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FeF_3 as a green catalyst for the synthesis of dihydropyrimidines via Biginelli reaction

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RESEARCH ARTICLE

ABSTRACT

A facile and highly efficient FeF_3-catalyzed method has been developed for the direct synthesis of functionalized dihydropyrimidines from readily available starting materials via Biginelli reaction. These reactions proceed at low-catalyst loadings with high functional group tolerance under mild conditions. This method provides efficient reusability of the catalyst and good to excellent yields of the products, making the protocol more attractive, economical, and environmentally benign. FeF_3 is an attractive catalyst for the Biginelli reaction because of its high acidity, thermal stability and water tolerance.

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1. Introduction

One of the major goals of organic chemistry is the development of environmentally benign and greener protocols for the synthesis of complex molecular frameworks. In this scenario, multicomponent reactions (MCRs) are one of the most straightforward and powerful tools for the production of diverse heterocyclic compounds in the various scientific disciplines [1,2]. Recently, much attention has been devoted to MCRs because they enable the combination of three or more reactants in a one-pot process to access complex product with most meaningful parts of the starting materials and the manipulation of several transformations in a single step [3-5]. Although a large number of MCR strategies have been investigated to explore their applications in organic and medicinal chemistry, the development of MCRs in an eco-friendly manner is still of promising interest. Of these MCRs, the Biginelli reaction is one of the most powerful MCRs that allows the condensation of aldehyde, ketoester, and urea to synthesize dihydropyrimidine derivatives [6,7]. Moreover, this efficient reaction was first discovered by Bigineli in 1893; unfortunately, it was ignored for many years by organic chemists. Later on, various research groups have focused on novel approaches and mechanistic studies to improve this attractive Biginelli reaction [8-14].

On the other hand, dihydropyrimidines (DHPMs) are privileged and significant pharmacophores among nitrogen-containing heterocyclic frameworks and are widely found in a wide range of natural products, agrochemicals, biologically active systems, and drug candidates (Figure 1) [15-23]. In particular, functionalized DHPMs have attracted considerable attention because of their interesting biological activities, such as antibacterial, antiviral, antimalarial, antitumor, anti-inflammatory, antitubercular, antidiabetic, antileishmanial, antiepileptic, and antiproliferative activities [24]. Moreover, DHPMs have been used as potent calcium channel blockers [25], neuropeptide Y antagonists [26], antihypertensive agents [27], mitotic kinesin inhibitors [28], mPGES-1 inhibitors [29], adrenergic antagonists [30], and A_{2B} receptor antagonists [31]. Indeed, they are versatile and crucial building blocks in organic synthesis and recognized as a new lead for drug discovery [15-24].

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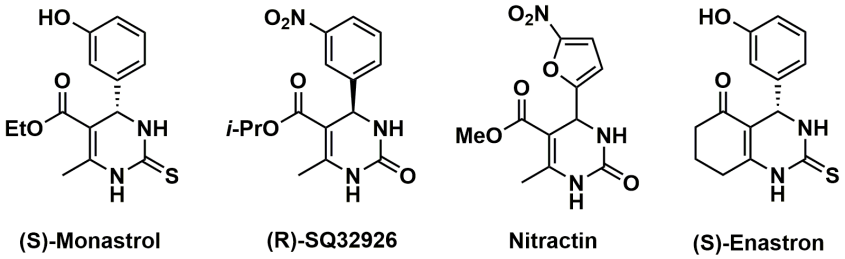


Figure 1. Biologically active dihydropyrimidines.

Despite their fascinating pharmaceutical applications, DHPMs have also been found in the development of functional materials, such as polymers, adhesives, optical materials, and dyes [32-34].

Recently, considering the synthetic and biological importance of Biginelli reaction, various efficient strategies have been explored for the expansion of Biginelli reaction to synthesize functionalized dihydropyrimidine derivatives that use a variety of Brönsted acids, metal-based Lewis acids, ionic liquids, polymer supported catalysts, microwave-assisted conditions, and base-mediated conditions [35-58]. Although the significant advances have been achieved in the synthesis of dihydropyrimidines, most of these are expensive, environmentally unfriendly, and difficult to handle large-scale reactions. Therefore, there is a need for the investigation of recyclable and reusable catalytic conditions for this reaction, which can overcome limitations for large-scale reactions.

Among the transition metal catalysts, iron catalysts play an important role in the organic synthesis, owing to their indispensable advantages, such as relatively safe, inexpensive, stable, recyclable, less hazardous, low-catalyst loading, and environmentally benign nature [59]. Moreover, iron-catalyzed tandem sequences have gained considerable attention [60]. Recently, Surasani *et al.* reported a FeF_3-catalyzed method for the synthesis of polyhydroquinoline derivatives via unsymmetrical Hantzsch reaction [61]. In this context, as a part of ongoing research efforts [62,63], we envisaged accessing pharmaceutically active dihydropyrimidines via Biginelli reaction using FeF_3 as a catalyst. Therefore, we wish to report an efficient and eco-friendly MCR protocol for the one-pot facile synthesis of functionalized dihydropyrimidine scaffolds by the reaction of aldehydes, ketoesters, and urea or thiourea in ethanol at reflux temperature using FeF_3 as an environmentally benign catalyst. The present study also explores good recyclability and reusability of the catalyst.

