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Short Communication

Metal-organic framework Cu_3 $(BTC)_2(H_2O)_3$ catalyzed Aldol synthesis of pyrimidine-chalcone hybrids

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ABSTRACT

A typical metal organic framework, [Cu_3 $(BTC)_2(H_2O)_3$, BTC = 1,3,5-benzene tricarboxylate] has been used for the synthesis of pyrimidine-chalcones. We have explored a green synthesis of pyrimidine chalcones under Cu_3 $(BTC)_2$ catalysis by Aldol condensation. Easy isolation of product, excellent yield, and recyclable catalyst makes this reaction eco-friendly. The technology was demonstrated to be applicable to the synthesis of a host of chemical hybrids.

1. Introduction

Extensive research on diverse biological activities of heterocycles has confirmed their immense significance in pathophysiology of diseases. The amalgamation of two pharmacologically important structural scaffolds leads to a new library of heterocycles, possessing broad spectrum of activities against numerous pathogenic strains and also striking activities against cancer. We have developed an extensive research program on the synthesis and biological evaluations of Chemical Hybrids (as "Molecular Lego Sets") incorporating diverse architecture of nuclei within their molecular framework and to explore synergistic therapeutic relevance as thrombin inhibitors, prostate specific antigen inhibitors, and anticancer drugs. We have exemplified synthesis of an array of hybrid molecules: We combined substituted pyrimidines with isoxazoline residues in hybrid scaffolds in a single molecular framework to secure enhanced and systematically attenuated and accentuated biological activity. Synthesis of hybrid molecules is of interest as a way of synergistically increasing drug discovery portfolios.

Because of their biological and therapeutic significance, chalcones have been versatile key precursors of many heterocyclic compounds of pharmaceutical relevance [1,2]. Pyrimidines, exhibit diverse pharmacological properties as effective bactericides, fungicides, viricides, insecticides, certain pyrimidine and annulated pyrimidine derivatives are also known to display anticancer, antimalarial, antileshmaniel and antifilarial activity [3]. Our research encompasses the synthesis of pyrimidine-chalcone hybrids.

The pioneering papers and reports of the yesteryears that described base catalyzed synthesis of chalcones by the Claisen Schmidt condensation were fraught with several limitations, such sub-optimal purity and inefficiency of the methods for purification and evaluation of synthesized compounds, undesirable side products, long reaction times and low yields. In the Claisen Schmidt chalcone synthesis, various bases like NaOH [4,5], KOH [6], solid base KF-Al_2O_3 under ultrasound irradiation [7] have been used. In addition, acid catalyzed reactions involves the use of $AlCl_3$ [8], BF_3 [9] and dry HCl [10], extended reaction times, difficulty in the catalyst preparation, high temperatures, use of special apparatus, costly reagents and formation of side products. Development of catalytic green chemical processes with organometalic complexes is of growing interest because of the need to obviate use of corrosive and hazardous liquid acids. Recently, use and utility of a wide range of catalysts such as acidic alumina [11], acidic clays [12], organometallic compounds [13], zeolites [14], ionic liquids [15], ion exchange resins [16] and metal oxides [17] have been reported.

MOFs are crystalline solids wherein the structure is built by metal ions or clusters of metal ions held in place by organic di- or multitopical linkers [18,19]. In MOF, the transition metals have free coordination positions that are not compromised in the construction of MOFs. These materials are expected to have similarities with zeolites & related microporous solids. $Cu_3(BTC)_2$(BTC = 1,3,5-benzene tricarboxylate), MOF combined with TEMPO [(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl, $(CH_2)_3(CMe_2)_2NO$] as cocatalyst has been used as an effective and reusable heterogeneous catalyst for the aerobic oxidation of benzylic alcohol [19]. Metal organic framework Fe (BTC) (BTC = 1,3,5-benzene

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tricarboxylate), heterogeneous catalyst has been used for chalcone synthesis in high yield and reduced reaction times via Claisen Schmidt condensation [20].

TiO_2–SO_4^{2-} [21] was used for the synthesis of chalcones under microwave irradiation in which sulphate loading by H_2SO_4 increased the Lewis acidity of TiO_2. $Cu_3(BTC)_2(H_2O)_3$ exhibit hard Lewis acid character [22,23] and is found to be the first MOF catalyst deployed for the Friedlander reaction between 2-aminobenzophenones and acetylacetone under mild reaction conditions, leading to the corresponding quinolines with excellent yield. $Cu_3(BTC)_2$ has attracted lavish attention because of its interesting structural diversity, geometrical control and flexibility arising from an axial Cu^{2+} and 1,3,5-benzene tricarboxylate (H_3BTC) (Crystal structure [24] in Scheme 1). Herein, we report use of a recyclable, easily separable, eco-friendly and highly effective solid acid catalyst, $Cu_3(BTC)_2$ for the synthesis of pyrimidine chalcones at 40 °C. When conducted with solid acids this leads to better selectivity, increased productivity and high yield of pyrimidine-chalcones.

