105.8, 70.9, 59.7, 55.9, 37.0, 35.5, 27.2, 20.9, 19.2, 14.2 cm^{-1} ; **IR** (KBr): 3293, 1692, 1074 cm^{-1} ; **ESI** (M^+ -1): 446; Yield: 79%

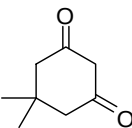
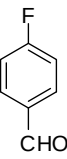
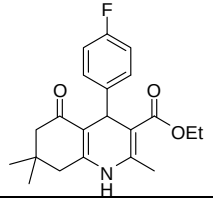
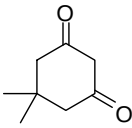
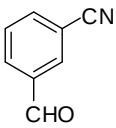
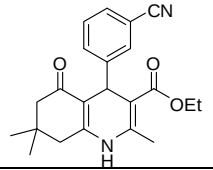
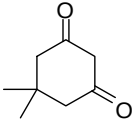
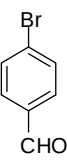
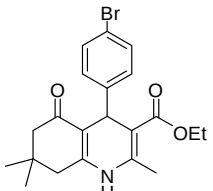
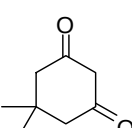
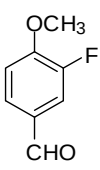
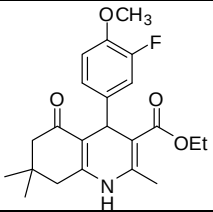
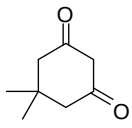
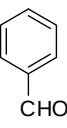
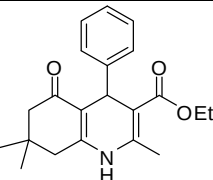
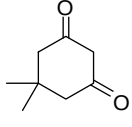
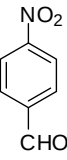
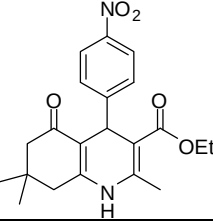
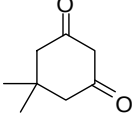
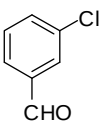
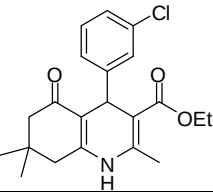
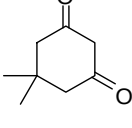
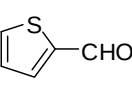
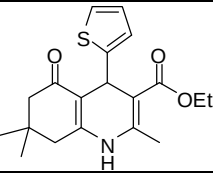
ethyl 4-(4-methoxyphenyl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (10i): Yellow solid, **M.P.**: 217-218 °C; ^1H **NMR** (400 MHz, CDCl_3): δ 7.22-7.20 (d, J = 8.8 Hz, 2H), 6.73 (d, J = 8.0 Hz, 2H), 6.14 (s, 1H), 5.03 (s, 1H), 4.06 (q, J = 14.0, 7.2 Hz, 2H), 3.73 (s, 3H), 1.90-2.43 (m, 6H), 2.40 (s, 3H), 1.19 (t, J = 14.4 Hz, 3H); ^{13}C **NMR** (100 MHz, CDCl_3): δ