2. Experimental

Unless stated otherwise, reactions were performed under nitrogen atmosphere using oven dried glassware. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates ($60F_{254}$), visualizing with ultraviolet light or iodine spray. Flash chromatography was performed on silica gel (230-400 mesh) using distilled hexane, ethyl acetate, and dichloromethane. ^{1}H NMR and ^{13}C NMR spectra were determined in $CDCl_3$ or DMSO-d_6 solution by using 400 or 100 MHz spectrometers, respectively. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, δ = 0.00) as internal standard and expressed in ppm. 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. Melting points were determined using melting point B-540 apparatus and are uncorrected. HRMS was determined using waters LCT premier XETOF ARE-047 apparatus.

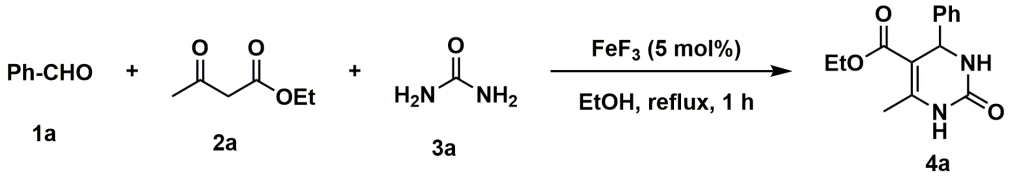
2.1. General procedure for the synthesis of 3,4-dihydro pyrimidin-2(1H)-one or thione (DHPMs) derivatives (4)

A mixture of aldehyde **1** (1.0 mmol), urea or thiourea **2** (1.0 mmol), alkyl acetoacetate **3** (1.0 mmol), and FeF_3 (5 mol%) in ethanol (5 mL) was stirred at room temperature. Then the reaction mixture was slowly heated to 75-80 °C, and the reaction was completed within one hour. After completion of the reaction (TLC), the mixture was cooled and diluted with 15 mL of ethyl acetate and 10 mL of water. The organic layer was separated and washed with cold water (20 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to afford the crude product, which was finally recrystallized from ethanol to afford the pure product **4**. The aqueous layer containing the catalyst (FeF_3) was evaporated under reduced pressure to give a solid [62]. Then the recovered catalyst was dried in an oven at 120 °C for 3-5 h and reused in subsequent reactions without loss its catalytic activity. The products obtained were identified by comparison of their NMR, IR, and mass spectra. The spectroscopic data of all the desired products were identical with those were reported in the literature [64-70].

Ethyl-6-methyl-2-oxo-4-phenyl-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate (**4a**): Color: Colorless solid. Yield: 93%. M.p.: 202-204 °C. FT- IR (KBr, ν, cm^{-1}): 3375, 3329, 3106, 1670, 1574, 1465, 1327, 1284, 1196, 1118, 1028, 760, 693. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.10 (t, *J* = 7.4 Hz, 3H, CH_3), 2.24 (s, 3H, CH_3), 4.00-3.95 (q, *J* = 6.8 Hz, 2H, OCH_2), 5.14 (d, *J* = 3.0 Hz, 1H, C-H), 7.33-7.22 (m, 5H, Ar-H), 7.72 (s, 1H, N-H), 9.17 (s, 1H, N-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 165.3, 152.2, 148.3, 144.8, 128.3, 127.2, 126.2, 99.2, 59.2, 53.9, 17.7, 14.0. HRMS (ESI, *m/z*) calcd. for $C_{14}H_{16}N_2O_3$ [M+H]: 261.1239. Found 261.1229.

Ethyl-6-methyl-2-oxo-4-(o-tolyl)-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate (**4b**): Color: Colorless solid. Yield: 91%. M.p.: 208-210 °C. FT- IR (KBr, ν, cm^{-1}): 3672, 3291, 2958, 2811, 1927, 1707, 1454, 1228, 1025. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.07 (t, *J* = 6.9 Hz, 3H, CH_3), 2.29 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 3.91-3.87 (q, *J* = 2.8 Hz, 2H, OCH_2), 5.40 (d, *J* = 2.5 Hz, 1H, CH), 7.16-7.11 (m, 4H, Ar-H), 7.61 (s, 1H, N-H), 9.13 (s, 1H, N-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 165.2, 151.6, 148.4, 143.3, 134.6, 130.1, 127.2, 126.5, 99.2, 59.1, 50.5, 18.6, 17.9, 13.9. HRMS (ESI, *m/z*) calcd. for $C_{15}H_{18}N_2O_3$ [M+H]: 275.1396. Found 275.1389.

Ethyl-4-(4-hydroxyphenyl)-6-methyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate (**4c**): Color: Colorless solid. Yield: 88%. M.p.: 226-228 °C. FT- IR (KBr, ν, cm^{-1}): 3683, 3514, 3106, 2695, 1688, 1655, 1514, 1460, 1318, 1229, 1172, 1098, 967, 752. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.10 (t, *J* = 7.3 Hz, 3H, CH_3), 2.22 (s, 3H, CH_3), 4.02-3.95 (q, *J* = 6.9 Hz, 2H, OCH_2), 5.07 (d, *J* = 2.9 Hz, 1H, C-H), 6.68 (d, *J* = 8.3 Hz, 2H, Ar-H), 7.03 (d, *J* = 8.3 Hz, 2H, Ar-H), 7.60 (s, 1H, N-H), 9.09 (s, 1H, N-H), 9.31 (s, 1H, O-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 165.5, 156.6, 152.3, 147.8, 135.5, 127.5, 115.0, 99.8, 59.2, 53.5, 17.8, 14.1. HRMS (ESI, *m/z*) calcd. for $C_{14}H_{16}N_2O_4$ [M+H]: 277.1188. Found 277.1180.