We embarked on the synthesis of pyrimidine chalcones by conventional and non-conventional methods and synthesized a library of new pyrimidine chalcones under base and acid catalysis. The Claisen Schmidt condensation and Aldol condensation were our methods of choice. The formyl pyrimidine constitutes an electron rich nucleus; with a deactivated N-*CHO centre, making the molecule more stable but less reactive. Enroute to our goals of developing green processes, we explored a pathway of synthesis of biologically active pyrimidine chalcone hybrids under catalysis of $Cu_3(BTC)_2(H_2O)_3$ (MOF) in toluene at 40 °C with constant stirring for 12 h. We optimized the reaction conditions in order to check the authenticity of the reaction which was carried out under catalysis of $Cu_3(BTC)_2(H_2O)_3$

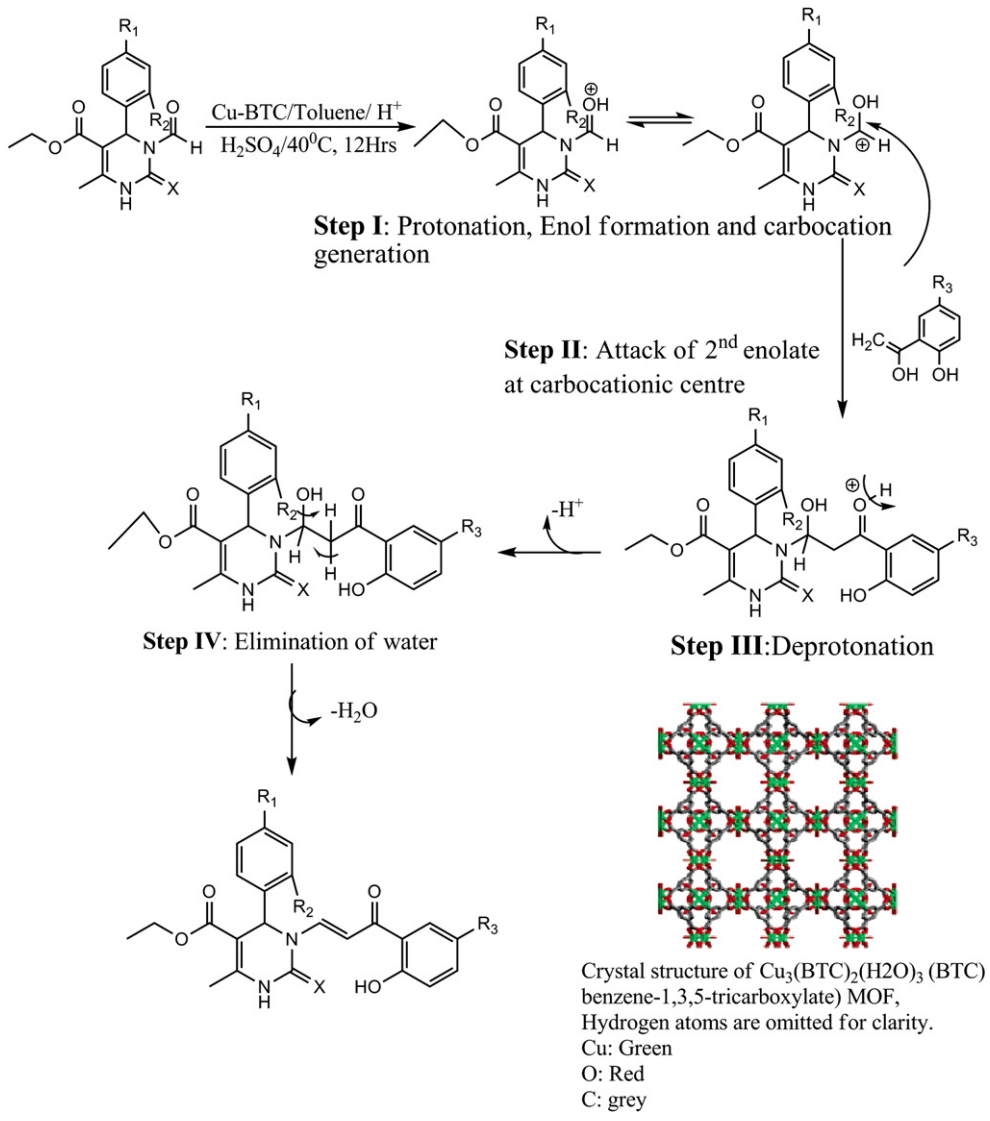
2. Experimental

2.1. Materials and methods

Substituted acetophenone viz., 4-chloro-2-hydroxy acetophenone, 2-hydroxy-4-methyl acetophenone, differently substituted formyl pyrimidine were made using analytical grade benzaldehyde, chlorobenzaldehyde, anisaldehyde, nitrobenzaldehyde (S. D. Fine Chem. 98.0%), urea/thiourea, absolute alcohol (99%), H_2SO_4 (Fischer 98%), DMF, $POCl_3$ (Thomas baker, 98%), hydrated form of cupric acetate, benzene-1,3,5-tricarboxylic acid.

2.2. Apparatus

Thin layer chromatography was performed on silica gel G. Melting points were determined by open-capillary method. IR spectra were



Scheme 1. Proposed mechanism of *Aldol condensation* of acetophenone with formylpyrimidine under Cu-BTC catalysis.

recorded using Shimadzu FT-IR spectrometer using KBr pellets. GC/MS analysis was carried out using GC model: Shimadzu gas chromatograph coupled with QP5050 spectrometer at 1–1.5 ev. Proton and carbon NMR spectra were recorded on a Brucker AVII FT-NMR spectrometer operating at 400 MHz for the entire sample.

