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Synthesis, characterization and application of $ZnFe_2O_4$ nanoparticles as a heterogeneous ditopic catalyst for the synthesis of pyrano[2,3-*d*] pyrimidines†

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In the present work, $ZnFe_2O_4$ nanopowder, as a highly efficient and heterogeneous catalyst, was prepared and fully characterized by IR, UV, XRD, EDX and SEM analysis. The nanocatalyst was employed as a highly stable and reusable catalyst for the synthesis of pyrano[2,3-*d*]pyrimidines by the one-pot three-component condensation reaction of 1,3-dimethylbarbituric acid and malononitrile with aromatic aldehydes under solvent-free conditions. $ZnFe_2O_4$ nanoparticles with Lewis acidic properties (by the Fe^{3+} of Fe_2O_3) and basic character (related to the O^{2-} of ZnO), can catalyze this reaction. This procedure has some advantages, such as efficiency, generality, high yield, short reaction time, cleaner reaction profiles, ease of product isolation and simplicity.

Introduction

Multi-component reactions are efficient and powerful procedures for the rapid synthesis of highly selective products containing portions of all inputs in a single reaction vessel. MCRs are a notable synthetic methodology and they enable simple and fast achievement of large ranges of organic compounds.

Recently, pyran and substituted 4*H*-pyrans have attracted wide notices. They perform the major construction blocks of several natural products and form the core of noteworthy compounds are displaying broad biological activities such as antimicrobial,[1] antiviral[2] activities and antiproliferation agents.[3]

Because of the broad range of biological activity, pyrano[2,3-*d*]pyrimidine derivatives have received substantial consideration over the last decade. These cyclic systems have various pharmacological activities including hepatoprotactive,[4] antitumour,[5] antihypertensive,[5] cardiotonic[6] and antifungal activities.[7] Therefore, for the preparation of the important compounds large assays have been occurred. The syntheses of 2-amino-4*H*-pyran derivatives have been carried out in the presence of *N*-methyl-imidazole,[8] 4-(dimethylamino) pyridine (DMAP),[9] tetrabutyl-ammonium fluoride (TBAF),[10] 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU),[11] triethyl amine and ultrasonic-irradiation,[12] PEG-Ni NPs[13] and microwave.[14] However, some of the reported methods have some disadvantages such as low yield, long reaction time, toxic and corrosive solvent, high reaction temperature and using of expensive and large amount of catalysts. Due to the importance of these compounds, it is important to find a milder, faster and more eco-friendly procedure with higher yields for the preparation of pyrano[2,3-*d*]pyrimidines.

Mixed metal oxide nanoparticles (MMONs) have attracted much attention in the recent years and the improvements of modern organic synthesis are followed.[15–18] Simple synthesis conditions, cheap and economically efficient, high surface area heterogeneous catalyst, insolubility in reaction solvents and easy separation are some advantages of these catalysts. Remarkably, because of high catalytic activity of MMONs, they are preferable than individual component oxides in diverse reactions.[19,20] Considering above facts and as a part of our research programs to develop mild and greener methodologies involving these mixed nanoparticle,[21] we have reported here, the application of $ZnFe_2O_4$ nanoparticles for the synthesis of pyrano[2,3-*d*]pyrimidines.

Moreover, limited catalytic applications of heterogeneous ditopic $ZnFe_2O_4$ have been reported so far. It has been a as catalyst in the synthesis of 4*H*-pyrans and 1,4-DHPs[22] and *O*-acylation of alcohol and phenol.[23]

Herein, it has been applied $ZnFe_2O_4$ nanoparticles as an efficient and heterogeneous catalyst for the synthesis of pyrano[2,3-*d*]-pyrimidines by the one-pot three-component condensation reaction of 1,3-dimethylbarbituric acid and malononitrile with aromatic aldehydes at 75 °C under solvent-free conditions (Scheme 1).

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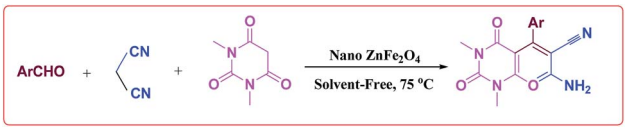


Scheme 1 The synthesis of pyrano[2,3-*d*]pyrimidines.