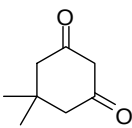
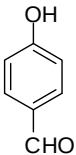
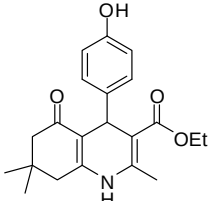
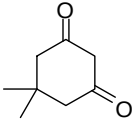
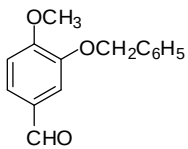
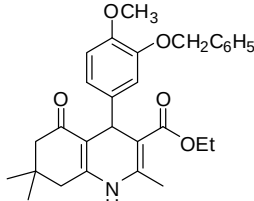
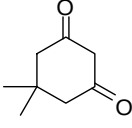
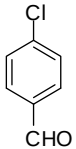
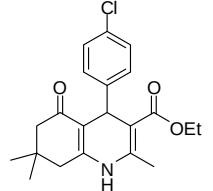
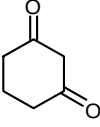
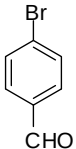
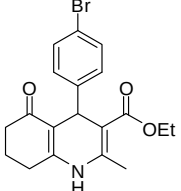
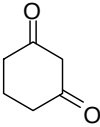
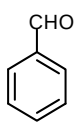
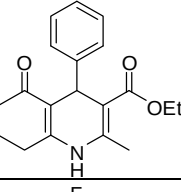
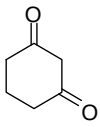
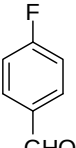
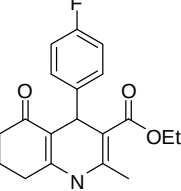
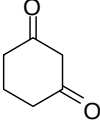
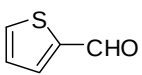
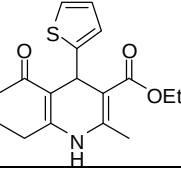
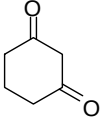
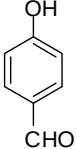
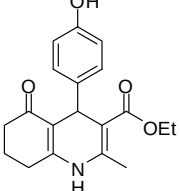
The authors thank Institute of Life Sciences for its support.



Scheme 1: Amberlite IR-120 catalyzed one pot four component reaction to synthesize 1,4-dihydropyrimidines.

Entry	Diketone	Aldehyde	Product	Yield (%) ^a	Observed Melting point (°C)	Reported Melting point (°C)
9a				83	251-252	257-259

9b				80	187-189	184-186
9c				84	176-178	-
9d				78	252-254	253-255
9e				80	234-235	-
9f				81	220-221	202-203
9g				91	103-105	-
9h				85	200-202	206-207
9i				85	237-239	238-240

9j				79	233-235	232-234
9k				76	76-78	-
9l				78	231-232	234-235
10a				80	242-244	253-255
10b				94	233-235	240-241
10c				81	208-210	243-244
10d				94	224-226	233-234
10e				78	247-249	220-222

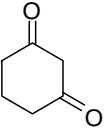
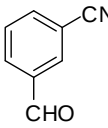
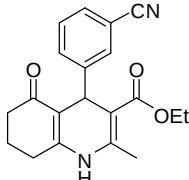
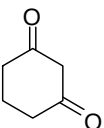
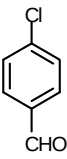
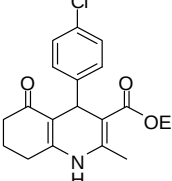
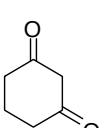
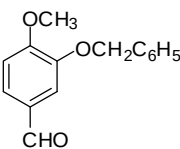
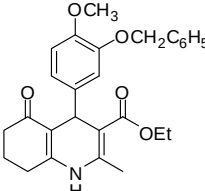
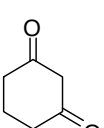
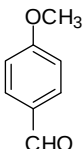
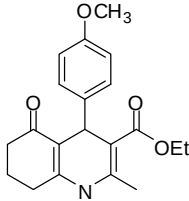
10f				76	209-210	-
10g				75	248-249	-
10h				79	172-174	-
10i				80	217-218	193-195

Table-1: Amberlite IR-120 catalyzed one pot four component reaction to synthesize 1,4-dihydropyrimidines.