2.3. Claisen–Schmidt condensation: base catalyzed synthesis of substituted ethyl 1,2,3,6-tetrahydro-1-(3-(2-hydroxyphenyl)-3-oxoprop-1-enyl)-4-methyl-2-oxo/thioxo-6-phenyl pyrimidin-5-carboxylates

Substituted 2′-hydroxy acetophenone (0.11 mmol) and ethyl 1-formyl-1, 2, 3, 6-tetrahydro-4-methyl-2-oxo/thioxo-6-phenylpyrimidine-5-carboxylate (**1a**–**g**) (0.1 mmol) were dissolved in ethanol 20 mL and the mixture was heated up to 60 °C. Then a solution of 0.3 mmol of NaOH (40%) was added till a red mass obtained and the reaction mixture was kept for 24 h. It was subsequently decomposed by ice cold 1:1 HCl till the reaction mixture became acidic. It was further filtered, washed with dil. $NaHCO_3$. The product was recrystallized from ethanol: acetic acid (8:2) (**2a**–**k**). The purity of the synthesized compounds was evaluated by using hexane: ethyl acetate (7:3) as eluent.

2.4. Aldol condensation: $Cu_3(BTC)_2$ catalyzed synthesis of substituted ethyl 1,2,3,6-tetrahydro-1-(3-(2-hydroxyphenyl)-3-oxoprop-1-enyl)-4-methyl-2-oxo/thioxo-6-phenylpyrimidin-5-carboxylates

$Cu_3(BTC)_2$ was prepared by known method [22] and was ground by mortar & pestle. To a mixture of substituted acetophenone (1 mmol) and substituted ethyl 1-formyl-1,2,3,6-tetrahydro-4-methyl-2-oxo/thioxo-6-phenyl pyrimidin-5-carboxylate (**1a**–**g**) (1.1 mmol) in toluene, 0.075 g of $Cu_3(BTC)_2$ was added with one-two drops of conc. H_2SO_4 in order to accelerate the reaction in a forward direction. The mixture was stirred at 40 °C for 10–12 h (Scheme 1). Completion of the reaction was monitored by TLC. Ethyl acetate was added to the solid mass and the insoluble catalyst was separated by filtration. The filtrate was dried over anhydrous Na_2SO_4. The solvent was evaporated and the product was obtained. The crude product was purified by column chromatography using hexane: ethyl acetate (7:3) as mobile phase. The catalyst recovered from the reaction mixture was reused for the 2nd cycle of Aldol condensation. All compounds (**2a**–**k**) were synthesized by using $Cu_3(BTC)_2$ up to 11th cycle.

The impact of variation of the quantity of $Cu_3(BTC)_2$ on Aldol synthesis was investigated. The experiments were repeated by varying the quantities of the catalyst for optimization of reaction conditions. The results are depicted in Table 1.

2.4.1. Reusability of $Cu_3(BTC)_2$

The reusability of $Cu_3(BTC)_2$ was tested by recovering the catalyst from every cycle. The insoluble catalyst was filtered out, dried and reused with two drops of conc. H_2SO_4 without further purification for second run. The procedure was repeated and the efficiency of the catalyst was checked up to the 11th cycle. The results are depicted in Table 2.

Table 1
Variation of quantities of $Cu_3(BTC)_2$ on Aldol Synthesis of Ethyl 1,2,3,6-tetrahydro-1-(3-(2-hydroxy-5-methylphenyl)-3-oxoprop-1-enyl)-4-methyl-2-oxo-6-phenylpyrimidin-5-carboxylate (2a).

Entry	$Cu_3(BTC)_2$ in mg	$Cu_3(BTC)_2$ in mmol	Isolated yield (%)
1	20	0.0976	No reaction
2	40	0.1952	No reaction
3	50	0.244	30
4	60	0.292	60
5	75	0.366	87
6	100	0.488	87
7	150	0.732	87

All synthesized compounds were structurally characterized by FT-IR, ^{1}HNMR, ^{13}CNMR and GC–MS analyses (Table 3).

2.4.1.1. Ethyl 1,2,3,6-tetrahydro-1-(3-(2-hydroxy-5-methylphenyl)-3-oxoprop-1-enyl)-4-methyl-2-oxo-6-phenylpyrimidin-5-carboxylate (2a). Light Yellow crystal mp140 °C [$C_{24}H_{24}N_2O_5$]; IR (KBr disc) λ cm^{-1} 3460, 3190, 1720, 1695, 1450; ^{1}HNMR ($CDCl_3 + CCl_4$, 400 MHz) δ 1.14 (t, 3 H, $J = 8.4$), 1.6 (s, 3 H), 2.35 (s, 3 H), 4.0 (q, 2 H, $J = 4.6$), 5.4 (d, 1 H, $J = 4.1$), 5.5 (s, 1 H), 7.3–7.5 (m, 8 H), 8.2 (d, 1 H, $J = 4.2$); DI-MS: *m/z* 420 $[M+H]^+$.

2.4.1.2. Ethyl 6-(4-chlorophenyl)-1,2,3,6-tetrahydro-1-(3-(2-hydroxy-5-methyl phenyl)-3-oxoprop-1-enyl)-4-methyl-2-oxopyrimidin-5-carboxylate (2b). Yellow crystal mp125 °C [$C_{24}H_{23}N_2O_5Cl$]; IR (KBr disc) λ cm^{-1} 3465, 3185, 1715, 1690, 1455, 800; ^{1}HNMR ($CDCl_3 + CCl_4$, 400 MHz) δ 1.12 (t, 3 H, $J = 8.6$), 1.7 (s, 3 H), 2.32 (s, 3 H), 4.1 (q, 2 H, $J = 4.6$), 5.2 (d, 1 H, $J = 4.1$), 5.3 (s, 1 H), 7.2–7.5 (m, 8 H), 8.2 (d, 1 H, $J = 4.2$), 8.4 (s, 1 H); DI-MS: *m/z* 454 $[M+H]^+$.

