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Greener [3+3] Tandem Annulation-Oxidation Approach towards Synthesis of Substituted Pyrimidines

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This work is dedicated to Prof. M. M. Salunkhe, Vice Chancellor, Yashwantrao Chavan Maharashtra Open University on his 60th birthday

Abstract:

An economical and green synthesis of partly and fully substituted pyrimidines is described from α,β-unsaturated ketones and benzamidine hydrochloride using greener and recyclable choline hydroxide (ChOH) as a catalyst as well as a reaction medium. The remarkable features of this method are mild reaction conditions, short reaction times, easy workup procedure, recyclability of the catalyst and excellent yields of the products. The reaction involves [3+3] annulation-oxidation sequence and the protocol is useful for synthesizing a broad range of biologically significant pyrimidine derivatives.

Keywords:

Greener, [3+3] Annulation-oxidation, Pyrimidines, α,β-Unsaturated ketones, Benzamidine hydrochloride, Choline hydroxide

Introduction:

Pyrimidine is the privileged scaffold owing to its significant chemical and pharmacological properties.[1,2] Furthermore, pyrimidine derivatives exhibit a broad range of biological activities such as antitumor, antibacterial, antifungal, antimalarial and anticonvulsant.[1-5] Notably, pyrimidine is a key constituent of some important drugs used for the treatment of hyperthyroidism, acute leukamia in children and adult granulocytic leukamia.[5] In addition, several pyrimidines display wide-spread pharmacological activities such as analgesic, antiarrhythmic and anticancer.[6-8] Pyrimidines also find broad applications in polymer and supramolecular chemistry.[9,10] The compounds with extended conjugation having pyrimidine

nucleus are vital as they are potential candidates for light emitting devices[11] and molecular wires.[12]

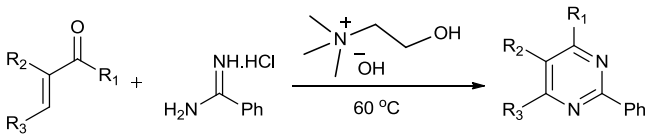
Conventionally, pyrimidines are prepared by the reaction of amidines with α,β-unsaturated ketones,[13] dimerization-oxidative fragmentation of aryl-β-arylvinylimines,[14] condensation of phenacyldimethylsulfonium salts, aldehydes and ammonia,[15] reaction of alkynes and nitriles using TfOH,[16] the one-pot, three-component reaction of aryl halides, terminal propargyl alcohols and amidinium salts by means of a coupling-isomerization-cyclocondensation sequence,[17] arylation of halogenated pyrimidines via a Suzuki coupling reaction,[18] reaction of α,α-dibromo oxime ethers with Grignard reagents,[19] and microwave-assisted reaction of amidines and alkynones.[20] Recently Zhan *et al*.[21] and Bagley *et al*.[22] reported the tandem synthesis of pyrimidines from propargylic alcohols and amidines using transition metal catalysts such as $Cu(OTf)_2$ and MnO_2 respectively. Obora *et al*.[23] synthesized tetrasubstituted pyrimidines *via* [2+2+2] intermolecular cycloaddition of alkynes with aryl nitriles in presence of $NbCl_5$ while Campagne *et al*.[24] prepared the disubstituted pyrimidines by cyclocondensation of β-enaminones with carboxamides using a strong base.

However these methods suffer from one or another drawback such as use of metal mediated catalysis, starting materials which require multistep synthesis, expensive and moisture sensitive reagents, strong basic conditions, longer reaction time, higher reaction temperature, low yield of products and non recyclability of catalyst which limits their practical utility in organic synthesis. Hence, the development of a more practical, economical and environmentally friendly method for the synthesis of substituted pyrimidines is of great interest.

On the eve of environmental consciousness in chemical research, the challenge for designing of sustainable environment procedures is the replacement of toxic and hazardous organic solvents by green solvents. In this context, in past few years ionic liquids (ILs) have emerged as green alternatives to conventional organic solvents due to ease in their synthesis. Inspite of this, they do have some limitations such as their toxicity to aquatic environment, use of costly starting materials, etc. In these circumstances, eutectic mixture is more eco- and environmentally friendly. Eutectic mixture is the combination of ammonium based chloride and hydrogen bond donors like urea. Bio-compatible nature of the constituents, their easy availability at low cost and easy preparation makes large-scale application more feasible. They possess significant properties such as low vapor pressure, high stability, wide liquid range, non-flammability, wide-range of

electrochemical window, biodegradable nature and tunable solvency. Considering all of these desirable properties, eutectic mixtures have been successfully used for extraction of glycerol from biodiesel,[25] hydrolase catalysed biotransformations[26] and as electrolytes for dye sensitized solar cell[27], etc. Pioneer work of Abbott *et al.*[28-30] in these low melting liquid systems attracted the attention of research fraternity.

