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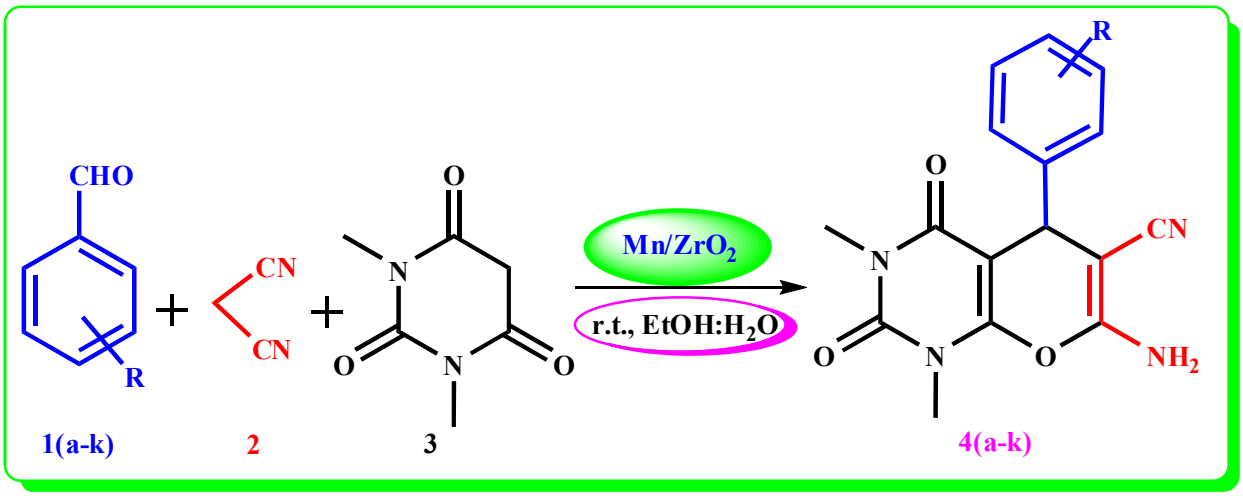
Surya Narayana Maddila, Suresh Maddila, Werner E. van Zyl*, Sreekantha B. Jonnalagadda*

**School of Chemistry & Physics, University of KwaZulu-Natal, Westville Campus, Chiltern Hills, Durban-4000, South Africa.*

Graphical Abstract:



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COMMUNICATION

Mn doped ZrO_2 as a green, efficient and reusable heterogeneous catalyst for the multicomponent synthesis of pyrano[2,3-d]-pyrimidine derivatives

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A simple and an efficient method has been developed for the one-pot multicomponent synthesis of pyrano[2,3-d]-pyrimidine derivatives. This was achieved through the condensation reaction between dimethylbarbituric acid, aromatic aldehyde and malononitrile in the presence of a Mn/ZrO_2 heterogeneous catalyst with ethanol/water mixture as solvent over only 1 hour. Further advantages to this synthesis methodology include excellent yields, mild reaction conditions, atom economy, environment friendly, reusable catalyst and no need for chromatographic separations.

Multicomponent reactions (MCRs) have emerged as an exciting field of research where three or more reactants are all added together in a single-step to afford pure products in high yield. MCRs are mostly used in organic synthesis, biological discovery, combinatorial library and agrochemical synthesis.[1-4] The simple protocols, inexpensive reactants and green principles involved make MCRs and attractive field of study.4 Well planned MCRs afford higher chemical yields than multiple-step syntheses, resulting in conservation of energy and manpower and are often complete in relatively short reaction times[5] making it an environmentally benign and elegant process.[1,6,7]

The use of heterogeneous catalysts with recyclability and reusability potential add value to the one-pot reactions involving MCRs.[8] The use of heterogeneous catalysts has gained prominence in the field of heterocyclic synthesis because of simple work-up, cost effectiveness, mild reaction conditions, atom economy, good activity, easy recyclability and scope to modify the surface properties.[9,10] Heterogeneous materials are used as green reaction media due to their distinct chemical and physical properties such as non-volatility, thermal stability, non-inflammability, controlled miscibility[10] and playing a vital role as catalysts in the MCRs. Metal oxides are good contenders in this regard as they have a proven track record as catalysts and supports. Thermal calcination of such materials at 773 K, lead to the formation of acidic/basic mixed metallic oxides with moderate surface-area and can act as catalysts for various condensation reactions.

Zirconia (ZrO_2) is an interesting support material where a particular zirconia phase (cubic, tetragonal etc.) can be stabilized down to room temperature by the amount of dopant added and this can promote the activity of the supported metal catalysts. ZrO_2 has good redox and chemical stability and is an acid–based bi-functional catalyst, which is stable in alkaline or acidic solutions.[11] ZrO_2 in combination with metals (cermets) have been used in organic synthesis[12] and manganese has previously been used as dopant in zirconia. The crystalline structure of ZrO_2 is one of the key factors affecting the structure-activity relationships of Mn-based catalysts.[13] The Mn/ZrO_2 solid material possesses both Bronsted and Lewis acids centers.