2.4.1.3. Ethyl 1,2,3,6-tetrahydro-1-(3-(2-hydroxy-5-methylphenyl)-3-oxoprop-1-enyl)-6-(4-methoxyphenyl)-4-methyl-2-oxopyrimidin-5-carboxylate (2c). Brown crystal mp145 °C [$C_{25}H_{26}N_2O_6$]; IR (KBr disc) λ cm^{-1} 3416, 3155, 1715, 1670, 1455; ^{1}HNMR ($CDCl_3 + CCl_4$, 400 MHz) δ 1.14 (t, 3 H, $J = 8.3$), 2.3 (s, 3 H), 3.73 (s, 3 H), 3.8 (s, 3 H), 4.0 (q, 2 H, $J = 4.4$), 5.2 (s, 1 H), 6.5 (m, 8 H), 6.8 (d, 1 H, $J = 4.1$), 7.8 (d, 1 H, $J = 4.2$), 8.9 (s, 1 H), 10.8 (s, 1 H); DI-MS: *m/z* 450 $[M+H]^+$.

2.4.1.4. Ethyl 1,2,3,6-tetrahydro-1-(3-(2-hydroxy-5-methylphenyl)-3-oxoprop-1-enyl)-4-methyl-6-phenyl-2-thioxopyrimidin-5-carboxylate (2 d). Yellow crystal mp135 °C[$C_{24}H_{24}N_2O_4S$]; IR (KBr disc) λ cm^{-1} 3450, 3155, 1710, 1695, 1450; ^{1}HNMR ($CDCl_3 + CCl_4$, 400 MHz) δ 1.12 (t, 3 H, $J = 8.3$), 1.5 (s, 3 H), 2.2 (s, 3 H), 4.1(q, 2 H, $J = 4.6$), 5.2 (d, 1 H, $J = 4.0$), 5.4 (s, 1 H), 7.2–7.6 (m, 8 H), 8.6 (d, 1 H, $J = 4.2$), 8.9 (s, 1 H); DI-MS: *m/z* 436 $[M+H]^+$.

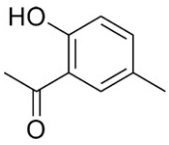
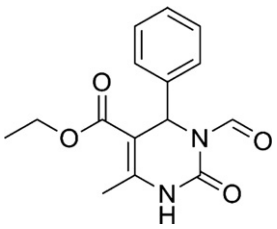
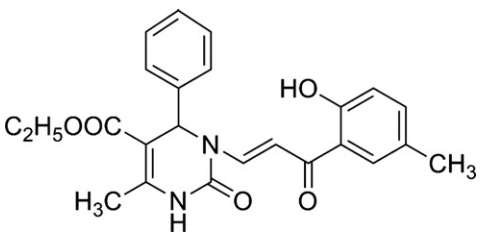
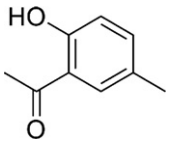
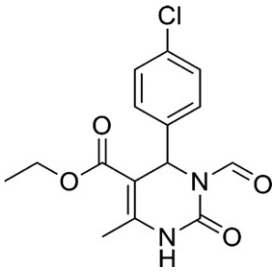
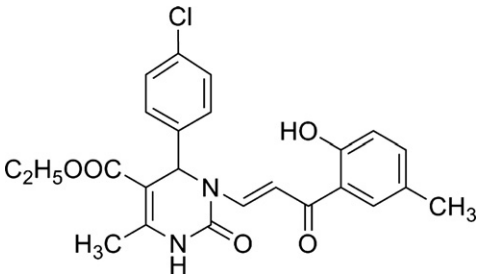
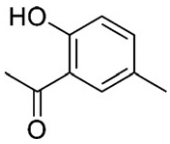
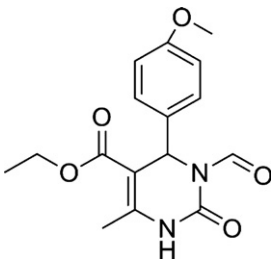
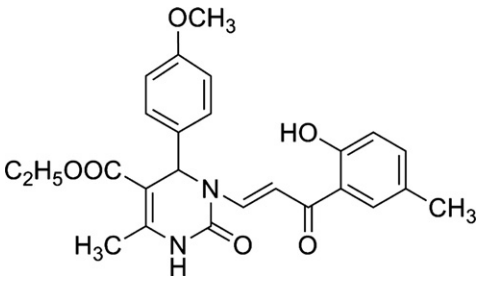
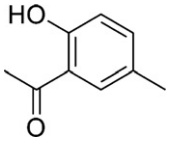
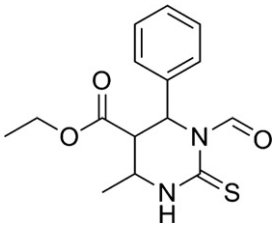
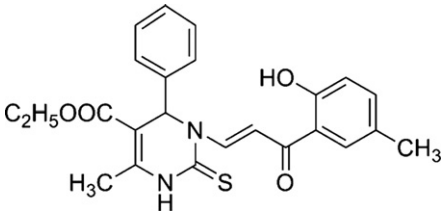
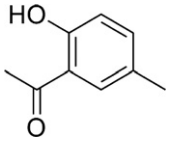
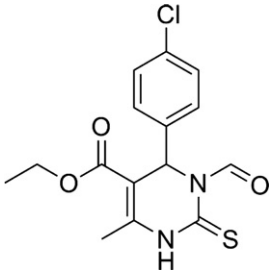
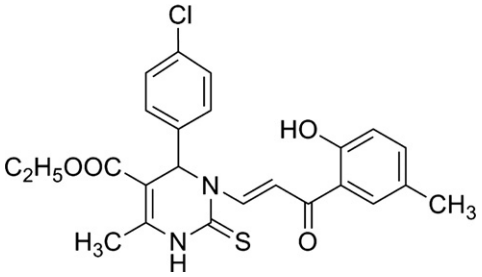
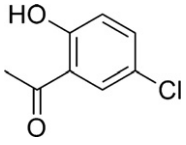
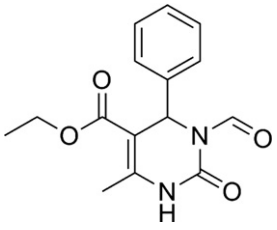
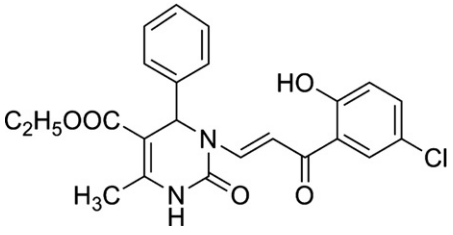
2.4.1.5. Ethyl 6-(4-chlorophenyl)-1,2,3,6-tetrahydro-1-(3-(2-hydroxy-5-methyl phenyl)-3-oxoprop-1-enyl)-4-methyl-2-thioxopyrimidin-5-carboxylate (2e). Yellow crystal mp115 °C [$C_{24}H_{23}N_2O_4SCl$]; IR (KBr disc) λ cm^{-1} 3315, 3145, 1715, 1695, 1455; ^{1}HNMR ($CDCl_3 + CCl_4$, 400 MHz) δ 1.1 (t, 3 H, $J = 8.4$), 1.6 (s, 3 H), 2.1 (s, 3 H), 4.1(q, 2 H, $J = 4.6$), 5.1(d, 1 H, $J = 4.1$), 5.4 (s, 1 H), 7.2–7.5(m, 8 H), 8.3 (d, 1 H, $J = 4.2$), 8.4 (s, 1 H); DI-MS: *m/z* 470 $[M+H]^+$.

