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Synthesis and Characterization of Tetrahydropyrazolo Pyridine Analogous By Using Zn-O Nano Catalyst as a One-Pot Tandem Multicomponent Reactions

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ABSTRACT:
A various substituted aromatic aldehydes are treated with hydrazine hydrate/phenyl hydrazine, EAA, ammonium acetate results in formation of different Tetrahydropyrazolopyridine derivatives. The convensional and non-convensional methods are used for synthesis. These derivatives are further characterized by various techniques such as NMR, IR etc.We were successfully accomplished 'Green' synthesis of tetrahydropyrazolopyridine derivatives. Use of Zn-O nanocatalystswas found to be an efficient catalyst for heterogeneous multicomponent reaction. The catalyst was used environmentally free and yield of product is also increased. Finely catalyst is recovered. We were reused the catalysts for next reactions.

Keywords: Phenyl hydrazine, EAA, Tetrahydropyrazolopyridine, Zn-O nanocatalysts

I. INTRODUCTION

Pyrazoles are an important class of bio active drug targets in the pharmaceutical industry[1], as they are the core structure of numerous biologically active compounds.[2] For example; they exhibit ant anxiety, antipyretic, analgesic, and anti-inflammatory properties. On account of its variety of biological activity, the chemistry of pyrazoles has attracted much attention and many methods for their synthesis have been extended. Nowadays, the pyrazolone derivatives were paid much attention for their various biological activities, such as antitumor, selective COX-2 inhibitory.[3-4] Besides; they can be used as cytokine inhibitors, potent catalytic activity inhibitor of human telomerase,[5]therapeutics for kinase mediated inflammatory disorders [6] and dyes. The compounds that contain two pyrazolone rings can be used as extracting for some metal ions[7] and ligands.[8]

Pyrazolopyridines and their derivatives have a wide range of biological activities.[9,10] For example, a number of pyrazolo[3,4-b]pyridines exhibit biological activities, including anxiolytic (eg., tracazolate), antiallergic and antiherpetic properties.[11] The research on organic light emitting diodes (OLEDs) has exploded and progressed considerably in recent years. Dipyrazolopyridines are a new class of fluorescent materials. Preliminary electroluminescence properties were reported in their polymer systems.[12-13],

Owing to their pharmacological and biological properties, 1,4-dihydropyridines (1,4-DHPs) have generated particular attention in both synthetic and medicinal research.[14]1,4-DHPs, as a class of calcium modulators, are extensively investigated for their pharmacological activities as antioxidant, anti-tumor, anti-atherosclerosis, anti-diabetes, anti-mutagenic, anti-vasodilator, neuromodulator, hepatoprotector, neuroprotector and memory enhancer.[15] The Hantzsch synthesis, one of the most famous MCRs involving an aldehyde, two equivalents of a β-ketoester and a nitrogen donor such as ammonia or ammonium acetate, is most often used for the construction of 1,4-dihydropyridines.[16]Several modifications have been developed to allow for the synthesis of different 1,4-DHP derivatives.[17]

The importance of green chemistry and also the existing attraction in the design and synthesis of heterocyclic compounds through MCRs, motivated us to design a one-pot 2A+2B+C+D four component reaction for the synthesis of dipyrazolo-1,4-dihydropyridines under green reaction conditions. Although, the synthesis of dipyrazolopyridines starting from pyrazole containing building blocks have been already reported. Herein, we introduce the first example of simultaneous assembly of all three heterocyclic rings from four acyclic building blocks. We employed in situ preparation of the pyrazolone ring through the reaction between hydrazine and ethyl acetoacetate and subsequent reaction with aldehyde and ammonium acetate. We note that, the in situ formation of pyrazolone as pronucleophiles in MCRs has already been developed.

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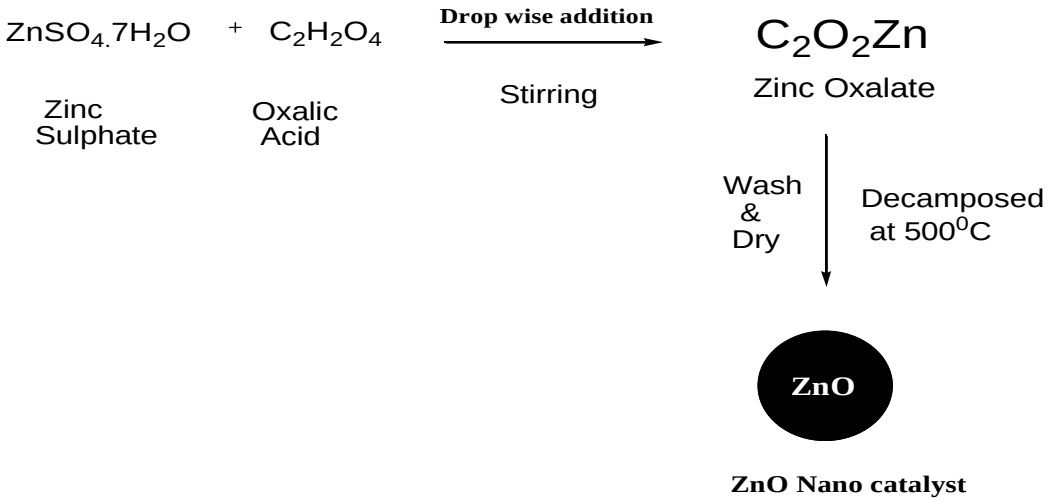
II. METHODS AND MATERIALS