Pyranes and pyrimidine derivatives are an important class of heterocyclic compounds that feature in a number of pharmaceutical drugs and natural products of medicinal interest. This class of compounds exhibit a range of sought after features including antimicrobial,[14] antioxidant,[15] anti-tumor,[16] antimalarial,[17] antimetabolite,[17] antileishmanial,[18] antiviral,[19] antihypertensive,[20] anti-convulsant,[21] and anti-inflammatory activities.[22] The computational chemistry of many of pyrimidine derivatives has also been documented.[23]

Literature search shows several described methods for synthesis of various pyrano[2,3-*d*]pyrimidine derivatives. Such protocols employed $[Ch\text{-}OSO_3H]_3W_{12}PO_{40}$,[24] diammoniunhydrogenphosphate[25] microwave irradiation,[26,27] DABCO,[28] electrolysis,[29,30] γ-Fe_2O_3@HAp-$Si(CH_2)_3SO_3H$,[31] L-proline,[32] $NaHCO_3$[33] and urea[34] etc. as catalysts. In general terms, many of these approaches face few or more of the limitations such as using toxic reagents, strong acidic or basic conditions, costly reagents and catalysts, strict reaction conditions, tedious steps, and low product yields or long reaction times, which limit their use in practical applications. Thus, researchers are compelled to find new and improved approaches for environmental friendly synthesis of these heterocyclic molecules with impressive yields. The best of our knowledge there are no reports on the multicomponent facile one-pot synthesis of pyrano[2,3-*d*]pyrimidine derivatives and with EtOH/water mixture as solvent system. In this manuscript we report the synthesis of pyrano[2,3-*d*]-pyrimidine derivatives by using Mn/ZrO_2 as a catalyst in the presence of equal ratio of EtOH:water for the first time. We report a novel protocol for the synthesis of those derivatives using an inexpensive and robust catalyst which accomplishes the reactions in short reaction times.

Reactions were carried out during preliminary investigations to screen for various catalysts and under catalyst-free conditions and varying solvents. Reactions with 1,3-dimethylbarbituric acid (1

mmol), substituted aldehyde (1 mmol) and malononitrile (1.1 mmol) and water or ethanol as solvent and no catalyst showed no reaction at RT even after 12 h under reflux conditions, (Table 1, entries 1-4). To obtain the most efficient catalytic conditions, the title reaction was investigated in the presence of different catalyst materials such as alumina, silica, $MnCl_2$, and $ZnCl_2$ and in the presence of EtOH and water (50:50 v/v). The obtained results are summarized in (Table 1, entries 5-8) and indicate that the reaction did not occur in the presence of alumina or silica, and the yield obtained was very low with $MnCl_2$ or $ZnCl_2$. Further, we tested the scope of reaction in the presence of ionic liquids such as L-proline, (Bmim)BF_4 and (Bmim)OH, but yields were low (Table 1, entry 9-11).

The reactions were also investigated using 30 mg of CuO, MnO_2, ZrO_2, as catalysts under room temperature conditions in 1:1 ethanol/water mixture. The CuO, MnO_2 and ZrO_2 gave yields of 42%, 53% and 48%, respectively (Table 1 entry 12-14). The reaction was repeated under similar conditions using Mn/ZrO_2 which gave an excellent yield of 90% in 1 h once optimum dopant percentage had been established. The impact of Mn loading on zirconia in tuning its catalytic efficiency was further investigated. To find the ideal loading of Mn on ZrO_2 on catalyst activity, reactions with 1%, 2% and 5% Mn doped ZrO_2 were carried out under otherwise comparable conditions. The percentage of Mn loading was found to have an influence on the reaction yield as well as reaction time (Table 1, entries 15-17). Using 1% Mn/ZrO_2 catalyst yielded 76% product in 3 h under EtOH/water mixture solvent conditions (Table 1, entry 15). A 2.5% Mn loading was found optimal with 90 % yield in 1 h (Table 1, entry 16). A further increase of metal (5%) loading led to a slight decreased yield (88%) (Table 1, entry 17).

In an effort to find the optimal reaction conditions, the reaction was carried out using various amounts of catalyst at RT. It was found that 30 mg catalyst gave a maximum yield of 90% in 1 h. Using more than 30 mg of catalyst for the reaction had no significant improvement on the yield or the reaction time. However, the decrease in amount of the catalyst to 20 and 10 mg, decreased the product yield to 89%, 87%, 73% and 67%, respectively (Table 1, entries 18-21).