2.4.1.6. Ethyl 1-(3-(5-chloro-2-hydroxyphenyl)-3-oxoprop-1-enyl)-1,2,3,6-tetrahydro-4-methyl-2-oxo-6-phenylpyrimidin-5-carboxylate (2f). Yellow crystal mp180 °C [$C_{23}H_{21}N_2O_5Cl$]; IR (KBr disc) λ cm^{-1} 3420, 3130, 1720, 1650, 1435; ^{1}HNMR ($CDCl_3 + CCl_4$, 400 MHz) δ 1.1 (t, 3 H, $J = 8.4$), 1.63 (s, 3 H), 4.0 (q, 2 H, $J = 4.5$),5.2 (d, 1 H, $J = 4.0$), 5.5

Table 2
Recycling of $Cu_3(BTC)_2$ in Aldol Synthesis of Ethyl 1,2,3,6-tetrahydro-1-(3-(2-hydroxy-5-methylphenyl)-3-oxoprop-1-enyl)-4-methyl-2-oxo-6-phenylpyrimidin-5-carboxylate (2a).

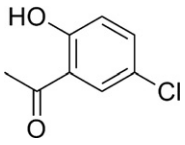
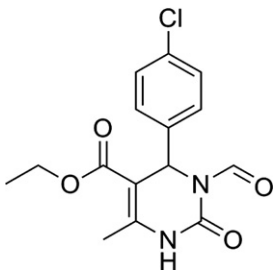
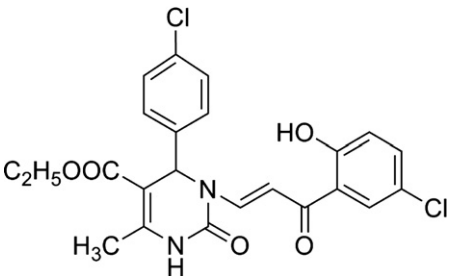
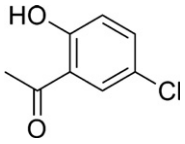
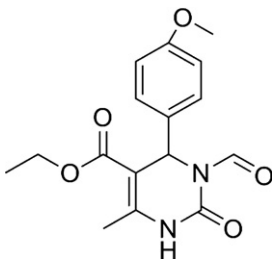
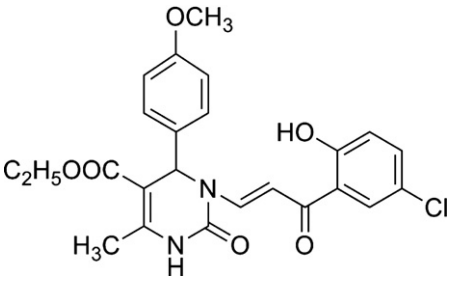
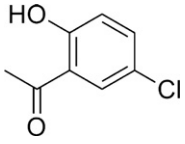
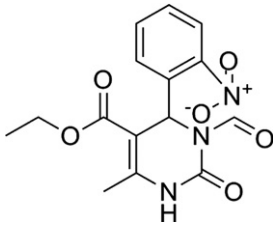
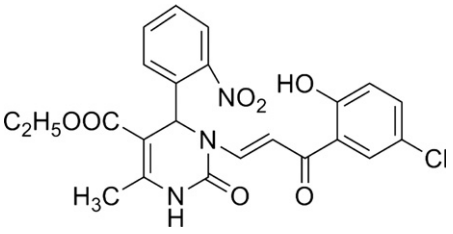
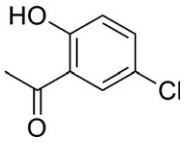
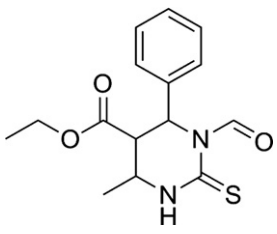
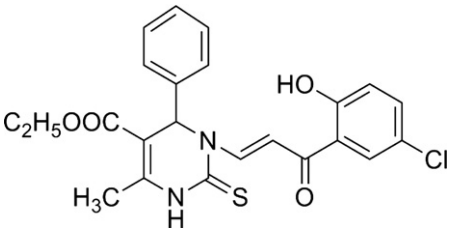
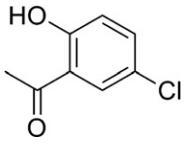
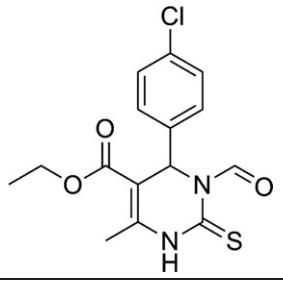
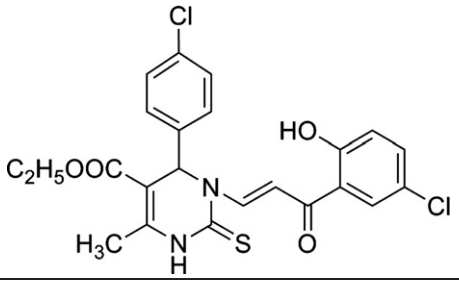
Entry	No. of cycles	Isolated yield (%)
1	1st	87
2	2nd	87
3	3 rd	85
4	4th	85
5	5th	85
6	6th	83
7	7th	83
8	8th	80
7	9th	80
10	10th	78
11	11th	78
12	12th	64