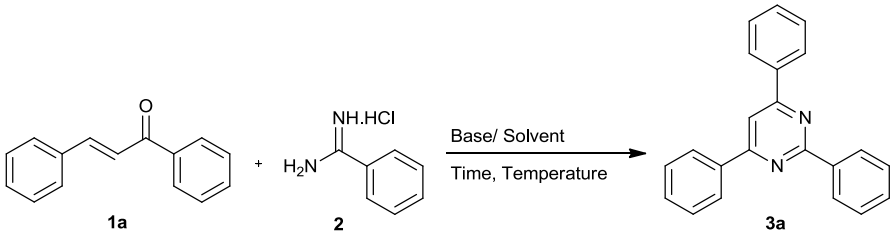
Deep eutectic mixtures have seldom been used as catalysts as well as reaction media for organic reactions. In this context, in pursuit of our research on the development of economical and environmentally friendly protocols[31-36] for the synthesis of biologically important heterocyclic compounds, herein we report our investigation concerning the synthesis of substituted pyrimidines from α,β-unsaturated ketones and benzamidine hydrochloride using choline hydroxide (ChOH) in the dual role.



Scheme 1. Greener synthesis of substituted pyrimidines

Results and discussion

Table 1. Optimization of reaction conditions[a-e]



Entry	Base/ Solvent	Temp. °C	Time (h)	Yield[f] (%)
1[a]	Without base-EtOH	80	24	NR
2[b]	K_2CO_3-CH_3CN	80	4	25
3[b]	K_3PO_4-CH_3CN	80	4	19
4[b]	Cs_2CO_3-CH_3CN	80	4	38
5[b]	NaOH-EtOH	80	1.5	83
6[b]	KOH-EtOH	80	1.5	85
7[b]	CsOH-DMF	80	1	86

8[b]	KtBuO-THF	80	5	63
9[b]	NaH-THF	80	5	59
10[b]	DBU-CH_3CN	80	4	31
11[b]	Pyridine-THF	80	3	52
12[b]	Piperidine-EtOH	80	3	67
13[b]	NEt_3-CH_3CN	80	4	74
14[c]	ChCl: Urea	80	6	12
15[c]	ChCl: PTSA	80	12	NR
16[d]	ChOH	RT	1	48
17[d]	ChOH	40	30 min	69
18[d]	ChOH	60	30 min	90
19[d]	ChOH	80	30 min	87
20[e]	Water	100	8	28
21[e]	EtOH	80	1	65
22[e]	CH_3CN	80	1.5	60
23[e]	1,2-DCE	80	5	47
24[e]	THF	80	3	52
25[e]	1,4-dioxane	102	3	38
26[e]	Toluene	110	2.5	43

[a]Reaction conditions: **1a** (1.0 mmol), **2** (1.0 mmol) in EtOH (5 mL) at 80 ^oC. [b]Reaction conditions: **1a** (1.0 mmol), **2** (1.0 mmol), base (2.0 mmol) and solvent (5 mL) at 80 ^oC. [c]Reaction conditions: **1a** (1.0 mmol), **2** (1.0 mmol), DES (3 mL) at 80 ^oC. [d]Reaction conditions: **1a** (1.0 mmol), **2** (1.0 mmol), ChOH (3 mL) at RT to 80 ^oC. [e]Reaction conditions: **1a** (1.0 mmol), **2** (1.0 mmol), ChOH (1.0 mmol) and solvent (5 mL) under reflux. [f]Isolated yields.

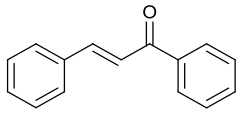
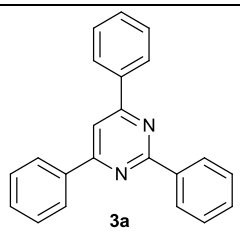
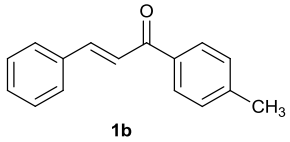
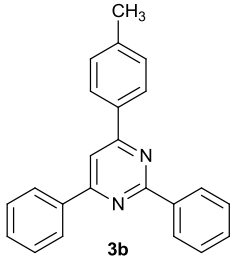
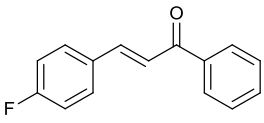
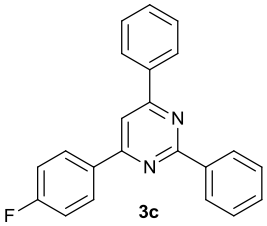
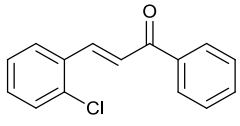
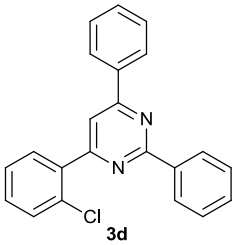
Initially, the reaction of 1,3-diphenyl-2-en-1-one **1a** with benzamidine hydrochloride **2** was selected as a model, wherein the effect of different bases, solvents and temperature was investigated. The reaction of α,β-unsaturated ketone **1a** with benzamidine hydrochloride **2** in EtOH at 80 ^oC was performed in absence of base but it was failed to give the desired product even after prolonged reaction time of 24 h (Table 1, entry 1). Then, the reaction of chalcone **1a** with benzamidine hydrochloride **2** was carried out in presence of different inorganic bases such as K_2CO_3, K_3PO_4, Cs_2CO_3, NaOH, KOH, CsOH, KtBuO and NaH (Table 1, entries 2-9). The