An interrogation of the experimental results and the effect of various polar and non-polar solvents on the three component reaction clearly indicate that the EtOH/water solvent system plays a vital role in facilitating the reaction (Table 1), comparatively less polar solvents like CH_3CN, DMF afforded poor yields (Table 1, entries 22,23). The protic polar (ethanol, water) solvents on their own failed to produce the anticipated high yield (Table 1, entry 24, 25) but interestingly, the miscible mixture of EtOH:H_2O (50:50 v/v) gave a high 90% yield. This effect can be explained by a simple acid-base bi-functional catalysis mechanism facilitated by the strong hydrogen bond interaction at the organic–aqueous ethanol interface which stabilizes the reaction intermediate. A highly-polar solvent which dissipates heat faster possibly provide optimum conditions for the formation of intermediates, and their conversion to final products on the catalyst surface.

Table 1. Optimization of reaction conditions of the three-component synthesis.[a]

Entry	Catalyst	Solvent	Condition	Time (h)	Yield (%)[b]
1	No catalyst	H_2O	R.T	24	--
2	No catalyst	EtOH	R.T	24	--
3	No catalyst	H_2O	Reflux	12	Trace
4	No catalyst	EtOH	Reflux	12	Trace
5	Al_2O_3	EtOH:H_2O	R.T	10	--
6	SiO_2	EtOH:H_2O	R.T	10	--
7	$MnCl_2$	EtOH:H_2O	R.T	5	28
8	$ZnCl_2$	EtOH:H_2O	R.T	8	18
9	L-proline	EtOH:H_2O	Reflux	3	48
10	(Bmim)BF_4	EtOH:H_2O	Reflux	4	44
11	Bmim)OH	EtOH:H_2O	Reflux	3.5	51
12	CuO (30 mg)	EtOH:H_2O	R.T	6	42
13	MnO (30 mg)	EtOH:H_2O	R.T	3.5	53
14	ZrO_2 (30 mg)	EtOH:H_2O	R.T	4	48
15	1% Mn/ZrO_2 (30 mg)	EtOH:H_2O	R.T	3	76
16	2.5% Mn/ZrO_2 (30 mg)	EtOH:H_2O	R.T	1	90
17	5% Mn/ZrO_2 (30 mg)	EtOH:H_2O	R.T	1	88
18	2.5% Mn/ZrO_2 (40 mg)	EtOH:H_2O	R.T	1	89
19	2.5% Mn/ZrO_2 (50 mg)	EtOH:H_2O	R.T	1.5	87
20	2.5% Mn/ZrO_2 (20 mg)	EtOH:H_2O	R.T	2	73
21	2.5% Mn/ZrO_2 (10 mg)	EtOH:H_2O	R.T	2	67
22	2.5% Mn/ZrO_2 (40 mg)	CH_3CN	R.T	3.5	46
23	2.5% Mn/ZrO_2 (40 mg)	DMF	R.T	4	35
24	2.5% Mn/ZrO_2 (30 mg)	EtOH	R.T	3	74
25	2.5% Mn/ZrO_2 (30 mg)	H_2O	R.T	3.5	69

[a]Reaction conditions: dimethylbarbituric acid (1 mmol), substituted aldehyde (1 mmol) and malononitrile (1.1 mmol) and EtOH:water (1:1 v/v, 10 mL), R.T.

[b]Isolated yields;

-- No reaction

Table 2. Synthesis of pyrano[2,3-d]-pyrimidines derivatives catalyzed by Mn/ZrO2 catalyst.

Entry	R	Product	Yield (%)	Mp °C	Lit Mp °C
1	4-MeO-Ph	4a	85	225-226	225-227 [29,3
2	2,3-$(MeO)_2$-Ph	4b	86	216-218	--
3	2,5-$(MeO)_2$-Ph	4c	85	231–233	--
4	2-Br-Ph	4d	84	202-203	--
5	4-Br-Ph	4e	79	210-211	--
6	2-Cl-Ph	4f	78	235-237	237-238 [29]
7	3-NO_2-Ph	4g	83	221-223	--
8	3-OH-Ph	4h	79	196-198	--
9	Ph	4i	84	219-220	219-222 [29]
10	2-F-Ph	4j	90	237-238	--
11	3-F-Ph	4k	84	214-215	--

[a]Reaction conditions: 1,3-dimethylbarbituric acid (1 mmol), substituted aldehyde (1 mmol) and malononitrile (1.1 mmol) and EtOH:water (1:1 v/v, 10 mL), R.T.

[b]All synthesized compounds are identified and their structures were conformed with IR, ^{1}HNMR, ^{13}C NMR spectral data and melting points as compared with literature values.

-- New compounds/no literature available.

