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CuO Nanocatalyzed Improved Synthesis of Some 2-Aminopyrimidines

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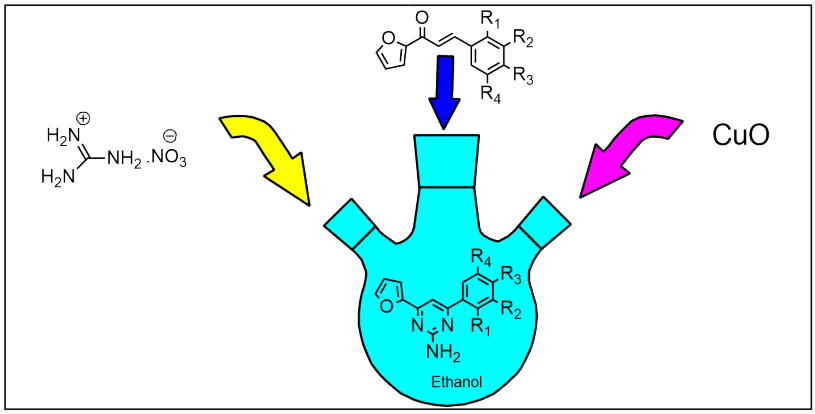
An effective and simple method for the synthesis of substituted 2- aminopyrimidines has been developed using chalcones, guanidine nitrate and aqueous sodium hydroxide in the presence of CuO nanoparticle as catalyst. The developed strategy has various advantages such as short reaction time, improved yields and the catalyst used is recyclable and inexpensive.

Graphical abstract



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1. Introduction

Heterocyclic compounds are found in nature abundantly and are of great importance to life due to their structural scaffolds that exist in various natural products such as hormones, antibiotics and vitamins [1, 2] and they are widely used to design biologically active compounds. Pyrimidines are heterocyclic compounds which have nitrogen atom at positions first and third of six membered ring. Pyrimidines are found in many bioactive natural products. The pyrimidine skeleton is a key nucleus in DNA and RNA and associated with various biological and pharmaceutical activities such as anthelmintic [3], cell inhibitor [4], anti-cancer [5], antimicrobial [6], anti-fungal [7], anti-leishmanial [8], etc. The property of aminopyrimidine derivatives to inhibit the protein kinase makes it an important class in organic synthesis [9, 10]. Substituted aminopyrimidine nuclei are one of the commonly marketed drugs. The synthesis of 2-aminopyrimidines and its derivatives through various methods are reported [11, 12].

Chalcone, which is commonly known as α,β-unsaturated carbonyl compounds occupy a special place in organic and medicinal chemistry. Chalcones are abundantly found in edible plants and are assumed to be the pioneer of flavonoids and isoflavanoids. Chalcones are coloured compounds due to the presence of auxochrome and chromophore. Chalcones act as an excellent precursor for the synthesis of various heterocycles. Compounds having chalcone skeleton possess numerous ranges of biological activities [13-17].

Nowadays, nanocatalyst is used more frequently than the conventional catalyst because of their unique properties such as reactive morphologies, high-surface area and recyclability [18-21]. Copper nanocatalysts have gained much attention among metal nanocatalysts due to their unfamiliar properties and potential applications in various fields. CuO has been

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used as catalyst to catalyze carbon-carbon and carbon-heteroatom bond formation [22]. We, herein report a simple procedure for the synthesis of substituted 2-aminopyrimidines using chalcones, guanidine nitrate and aqueous sodium hydroxide in the presence of CuO nanoparticles as nanocatalyst.

2. Results and Discussion

Initially the desired chalcones (**3a-j**) were synthesized by the Claisen-Schmidt condensation of 2-acetylfuran and substituted benzaldehydes in the presence of aq. KOH (Scheme 1). CuO nanocatalyst was synthesized by using the reported method [23]. The synthesized CuO catalyst was characterized by FESEM and XRD techniques. (Figure 1 and 2) The XRD analysis shows that the sample consists pure phase of CuO, i.e., monoclinic crystal system. The dimension of the crystallite sites is estimated using full width half max (FWHM) of the most intense peak which is (111) by using Scherrer formula.