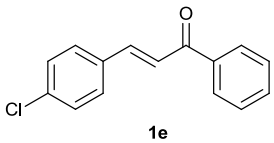
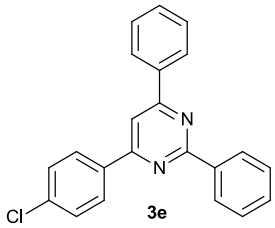
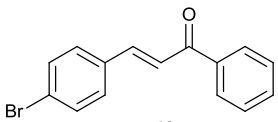
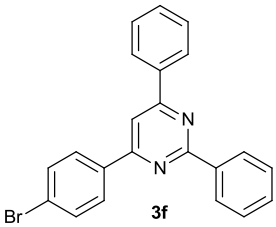
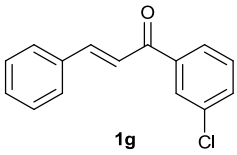
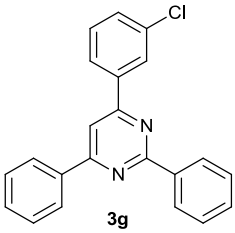
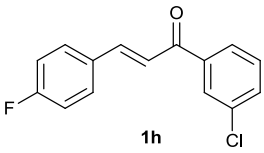
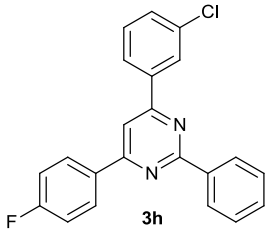
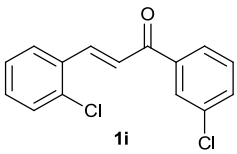
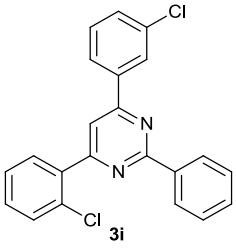
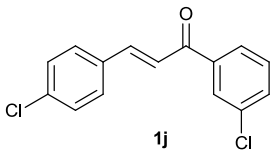
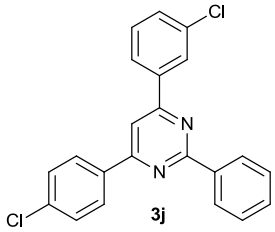
reactions using weak bases such as K_2CO_3, K_3PO_4 and Cs_2CO_3 offered pyrimidine **3a** in low yields whereas the use of KtBuO and NaH resulted in formation of product **3a** in 63 and 59% yield respectively. To our delight, the reaction in presence of strong bases such as NaOH, KOH and CsOH proceeded smoothly to afford product **3a** in excellent yields. The reaction involving the use of CsOH as a base and DMF as a solvent took only 1 h for completion and formed pyrimidine **3a** in 86% yield (Table 1, entry 7). Similarly we also screened different organic bases such as DBU, pyridine, piperidine and NEt_3 for this reaction but all of these bases resulted in lower yields (Table 1, entries 10-13) as compared to inorganic bases. The reaction between chalcone **1a** and benzamidine hydrochloride was performed using deep eutectic solvents (DES) which possess intrinsic advantages over organic solvents as green catalysts. The reaction in a mixture of choline chloride / urea DES formed pyrimidine **3a** in low yield of 12% (Table 1, entry 14) whereas the reaction in a mixture of choline chloride / PTSA DES did not form the desired product even after 12 h heating (Table 1, entry 15). When we carried out the reaction in choline hydroxide (ChOH) at room temperature, it produced pyrimidine **3a** in 48% yield with reaction time of 1 h (Table 1, entry 16). Encouraged with this result we attempted the same reaction under varying temperature conditions (Table 1, entries 17-19). To our surprise, the reaction at 60 ^oC temperature formed pyrimidine **3a** in 90% yield with a lower reaction time of 30 minutes (Table 1, entry 18). We also screened different solvents such as water, EtOH, acetonitrile, 1,2-dichloroethane, THF, 1,4-dioxane and toluene for this reaction using 1.0 equiv. of ChOH under reflux conditions. A low yield (28%) of product was obtained for the reaction in water (Table 1, entry 20). We found that the reaction in polar solvents such as ethanol and acetonitrile (Table 1, entries 21 and 22) resulted in higher yields of the product as compared to non polar solvents (Table 1, entries 23-26). The reaction involving the use of choline hydroxide as a catalyst as well as reaction medium at 60 ^oC temperature was found to be the optimal reaction condition for formation of pyrimidine **3a**.