Scheme 1. FeF_3-catalyzed synthesis of dihydropyrimidines.

Ethyl-4-(3-(benzyloxy)phenyl)-6-methyl-2-oxo-1, 2, 3, 4-tetra hydropyrimidine-5-carboxylate (**4d**): Color: Colorless solid. Yield: 92%. M.p.: 230-234 °C. FT- IR (KBr, ν, cm^{-1}): 3291, 2958, 2697, 1927, 1707, 1641, 1454, 1228, 1141, 1098, 1025, 805. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.11 (t, *J* = 6.8 Hz, 3H, CH_3), 2.23 (s, 3H, CH_3), 4.01-3.95 (q, *J* = 6.8 Hz, 2H, OCH_2), 5.06 (s, 2H, OCH_2), 5.11 (d, *J* = 1.5 Hz, 1H, C-H), 6.91-6.81 (m, 3H, Ar-H), 7.44-7.21 (m, 6H, Ar-H), 7.71 (s, 1H, N-H), 9.17 (s, 1H, N-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 165.3, 158.4, 152.2, 148.5, 146.4, 137.0, 129.5, 128.4, 127.9, 127.7, 118.6, 113.2, 99.1, 69.2, 59.2, 53.8, 17.8, 14.1. HRMS (ESI, *m/z*) calcd. for $C_{21}H_{22}N_2O_4$ [M+H]: 367.1658. Found 367.1649.

Ethyl-4-(3-hydroxyphenyl)-6-methyl-2-oxo-1, 2, 3, 4-tetrahyd ropyrimidine-5-carboxylate (**4e**): Color: Colorless solid. Yield: 85%. M.p.: 168-170 °C. FT- IR (KBr, ν, cm^{-1}): 3655, 3230, 2932, 2795, 1702, 1645, 1228, 1079, 1027, 786, 745, 682. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.13 (t, *J* = 7.4 Hz, 3H, CH_3), 2.23 (s, 3H, CH_3), 4.02-3.96 (q, *J* = 7.3 Hz, 2H, OCH_2), 5.05 (d, *J* = 1.9 Hz, 1H, C-H), 6.67-6.60 (m, 3H, Ar-H), 7.10 (t, *J*= 7.8 Hz, 1H, Ar-H), 7.66 (s, 1H, N-H), 9.13 (s, 1H, N-H), 9.34 (s, 1H, O-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 165.4, 157.4, 152.2, 148.1, 146.3, 129.3, 116.9, 114.2, 113.1, 99.4, 59.2, 53.8, 17.8, 14.1. HRMS (ESI, *m/z*) calcd. for $C_{14}H_{16}N_2O_4$ [M+H]: 277.1188. Found 277.1199.

Ethyl-4-(3-bromophenyl)-6-methyl-2-oxo-1, 2,3,4-tetrahydro pyrimidine-5-carboxylate (**4f**): Color: Colorless solid. Yield: 88%. M.p.: 185-187 °C. FT- IR (KBr, ν, cm^{-1}): 3291, 2958, 2697, 2065, 1927,1707,1641,1454, 1346, 1228, 1098, 965, 798, 752, 652. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.10 (t, *J* = 7.4 Hz, 3H, CH_3), 2.25 (s, 3H, CH_3), 4.01-3.98 (q, *J* = 7.4 Hz, 2H, OCH_2), 5.14 (d, *J* = 3 Hz, 1H, CH), 7.46-7.22 (m, 4H, Ar-H), 7.78 (s, 1H, N-H), 9.26 (s, 1H, N-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 165.2, 151.9, 148.9, 147.5, 130.8, 130.1, 129.2, 129.1, 125.3, 121.6, 98.6, 59.3, 53.5, 17.8, 14.1. HRMS (ESI, *m/z*) calcd. for $C_{14}H_{15}BrN_2O_3$ [M+H]: 339.0344. Found 339.0366.

Ethyl-6-methyl-4-(4-nitrophenyl)-2-oxo-1, 2, 3, 4-tetrahydro pyrimidine-5-carboxylate (**4g**): Color: Yellow solid. Yield: 85%. M.p.: 205-207 °C. FT- IR (KBr, ν, cm^{-1}): 3434, 2920, 2065, 1639, 1346, 1226, 1049. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.10 (t, *J* = 6.9 Hz, 3H, CH_3), 2.26 (s, 3H, CH_3), 4.01-3.96 (q, *J* = 6.9 Hz, 2H, OCH_2), 5.27 (d, *J* = 3 Hz, 1H, C-H), 7.51 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.80 (s, 1H, N-H), 8.22 (d, *J* = 8.4 Hz, 2H, Ar-H), 9.34 (s, 1H, N-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 165.0, 151.9, 151.7, 149.4, 146.7, 127.6, 123.8, 98.2, 59.4, 53.7, 17.8, 14.0.