$D = K\lambda/\beta \cos\theta$

$\beta = 0.0050$ radian, $\theta = 17.872$, $\cos\theta = 0.9517$

D is crystallite size, K is shape factor, which is 0.9, λ is wavelength of the X-ray source 0.14nm, β is FWHM of the intense peak in radian unit and θ is angle.

The model reaction of chalcone (**3a-j**), guanidine nitrate (**4**) and aqueous sodium hydroxide was refluxed for 6 hours in the presence of CuO nanocatalyst in ethanol afforded title product in good yields (Scheme 2). To check the effective participation of CuO nanocatalyst during this chemical transformation, the same reaction was performed without using the catalyst and observed that the reaction time was much longer (16 hrs) compared to the reaction carried out with catalyst. The concentration of the catalyst was studied with different concentrations from 5 to 20 mol% of its amount. At 15 mol%, maximum amount of the product was obtained. Therefore, 15 mol% was assumed to be the optimum catalyst concentration (Table 1).

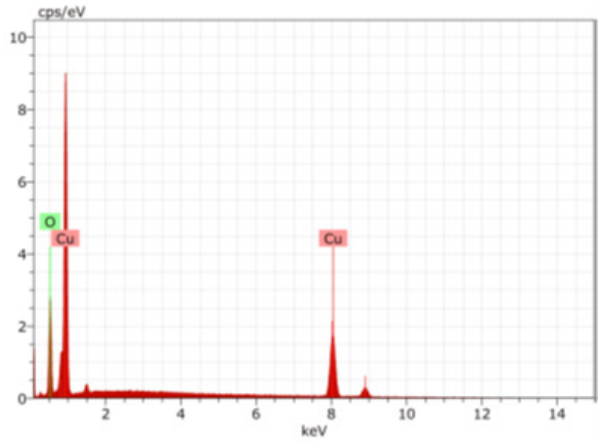


Fig. 1. FESEM of CuO catalyst.

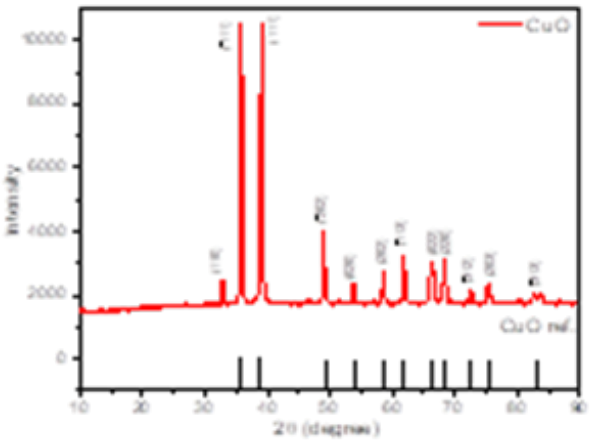
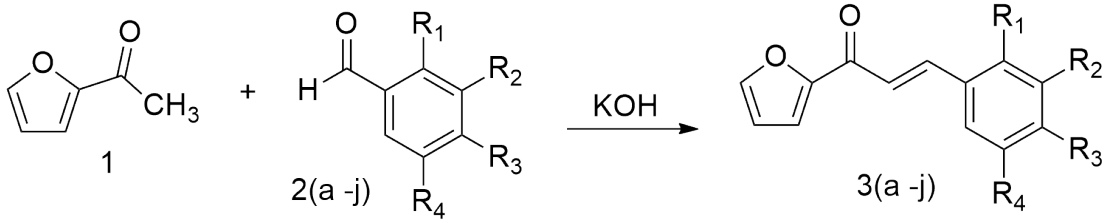
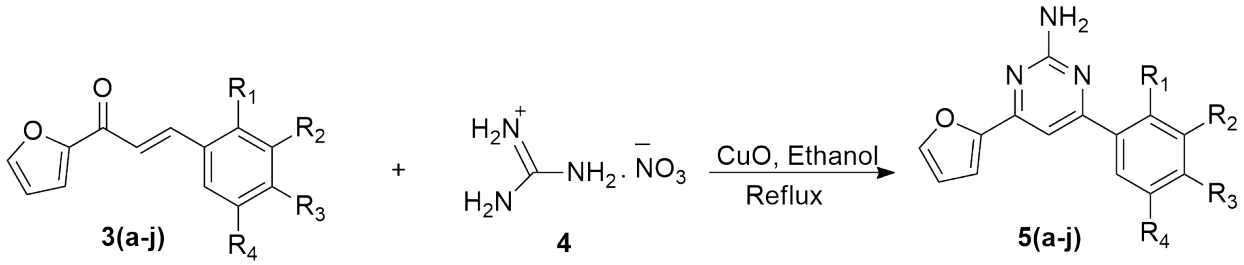