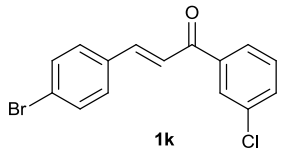
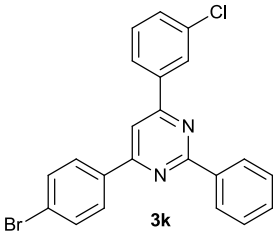
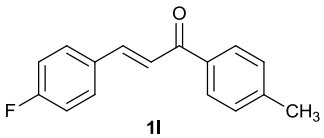
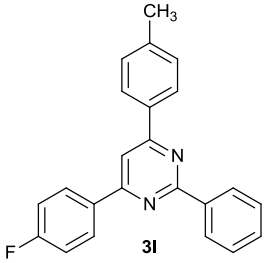
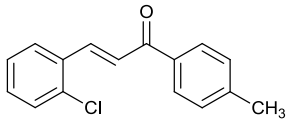
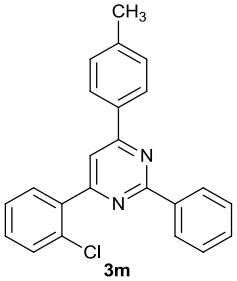
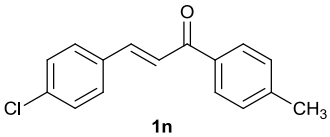
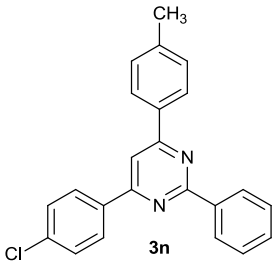
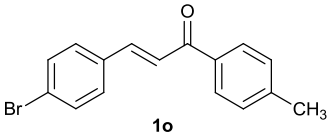
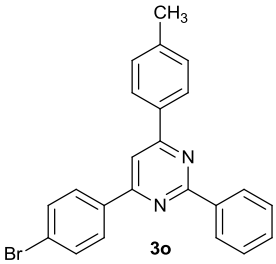
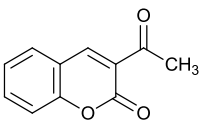
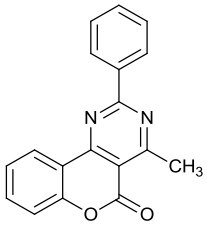
With optimal conditions in hand, we next explored the scope and limitations of this transformation by using various α,β-unsaturated ketones (Table 2). Chalcone **1b** bearing no substituent on the styryl moiety resulted in formation of pyrimidine **3b** in 86% yield. α,β-Unsaturated ketones (**1c**-**1o)** bearing a halogen group on the styryl moiety offered pyrimidine derivatives (**3c**-**3o)** in good to excellent yield (82-93%, Table 2). Steric hindrance as well as the inductive effect due to a halogen group near the double bond of unsaturated ketones (**1d**, **1i**, **1m**)

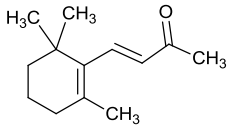
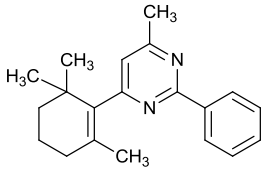
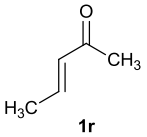
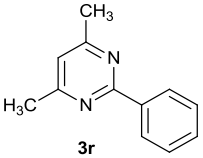
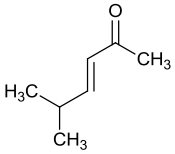
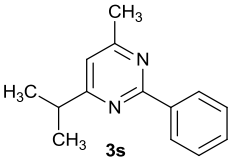
hampered the reaction and afforded low yields. The reaction of 3-acetyl coumarin (**1p**) with benzamidine hydrochloride (**2**) under similar reaction conditions produced tetrasubstituted pyrimidine (**3p**) in 85% yield with slightly longer reaction time of 50 minutes. The extended conjugation in β-ionone adversely influenced the reaction rate and formed **3q** in 83% yield. (*E*)-Pent-3-en-2-one (**1r**) and (*E*)-5-methylhex-3-en-2-one (**1s**) also reacted smoothly with benzamidine hydrochloride (**2**) to offer the corresponding pyrimidines **3r** and **3s** in 86 and 82% yields, respectively.

Table 2. Choline hydroxide mediated synthesis of substituted pyrimidines[a]

Entry	Starting Material	Product	Time (min)	Yield[b] (%)
1	 **1a**	 **3a**	30	90
2	 **1b**	 **3b**	40	86
3	 **1c**	 **3c**	30	92
4	 **1d**	 **3d**	35	84

5	 1e	 3e	25	91
6	 1f	 3f	25	93
7	 1g	 3g	30	89
8	 1h	 3h	30	88
9	 1i	 3i	40	85
10	 1j	 3j	30	90

11	 1k	 3k	30	92
12	 1l	 3l	35	87
13	 1m	 3m	40	82
14	 1n	 3n	40	84
15	 1o	 3o	40	86
16	 1p	 3p	50	85

17	 1q	 3q	90	83
18	 1r	 3r	45	86
19	 1s	 3s	45	82

[a]Reaction conditions: chalcone **1** (1.0 mmol), benzamidine hydrochloride **2** (1.0 mmol) and ChOH (3.0 mL) at 60 ℃ temperature, [b]Isolated yields.