Results and discussion

In continuation of previous investigations on the synthesis of pyrano[2,3-*d*]pyrimidines,[8–12] $ZnFe_2O_4$ nanoparticles has been reported as an efficient heterogeneous catalyst. According to previous literatures in the synthesis of pyrano[2,3-*d*]pyrimidines, acid–base ditopic catalysts are more effective than acidic[24,25] or basic catalysts lonely.[9,12] Mixed metal oxides show suitable activity and selectivity toward individual oxides. Also, mixing of a metal oxide with another metal oxide improves chemical properties and performances of the catalyst. For example, modifying of iron oxide by zinc oxide cause to produce spinel zinc ferrite ($ZnFe_2O_4$) with acidic and basic characters. The basic part catalyzed Knoevenagel condensation and other steps such as addition, cyclization and dehydration proceed by acidic part of the catalyst. The Lewis acidic behavior of $ZnFe_2O_4$ is derived by the Fe^{3+} of Fe_2O_3 and its basic character is related to the O^{2-} of ZnO.

According to the previous literature, $ZnFe_2O_4$ nanoparticles have been prepared from the reaction of $ZnCl_2$ and $FeCl_3 \cdot 6H_2O$[26] and characterized by FTIR and solid state UV spectroscopy, XRD, EDS and SEM analysis.

IR spectrum of $ZnFe_2O_4$ nanoparticles has been indicated in Fig. 1. Due to interaction between oxygen and cations in tetrahedral and octahedral positions, three vibrational frequencies were exhibited in spinel structure of zinc ferrites ($\nu_1 = 666$, $\nu_1 = 544$, $\nu_1 = 453$ cm^{-1}). The high frequency bands 666 and 544 cm^{-1} corresponds to vibrations of the metal at the tetrahedral site (tetrahedral Zn^{2+} stretching), and the low frequency band 453 cm^{-1} is related to Fe^{3+} vibration frequencies in octahedral groups.

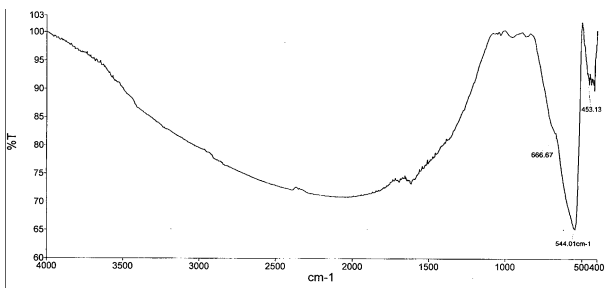


Fig. 1 FT-IR spectrum of $ZnFe_2O_4$ nanoparticles.

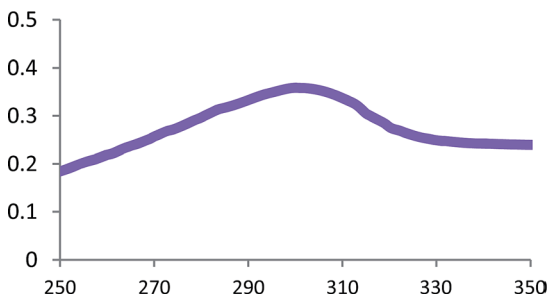


Fig. 2 UV spectrum of $ZnFe_2O_4$ nanoparticles.

In another study, to examine the optical properties of nanoparticles, UV-vis diffuse reflectance of $ZnFe_2O_4$ nanoparticles was carried out (Fig. 2) at room temperature. It could be seen that the intensity of absorbance of nanoparticles increased in the range of 250–310 nm and showed a steep absorption edge.

The X-ray diffraction (XRD) pattern of nanocatalyst was examined in a domain of 5–90° (Fig. 3).[27] As shown at Fig. 3, XRD pattern displayed diffraction lines of a high crystalline nature at $2\theta \approx 30.00°$, 35.50°, 43.00°, 53.50°, 57.10°, 62.5°, and several small lines in the 15–90° range.

Scanning electron microscopy (SEM) and energy dispersive X-ray spectroscopy (EDX), are the best known and most widely-used of the surface analytical techniques. The elemental

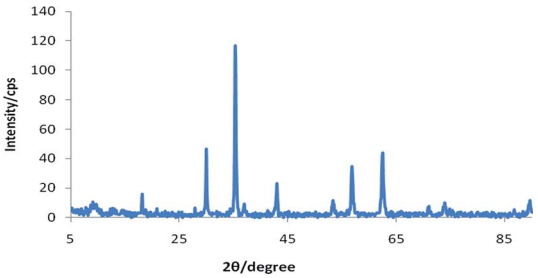


Fig. 3 XRD pattern of $ZnFe_2O_4$ nanoparticles.