Fig. 2. XRD pattern of the synthesizes CuO catalyst. Average crystallite size = 29.12 nm.



Scheme 1. Synthesis of substituted (2*E*)-1-(2-furyl)-3-phenylprop-2-en-1-one (**3a-j**).



3a, 5a: R_1, R_2, R_4 = H, R_3= Br
3b, 5b: R_1, R_2, R_4 = H, R_3= $N(CH_3)_2$
3c, 5c: R_1, R_2, R_4 = H, R_3= $C(F)_3$
3d, 5d: R_1, R_2, R_4 = H, R_3= F
3e, 5e: R_1, R_2, R_4 = H, R_3= Cl
3f, 5f: R_1, R_2, R_4 =H, -N-R_3
3g, 5g: R_1, R_2, R_3, R_4 = H
3h, 5h: R_1= H, R_2, R_3, R_4 = OCH_3
3i, 5i: R_1 = OH, R_2, R_3 = H, R_4 =Br
3j, 5j: R_1, R_2, R_4= H, R_3= CH_3

Scheme 2. Synthesis of 2-aminopyrimidines (**5a-j**).

Table 1. Effect of amount of CuO catalyst for the synthesis of 2-aminopyrimidines[a].

Entry	CuO mol %	Yield (%)
1	5	33
2	10	60
3	15	87
4	20	87

[a]Reaction conditions: chalcone (0.001 mol), guanidine nitrate (0.001 mol) and CuO (15 mol%) in ethanol (10 mL) reflux for 6 h.

The most advantage of the CuO catalyst is its recyclability. In this study, we have found that the catalyst used can be regained by filtrating the reaction mixture and reused it for the three successive runs without any remarkable loss of action for a similar reaction (Figure 3).

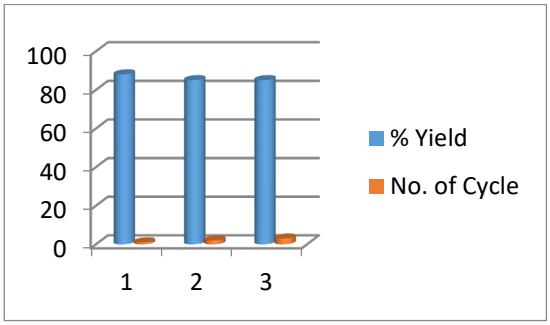


Fig. 3. Recyclability of the catalyst.

3. Material and Methods

Chemicals brought from the Sigma-Aldrich and Merck were used without further purification. ^{1}H and ^{13}C NMR spectra were recorded (DMSO-d_6) with 500MHz and 100 MHz respectively on spectrometer Bruker Avance NEO. The value of chemical shifts are represented in δ units (ppm) relative to TMS (δ = 0.00). Melting points (◦C) were taken in capillaries using a Veego (VMP-MP) melting point apparatus and are uncorrected. The purity of the titled products were recorded by thin layer chromatography (TLC) using silica gel.