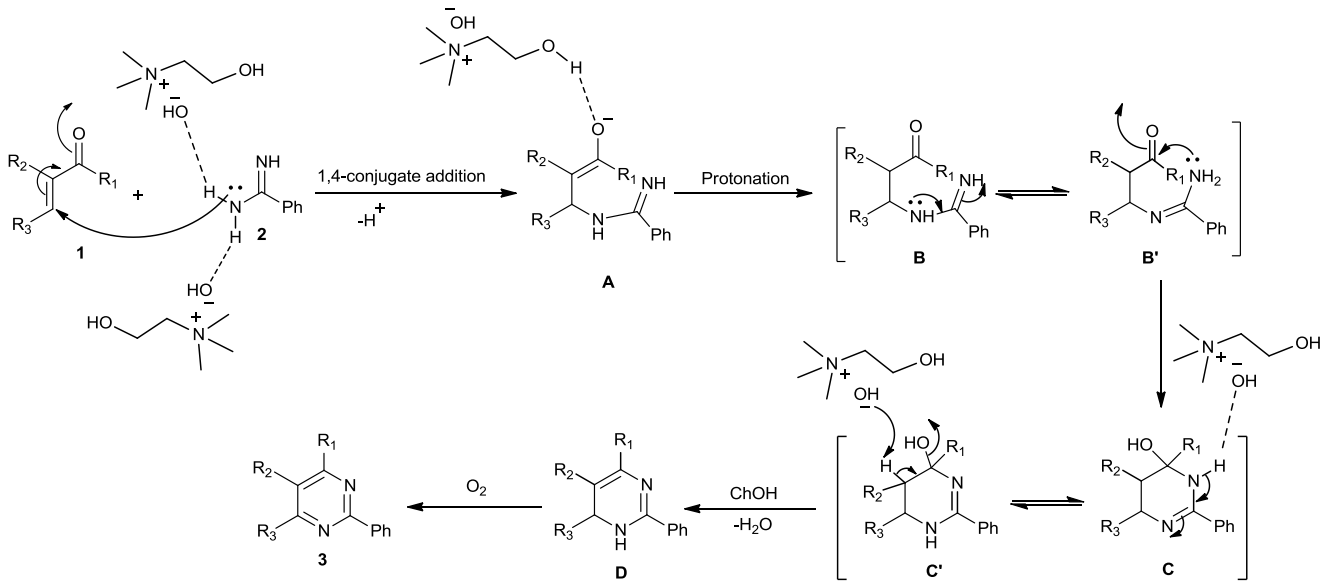
Recyclability of choline hydroxide (ChOH):

For large-scale operations, recovery and reuse of the DES is essential. In this context, the reaction between 1,3-diphenyl-2-en-1-one (**1a**) and benzamidine hydrochloride (**2**) was examined under optimized reaction conditions. After completion, the reaction mass was filtered to obtain crude solid product which was washed with water. DES was recovered by evaporation of water under vacuum from the filtrate. The recovered DES was reused for the next run. As summarized in Table 3, DES can be recycled and reused up to four times without significant loss in activity.

Table 3. Recyclability studies of DES for the synthesis of pyrimidine **3a**

Entry	Number of runs	Yield[b] (%)
1	Fresh, non recycled	90
2	First	89
3	Second	88
4	Third	88
5	Fourth	87

[a]Reaction conditions: chalcone **1a** (1.0 mmol), benzamidine hydrochloride **2** (1.0 mmol) and ChOH (3.0 mL) at 60 ℃ temperature, [b]Isolated yields.



Scheme 2. Plausible reaction mechanism for synthesis of substituted pyrimidines using DES as catalyst

A plausible mechanism for the pyrimidine ring formation is depicted in Scheme 2. Initially, conjugate addition of benzamidine to the α,β-unsaturated ketone forms intermediate **A** (enolate) which is stabilized by hydrogen bonding. This intermediate on tautomerization generates an imine **B** which is in equilibrium with its tautomer **B'**. An 1,2-intramolecular addition produces cyclic tertiary alcohol **C** which is in equilibrium with its tautomer **C'.** Intermediate **C'** undergoes dehydration to produce dihydropyrimidine **D**. **D** get aromatized in presence of molecular oxygen to form substituted pyrimidine.

Conclusion

We have developed a simple, practical, environmentally friendly and economically viable procedure for the synthesis of pyrimidine derivatives from readily available chalcones and benzamidine hydrochloride using choline hydroxide (ChOH). This green protocol offered good to excellent yield of the product ranging from 82-93%. Further use of these substituted pyrimidines in the synthesis of D-A type molecules for optoelectronic applications is currently underway in our laboratory.