^a isolated yields

Entry	Catalyst ^b	Solvent	Temp (°C)	Time (h)	Yield ^c (%)
1	Amberlite	EtOH	rt	3	81
2	Amberlite	EtOH	reflux	1.5	80
3	Amberlite	Toluene	rt	2.5	76
4	Amberlite	Toluene	reflux	0.5	64
5	Amberlite	DCM	rt	2.5	80
6	Amberlite	DCM	reflux	1	76

Table 2: Optimization of amberlite IR-120 catalyzed reaction of 1,4-dihydropyrimidines ^a

^a The reactions were conducted with benzaldehyde, 1,3-dimedone, ethyl acetoacetate and ammonium acetate

^b Catalyst 10 mol%

^c Isolated yields

Cycle	Amberlite IR-120 (mg)	% Yield
1	10	81
2	9	81
3	8	81

Table 3: Recycling of amberlite IR-120 catalyst

References

- [1] (a) N. K. Terrett, M. Gardner, D. W. Gordon, R. J. Kobylecki, J. Steele, *Tetrahedron* 1995, 51, 8135-8173. (b) R. W. Armstrong, A. P. Combs, P. A. Tempest, S. D. Brown, T. A. Keating, *Acc. Chem. Res.* 1996, 29, 123-131. (c) D. J. Ramón, M. Yus, *Angew. Chem., Int. Ed.* 2005, 44, 1602-1634. (d) A. Dömling, *Chem. Rev.* 2006, 106, 17-89.
- [2] (a) V. Klusa, *Drugs Future* 1995, 20, 135-138. (b) R. G. Bretzel, C. C. Bollen, E. Maeser, K. F. Federlin, *Am. J. Kidney Dis.* 1993, 21, 53-64. (c) R. G. Bretzel, C. C. Bollen, E. Maeser, K. F. Federlin, *Drug Future* 1992, 17, 465-468. (d) R. Boer, V. Gekeler, *Drug Future* 1995, 20, 499-509. (e) H. L. Davis, T. E. Davis, *Cancer Treat. Rep.* 1979, 63, 809-815.
- [3] I. Pastan, M. Gottesman, *N. Engl. J. Med.* 1987, 316, 1388-1393.
- [4] S. Ko, M. N. V. Sastry, C. Lin, C.-F. Yao, *Tetrahedron Lett.* 2005, 46, 5771-5774.
- [5] S.-J. Ji, Z.-Q. Jiang, J. Lu, T.-P. Loh, *Synlett* 2004, 831-835.
- [6] J. L. Donelson, R. A. Gibbs, S. K. De, *J. Mol. Catal. Chem.* 2006, 256, 309-311.
- [7] M. Maheswara, V. Siddaiah, G. L. V. Damu, C. V. Rao, *Arkivoc* 2006, 201-206.
- [8] B. Das, B. Ravikanth, R. Ramu, B. V. Rao, *Chem. Pharm. Bull.* 2006, 54, 1044-1045.
- [9] S. S. Katkar, P. H. Mohiteb, S. Lakshman, L. S. Gadekara, B. R. Arbada, M. K. Landea, *Green Chem. Lett. Rev.* 2010, 3, 287-292.
- [10] G. Sabitha, G. S. K. K. Reddy, C. S. Reddy, J. S. Yadav, *Tetrahedron Lett.* 2003, 44, 4129-4131.
- [11] S. Ko, C.-F. Yao, *Tetrahedron* 2006, 62, 7293-7299.
- [12] S. Kumar, P. Sharma, K. K. Kapoor, M. S. Hundal, *Tetrahedron* 2008, 64, 536-542.
- [13] G. Shengrong, Y. Yanqin, *Chin. J. Chem.* 2010, 28, 811-817.
- [14] G. Song, B. Wang, X. Wu, Y. Kang, L. Yang, *Synth. Commun.* 2005, 35, 2875-2880.
- [15] A. Kumar, R. A. Maurya, *Synlett* 2008, 883-885.
- [16] (a) J. G. Breitenbucher, G. Figliozzi, *Tetrahedron Lett.* 2000, 41, 4311-4315. (b) A. Dondoni, A. Massi, E. Minghini, V. Bertolasi, *Tetrahedron* 2004, 60, 2311-2326.
- [17] M. M. Heravi, M. Hosseini, H. A. Oskooie, B. Baghernejad, F. Farzaneh, *Chin. J. Chem.* 2010, 28, 2045-2048.