Procedure for the synthesis of substituted (2E)-1-(2-furyl)-3-phenylprop-2-en-1-one (3a-j):

Equimolar quantities of 2-furylacetophenone (0.01mL) and substituted aryl aldehydes (0.01 mL) were added in ethanol (30mL) and stirred at room temperature. With continuous stirring, aqueous solution of potassium hydroxide (15 mL, 40%) was added to the reaction mixture. The reaction mixture was kept overnight and poured onto ice water and acidified with dilute HCl. The solid obtained was filtered off and recrystallized from ethanol to give chalcones (**3a-j**).

Procedure for the synthesis of substituted 2-aminopyrimidines (5a-j):

The starting chalcones (**3a-j**) were synthesized by Claisen-Schmidt condensation [24]. The substituted chalcones (0.001 mol), guanidine nitrate (0.001 mol) and CuO (15 mol%) in ethanol (10 mL) was taken in a 100 mL round bottomed flask. Aqueous sodium hydroxide solution (40%, 2 mL) was added and refluxed. After 3 hours, further instalments of sodium hydroxide (3x 2 mL) were added to the refluxing solution under continuous stirring. The formation of the product was monitored by TLC using benzene: ethylacetate (9:1v/v) as eluent. The reaction mixture was allowed to cool at room temperature and filtered to separate the catalyst. After separation of the catalyst, the reaction mixture was poured onto ice water and the solid obtained was recrystallized to afford the title products (**5a-j**).

Analysis data

3a. (2*E*)-3-(4-bromophenyl)-1-(2-furyl)prop-2-en-1-one: Yield: 92%; Cream; m.p. 103-105◦C; ^{1}H NMR (500 MHz DMSO-d_6): δ 7.82-7.64 (d, 4H, Ar-Br), 7.57 (d, β H, J=15.58), 7.54-7.17 (d, 2H, -OC_4H_3), 7.05 (d, α H, J=15.58), 6.50 (dd, 1H, -OC_4H_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 111.38, 114.64, 123.89, 131.58, 132.81, 134.98, 144.94, 146.90, 152.73, 177.49. MS: m/z 277.01 (M+), Calcd. for $C_{13}H_9BrO_2$.

3b. (2*E*)-3-[4-(dimethylamino)phenyl]-1-(2-furyl)prop-2-en-1-one: Yield: 89%; Orange; m.p. 95-97◦C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.57 (d, β H, J=15.58), 7.54-7.17 (d, 2H, -OC_4H_3), 7.41-6.69 (d, 4H, Ar-H$(CH_3)_2$), 7.05 (d, α H, J=15.58), 6.50 (dd, 1H, -OC_4H_3), 2.97 (s, 2H, Ar-N$(CH_3)_2$); ^{13}C NMR (100 MHz, DMSO-d_6): δ 39.96, 111.38, 112.02, 114.64, 123.89, 126.53, 132.18, 144.94, 146.90, 152.73 177.49. MS: m/z 266.11 (M+), Calcd. for $C_{15}H_{15}NO_2$.

3c. (2*E*)-1-(2-furyl)-3-[4-(trifluoromethyl)phenyl]prop-2-en-1-one: Yield: 88%; Brown; m.p. 98-100◦C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.88-7.80 (d, 4H, Ar-C$(F)_3$), 7.57 (d, β H, J=15.58), 7.54-7.17 (d, 2H, -OC_4H_3), 7.05 (d, α H, J=15.58), 6.50 (dd, 1H, -OC_4H_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 111.38, 113.68, 123.89, 126.26, 129.83, 131.24, 136.08, 144.94, 146.90, 152.73, 177.49. MS: m/z 241.18 (M+), Calcd. for $C_{14}H_9F_3O_2$.

3d. (2*E*)-3-(4-fluorophenyl)-1-(2-furyl)prop-2-en-1-one: Yield: 84%; Cream; m.p. 127-129◦C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.57 (d, β H, J=15.58), 7.54-7.17 (d, 2H, -OC_4H_3), 7.33 (d, 4H, Ar-F), 7.05 (d, α H, J=15.58), 6.50 (dd, 1H, -OC_4H_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 111.38, 114.64, 116.86, 123.89, 131.86, 144.94, 146.90, 152.73, 177.49. MS: m/z 216.10 (M+), Calcd. for $C_{13}H_9FO_2$.