Table 3
Physical Characteristic data of the Substituted ethyl 1,2,3,6-tetrahydro-1-(3-(2-hydroxyphenyl)-3-oxoprop-1-enyl)-4-methyl-2-oxo/thioxo-6-phenylpyrimidin-5-carboxylates (2a-k).

Entry	Ketone	Formylpyrimidine	Pyrimidine chalcone	Mp. (°C)	Isolated yield (%) a/b
2a				140	87/76
2b				125	80/72
2c				145	72/69
2d				135	82/74
2e				115	76/69
2f				180	84/68

(continued on next page)

Table 3 (*continued*)

Entry	Ketone	Formylpyrimidine	Pyrimidine chalcone	Mp. (°C)	Isolated yield (%) a/b
2g				120	85/68
2h				120	80/70
2i				155	70/62
2j				115	84/71
2k				105	71/66

a = Cu-BTC catalyzed *Aldol condensation.*
b = Base catalyzed Claisen Schmidt condensation.

(s, 1 H), 7.37.5 (m, 8 H), 8.4 (d, 1 H, $J = 4.2$), 8.6 (s, 1 H); DI-MS: *m/z* 440 $[M+H]^+$.

2.4.1.7. Ethyl 1-((E)-3-(5-chloro-2-hydroxyphenyl)-3-oxoprop-1-enyl)-6-(4-chloro-phenyl)-1,2,3,6-tetrahydro-4-methyl-2-oxopyrimidin-5-carboxylate (2 g). Yellow crystal mp120 °C [$C_{23}H_{20}N_2O_5Cl_2$] ; IR (KBr disc) λ cm^{-1} 3416, 3135, 1720, 1665, 1445; ^{1}HNMR ($CDCl_3 + CCl_4$, 400 MHz) δ 1.13 (t, 3 H, $J = 8.4$), 1.45 (s, 3 H), 4.1 (q, 2 H, $J = 4.6$), 5.1 (d, 1 H, $J = 4.1$), 5.3 (s, 1 H), 7.2–7.4 (m, 8 H), 8.2 (d, 1 H, $J = 4.2$), 8.4 (s, 1 H); DI-MS: *m/z* 475 $[M+H]^+$.

2.4.1.8. Ethyl 1-(3-(5-chloro-2-hydroxyphenyl)-3-oxoprop-1-enyl)-1,2,3,6-tetrahydro-6-(4-methoxyphenyl)-4-methyl-2-oxopyrimidin-5-carboxylate (2 h). Dark yellow crystal mp120 °C[$C_{24}H_{23}N_2O_6Cl$]; IR (KBr disc) λ cm^{-1} 3415, 3145, 1720, 1665, 1440; ^{1}HNMR ($CDCl_3 + CCl_4$, 400 MHz) δ 1.1 (t, 3 H, $J = 8.4$), 2.3 (s, 3 H), 3.7 (s, 3 H), 4.0 (q, 2 H,

$J=4.6$), 5.5 (s, 1 H), 7.3–7.5 (m, 8 H), 6.8 (d, 1 H, $J=4.1$), 7.8 (d, 1 H, $J=4.2$), 8.8 (s, 1 H), 11.8 (s, 1 H); DI-MS: *m/z* 470 $[M+H]^+$.