Ethyl-4-(4-chlorophenyl)-6-methyl-2-oxo-1, 2,3,4-tetrahydro pyrimidine-5-carboxylate (**4h**): Color: Colorless solid. Yield: 86%. M.p.: 212-214 °C. FT- IR (KBr, ν, cm^{-1}): 3564, 3176, 3105, 2998, 2798, 2053, 1673, 1574, 1456, 1347, 1285,1 181, 941. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.08 (t, *J* = 6.9 Hz, 3H, CH_3), 2.29 (s, 3H, CH_3), 3.91-3.87 (q, *J* = 6.9 Hz, 2H, OCH_2), 5.62 (d, *J* = 2.4 Hz, 1H, CH), 7.41-7.26 (m, 4H, Ar-H), 7.68 (s, 1H, N-H), 9.25 (s, 1H, N-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 164.9, 151.3, 149.3, 141.7, 131.6, 129.3, 129.0, 128.8, 127.7, 97.9, 59.1, 51.4, 17.6, 13.9.

Ethyl-4-(4-acetylphenyl)-6-methyl-2-oxo-1, 2, 3,4-tetrahydro pyrimidine-5-carboxylate (**4i**): Color: Colorless solid. Yield: 90%. M.p.: 201-203 °C. FT- IR (KBr, ν, cm^{-1}): 3315, 3171, 2983, 1891, 1668, 1575, 1463, 1372, 1285, 1269, 1252, 1196, 1171, 1028, 766. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.13 (t, *J* =6.8 Hz, 3H, CH_3), 2.25 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 4.01-3.95 (q, *J* = 6.8 Hz, 2H, OCH_2), 5.21 (d, *J* = 2.4 Hz, 1H, CH), 7.36 (d, *J* = 7.3 Hz, 2H, Ar-H), 7.93 (d, *J* = 8.3 Hz, 2H, Ar-H), 8.13 (s, 1H, N-H), 9.29 (s, 1H, N-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 197.4, 165.2, 151.9, 149.7, 148.9, 135.9, 129.0, 128.5, 126.5, 98.6, 59.3, 53.8, 26.7, 17.8, 14.0.

Ethyl-4-(2,4-difluorophenyl)-6-methyl-2-oxo-1, 2, 3, 4-tetra hydropyrimidine-5-carboxylate (**4j**): Color: Colorless solid. Yield: 88%. M.p.: 150-152 °C. FT- IR (KBr, ν, cm^{-1}): 3171, 3108, 2937, 2836, 2501, 1891, 1668, 1463, 1269, 1171, 1028, 767. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.10 (t, *J* = 6.9 Hz, 3H, CH_3), 2.25 (s, 3H, CH_3), 4.03-3.95 (q, *J* = 6.9 Hz, 2H, OCH_2), 5.15 (d, *J* = 3.5 Hz, 1H, CH), 7.08-7.05 (m, 1H, Ar-H), 7.23-7.18 (m, 1H, Ar-H), 7.41-7.23 (m, 1H, Ar-H), 7.79 (s, 1H, N-H), 9.27 (s, 1H, N-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 165.1, 158.9, 149.1, 142.5, 122.93, 117.5, 115.37, 98.5, 59.3, 53.2, 17.8, 14.06. HRMS (ESI, *m/z*) calcd. for $C_{14}H_{14}F_2N_2O_3$ [M+H]: 297.1051. Found 297.1046.

Ethyl-4-(3,4-dimethoxyphenyl)-6-methyl-2-oxo-1, 2,3,4-tetra hydropyrimidine-5-carboxylate (**4k**): Color: Colorless solid. Yield: 96%. M.p.: 176-178 °C. FT- IR (KBr, ν, cm^{-1}): 3176, 2996, 2798, 2590, 1926, 1673, 1574, 1506, 1285, 1198, 1119, 838, 762. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.11 (t, *J* = 6.9 Hz, 3H, CH_3), 2.24 (s, 3H, CH_3), 3.71 (s, 6H, OCH_3), 4.02-3.97 (q, *J* = 6.9 Hz, 2H, OCH_2), 5.09 (d, *J* = 3.0 Hz, 1H, C-H), 6.72 (d, *J* = 6.4 Hz, 1H, Ar-H), 6.73 (s, 1H, Ar-H), 6.89 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.66 (s, 1H, N-H), 9.13 (s, 1H, N-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 165.5, 152.3, 148.5, 148.1, 148.0, 137.3, 117.9, 111.7, 110.4, 99.4, 59.2, 55.5, 55.4, 53.5, 17.8, 14.2. HRMS (ESI, *m/z*) calcd. for $C_{16}H_{20}N_2O_5$ [M+H]: 321.1450. Found 321.1452

Ethyl-4-(benzo[d][1, 3]dioxol-4-yl)-6-methyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate (**4l**): Color: Colorless solid. Yield: 91%. M.p.: 180-182 °C. FT- IR (KBr, ν, cm^{-1}): 3694, 3354, 3221, 3100, 2962, 1702, 1641, 1490, 1451, 1225, 1092, 1040, 928, 795, 675. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.12 (t, *J* = 6.9 Hz, 3H, CH_3), 2.24 (s, 3H, CH_3), 3.96-4.01 (q, *J* = 6.9 Hz, 2H, OCH_2), 5.06 (d, *J* = 3.4 Hz, 1H, CH), 5.98 (s, 2H, -OCH_2O-), 6.69 (d, *J* = 1.4 Hz, 1H, Ar-H), 6.74 (d, *J* = 1.4 Hz, 1H, Ar-H), 6.83 (t, *J* = 8.4 Hz, 1H, Ar-H), 7.67 (s, 1H, N-H), 9.16 (s, 1H, N-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 165.4, 152.1, 148.3, 147.3, 146.9, 138.9, 119.3, 108.0, 106.7, 100.9, 99.3, 59.2, 53.7, 17.8, 14.1. HRMS (ESI, *m/z*) calcd. for $C_{15}H_{16}N_2O_5$ [M+H]: 305.1137. Found 305.1129.