Using the optimised reaction conditions, the applicability of the protocol was evaluated for the synthesis of other pyrano[2,3-d]pyrimidine derivatives with various aromatic aldehydes. The Mn/ZrO_2 heterogeneous catalyst proved to be an ideal material to catalyse the facile one-pot synthesis of pyrano[2,3-d]-pyrimidine derivatives with good to excellent yields. All the reaction products with other details are depicted in Table 2. Interestingly, the substrates used and reaction yields obtained suggest that irrespective of electron-withdrawing and electron donating groups in ortho, meta and para positions of the aromatic ring, using Mn/ZrO_2 as catalyst, all the substrates gave good to excellent yields of desired pyrano[2,3-d]-pyrimidine derivatives (Table 2). The plausible reaction pathway is shown in Mechanism 1. All the resultant products were characterized and molecular structures were confirmed by FTIR, ^{1}H NMR, ^{13}C NMR and ^{15}N NMR (GHSQC) spectral analysis (Electronic Supplementary Information).

BET surface and ICP analysis:

Figure 1 illustrates the N_2 adsorption–desorption isotherms and pore size distribution curves for the Mn doped ZrO_2. The catalyst displays the characteristic hysteresis loop of a Type IV isotherm (IUPAC) lying in the p/p_o range of 0.6-0.95 typical for mesoporous materials. The pore size distribution and specific area was calculated from the Barrett-Joyner-Halenda (BJH adsorption) and Brunauer-Emmett-Teller methods respectively. The BET surface area of Mn/ZrO_2 was confirmed to be 188.47 m^2/g with an average pore size and volume of 11.9 nm and 0.567 cm^3/g respectively. The metal wt % obtained from ICP is in correlation with the nominal weight loading.

Powder X-ray diffractogram (XRD) analysis:

The XRD patterns of the calcined 2% Mn on ZrO_2 catalyst are demonstrated in Figure 2. The high intensity of the peaks suggested that all the prepared catalysts are polycrystalline in nature. The *d*-spacing's at 2 theta angles of 25.3, 34.9, 38.9, and 55.3 for Mn_2O_3 respectively. This is in good agreement with the ICDD PDF No. 65-7467. From the XRD diffractograms it is evidenced that Mn_2O_3 is the major phase in all the catalysts. There is a formation of additional phase i.e Mn_3O_4 is observed. The d-spacing's at a 2 theta angles of 32.5, 54.6 and 63.1 for Mn_3O_4 which is correspond to the ICDD PDF No. 39-1218 for Mn_3O_4 phase. The ZrO_2 showed the sharp peaks corresponding to tetragonal ZrO_2 (ICDD PDF No. 88-1007, 2θ = 25.7, 38.2, 49.8, and 55.7.

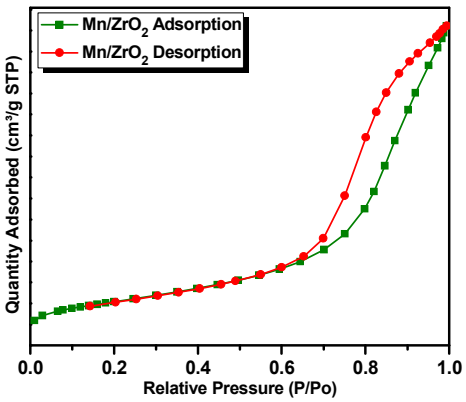

Figure 1: BET surface of Mn/ZrO_2 catalyst

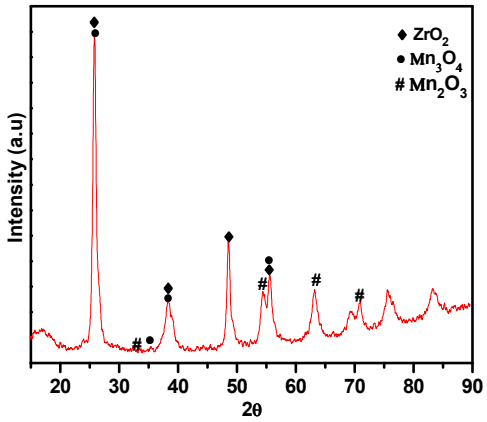

Figure. 2. Powder X-ray diffractogram spectra of Mn/ZrO_2 catalyst

Infrared-spectra (FT-IR):

Figure 3 displays FT-IR spectra of mesoporous Mn on ZrO_2 catalyst exhibited characteristic absorption band at 3368.6 cm^{-1}, 1655.4 cm^{-1} and 1368.3 cm^{-1} corresponding to the vibration of hydroxyl group, which involve the O-H vibrating mode of traces of adsorbed water. Absorption band at 749.8 cm^{-1} and 492.3 cm^{-1} was due to stretching peaks of Mn-O-Mn and Mn-O vibrations, respectively in accord with literature values.[35] A strong absorption band was observed at 1136.3 cm^{-1} for the asymmetric stretching of Zr–O group, supporting the formation of ZrO_2 groups on their surfaces. No organic groups were found to be surface adsorbed based on IR results.