2.4.1.9. Ethyl1-((E)-3-(5-chloro-2-hydroxyphenyl)-3-oxoprop-1-enyl)-1,2,3,6-tetrahydro-4-methyl-6-(2-nitrophenyl)-2-oxopyrimidin-5-carboxylate (2i). Yellow crystal mp155 °C [$C_{23}H_{20}N_3O_7Cl$]; IR (KBr disc) λ cm^{-1} 3450, 3155, 1715, 1695, 1465; ^{1}HNMR ($CDCl_3+CCl_4$, 400 MHz) δ 1.1 (t, 3 H, $J=8.4$), 1.5 (s, 3 H), 4.1 (q, 2 H, $J=4.7$), 5.2 (d, 1 H, $J=4.3$), 5.4 (s, 1 H), 7.3–7.8 (m, 8 H), 8.2 (d, 1 H, $J=4.2$), 8.8 (s, 1 H), 10.8 (s, 1 H); DI-MS: *m/z* 485 $[M+H]^+$.

2.4.1.10. Ethyl1-(3-(5-chloro-2-hydroxyphenyl)-3-oxoprop-1-enyl)-1,2,3,6-tetrahydro-4-methyl-6-phenyl-2-thioxopyrimidin-5-carboxylate (2j). Yellow crystal mp115 °C [$C_{23}H_{21}N_2O_4SCl$]; IR (KBr disc) λ cm^{-1} 3460, 3190, 1720, 1695, 1450; ^{1}HNMR ($CDCl_3+CCl_4$, 400 MHz) δ 1.14 (t, 3 H, $J=8.4$), 1.6 (s, 3 H), 4.0 (q, 2 H, $J=4.6$), 5.4 (d, 1 H, $J=4.1$), 5.5 (s, 1 H), 7.3–7.5 (m, 8 H), 8.2 (d, 1 H, $J=4.2$); DI-MS: *m/z* 456 $[M+H]^+$.

2.4.1.11. Ethyl 1-((E)-3-(5-chloro-2-hydroxyphenyl)-3-oxoprop-1-enyl)-6-(4-chloro-phenyl)-1,2,3,6-tetrahydro-4-methyl-2-thioxopyrimidin-5-carboxylate (2 k). Yellow crystal mp105 °C [$C_{23}H_{20}N_2O_4SCl_2$]; IR (KBr disc) λ cm^{-1} 3465, 3185, 1720, 1690, 1455; ^{1}HNMR ($CDCl_3+CCl_4$, 400 MHz) δ 1.1 (t, 3 H, $J=8.4$), 1.5 (s, 3 H), 4.1 (q, 2 H, $J=4.6$), 5.2 (d, 1 H, $J=4.1$), 5.4 (s, 1 H), 7.2–7.6 (m, 8 H), 8.6 (d, 1 H, $J=4.2$), 8.9 (s, 1 H); DI-MS: *m/z* 491 $[M+H]^+$.

3. Result and discussion

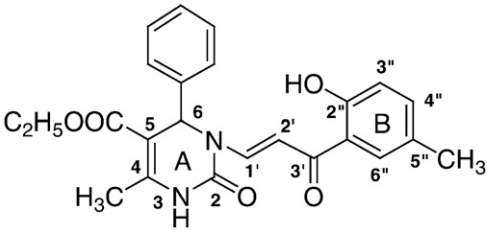
A novel, efficient methodology of synthesis of pyrimidine chalcone has been developed by using acetophenone and substituted ethyl 1-formyl-1,2,3,6-tetrahydro-4-methyl-2-oxo/thioxo-6-phenyl pyrimidin-5-carboxylate (**1a–g**) in Aldol condensation under catalysis of $Cu_3(BTC)_2(H_2O)_3$ .The results are presented in Table 3. Initially no reaction was observed when a base catalyzed reaction was carried out at ambient temperature. Generally Claisen Schmidt condensation is initiated via nucleophilic addition reaction. We observed that formyl pyrimidines did not undergo nucleophilic addition reaction very easily. To progress the reaction in forward direction, we increased the reaction time and temperature. The desired products were obtained by the conventional method with poor to moderate yield. This observation prompted us to explore new, efficient method of the synthesis of chalcones. Surprisingly, addition of a catalytic amount of $Cu_3(BTC)_2$ to the mixture of acetophenone & formylpyrimidine in toluene at 40 °C with constant stirring for 12 h produced corresponding pyrimidine-chalcones. Condensation was initiated with the formation of an enolate ion. The mechanistic pathway appears to involve acidic media which activates the carbonyl function, thereby making the carbonyl group of formyl pyrimidine readily enolisable in the presence of $Cu_3(BTC)_2$. $Cu_3(BTC)_2$ is a strong Lewis acid & functions as a heterogeneous catalyst; we however observed negligible conversion of **2** in absence of conc. H_2SO_4. The Lewis acidity of $Cu_3(BTC)_2$ was modulated by adding 2 drops of conc. H_2SO_4 in order to accelerate the reaction. Presumably the Lewis acid sites within the micropores of $Cu_3(BTC)_2$ were activated. This addition facilitated protonation leading to formation of enolates: the enolic form of acetophenone easily approached the carbocation of the enolate of formyl pyrimidine and attached itself to the centre (Scheme 1).

The heterogeneous catalytic activity of $Cu_3(BTC)_2$ was investigated for the Aldol condensation. The reaction was carried out under optimized conditions described in Table 1; the reaction mixture was filtered after 2 h to remove $Cu_3(BTC)_2$. The acidic filtrate was kept for 24 h without catalyst, complete recovery of initial substrate **1** with no conversion of **2** confirmed that conc. H_2SO_4 only enhanced the performance of $Cu_3(BTC)_2$ and did not catalyze the reaction in the absence of $Cu_3(BTC)_2$.