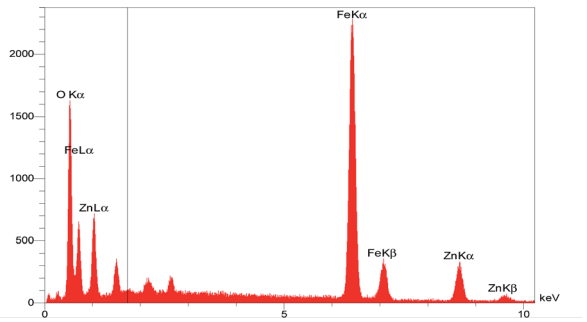


Fig. 4 EDX analysis of $ZnFe_2O_4$ nanoparticles.

Table 1 The atomic abundance of elements measured in $ZnFe_2O_4$ nanoparticles

Elements	Atomic abundance (%)
Zn	26.85
Fe	46.76
O	26.39

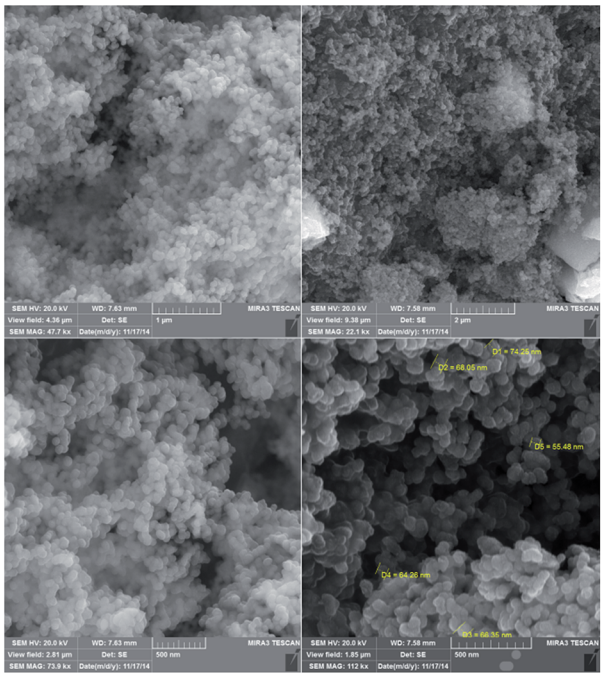


Fig. 5 SEM images for ZnFe nanoparticles with different magnifications.

analysis of $ZnFe_2O_4$ nanoparticles is recorded by Energy dispersive X-ray (EDX) on the surface of solid.

The results of the EDX measurement of $ZnFe_2O_4$ nano particles are approved the existence of Zn, Fe and O atoms (Fig. 4).

The actual chemical composition of the nanoparticles and the abundance of the elements were specified using the ICP-OES (inductively coupled plasma optical emission spectroscopy) method (Yvon-Jobin, France). The relative atomic abundance of Zn, Fe and O species is displayed in Table 1.

Scanning electron microscopy (SEM) of $ZnFe_2O_4$ nanoparticle with different magnifications is shown in Fig. 5. As it is shown in Fig. 5, the spherical structure with only one type of particle morphology, has almost particle of 55–74 nm in size.

In another step, catalytic activity of $ZnFe_2O_4$ nanoparticles as an efficient and heterogeneous catalyst was investigated in the synthesis of pyrano[2,3-*d*]pyrimidines by the one-pot, three-component condensation of 1,3-dimethylbarbituric acid and malononitrile with various aromatic aldehydes (Scheme 1).

To optimize the reaction conditions, the reaction of 1,3-dimethylbarbituric acid (1 mmol), benzaldehyde (1 mmol) and malononitrile (1.2 mmol) was selected as a model reaction, and tested in the presence of several nano-magnetic catalysts such as Fe_3O_4, $ZnFe_2O_4$ and $Ni_{0.5}Zn_{0.5}$ Fe_2O_4 under thermal solvent-free conditions. The results are summarized in Table 2.

As it is shown in Table 2, indicates that nano-magnetic $ZnFe_2O_4$ is the most effective catalyst among other magnetic nanoparticles. Therefore, $ZnFe_2O_4$ was selected as a catalyst for this reaction and continued optimal conditions. It was observed that higher yield and shorter reaction time were achieved using 5 mol% of catalyst at 75 °C under solvent-free conditions. No improvement in the reaction results was observed by increasing the value of the catalyst and the temperature.