Ethyl-6-methyl-4-(naphthalen-1-yl)-2-oxo-1, 2, 3, 4-tetrahyd ropyrimidine-5-carboxylate (**4m**): Color: Colorless solid. Yield: 94%. M.p.: 246-248 °C. FT- IR (KBr, ν, cm^{-1}): 3250, 3121, 2978, 2817, 1708, 1602, 1466, 1384, 1229, 1094, 770, 690. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.09 (t, *J* = 6.9 Hz, 3H, CH_3), 2.28 (s, 3H, CH_3), 3.99-3.94 (q, *J* = 6.9 Hz, 2H, OCH_2), 5.32 (d, *J* = 2.9 Hz, 1H, CH), 7.50-7.43 (m, 3H, Ar-H), 7.67 (s, 1H, N-H), 7.86-7.90 (m, 4H, Ar-H), 9.24 (s, 1H, N-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 165.4, 152.2, 148.6, 142.2, 132.7, 132.3, 128.3, 127.8, 127.5, 126.3, 125.9, 124.9, 124.5, 99.2, 59.2, 54.4, 17.9, 14.1. HRMS (ESI, *m/z*) calcd. for $C_{18}H_{18}N_2O_3$ [M+H]: 311.1396. Found 311.1409.

Ethyl-4-(furan-2-yl)-6-methyl-2-oxo-1, 2, 3, 4-tetrahydropyri midine-5-carboxylate (**4n**): Color: Colorless solid. Yield: 92%. M.p.: 204-206 °C.

Table 1. The reaction of benzaldehyde (**1a**), ethylacetoacetate (**2a**) and urea (**3a**): screening of fluoride sources [a].

Entry	Catalyst (Fluoride source)	Temp. (°C)	Time (h)	Yield (%) [b]
1	CsF	80	1	34
2	CaF_2	80	1	30
3	KF	80	1	28
4	NH_4F	80	1	20
5	TBAF	80	1	35
6	FeF_3	80	1	93
7	None	80	1	None

[a] Reaction conditions: **1** (1.0 mmol), **2** (1.0 mmol), **3** (1.0 mmol), catalyst (5 mol%), ethanol (5 mL), at 75-80 °C.
[b] Isolated yields.

^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.15 (t, *J* = 6.4 Hz, 3H, CH_3), 2.22 (s, 3H, CH_3), 4.05-3.99 (q, *J* = 6.4 Hz, 2H, OCH_2), 5.20 (d, *J* = 3.4, Hz, 1H, CH), 6.09 (d, *J* = 3.5 Hz, 1H, Ar-H), 6.35 (t, *J* = 2.0 Hz, 1H, Ar-H), 7.55 (d, *J* = 1.0 Hz, 1H, Ar-H), 7.74 (s, 1H, N-H), 9.23 (s, 1H, N-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 165.0, 155.9, 152.4, 149.4, 142.2, 110.4, 105.3, 96.7, 59.2, 47.7, 17.7, 14.1. HRMS (ESI, *m/z*) calcd. for $C_{12}H_{14}O_4N_2$ [M+H]: 251.1032. Found 251.1038.

Methyl-6-methyl-2-oxo-4-phenyl-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate (**4o**): Color: Colorless solid. Yield: 91%. M.p.: 211-213 °C. FT- IR (KBr, ν, cm^{-1}): 3514, 3106, 2608, 1655, 1460, 1318, 1229, 1093, 965, 652. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.23 (s, 3H, CH_3), 3.51 (s, 3H, OCH_3), 5.13 (d, *J* = 2.9 Hz, 1H, C-H), 7.32-7.20 (m, 5H, Ar-H), 7.73 (s, 1H, N-H), 9.20 (s, 1H, N-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 166.1, 165.6, 152.5, 148.8, 144.8, 128.7, 127.6, 126.4, 99.3, 54.1, 51.09, 17.9. HRMS (ESI, *m/z*) calcd. for $C_{13}H_{14}N_2O_3$ [M+H]: 247.1083. Found 247.1094.

Ethyl-6-methyl-4-phenyl-2-thioxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate (**4p**): Color: Colorless solid. Yield: 92%. M.p.: 208-210 °C. FT- IR (KBr, ν, cm^{-1}): 3329, 3178, 2980, 2806, 1964, 1670, 1574, 1465, 1327, 1284, 1118, 693. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.12 (t, *J* = 6.9 Hz, 3H, CH_3), 2.20 (s, 3H, CH_3), 4.03-3.98 (q, *J* = 6.9 Hz, 2H, OCH_2), 5.17 (d, *J* = 3.4 Hz, 1H, C-H), 7.36-7.21 (m, 5H, Ar-H), 9.64 (s, 1H, N-H), 10.32 (s, 1H, N-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 174.3, 165.1, 145.0, 143.5, 128.5, 127.7, 126.4, 100.7, 59.6, 54.1, 17.2, 14.0. HRMS (ESI, *m/z*) calcd. for $C_{14}H_{16}N_2O_2S$ [M+H]: 277.1011. Found 277.1008.