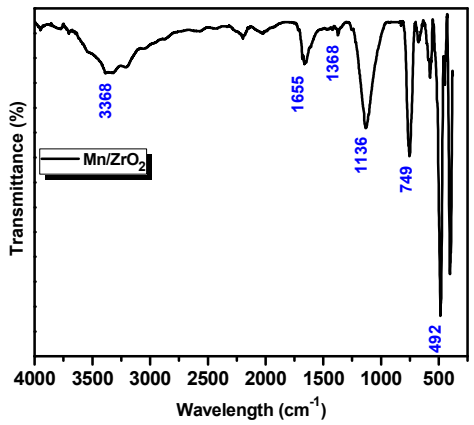

Figure 3. FT-IR image of Mn/ZrO_2 catalyst

SEM & TEM analysis:

The SEM image of the prepared catalyst is shown in Figure 4. The catalyst was crystalline in nature but with a coarse surface morphology. The manganese oxide particles were observed as hexagonal-shaped particles which were dispersed on the surface of the zirconia. The manganese oxide particles are shown in a red colour circles in Figure 4. These observations are also in agreement with literature.[36] The TEM images showed that the zirconia particles are irregular and oval-shaped. The red circles in Figure 5 shows the manganese oxide particles which might be agglomerated on the surface of zirconia.

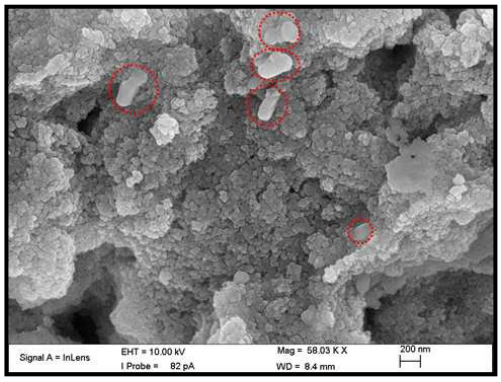

Figure 4. SEM image of Mn/ZrO_2 catalyst

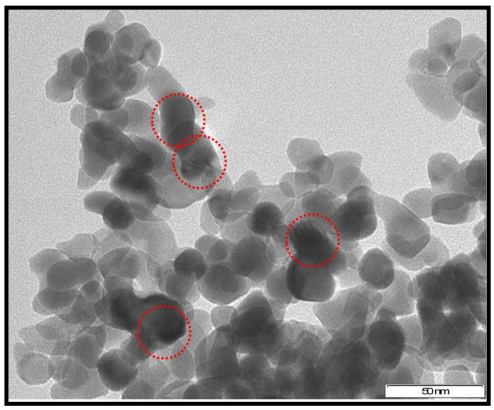

Figure 5. TEM image of Mn/ZrO_2 catalyst

Reusability of Mn/ZrO_2

To test reusability, a recycling experiment was employed using a model reaction. Thus, after completion of reaction, the catalyst was recovered by filtration, washed with ethanol and dried under vacuum. The recovered catalyst was re-used for six times with a slight loss in catalytic activity (Figure 6). The minor loss perceived in the catalytic activity after 6th run could be due to poisoning by organic impurities.

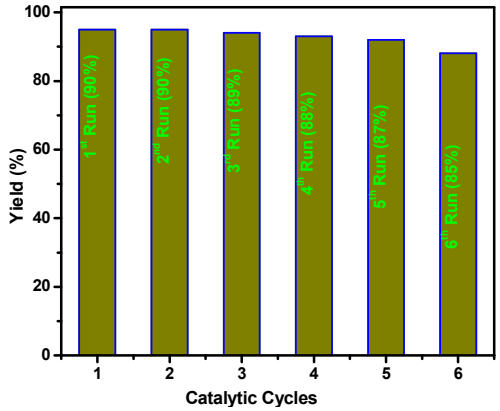

Figure 6. Recyclability of Mn/ZrO_2 catalyst

Conclusions

In conclusion, we report an environmentally benign and an efficient one-pot multicomponent green synthesis of pyrano-[2,3-d]-pyrimidine derivatives using Mn/ZrO_2 as catalyst in green solvent media and with good atom efficiency. This simple and recyclable heterogeneous catalyst, Mn/ZrO_2 shows high catalytic activity for multicomponent reactions. The current method deals several advantages such as short reaction time, cost-effectiveness, purity of products, excellent yields, use of small amount of inexpensive catalyst and environmentally benign green solvent.