After optimization of the reaction conditions, to show the performance and the aim of the presented protocol, 1,3-dimethylbarbituric acid (1 mmol) and malononitrile (1.2 mmol) were treated with different arylaldehydes (1 mmol) in the presence of $ZnFe_2O_4$ as a catalyst. In continues, the effect of electron-releasing, electron-withdrawing and halogens groups in different positions on the aromatic ring of aldehydes in the synthesis of pyrano[2,3-*d*]pyrimidines were studied and illustrated in Table 3.

Aldehydes bearing electron-releasing groups increased the reaction times but no outstanding effect on the yields. Consequently, this protocol gives the desired products in good yields and in relatively short reaction times.

In the proposed mechanism, complex **I** produces by the reaction of aldehyde with nanocatalyst (Scheme 2). In next step, by the Knoevenagel reaction of intermediate **I** and malonitrile, intermediate **II** is generated. This intermediate as a Michael

Table 2 Optimization of kinds of catalyst, the quantity of nanoparticles and the reaction temperature for the preparation of 7-amino-5-phenyl-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1*H*-pyrano[2,3-*d*]pyrimidine-6-carbonitrile

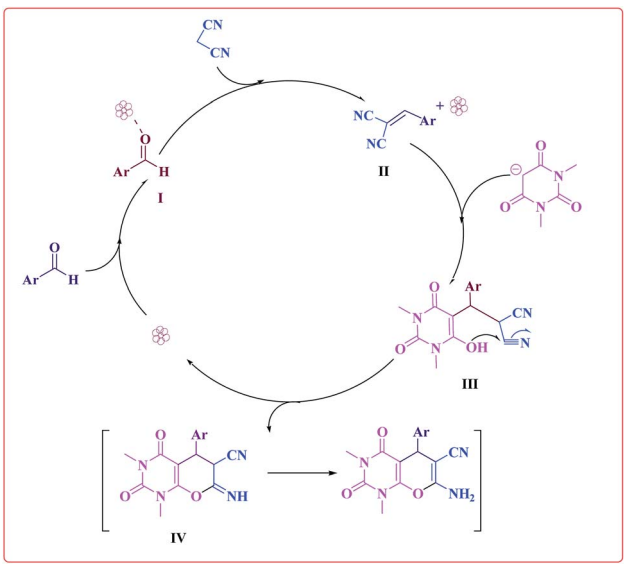
Entry	Catalyst	Catalyst (mol%)	Temp (°C)	Time (min)	Yield[a] (%)
1	Fe_3O_4	5	75	30	91
2	$Ni_{0.5}Zn_{0.5}Fe_2O_4$	5	75	25	93
3	ZnO	5	75	13	94
4	$ZnFe_2O_4$	5	75	10	96
5	$ZnFe_2O_4$	2	75	35	86
6	$ZnFe_2O_4$	3	75	30	90
7	$ZnFe_2O_4$	4	75	22	93
8	$ZnFe_2O_4$	6	75	10	96
9	$ZnFe_2O_4$	5	90	10	96
10	$ZnFe_2O_4$	5	80	10	96
11	$ZnFe_2O_4$	5	70	18	93
12	$ZnFe_2O_4$	5	60	40	90
13	$ZnFe_2O_4$	5	50	45	89

[a] Isolated yield.

Table 3 The synthesis of pyrano[2,3-*d*]pyrimidines using $ZnFe_2O_4$ at 75 °C

Entry	Ar	Time (min)	Yield[a] (%)	M.p. °C (Lit.)
1	C_6H_5	10	96	218–220(210)[28]
2	3-$NO_2C_6H_4$	12	91	204
3	4-$NO_2C_6H_4$	12	92	217–219(212)[13]
4	2-ClC_6H_4	12	87	243–244(238–239)[12]
5	3-ClC_6H_4	15	90	247–248
6	4-ClC_6H_4	20	90	206(206–208)[29]
7	2,3-$DiClC_6H_3$	7	92	238
8	2,4-$DiClC_6H_3$	12	93	211–212
9	4-Cl-3-$NO_2C_6H_4$	7	94	209–210
10	2-FC_6H_4	12	91	238–239
11	3-FC_6H_4	15	89	228–229
12	4-FC_6H_4	15	89	227–228(230–232)[12]
13	2-BrC_6H_4	22	89	237–238
14	3-BrC_6H_5	18	90	209(217–218)[12]
15	4-BrC_6H_5	12	92	235(235–237)[30]
16	2-Naphtyl	20	92	218–219(218)[13]
17	4-MeC_6H_4	30	89	217–218(221–223)[31]
18	2-$MeOC_6H_5$	25	86	209–210
19	4-$MeOC_6H_5$	25	87	226–227(225–227)[32]

[a] Isolated yield.