The reusability of $Cu_3(BTC)_2$ was investigated for Aldol condensation. The XRD pattern of used $Cu_3(BTC)_2$ when compared with fresh $Cu_3(BTC)_2$ displayed no structural variations. In the second cycle, the $Cu_3(BTC)_2$ showed deactivation in the absence of added H_2SO_4. After addition of conc. H_2SO_4, there was considerable enhancement in the efficiency of the reaction. These observations suggested that the activity of Lewis acidity center in $Cu_3(BTC)_2$ diminished after every use but that its activity could be modulated and regenerated by adding conc. H_2SO_4.

In $Cu_3(BTC)_2$ catalyzed Aldol condensation, the reaction was terminated by the removal of water molecule and desired α, β unsaturated product was achieved. No side reactions were observed, although the yield was highly dependent on the substituents. Fig. 1 shows the time conversion plot for formyl pyrimidine **1** to pyrimidine chalcone **2** under catalysis of $Cu_3(BTC)_2$ for Aldol condensation.

Therefore, $Cu_3(BTC)_2$ is the MOF showing best catalytic activity for Aldol condensation in the presence of conc. H_2SO_4. Electron withdrawing substituents like –Cl formyl pyrimidines, *o*-nitro formyl pyrimidines gave much better yields than *p*-nitro formyl pyrimidine under identical conditions: the reaction for the p-nitro substituent proceeded in negligible yield. Aldol condensation of chloro substituted substrates resulted in excellent product formation in high yields. Electron withdrawing groups at the phenyl ring of substituted formyl pyrimidines favored formation of product whereas electron donating groups lowered the yields.



The desired structure of synthesized ethyl 1,2,3,6-tetrahydro-1-(3-(2-hydroxy-5-methyl phenyl)-3-oxoprop-1-enyl)-4-methyl-2-oxo-6-phenylpyrimidin-5-carboxylate **2a** has been elucidated by the IR spectrum showing the presence of O–H stretching and N–H absorption band at 3320 cm^{-1} and 3190 cm^{-1} respectively. A strong band at 1670 cm^{-1} showed the presence of conjugated carbonyl group (>C=O). In ^{1}HNMR spectrum of **2a** the two different signals appeared at δ 1.1 & triplet at δ 2.1 confirming the presence of two methyl groups A singlet at δ 2.31 indicated the presence of $-CH_3$ that derived from ring B. Disappearance of a singlet of –CHO at δ 9.9 and appearance of two new doublets at δ 6.8 (*J=4.1 Hz*) and δ 8.2 (*J=4.2 Hz*) integrating $C_{2'}$–H_α and $C_{1'}$–H_β protons from olefinic region. A characteristic singlet at δ 11.8 indicated the presence of Ar–OH. ^{13}CNMR spectrum displayed two different peaks for carbon carbon double bond [$C_{2'}$–H_α and $C_{1'}$–H_β] at δ 109.6 and δ 144.4 also the presence of two signals at δ 189.6 for $C_{3'}=O$ and at δ 145.6 for carbonyl group of pyrimidine that confirmed the

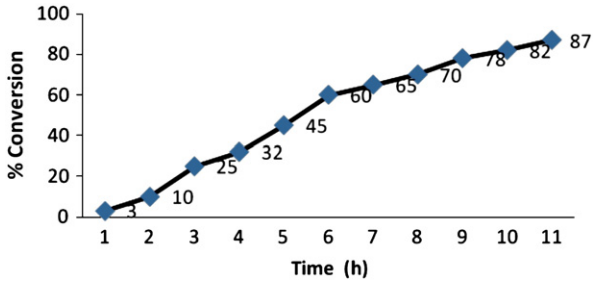


Fig. 1. Time conversion plot for the *Aldol Condensation* of formyl pyrimidine **1a** to pyrimidine chalcone **2a** under catalysis of $Cu_3(BTC)_2$ (reaction condition: substituted formyl pyrimidine (0.1 mmol), substituted hydroxyphenone (0.11 mmol), catalyst (0.075 g), toluene, 12 h, 40 °C).

assigned structure. The product **2a** was analyzed for $C_{24}H_{24}N_2O_5$ which exhibited molecular ion at *m/e* 420 [M^{+1}].

3.1. Reusability of $Cu_3(BTC)_2$

To check the versatility of this catalyst, we selected two reactants: 4-chloro-2-hydroxy acetophenone and ethyl 1,2,3,6-tetrahydro-1-(3-(2-hydroxy-5-methyl phenyl)-3-oxoprop-1-enyl)-4-methyl-2-oxo-6-phenylpyrimidin-5-carboxylate as model substrates. The Aldol condensation was repeatedly carried out in presence of reused and recovered Cu_3 $(BTC)_2$ with two drops of added conc. H_2SO_4 to modulate the Lewis acidity of the catalyst in the same reactant system. The catalyst was reused up to 11th cycle. The results summarized in Table 2 suggested that there was no appreciable loss in catalytic activity of $Cu_3(BTC)_2$ up to 10th cycle. (Table 2)

4. Conclusion

We have developed green synthesis of chalcones and related hybrids by using $Cu_3(BTC)_2$ as heterogeneous catalyst, under suitable temperature conditions for Aldol condensation. Overall, mild reaction conditions, enhanced rates, improved efficiency of reaction with maximum atom economy, recyclable and inexpensive catalyst, use of green solvent system and reduced reaction time are the remarkable features exhibited by our process.

Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.catcom.2011.03.040.

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