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Notes and references

School of Chemistry & Physics, University of KwaZulu-Natal, Westville Campus, Chiltern Hills, Durban-4000, South Africa. Fax: +27 31 260 3091; Tel: +27 31 260 7325/3090; E-mail: jonnalagaddas@ukzn.ac.za

† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

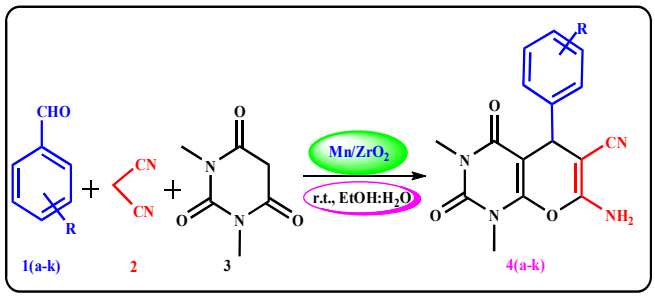
Catalyst Preparation

Mn doped ZrO_2 of various wt.% was prepared by a wet impregnation technique as described in our earlier reports.[37,38] 5.0 g of zirconium oxide powder (Alfa Aesar Chemical) was suspended in 250 mL of double distilled water and mixed with the desired masses of $MnCl_2$ (Manganese (II) chloride tetrahydrate, Aldrich) based on the weight percentages of interest. The mixture was stirred for 4 h using a magnetic stirrer at room temperature (RT) and then heated to 90 °C for 4 h. The precipitate was dried in an air oven at 110-120 °C for 12 h, followed by calcination at 450

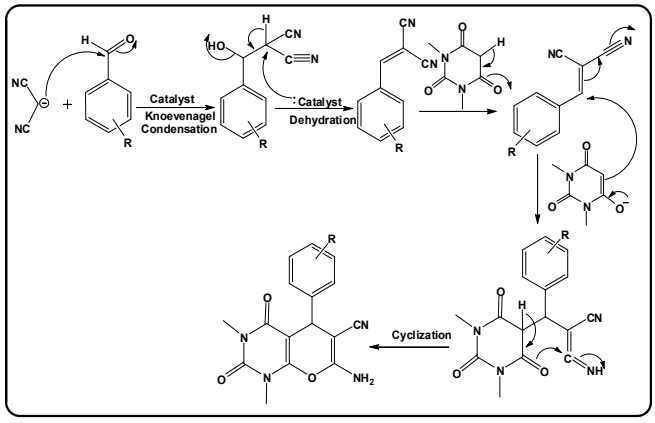
°C for 5 h to afford the 1%, 2.5% & 5% w/w of the Mn/ZrO_2 catalysts.

General Procedure for the synthesis of pyrano[2,3-d]-pyrimidines:

A solution containing dimethylbarbituric acid (1 mmol), substituted aldehyde (1 mmol), malononitrile (1.1 mmol) and Mn/ZrO_2 (30 mg) in mixture of EtOH:H_2O (1:1 v/v, 10 mL) was continuously stirred for 1.0 h at RT using a magnetic stirrer (Scheme 1). The progress and completion of the reaction was monitored by TLC. The reaction mixture was then filtered, and the filtrate was subsequently evaporated under reduced pressure to obtain the crude product which was recrystallized with ethanol to afford pure product (4a-k). The recovered catalyst was subjected to washing with ethanol, dried and re-used for up to six cycles.



Scheme 1: *Synthesis of pyrano[2,3-d]-pyrimidine derivatives*



Mechanism 1. *Plausible reaction mechanism for the formation of pyrano[2,3-d]-pyrimidine derivatives*

7-Amino-5-(4-methoxyphenyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]-pyrimidine-6-carbonitrile (4a): ^{1}H NMR (400 MHz, DMSO-d_6) δ = 3.07 (s, 3H, NCH_3), 3.36 (s, 3H, NCH_3), 3.72 (s, 3H, OCH_3), 4.31 (s, 1H, CH), 6.83 (d, *J* = 8.2 Hz, 2H, ArH), 7.14 (d, *J* = 8.04 Hz, 2H, ArH), 7.29 (s, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.64, 29.74, 35.81, 55.02, 58.55, 89.09, 113.64, 119.17, 128.18, 136.81, 149.95, 150.87, 157.88, 158.38, 160.45; ^{15}N NMR (40.55 MHz, DMSO-d_6) δ 7.29 (s, 2H, NH_2); IR (KBr, cm^{-1}): 3368, 3307, 3181, 2965, 2188, 1682, 1680, 1605, 1508; HRMS of [$C_{17}H_{16}N_4O_4$ ─ H] (m/z): 339.2011; Calcd.: 339.2021.