Ethyl-4-(4-methoxyphenyl)-6-methyl-2-thioxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate (**4q**): Color: Colorless solid. Yield: 93%. M.p.: 151-153 °C. FT-IR (KBr, ν, cm^{-1}): 3315, 3171, 3108, 2983, 2836, 1891, 1668, 1575, 1509, 1463, 1285, 1196, 1122, 1028, 766. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.12 (t, *J* = 6.8 Hz, 3H, CH_3), 2.28 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 4.03-3.97 (q, *J* = 6.8 Hz, 2H, OCH_2), 5.11 (d, *J* = 3.4 Hz, 1H, C-H), 6.91 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.13 (d, *J* = 8.8 Hz, 2H, Ar-H), 9.59 (s, 1H, N-H), 10.25 (s, 1H, N-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 174.0, 165.2, 158.7, 144.7, 135.7, 127.6, 113.8, 100.9, 59.5, 55.1, 53.4, 17.14, 14.0. HRMS (ESI, *m/z*) calcd. for $C_{15}H_{18}N_2O_3S$ [M+H]: 307.1116. Found 307.1104.

Ethyl-4-(benzo[d][1, 3]dioxol-4-yl)-6-methyl-2-thioxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate (**4r**): Color: Colorless solid. Yield: 88%. M.p.: 172-174 °C. FT- IR (KBr, ν, cm^{-1}): 3672, 3291, 2958, 2811, 1927, 1707, 1454, 1228, 1025. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.11 (t, *J* = 7.3 Hz, 3H, CH_3), 2.28 (s, 3H, CH_3), 4.04-3.99 (q, *J* = 7.3 Hz, 2H, OCH_2), 5.09 (d, *J* = 3.9 Hz, 1H, CH), 5.99 (s, 2H, -OCH_2O-), 6.66 (d, *J* = 6.4 Hz, 1H, Ar-H), 6.72 (m, 1H, Ar-H), 6.88 (t, *J* = 7.8 Hz, 1H, Ar-H), 9.59 (s, 1H, N-H), 10.31(s, 1H, N-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 174.0, 165.1, 147.4, 146.7, 145.0, 137.5, 119.6, 108.1, 106.7, 101.0, 100.7, 59.6, 53.7, 17.1, 14.0. HRMS (ESI, *m/z*) calcd. for $C_{15}H_{16}O_4N_2S$ [M+H]: 321.0909. Found 321.0906.

Ethyl-4-(3, 5-bis(trifluoromethyl)phenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**4s**): Color: Colorless solid. Yield: 90%. M.p.: 105-107 °C. FT- IR (KBr, ν, cm^{-1}): 3315, 2937, 2836, 1668, 1463, 1285, 1198, 1095, 762. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.08 (t, *J* = 7.4 Hz, 3H, CH_3), 2.25 (s, 3H, CH_3), 4.05-3.95 (q, *J* = 7.3 Hz, 2H, OCH_2), 5.38 (d, *J* = 2.9 Hz, 1H, C-H), 7.92-7.85 (m, 3H, Ar-H), 8.05 (s, 1H, N-H), 9.41 (s, 1H, N-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 164.9, 157.7, 151.59, 149.9, 148.2, 130.5, 129.9, 129.7, 127.3, 124.6, 121.8, 97.8, 59.4, 53.5, 17.8, 13.8.

Methyl-6-methyl-4-phenyl-2-thioxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate (**4t**): Color: Colorless solid. Yield: 90%. M.p.: 222-225 °C. FT- IR (KBr, ν, cm^{-1}): 3321, 3176, 2998, 2798, 2590, 1900, 1673, 1456, 1347, 1198, 1043, 941. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.27 (s, 3H, CH_3), 3.54 (s, 3H, OCH_3), 5.15 (d, *J* = 3.4 Hz, 1H, CH), 7.35-7.19 (m, 5H, Ar-H), 9.64 (s, 1H, N-H), 10.20 (s, 1H, N-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 174.2, 165.6, 145.3, 143.3, 128.6, 127.7, 126.3, 100.5, 53.9, 51.09, 17.2. HRMS (ESI, *m/z*) calcd. for $C_{13}H_{14}N_2O_2S$ [M+H]: 263.0854. Found 263.0842.

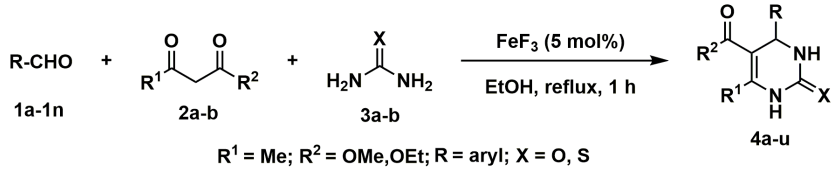
Methyl-4-(4-fluorophenyl)-6-methyl-2-thioxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate (**4u**): Color: Colorless solid. Yield: 89%. M.p.: 184-186 °C. FT- IR (KBr, ν, cm^{-1}): 3308, 3176, 2998, 2851, 2796, 1900, 1673, 1574, 1456, 1347, 1285, 1119, 941, 852. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.29 (s, 3H, CH_3), 3.55 (s, 3H, OCH_3), 5.18 (d, *J* = 3.4 Hz, 1H, C-H), 7.26-7.15 (m, 4H, Ar-H), 9.67 (s, 1H, N-H), 10.3(s, 1H, N-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 174.2, 165.5, 162.8, 160.4, 145.5, 139.6, 128.4, 115.5, 1153, 100.4, 53.3, 51.1, 17.2. HRMS (ESI, *m/z*) calcd. for $C_{13}H_{13}FN_2O_2S$ [M+H]: 281.0760. Found 281.0755.