- [18] C. G. Evans, J. E. Gestwicki, *Org. Lett.* 2009, 11, 2957-2959.
- [19] N. N. Karade, V. H. Budhewar, S. V. Shinde, W. N. Jadav, *Lett. Org. Chem.* 2007, 4, 16-24.
- [20] A. Kumar, R. A. Maurya, *Tetrahedron Lett.* 2007, 48, 3887-3890.
- [21] C. S. Reddy, M. Raghu, *Indian J. Chem.* 2008, 47B, 1578-1582.
- [22] L. Nagarapu, M. D. Kumari, N. V. Kumari, S. Kantaveri, *Catal. Commun.* 2007, 8, 1871-1875.
- [23] R. A. Mekheimer, A. A. Hameed, K. U. Sadek, *Green Chem.* 2008, 10, 592-593.
- [24] M. Hong, C. Cai, W.-B. Yi, *J. Fluorine Chem.* 2010, 131, 111-114.
- [25] L.-M. Wang, J. Sheng, L. Zhang, J.-W. Han, Z.-Y. Fan, H. Tian, C.-T. Qian, *Tetrahedron* 2005, 61, 1539-1543.
- [26] K. K. Pasunooti, C. N. Jensen, H. Chai, M. L. Leow, D.-W. Zhang, X.-W. Liu, *J. Comb. Chem.* 2010, 12, 577-581.
- [27] A. Debache, W. Ghalem, R. Boulcina, A. Belfaitah, S. Rhouati, B. Carboni, *Tetrahedron Lett.* 2009, 50, 5248-5250.
- [28] X.-L. Zhang, S.-R. Sheng, X.-L. Liu, *Arkivoc* 2007, 8, 79-86.
- [29] M. Saha, A. K. Pal, *Tetrahedron Lett.* 2011, 52, 4872-4877.
- [30] M. Anniyappan, D. Muralidharan, P. T. Perumal, *Synth. Commun.* 2002, 32, 659-663.
- [31] R. F. Affeldt, E. V. Benvenutib, D. Russowsky, *New J. Chem.* 2012, 36, 1502-1511.
- [32] (a) R. Ananthakrishnan, S. Gazi, *Catal. Sci. Technol.* 2012, 2, 1463-1471. (b) P. P. Ghosh, S. Paul, A. R. Das, *Tetrahedron Lett.* 2013, 54, 138-142.
- [33] (a) M. Naveen, K. Bhaskar, Ismail, K. R. Rajesh, R. Pallavi, M. Chaitanya, S. K. Chitta, I. Javed, O. Srinivas, *Bioorg. Med. Chem. Lett.* 2012, 22, 5063-5066. (b) R. Pallavi, K. Saidulu, I. Javed, O. Srinivas, *Tetrahedron Lett.* 2012, 53, 5314-5317.
- [34] (a) N. Tewari, D. Katiyar, V. K. Tiwari, R. P. Tripathi, *Tetrahedron Lett.* 2003, 44, 6639-6642. (b) K. Akagawa, S. Sakamoto, K. Kudo, *Tetrahedron Lett.* 2007, 48, 985-987. (c) T.-J. Park, M. Weiwer, X. Yuan, S. N. Baytas, E. M. Munoz, S. Murugesan, R.

- Linhardt, J. Carbohydr. Res. 2007, 342, 614-620; (d) A. K. Bhattacharya, K. C. Rana, Tetrahedron Lett. 2008, 49, 2598-2601. (e) M. Naveen, Ismail, M. K. Kottur, K. R. Rajesh, K. Bhaskar, R. Pallavi, O. Srinivas, P. Manojit, Tetrahedron Lett. 2012, 53, 6004-6007.
- [35] Sulfonic acid resin (Amberlite-IR 120) was purchased from Sigma-Aldrich and regenerated as follows: 100 g of the resin was stirred with 10% sulfuric acid (500 mL) for 30 min, filtered, and washed with deionized water until the washings were free of acid. The resin was then washed with THF, acetone, or absolute alcohol (3 x 30 mL), dried in an oven at 75–80 °C for 12 h, and kept over P₂O₅ in a vacuum desiccator for a week.