7-Amino-5-(2,3-dimethoxyphenyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]-pyrimidine-6-carbonitrile (4b): ^{1}H NMR (400 MHz, DMSO-d_6) δ = 3.06 (s, 3H, NCH_3), 3.36 (s, 3H, NCH_3), 3.75 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.61 (s, 1H, CH), 6.71 (d, *J* = 7.04 Hz, 1H, ArH), 6.87 (d, *J* = 8.00, 1H, ArH), 6.94 (t, *J* = 7.96, 1H, ArH), 7.22 (s, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.59, 29.07, 31.06, 55.49, 58.15, 59.90, 83.77, 111.29, 119.07, 120.70, 123.60, 136.99, 146.32, 149.94, 151.28, 152.24, 157.85, 160.37; ^{15}N NMR (40.55 MHz, DMSO-d_6) δ 7.22 (s, 2H, NH_2); IR (KBr, cm^{-1}): 3317, 2937, 2188, 1681, 1645, 1474; HRMS of [$C_{18}H_{18}N_4O_5$ + Na] (m/z): 393.1166; Calcd.: 393.1175..

7-Amino-5-(2,5-dimethoxyphenyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]-pyrimidine-6-carbonitrile (4c): ^{1}H NMR (400 MHz, DMSO-d_6) δ = 3.07 (s, 3H, NCH_3), 3.38 (s, 3H, NCH_3), 3.65 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 4.58 (s, 1H, CH), 6.64 (d, *J* = 3.02 Hz, 1H, ArH), 6.74 (dd, *J* = 8.9, 3 Hz, 1H, ArH), 6.89 (d, *J* = 8.9 Hz, 1H, ArH), 7.15 (s, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.59, 29.00, 31.32, 55.22, 56.34, 57.63, 88.05, 111.51, 112.76, 115.37, 119.02, 130.99, 150.00, 150.23, 151.52, 153.15, 158.15, 160.34; ^{15}N NMR (40.55 MHz, DMSO-d_6) δ 7.15 (s, 2H, NH_2); IR (KBr, cm^{-1}): 3302, 3175, 2934, 2194, 1715, 1683, 1634, 1599, 1487; HRMS of [$C_{18}H_{18}N_4O_5$ ─ H] (m/z): 369.0389; Calcd.: 371.0395.

7-Amino-5-(2-bromophenyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]-pyrimidine-6-carbonitrile (4d): ^{1}H NMR (400 MHz, DMSO-d_6) δ = 3.05 (s, 3H, NCH_3), 3.36 (s, 3H, NCH_3), 4.86 (s, 1H, CH), 7.11-7.15 (m, 1H, ArH), 7.28 (d, *J* = 4.2 Hz, 2H, ArH), 7.33 (s, 2H, NH_2), 7.53 (d, *J* = 8.00 Hz, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.58, 29.12, 35.80, 57.36, 88.23, 118.42, 122.77, 128.07, 128.64, 130.25, 132.45, 149.97, 151.47, 157.64, 160.28; ^{15}N NMR (40.55 MHz, DMSO-d_6) δ 7.33 (s, 2H, NH_2); IR (KBr, cm^{-1}): 3310, 2930, 2913, 1684, 1637, 1470; HRMS of [$C_{16}H_{13}BrN_4O_3$ ─ H] (m/z): 387.0103; Calcd.: 387.0093..

7-Amino-5-(4-bromophenyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]-pyrimidine-6-carbonitrile (4e): ^{1}H NMR (400 MHz, DMSO-d_6) δ = 3.07 (s, 3H, NCH_3), 3.34 (s, 3H, NCH_3), 4.32 (s, 1H, CH), 7.21 (d, *J* = 8.00 Hz, 2H, ArH), 7.35 (s, 2H, NH_2), 7.47 (d, *J* = 8.00 Hz, 2H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.62, 29.09, 36.04, 58.03, 88.22, 118.85, 119.80, 129.67, 131.07, 143.54, 149.95, 151.15, 157.57, 160.43; ^{15}N NMR (40.55 MHz, DMSO-d_6) δ 7.35 (s, 2H, NH_2); IR (KBr, cm^{-1}): 3426, 3299, 2930, 2189, 1683, 1633, 1487.

7-Amino-5-(2-chlorophenyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]-pyrimidine-6-carbonitrile (4f): ^{1}H NMR (400 MHz, DMSO-d_6) δ = 3.06 (s, 3H, NCH_3), 3.36 (s, 3H, NCH_3), 4.86 (s, 1H, CH), 7.23-7.36 (m, 6H, ArH, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.59, 29.11, 33.52, 57.18, 87.97, 118.52, 127.46, 128.37, 129.24, 132.17, 141.08, 149.97, 151.50, 157.76, 160.28; ^{15}N NMR (40.55 MHz, DMSO-d_6) δ 7.30 (s, 2H, NH_2); IR (KBr, cm^{-1}): 3382, 3310, 3193, 2959, 2193, 1703, 1684, 1638, 1474; HRMS of [$C_{16}H_{13}ClN_4O_3$ ─ H] (m/z): 343.0992; Calcd.: 343.1008.