Scheme 2 The plausible mechanism for the synthesis of pyrano[2,3-*d*]-pyrimidines using of $ZnFe_2O_4$.

accepter reacts with barbituric acid in enolate form, to give **III** after tautomerization.

The intramolecular cyclization of intermediate **III**, produces intermediate **IV** and subsequently, from another tautomerization, the product is prepared.

Conclusions

In conclusion, an efficient and applicable procedure for the synthesis of pyrano[2,3-*d*]pyrimidines by the one-pot three-component condensation reaction of 1,3-dimethylbarbituric acid, malononitrile and aromatic aldehydes using heterogeneous $ZnFe_2O_4$ nanoparticles at 75 °C under solvent-free conditions was reported. The catalyst was synthesized and fully characterized by IR, UV, XRD, EDX and SEM analysis. The advantages of the presented method are simplicity, efficiency, generality, high yield, short reaction time, cleaner reaction profiles and easy work-up.[33–35]

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32 F. Seeliger and S. Berger, *J. Org. Chem.*, 2007, **72**, 9170–9180.
33 *Procedure for the synthesis of spinel $ZnFe_2O_4$ nanopowder:* a solution of $FeCl_3 \cdot 6H_2O$ (0.2 mol L^{-1}, 200 mL) was added into a stirring round bottomed flask (50 mL) containing a solution of $ZnCl_2$ (0.1 mol L^{-1}, 100 mL). After the addition was completed, the reaction mixture was neutralized by sodium hydroxide solution (1.5 mol L^{-1}). The reaction temperature was kept at 85 °C for 45 min under stirring. After this time, the pH of the reaction was adjusted on 12. The precipitates were washed with distilled water until the particles were free from sodium and chloride ions. The product was dried in an electric oven at a temperature of 800 °C for 3 h to remove water contents.[27]
34 *General procedure for the synthesis of pyrano[2,3-d] pyrimidines:* to a mixture of 1,3-dimethylbarbituric acid (1 mmol), malononitrile (1.2 mmol) and aromatic aldehyde (1 mmol) in a test tube $ZnFe_2O_4$ nanoparticles (0.0125 g, 5 mol%) was added and the resulting mixture was stirred in an oil-bath at 75 °C for the appropriate time. After completion of the reaction, as monitored by TLC, ethanol was added and the mixture stirred for 5 min. The magnetic $ZnFe_2O_4$ nanoparticles were separated from the products using an external magnet and then washed twice with acetonitril, dried in a desiccator and stored for another subsequent reaction runs (the catalyst reused seven times in subsequent reaction without any significant changes in the yield and reaction times). The solid product was filtered, washed with acetone and dried. The pure products (compounds 1–19) were identified by IR, ^{1}H, ^{13}CNMR and mass spectra.
35 *7-Amino-5-(3-chlorophenyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano [2,3-d] pyrimidine-6-carbonitrile*, white solid; M.p: 247–248 °C; IR (KBr, cm^{-1}) υ_{max} = 3395, 3312, 3192, 2194, 1707, 1689, 1641, 1488, 1389, 1232, 1190, 1036, 750, 570; ^{1}HNMR (400 MHz, DMSO-d_6): δ = 3.03 (s, 3H, NMe), 3.38 (s, 3H, NMe), 4.83 (s, 1H, CH), 7.21–7.34 (m, 6H, Ar–H and NH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 29.2, 30.7, 35.1, 58.7, 89.6, 120.1, 129.1, 130, 130.8, 131.80, 133.8, 142.7, 151.6, 153.1, 159.3, 161.9 ppm; MS: m/z = 345 (M^+), *7-Amino-5-(2,3-dichlorophenyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano [2,3-d] pyrimidine-6-carbonitrile*, white solid; M.p: 