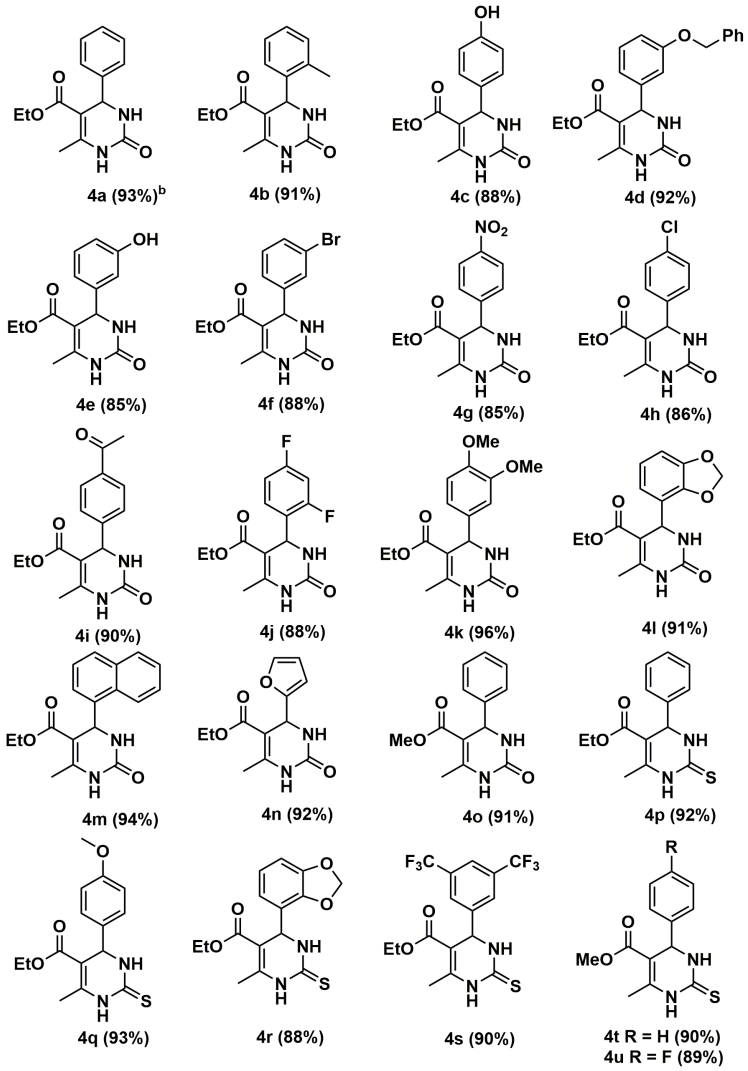
3. Results and discussion

Initially, benzaldehyde (**1a**), ethyl acetoacetate (**2a**), and urea (**3a**) were selected as model substrates to optimize the reaction. The reaction was carried out using 5 mol% of FeF_3 as a catalyst in ethanol at room temperature and reflux temperature (Scheme 1). It is worth mentioning that the reaction was slower at room temperature than at reflux temperature. Moreover, the desired product (**4a**) was obtained in 93% yield at the latter temperature within a short period (1 h). However, the increasing or decreasing the loading of the catalyst did not improve the product yield. In absence of the catalyst, no product could be detected within 1 h at 80 °C under the present experimental conditions (Table 1, entries 7).

With optimized reaction conditions in hand, we then investigated the scope and generality of aromatic aldehydes (**1a-n**) with ethyl acetoacetate (**2a**) and urea (**3a**), and the results are compiled in Table 1. To our delight, various aromatic aldehydes bearing electron-donating and electron-withdrawing groups were smoothly employed under these reaction conditions, thereby affording the desired products (**4a-i**) in good to excellent yields. Surprisingly, the sterically demanding ortho-2-tolualdehydealso worked well and gave the resulting product (**4b**) in 91% yield. The results suggested that the steric and electronic effects of the aromatic ring had negligible influence in this transformation. Notably, the reaction of disubstituted aldehydes also proceeded smoothly, providing the corresponding products (**4j-l**) in 88-96% yields. Moreover, extended aromatic aldehyde 1-naphthaldehydeand heterocyclic aldehyde 2-thiophenecarboxaldehydewere also found to be suitable reaction partners to give the resulting products (**4m-n**) in high yields.

Table 2. Substrate scope for the synthesis of dihydropyrimidines [a].





[a] Reaction conditions: **1** (1.0 mmol), **2** (1.0 mmol), **3** (1.0 mmol), catalyst (5 mol%), ethanol (5 mL), at 75-80 °C.
[b] Isolated yields.

As can be seen in Table 2, halogen substituents such as F, Cl, and Br were compatible in this reaction, which are the useful handle for further functionalization. Besides, a whole range of functional groups, such as ester, keto, ether, methyl, hydroxyl, and nitro could be efficiently tolerated with this catalytic system. Next, we also tested the reactivity of methyl acetoacetate (**2b**) with benzaldehyde (**1a**) and urea (**3a**) under optimized reaction conditions, and the reaction underwent efficiently to give the wanted product (**4o**) in 90% yield. Moreover, we also investigated the scope and generality of thiourea (**3b**) with various aldehydes and ethyl or methyl acetoacetate (**2a**-**b**) under optimized catalytic conditions, and the results are shown in Table 2. All the reactions proceeded smoothly and afforded the corresponding products (**4p**-**u**) in 88-93% yields.