Experimental section

Materials and Equipments

Chemical reagents were obtained from commercial companies. All reactions were done in a round bottom flask and monitored by TLC performed on aluminum plates (0.25 mm, E. Merck) precoated with silica gel (Merck 60 F-254). Developed TLC plates were visualized under a short-wavelength UV lamp. Reactions were conducted under open air atmosphere in solvents such as toluene, DCM, DCE, THF, 1,4-dioxan, acetonitrile, EtOH and water. Yields refer to spectroscopically (^{1}H, ^{13}C NMR) homogeneous material obtained after column chromatography, was performed on silica gel (100–200 mesh size) supplied by S. D. Fine Chemicals Limited, India. ^{1}H and ^{13}C NMR were recorded in $CDCl_3$ and DMSO-d_6 solution with a Brüker 400, Agilent 300 and 500 MHz spectrometers. Chemical shifts (δ) are quoted in ppm, relative to $SiMe_4$ (δ = 0.0) as an internal standard. The number of protons (*n*) for a given resonance is indicated by *n*H. Peak multiplicities are designated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublet; *J*, coupling constant in Hz. High-resolution mass spectra were obtained by using positive electrospray ionization (ESI) by Time of Flight (TOF) method. Melting points were recorded on a standard melting point apparatus from Sunder Industrial Product, Mumbai and uncorrected.

General Procedure for the Synthesis of choline hydroxide:

Choline chloride (1 mmol) and KOH (1 mmol) were dissolved in methanol at room temperature. This mixture was heated at 61 ^{o}C for 12 h with constant stirring. After cooling to room temperature, the reaction mixture was filtered to remove solid KCl and solution was obtained. This solution was concentrated under vacuum to remove methanol and used without further purification.

General Procedure for the Synthesis of substituted pyrimidines:

A round bottom flask was charged with the substituted chalcone **1** (1.0 mmol), benzamidine hydrochloride **2** (1.0 mmol) and choline hydroxide (3 mL). The mixture was heated to 60 ℃ for appropriate time. After completion of reaction, cold water (10 mL) was added to the reaction mixture. The precipitated crude solid product was filtered off and it was purified by silica gel

column chromatography (100–200 mesh) using *n*-hexane: Et_2O (95:05) as eluent to afford the corresponding pyrimidine **3**.

Product Characterization

2,4,6-Triphenylpyrimidine (3a). White solid; mp 184-186 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ = 7.52-7.59 (m, 9H), 8.03 (s, 1H), 8.29-8.31 (m, 4H), 8.73-8.75 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 110.38, 127.29, 127.37, 128.54, 129.00, 130.73, 130.86, 137.61, 138.23, 164.58, 164.82; **HRMS** (ESI-MS): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{17}N_2$: 309.1391; found: 309.1398.

2,4-Diphenyl-6-(*p*-tolyl)pyrimidine (3b). White solid; mp 150-152 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.46 (s, 3H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.55 (m, 6H), 7.99 (s, 1H), 8.21 (d, *J* = 8.0 Hz, 2H), 8.29 (d, *J* = 6.4 Hz, 2H), 8.74 (d, *J* = 6.8 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 21.58, 110.02, 127.26, 127.35, 128.51, 128.54, 128.97, 129.72, 130.65, 130.77, 134.78, 137.72, 138.32, 141.23, 164.49, 164.67, 164.74; **HRMS** (ESI-MS): *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{19}N_2$: 323.1548; found: 323.1559.

4-(4-Fluorophenyl)-2,6-diphenylpyrimidine (3c). White solid; mp 168-170 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.22-7.27 (m, 2H), 7.55 (d, *J* = 7.6 Hz, 6H), 7.96 (s, 1H), 8.28-8.32 (m, 4H), 8.71 (d, *J* = 5.6 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 109.96, 115.91, 116.12, 127.34, 128.52, 128.55, 129.01, 129.33, 129.42, 130.80, 130.93, 133.70, 137.49, 138.08, 163.47, 164.58, 164.92; **HRMS** (ESI-MS): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{16}FN_2$: 327.1297; found: 327.1303.

4-(2-Chlorophenyl)-2,6-diphenylpyrimidine (3d). White solid; mp 120-122 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.45-7.55 (m, 9H), 7.85 (d, *J* = 5.6 Hz, 1H), 8.03 (s, 1H), 8.28 (d, *J* = 4.4 Hz, 2H), 8.67 (d, *J* = 4.4 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 115.24, 127.31, 127.45, 128.55, 129.02, 130.57, 130.75, 130.78, 130.97, 131.77, 132.50, 137.33, 137.63, 138.01, 163.95, 164.70, 164.76; **HRMS** (ESI-MS): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{16}ClN_2$: 343.1002; found: 343.1005.

4-(4-Chlorophenyl)-2,6-diphenylpyrimidine (3e). White solid; mp 166-168 °C; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.51-7.55 (m, 8H), 7.95 (s, 1H), 8.22-8.28 (m, 4H), 8.71 (d, *J* = 5.2 Hz, 2H);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 110.01, 127.35, 128.53, 128.56, 128.62, 129.02, 129.21, 130.84, 130.98, 135.99, 137.04, 137.40, 138.02, 163.53, 164.61, 165.00; **HRMS** (ESI-MS): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{16}ClN_2$: 343.1002; found: 343.1009.