238 °C; IR (KBr, cm^{-1}) υ_{max} = 3406, 3317, 3198, 2929, 2194, 1707, 1692, 1639, 1489, 1387, 1230, 1185, 1045, 752; ^{1}HNMR (400 MHz, DMSO-d_6): δ = 3.07 (s, 3H, NMe), 3.40 (s, 3H, NMe), 4.92 (s, 1H, CH), 7.25–7.47 (m, 5H, Ar–H and NH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 29.2, 30.7, 58.2, 89.4, 120, 129.9, 130.4, 130.5, 131.9, 133.1, 151.5, 153.1, 159.4, 161.9 ppm; MS: m/z = 378 (M^+)*7-Amino-5-(3-fluorophenyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano [2,3-d] pyrimidine-6-carbonitrile*, white solid; M.p: 228–229 °C; IR (KBr, cm^{-1}) υ_{max} = 3381, 3309, 3191, 2199, 1708, 1691, 1640, 1493, 1387, 1232, 1191, 1037, 850, 751, 572; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.06 (s, 3H, NMe), 3.42 (s, 3H, NMe), 4.33 (s, 1H, CH), 7.09–7.35 (m, 6H, Ar–H and NH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 29.2, 30.7, 37.4, 60, 90.2, 116.4, 116.6, 120.5, 130.8, 130.9, 135.1, 141.9, 151.5, 152.6, 159.1, 161.4, 162.0 ppm; MS: m/z = 328 (M^+)7-*Amino-5-(2-fluorophenyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano [2,3-d] pyrimidine-6-carbonitrile*, white solid; M, 2196 white solid; M.p: 238–239 °C; IR (KBr, cm^{-1}) υ_{max} = 3390, 3312, 3194, 2196, 1705, 1687, 1641, 1490, 1390, 1235, 1192, 1039, 969, 760, 572; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.04 (s, 3H, NMe), 3.39 (s, 3H, NMe), 4.59 (s, 1H, CH), 7.10–7.36 (m, 6H, Ar–H and NH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 29.2, 30.7, 32, 58.7, 89.2, 116.7, 117, 120.4, 126.0, 130.4, 131.4, 132.2, 132.3, 151.5, 153, 159.5, 160.4, 161.9, 162.8 ppm; MS: m/z = 328 (M^+)7-*Amino-5-(4-chloro-3-nitrophenyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano [2,3-d] pyrimidine-6-carbonitrile*, white solid; M.p: 209–210 °C; IR (KBr, cm^{-1}) υ_{max} = 3395, 3316, 3198, 2201, 1716, 1690, 1639, 1489, 1392, 1231, 1186, 1047, 969, 752, 505; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.04 (s, 3H, NMe), 3.40 (s, 3H, NMe), 4.49 (s, 1H, CH), 7.47–7.95 (m, 5H, NH_2, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 29.2,30.7, 37.4, 58.7, 88.8, 120.2, 124.5, 125.7, 132.8, 134.6, 147.0, 149.3, 151.6, 153.1, 159.2, 162.1 ppm; MS: m/z = 389 (M^+)*7-Amino-5-(2-bromophenyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano [2,3-d] pyrimidine-6-carbonitrile,* white solid; M, 2194 white solid; M.p: 237–238 °C; IR (KBr, cm^{-1}) υ_{max} = 3396, 3311, 3190, 2194, 1709, 1687, 1641, 1488, 1389, 1232, 1189, 1026, 969, 749, 567; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.04 (s, 3H, NMe), 3.34 (s, 3H, NMe), 4.85 (s, 1H, CH), 7.13–7.53 (m, 6H, NH_2, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 29.2, 30.7, 37.4, 58.9, 89.8, 120, 124.4, 129.7, 130.2, 131.8, 134, 144.4, 151.6, 153, 159.2, 161.9 ppm; MS: m/z = 389 (M^+)*7-Amino-5-(2-methoxyphenyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano [2,3-d] pyrimidine-6-carbonitrile,* white solid and mp 209–210 °C, 2190 white solid; mp 209–210 °C; IR (KBr, cm^{-1}) υ_{max} = 3483, 3311, 3172, 2962, 2190, 1715, 1680, 1642, 1489, 1382, 1229, 1188, 1020, 753, 568; ^{1}H NMR (400 MHz, DMSO-d_6): δ =3.04 (s, 3H, NMe), 3.38 (s, 3H, NMe), 3.72 (s, 3H, CH_3), 4.61 (s, 1H, CH), 6.82–7.16 (m, 6H, NH_2, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 29.2, 30.6, 32.7, 57.2, 59.3, 89.8, 113.1, 120.7, 122, 129.6, 130.2, 133.2, 151.6, 153.1, 158.5, 159.8, 161.9 ppm; MS: m/z = 340 (M^+).