3e. (2*E*)-3-(4-chlorophenyl)-1-(2-furyl)prop-2-en-1-one: Yield: 90%; Cream; m.p. 117-120◦C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.61-7.47 (d, 4H, Ar-Cl), 7.57 (d, β H, J=15.57), 7.54-7.17 (d, 2H, -OC_4H_3), 7.05 (d, α H, J=15.57), 6.50 (dd, 1H, -OC_4H_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 111.38, 114.64, 123.89, 131.11, 134.61, 144.94, 146.90, 152.73, 177.49. MS: m/z 232.56 (M+), Calcd. for $C_{13}H_9ClO_2$.

3f. (2E)-1-(2-furyl)-3-pyridin-4-ylprop-2-en-1-one: Yield: 91%; Brown; m.p. 100-102◦C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.81-7.43 (d, 4H, Ar-N), 8.04 (d, β H, J=15.57), 7.54-7.17 (d, 2H, -OC_4H_3), 7.05 (d, α H, J=15.57), 6.50 (dd, 1H, -OC_4H_3),); ^{13}C NMR (100 MHz, DMSO-d_6): δ 111.38,114.64, 122.18, 123.89, 143.81, 146.90, 149.00, 152.73, 177.49. MS: m/z 199.10 (M+), Calcd. for $C_{12}H_9NO_2$.

3g. (2*E*)-1-(2-furyl)-3-phenylprop-2-en-1-one: Yield: 89%; Cream; m.p. 75-77 ◦C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.62 (d, 2H, Ar), 7.57 (d, β H, J=15.58), 7.54-7.17 (d, 2H, -OC_4H_3), 7.51 (dd, 3H, Ar), 7.05 (d, α H, J=15.58), 6.50 (dd, 1H, -OC_4H_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 111.38, 114.64, 123.81, 127.18, 129.66, 134.94, 144.94, 146.90, 153.73, 177.49. MS: m/z 198.11 (M+), Calcd. for $C_{13}H_{10}O_2$.

3h. (2*E*)-1-(2-furyl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one: Yield: 87%; Yellow solid; m.p. 102-104◦C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.07 (d, β H, J=15.58), 7.61-7.20 (d, 2H, -OC_4H_3), 7.69 (d, α H, J=15.58), 6.81 (s, 2H, Ar-$(OCH_3)_3$), 6.80 (dd, 1H, -OC_4H_3), 3.87-3.72 (s, 3H, -$(OCH_3)_3$; ^{13}C NMR (100 MHz, DMSO-d_6): δ 56. 20, 60.75, 107.79, 111.38, 114.64, 123.89, 131.69, 140.06, 149.90, 152.73, 177.49. MS: m/z

288.19 (M+), Calcd. for $C_{16}H_{16}O_5$.

3i. (2*E*)-3-(5-bromo-2-hydroxyphenyl)-1-(2-furyl)prop-2-en-1-one: Yield: 90%; Brown; m.p. 133-135 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.16 (d, β H, J=15.58), 7.66 (s, 1H, -OH), 7.55 (s, 1H, Ar-2-OH, 5-Br), 7.54-7.17 (d, 2H, -OC_4H_3), 7.31-6.97 (d, 2H, Ar-2-OH, 5-Br), 7.18 (d, α H, J=15.58), 6.50 (dd, 1H, -OC_4H_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 111.38, 114.64, 118.35, 123.35, 131.05, 144.82, 149.90, 152.73, 177.49. MS: m/z 293.01 (M+), Calcd. for $C_{13}H_9BrO_3$.

3j. (2*E*)-1-(2-furyl)-3-(4-methylphenyl)prop-2-en-1-one: Yield: 86%; Brown; m.p. 99-101 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.57 (d, β H, J=15.57), 7.54-7.17 (d, 2H, -OC_4H_3), 7.46-7.22 (d, 4H, Ar-CH_3), 7.05 (d, α H, J=15.57), 6.50 (dd, 1H, -OC_4H_3), 2.35 (s, 1H, -CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.35, 111.38, 114.64, 123.89, 130.11, 138.81, 144.94, 149.90, 152.73, 177.49. MS: m/z 277.21 (M+), Calcd. for $C_{14}H_{12}O_2$.