4-(4-Bromophenyl)-2,6-diphenylpyrimidine (3f). White solid; mp 168-170 ℃; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.54-7.55 (m, 6H), 7.68 (d, *J* = 8.4 Hz, 2H) 7.94 (s, 1H), 8.15 (d, *J* = 8.4 Hz, 2H), 8.27 (t, *J* = 3.2, 4.0 Hz, 2H), 8.70 (t, *J* = 2.0, 5.2 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 109.98, 125.49, 127.36, 128.53, 128.56, 128.85, 129.02, 130.85, 130.99, 132.17, 136.44, 137.38, 138.00, 163.60, 164.62, 165.02; **HRMS** (ESI-MS): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{16}BrN_2$: 387.0497; found: 387.0504.

4-(3-Chlorophenyl)-2,6-diphenylpyrimidine (3g). White solid; mp 146-148 ℃; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.47-7.56 (m, 8H), 7.97 (s, 1H), 8.15 (d, *J* = 6.4 Hz, 1H), 8.29 (s, 3H), 8.72 (d, *J* = 6.0 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 110.34, 125.41, 127.38, 127.49, 128.56, 128.58, 129.04, 130.23, 130.78, 130.89, 131.04, 135.16, 137.32, 137.93, 139.43, 163.38, 164.69, 165.12; **HRMS** (ESI-MS): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{16}ClN_2$: 343.1002; found: 343.1005.

4-(3-Chlorophenyl)-6-(4-fluorophenyl)-2-phenylpyrimidine (3h). White solid; mp 166-168 ℃; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.22-7.26 (m, 2H), 7.49-7.55 (m, 5H), 7.91 (s, 1H), 8.13 (d, *J* = 6.8 Hz, 1H), 8.27-8.31 (m, 3H), 8.69 (t, *J* = 2.8, 4.8 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 109.92, 115.97, 116.18, 125.40, 127.47, 128.53, 128.59, 129.37, 129.46, 130.25, 130.86, 130.97, 133.44, 135.18, 137.79, 139.30, 163.47, 163.97, 164.69; **HRMS** (ESI-MS): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{15}ClFN_2$: 361.0908; found: 361.0917.

4-(2-Chlorophenyl)-6-(3-chlorophenyl)-2-phenylpyrimidine (3i). White solid; mp 142-144 ℃; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.44-7.54 (m, 8H), 7.85 (t, *J* = 2.4, 6.0 Hz, 1H), 7.99 (s, 1H), 8.12 (d, *J* = 6.8 Hz, 1H), 8.29 (s, 1H), 8.66 (d, *J* = 4.0 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 115.26, 125.50, 127.36, 127.58, 128.56, 128.62, 130.27, 130.61, 130.91, 130.97, 131.77, 132.48, 135.22, 137.38, 137.72, 139.16, 162.52, 164.83, 165.09; **HRMS** (ESI-MS): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{15}Cl_2N_2$: 377.0612; found: 377.0621.

4-(3-Chlorophenyl)-6-(4-chlorophenyl)-2-phenylpyrimidine (3j). White solid; mp 140-142 ℃; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.50-7.53 (m, 7H), 7.87 (s, 1H), 8.10-8.24 (m, 4H), 8.67 (s, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 109.93, 125.39, 127.45, 128.53, 128.61, 129.24, 130.23, 130.90, 131.01, 135.18, 135.67, 137.25, 137.71, 139.18, 163.51, 163.79, 164.69; **HRMS** (ESI-MS): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{15}Cl_2N_2$: 377.0612; found: 377.0623.

4-(4-Bromophenyl)-6-(3-chlorophenyl)-2-phenylpyrimidine (3k). White solid; mp 130-132 ℃; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.49-7.55 (m, 5H), 7.68 (d, *J* = 8.4 Hz, 2H) 7.91 (s, 1H), 8.12-8.16 (m, 3H), 8.26 (s, 1H), 8.68 (t, *J* = 3.2, 4.4 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 109.97, 125.41, 125.72, 127.48, 128.54, 128.61, 128.86, 130.26, 130.92, 131.03, 132.24, 135.20, 136.17, 137.71, 139.21, 163.62, 163.94, 164.77; **HRMS** (ESI-MS): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{15}BrClN_2$: 421.0107; found: 421.0104.

4-(4-Fluorophenyl)-2-phenyl-6-(*p*-tolyl)pyrimidine (3l). White solid; mp 150-152 ℃; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.46 (s, 3H), 7.24 (distorted t, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 7.6 Hz, 2H), 7.54 (m, 3H), 7.92 (s, 1H), 8.19 (d, *J* = 7.6 Hz, 2H), 8.27-8.31 (distorted q, *J* = 1.6, 6.0 Hz, 2H), 8.71 (d, *J* = 6.0 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 21.57, 109.58, 115.86, 116.08, 127.24, 128.51, 129.30, 129.39, 129.73, 130.72, 133.79, 134.65, 138.18, 141.32, 163.36, 164.48, 164.81; **HRMS** (ESI-MS): *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{18}FN_2$: 341.1454; found: 341.1458.