7-Amino-5-(3-nitrophenyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]-pyrimidine-6-carbonitrile (4g): ^{1}H NMR (400 MHz, DMSO-d_6) δ = 3.01 (s, 3H, NCH_3), 3.34 (s, 3H, NCH_3), 5.12 (s, 1H, CH), 7.43 (d, *J* = 8.00 Hz, 1H, ArH), 7.48 (s, 2H, NH_2), 7.51 (s, 1H, ArH), 7.64 (t, *J* = 8.00, 1H, ArH), 7.83 (d, *J* = 8.00 Hz, 1H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.57, 29.11, 30.77, 56.62, 88.33, 118.40, 123.63, 128.02, 130.73, 133.42, 138.38, 149.05, 149.87, 151.82, 158.31, 160.50; ^{15}N NMR (40.55 MHz, DMSO-d_6) δ 7.48 (s, 2H, NH_2); IR (KBr, cm^{-1}): 3373, 3306, 3184, 2957, 2196, 1706, 1683, 1632, 1522, 1490; HRMS of [$C_{16}H_{13}N_5O_5$ ─ H] (m/z): 354.0844; Calcd.: 354.0838.

7-Amino-5-(3-hydroxyphenyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]-pyrimidine-6-carbonitrile (4h): ^{1}H NMR (400 MHz, DMSO-d_6) δ = 3.09 (s, 3H, NCH_3), 3.35 (s, 3H, NCH_3), 4.21 (s, 1H, CH), 6.58-6.66 (m, 3H, ArH), 7.06 (t, *J* = 8.00 Hz, 1H, ArH), 7.29 (s, 2H, NH_2), 8.42 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.65, 29.05, 36.35, 58.62, 88.98, 113.76, 114.15, 117.92, 119.05, 129.19, 145.48, 149.94, 150.96, 157.22, 160.43, 165.86; ^{15}N NMR (40.55 MHz, DMSO-d_6) δ 7.29 (s, 2H, NH_2); IR (KBr, cm^{-1}): 3370, 3303, 3199, 2965, 2197, 1783, 1636, 1598, 1484; HRMS of [$C_{16}H_{14}N_4O_4$ ─ H] (m/z): 325.0894; Calcd.: 325.0900.

7-Amino-1,3-dimethyl-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]-pyrimidine-6-carbonitrile (4i): ^{1}H NMR (400 MHz, DMSO-d_6) δ = 3.07 (s, 3H, NCH_3), 3.35 (s, 3H, NCH_3), 4.31 (s, 1H, CH), 7.18-7.28 (m, 5H, ArH), 7.30 (s, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.63, 29.07, 36.47, 58.63, 88.78, 119.01, 126.73, 127.28, 129.49, 130.44, 144.08, 149.97, 151.09, 157.63, 160.45; ^{15}N NMR (40.55 MHz, DMSO-d_6) δ 7.30 (s, 2H, NH_2); IR (KBr, cm^{-1}): 3380, 3307, 3193, 2866, 2196, 1703, 1682, 1639, 1607, 1493; HRMS of [$C_{16}H_{14}N_4O_3$ ─ H] (m/z): 309.0984; Calcd.: 309.0988.

7-Amino-5-(2-fluorophenyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]-pyrimidine-6-carbonitrile (4j): ^{1}H NMR (400 MHz, DMSO-d_6) δ = 3.06 (s, 3H, NCH_3), 3.35 (s, 3H, NCH_3), 4.61 (s, 1H, CH), 7.11 (t, *J* = 7.68 Hz, 2H, ArH), 7.24-7.27 (m, 2H, ArH), 7.35 (s, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.60, 29.07, 30.42, 57.16, 87.59, 115.36, 118.74, 124.43, 128.70, 128.78, 129.69, 149.95, 151.43, 157.93, 158.78, 160.75; ^{15}N NMR (40.55 MHz, DMSO-d_6) δ 7.35 (s, 2H, NH_2); IR (KBr, cm^{-1}): 3384, 3311, 3194, 2962, 2195, 1683, 1637, 1509, 1488; HRMS of [$C_{16}H_{13}FN_4O_3$ ─ H] (m/z): 327.0889; Calcd.: 327.0893.

7-Amino-5-(3-fluorophenyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]-pyrimidine-6-carbonitrile (4k): ^{1}H NMR (400 MHz, DMSO-d_6) δ = 3.07 (s, 3H, NCH_3), 3.34 (s, 3H, NCH_3), 4.36 (s, 1H, CH), 7.02-7.10 (m, 3H, ArH), 7.32-7.34 (m, 3H, ArH, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.62, 29.08, 36.20, 58.10, 88.11, 113.89, 114.50, 118.85, 123.45, 130.05, 147.01, 147.07, 149.99, 151.29, 157.62, 160.51; ^{15}N NMR (40.55 MHz, DMSO-d_6) δ 7.32 (s, 2H, NH_2); IR (KBr, cm^{-1}): 3382, 3305, 3192, 2194, 1711, 1683, 1635, 1613, 1490.

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