5a. 4-(4-bromophenyl)-6-(2-furyl)pyrimidin-2-amine: Yield: 85%; Brown solid; m.p. 165-167^{0}C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.99- 7.58 (d, 4H, Ar-Br), 7.16-6.90 (d, 2H, -OC_4H_3), 6.92 (s, 1H, -C=C-), 6.20 (dd, 1H, -OC_4H_3), 5.40 (s, 1H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ 104.97, 115.64, 123.04, 130.93, 132.86, 136.51, 143.40, 151.30, 163.49, 165.00, 180.39 ppm. MS: m/z 316.15 (M+), Calcd. for $C_{14}H_{10}BrN_3O$.

5b. 4-[4-(dimethylamino)phenyl]-6-(2-furyl)pyrimidin-2-amine: Yield: 87%; Red solid; m.p. 98-100^{0}C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.03-7.58 (d, 4H, Ar-N(CH_3)$_2$), 7.16-6.90 (d, 2H, -OC_4H_3), 6.87 (s, 1H, -C=C-), 6.20 (dd, 1H, -OC_4H_3), 5.40 (s, 1H, NH_2), 3.15 (s, 2H, (-CH_3)$_2$); ^{13}C NMR (100 MHz, DMSO-d_6): δ 40.70, 103.74, 105.00, 109.56, 115.64, 131.36, 143.40, 150.59, 158.93, 165.00, 180.39 ppm. MS: m/z 280.32 (M+), Calcd. for $C_{16}H_{16}N_4O$.

5c. 4-(2-furyl)-6-[4-(trifluoromethyl)phenyl]pyrimidin-2-amine: Yield: 89%; Brown solid; m.p. 140-142 ^{0}C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.09-7.63 (d, 4H, Ar-C(F)$_3$), 7.16-6.90 (d, 2H, -OC_4H_3), 6.93 (s, 1H, -C=C-), 6.20 (dd, 1H, -OC_4H_3), 5.40 (s, 1H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ 105.00, 113.43, 120.56, 125.64, 129.09, 134.83, 137.16, 143.40, 151.30, 162.79, 165.00, 180.39 ppm. MS: m/z 305.25 (M+), Calcd. for $C_{15}H_{10}F_3N_3O$.

5d. 4-(4-fluorophenyl)-6-(2-furyl)pyrimidin-2-amine: Yield: 85%; Cream solid; m.p. 130-132 ^{0}C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.20-7.27 (d, 4H, Ar-F), 7.16-6.90 (d, 2H, -OC_4H_3), 6.89 (s, 1H, -C=C-), 6.20 (dd, 1H, -OC_4H_3), 5.40 (s, 1H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ 103.97, 105.00, 113.76, 115.64, 133.09, 143.40, 151.30, 160.36, 165.00, 180.39 ppm. MS: m/z 255.24 (M+), Calcd. for $C_{14}H_{10}FN_3O$.

5e. 4-(4-chlorophenyl)-6-(2-furyl)pyrimidin-2-amine: Yield: 82%; Brown solid; m.p. 140-142^{0}C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.99-7.56 (d, 4H, Ar-Cl), 7.16-6.90 (d, 2H, -OC_4H_3), 6.82 (s, 1H, -C=C-), 6.20 (dd, 1H, -OC_4H_3), 5.40 (s, 1H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ 105.00, 115.64, 120.60, 129.71, 132.71, 143.40, 151.30, 161.54, 165.00, 180.39 ppm. MS: m/z 271.70 (M+), Calcd. for $C_{14}H_{10}ClN_3O$.