To further explore, the synthetic expediency and potential viability of this reaction, the scale-up reaction (10.0 mmol) was efficiently performed by using compound **1a**, ethyl acetoacetate and urea under optimized catalytic conditions to deliver the desired product **4a** in 88% yield. Moreover, we also studied the recyclability and reusability of the catalyst, which was checked with a model reaction. After completion of the reaction, the catalyst was recovered according to our previous procedure [62]. Then the recovered catalyst was dried in an oven at 120 °C for 3-5 h and reused in subsequent reactions up to five runs without significant loss its catalytic activity (Figure 2).

We have further compared the catalytic process of FeF_3 by screening other fluoride sources under the same reaction conditions (Table 1), it was found that FeF_3 is the most reactive than other fluoride sources (Table 1, entry 6). The corresponding product was obtained in low yield in the presence of CsF, CaF_2, KF, NH_4F and TBAF (Table 1, entries 1-5), respectively. The use of other solvents like toluene, dichloro-methane, cyclohexane, etc. was also examined among which ethanol and acetonitrile were found to be effective.

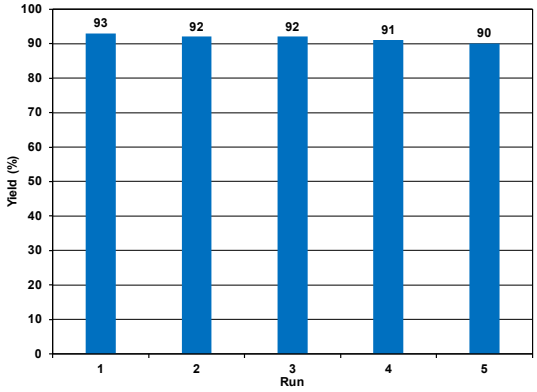


Figure 2. Reusability of catalyst in synthesis of compound **4a**.

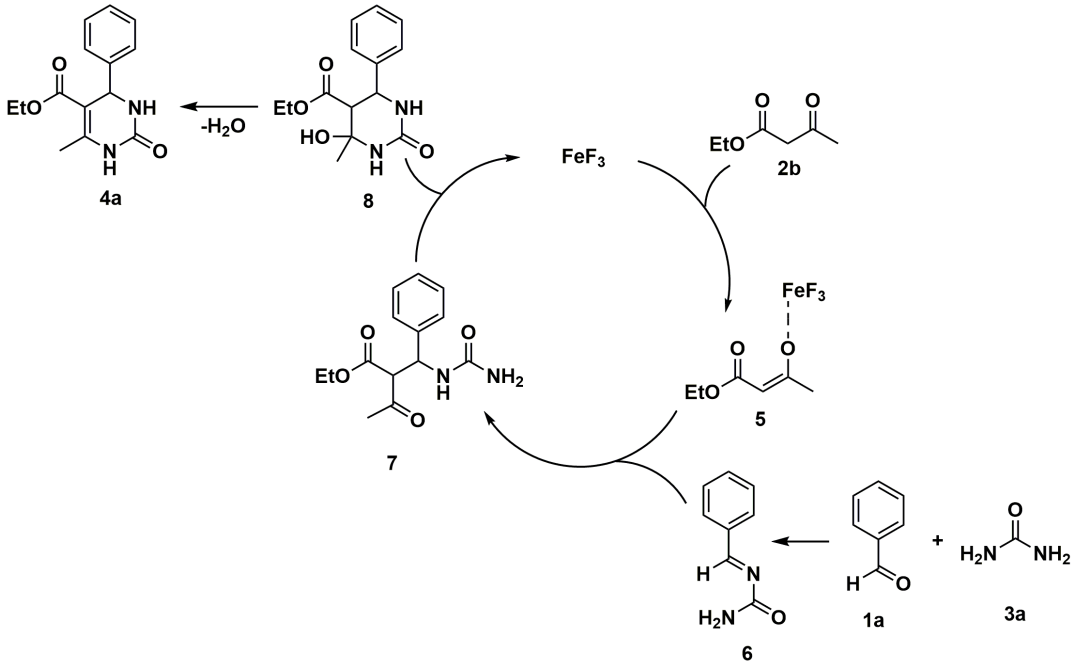


Figure 3. Proposed mechanism for the formation of ethyl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**4a**).

FeF_3 is more soluble in water than that in organic solvents. The catalyst was recovered almost quantitatively from the aqueous layer, which was subsequently reused for several runs. The yield of compound **4a** was found to be 93, 92, 92, 91 and 90 after the 1st, 2nd, 3rd, 4th and 3rd recovery and reuse of the catalyst. A comparison of the powder X-ray diffraction (XRD) spectrum obtained for fresh FeF_3 and the reused catalyst indicated no change in its crystalline nature [61].

Mechanistically, the reaction seems to proceed via a sequence (Figure 3) involving the FeF_3 promoted formation of the Schiff base **6** to form intermediate **7**, followed by cyclization **8** and dehydration to yield product **4a**.

4. Conclusion

We have developed an efficient multicomponent protocol for the synthesis of biologically active functionalized dihydro pyrimidines via Biginelli reaction using easily accessible FeF_3 as a catalyst. This method has several advantages, such as readily available starting materials, low-catalyst loading with high activity, good to excellent yields, high functional group tolerance, and environmentally benign conditions. The catalyst can be easily recycled and reused up to five runs with high performance. Furthermore, efficient strategies by using FeF_3 as a catalyst are now underway in our laboratory.

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Disclosure statement

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