4-(2-Chlorophenyl)-2-phenyl-6-(*p*-tolyl)pyrimidine (3m). White solid; mp 124-126 ℃; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.46 (s, 3H), 7.36 (d, *J* = 7.6 Hz, 2H), 7.43-7.56 (m, 6H), 7.85 (t, *J* = 2.0, 6.8 Hz, 1H), 7.99 (s, 1H), 8.19 (d, *J* = 8.0 Hz, 2H), 8.68 (t, *J* = 1.6, 5.2 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 21.59, 114.89, 127.29, 127.36, 128.53, 129.76, 130.56, 130.68, 130.71, 131.76, 132.50, 134.52, 137.73, 138.12, 141.37, 163.90, 164.61; **HRMS** (ESI-MS): *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{18}ClN_2$: 357.1158; found: 357.1152.

4-(4-Chlorophenyl)-2-phenyl-6-(*p*-tolyl)pyrimidine (3n). White solid; mp 166-168 ℃; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.46 (s, 3H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.53 (m, 5H), 7.93 (s, 1H), 8.20 (dd, *J* = 8.0, 8.4 Hz, 4H), 8.70 (d, *J* = 6.0 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 21.58, 109.66, 127.25, 128.51, 128.53, 128.61, 129.18, 129.74, 130.76, 134.58, 136.10, 136.94, 138.12,

141.38, 163.40, 164.54, 164.92; **HRMS** (ESI-MS): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{18}ClN_2$: 357.1158; found: 357.1159.

4-(4-Bromophenyl)-2-phenyl-6-(*p*-tolyl)pyrimidine (3o). White solid; mp 174-176 ℃; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.46 (s, 3H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.54 (m, 3H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.93 (s, 1H), 8.17 (m, 4H), 8.70 (t, *J* = 2.0, 5.6 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 21.59, 109.62, 125.38, 127.25, 128.52, 128.84, 129.74, 130.77, 132.14, 134.56, 136.56, 138.10, 141.39, 163.46, 164.55, 164.94; **HRMS** (ESI-MS): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{18}BrN_2$: 401.0653; found: 401.0652.

4-Methyl-2-phenyl-5*H*-chromeno[4,3-*d*]pyrimidin-5-one (3p). Yellow solid; mp 254-256 ℃; **^{1}H NMR** (300 MHz, DMSO-d_6): δ = 2.30 (s, 3H), 6.68 (t, *J* = 7.5, 7.2 Hz, 1H), 6.80 (d, *J* = 7.8 Hz, 1H), 6.92 (d, *J* = 6.9 Hz, 1H), 7.00 (t, *J* = 7.2, 6.9 Hz, 1H), 7.49-7.59 (m, 3H), 8.08 (d, *J* = 6.9 Hz, 2H); **^{13}C NMR** (75 MHz, DMSO-d_6): δ = 24.73, 115.34, 119.09, 120.72, 125.44, 127.08, 127.64, 128.66, 128.82, 131.44, 132.42, 153.91, 155.14, 164.18; **HRMS** (ESI-MS): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{13}N_2O_2$: 289.0977; found: 289.0991.

4-Methyl-2-phenyl-6-(2,6,6-trimethylcyclohex-1-en-1-yl)pyrimidine (3q). White solid; mp 74-76 ℃; **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.08 (s, 6H), 1.43 (s, 3H), 1.57-1.61 (m, 2H), 1.75-1.83 (m, 2H), 2.10 (t, *J* = 6.6, 6.0 Hz, 2H), 2.58 (s, 3H), 6.83 (s, 1H), 7.44-7.48 (m, 3H), 8.44-8.49 (m, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 19.27, 21.29, 24.45, 28.93, 32.00, 34.35, 39.47, 120.18, 128.47, 128.49, 128.75, 130.31, 131.21, 138.50, 139.28, 163.98, 166.10, 168.79; **HRMS** (ESI-MS): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{25}N_2$: 293.2017; found: 293.2068.

4,6-Dimethyl-2-phenylpyrimidine (3r). White solid; mp 82-84 ℃; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.51 (s, 6H), 6.89 (s, 1H), 7.42-7.47 (m, 3H), 8.40-8.43 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 24.06, 117.85, 128.12, 128.34, 130.16, 138.05, 164.08, 166.65; **HRMS** (ESI-MS): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{13}N_2$: 185.1079; found: 185.1093.

4-Isopropyl-6-methyl-2-phenylpyrimidine (3s). White solid; mp 102-104 ℃; **^{1}H NMR** (400 MHz, $CDCl_3$), δ 1.33 (d, *J* = 6.8 Hz, 6H), 2.54 (s, 3H), 2.96-3.03 (m, 1H), 6.90 (s, 1H), 7.45 (m,

3H), 8.46 (d, J = 7.2 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 21.73, 24.26, 35.82, 115.22, 128.16, 128.28, 130.07, 138.29, 163.79, 166.83, 175.22; **HRMS** (ESI-MS): m/z $[M + H]^+$ calcd for $C_{14}H_{17}N_2$: 213.1392; found: 213.1398.

Author Contributions

[a]These authors contributed equally to this work.

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