5f. 4-(2-furyl)-6-pyridin-4-ylpyrimidin-2-amine: Yield: 80%; Cream solid; m.p. 115-117^{0}C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.65-7.92 (d, 4H, Ar-(N)-), 7.16-6.90 (d, 2H, -OC_4H_3), 7.00 (s, 1H, -C=C-), 6.20 (dd, 1H, -OC_4H_3), 5.40 (s, 1H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ 105.00, 115.64, 125.09, 139.13, 143.40, 148.50, 151.30, 160.60, 166.62, 180.02 ppm. MS: m/z 238.24 (M+), Calcd. for $C_{13}H_{10}N_4O$.

5g. 4-(2-furyl)-6-phenylpyrimidin-2-amine: Yield: 83%; Cream solid; m.p. 110-112^{0}C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.77 (d, 2H, Ar), 7.66-7.58 (dd, 3H, Ar), 7.16-6.90 (d, 2H, -OC_4H_3), 6.87 (s, 1H, -C=C-), 6.20 (dd, 1H, -OC_4H_3), 5.40 (s, 1H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ 105.00, 115.64, 125.28, 130.15, 133.35, 143.40, 151.30, 161.51, 165.00, 180.39 ppm. MS: m/z 237.25 (M+), Calcd. for $C_{14}H_{11}N_3O$.

5h. 4-(2-furyl)-6-(3,4,5-trimethoxyphenyl)pyrimidin-2-amine: Yield: 88%; Brown solid; m.p. 123-125 ^{0}C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.46-6.71 (d, 2H, -OC_4H_3), 6.72 (s, 2H, Ar-(OCH_3)$_3$), 6.76 (s, 1H, -C=C-), 6.71 (dd, 1H, -OC_4H_3), 5.40 (s, 1H, NH_2), 3.89-3.73 (s, 3H, Ar-(OCH_3)$_3$); ^{13}C NMR (100 MHz, DMSO-d_6): δ 55.95, 60.02, 99.77, 104.11, 111.55, 90, 112.30, 132.51, 139.52, 145.10, 151.97, 152.92, 156.33, 163.59, 164.23, 180.16 ppm. MS: m/z 327.33 (M+), Calcd. for $C_{17}H_{17}N_3O_4$.

5i. 2-[2-amino-6-(2-furyl)pyrimidin-4-yl]-4-bromophenol: Yield: 87%; Brown solid; m.p. 150-152^{0}C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.87 (s, 1H, Ar-OH), 7.63 (s, 1H, Ar-OH), 7.63 (s, 1H, NH_2), 7.37-6.89 (d, 2H, Ar-OH), 7.16-6.90 (d, 2H, -OC_4H_3), 6.84 (s, 1H, -C=C-), 6.20 (dd, 1H, -OC_4H_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 101.09, 105.00, 114.87, 117.75, 132.80, 138.90, 143.90, 151.30, 158.29, 161.15, 166.27, 181.66 ppm. MS: m/z 332.15 (M+), Calcd. for $C_{14}H_{10}BrN_3O_2$.

5j. 4-(2-furyl)-6-(4-methylphenyl)pyrimidin-2-amine: Yield: 88%; Brown solid; m.p. 120-122 ^{0}C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.14-7.38 (d, 4H, Ar-CH_3), 7.16-6.90 (d, 2H, -OC_4H_3), 6.85 (s, 1H, -C=C-), 6.20 (dd, 1H, -OC_4H_3), 5.40 (s, 1H, NH_2), 2.44 (s, 1H, -CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ21.43, 105.00, 115.64, 120.97, 128.33, 139.47, 143.40, 151.30, 160.78, 165.00, 180.39 ppm. MS: m/z 251.28 (M+), Calcd. for $C_{15}H_{13}N_3O$.

4. Conclusions

The synthesis of pyrimidines is an active area of research and new protocols are often developed due to numerous biological activities linked to pyrimidines. Hence, we have developed an effective catalytic method for the preparation of substituted 2-aminopyrimidines in relatively short reaction time with improved yields using chalcones, guanidine nitrate and aqueous sodium hydroxide in the presence of catalytic amount of CuO nanocatalyst, which is recyclable, non-toxic and inexpensive.

Author Contributions

A.P.D. and K.L.A. designed and performed the research, analyzed the results and wrote the manuscript.

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