2.1 Synthesis of Zn-O Nano-Catalyst

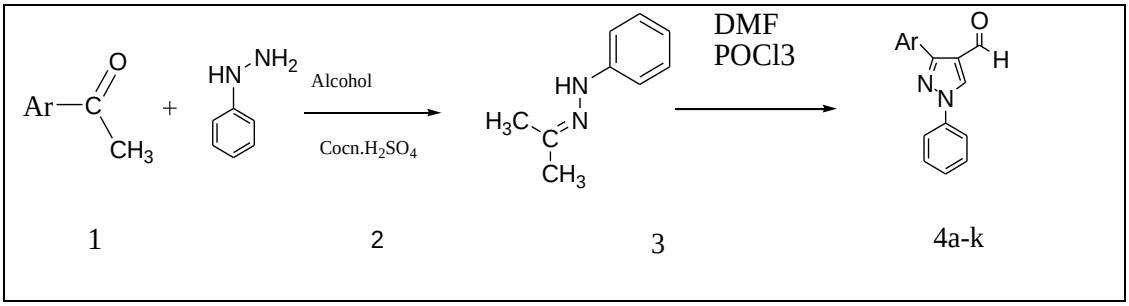
For synthesis of nanostructure Zn-O zinc sulphate (99.9%, sd-fine chemicals, 0.2M) and oxalic acid (99.9%, sd-fine chemicals, 0.2M) has beam used as a precursor material. The intermediate zinc oxalate was obtained by adding oxalic acid (0.2M) solution drop wise into zinc sulphate (0.2M) with constant stirring. The precipitate of intermediate zinc oxalate complex was washed with distilled water (~1 lit) and dried at 80^{o}C in heating oven. Further, intermediate powder material was decomposed at 500 ^{o}C in Muffal furnace in order to obtain nanostructured zinc oxide.



Scheme 2: Synthesis of Zinc Oxide (Zn-O) NPs.

2.2 Preparation of Pyrazole Aldehydes Formylation of Hydrazone

Take 45 ml DMF in dry R.B.F. with magnetic needle was taken.R.B.F. was kept in an ice bath and add 20 ml $POCl_3$ dropwise in above solution and temp. was maintained below the 100^{0}c. After the addition of POCl3pink colored complexwas appeared. Then the 0.1 moles (20gm) of hydzine in dry beaker was dissolved in a minimum amount of DMF .These hodrazones solution as added in to the above solution by dropwise addition and temp. as maintained under 20^{0}c . After the complete addition, solution was kept for stirring 45-60 minutes at R.T. and then stand for the over night. On the next day poured this solution on crushed ice slowly with constant stirring. Then we allowed this solution to stand for 90-120min. Then solution was filtered andrecrystallized in Ethyl Alcohol**(Scheme1).**



Scheme 1. Synthesis of Substituted Aromatic Aldehydes.

2.3 Synthesis of Tetrahydropyrazolo pyridine Derivatives by Non-conventional Method

The time required for synthesis of tetrahydropyrazolopyridine derivatives by convensional method is too high. So this is time consuming process and yield also decreases. Therefore this is not affordable. In order to increase the yield of this reaction I can use the Nano-

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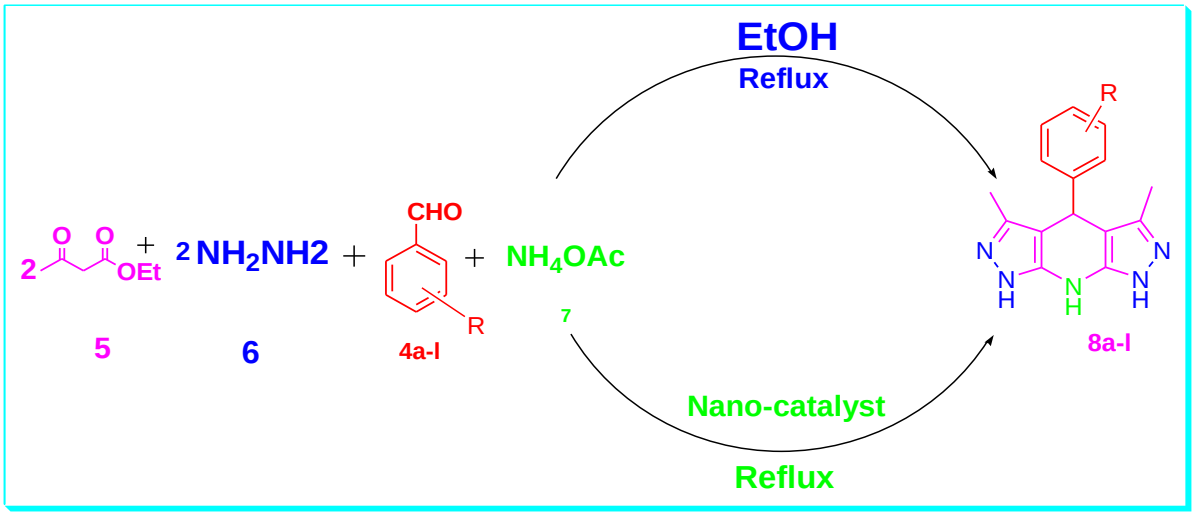
catalyst for this reaction. So the time is reduced and yield is increased. I can take a mixture of ethyl acetoacetate **1** (2 mmol) and hydrazine hydrate **2** (2 mmol) in ethanol (5mL) was magnetically stirred for 30 min at reflux condition followed by addition of aldehyde **3** (1 mmol), ammonium acetate **4** (4 mmol) and Nano catalyst. The reaction mixture was heated and then cooled to room temperature and water (20 mL) was added and the resulting mixture was stirred for 30 min. The precipitated product was filtered, washed with water and then dried under vacuum recrystallization from ethanol. Finally I observed that time is reduced almost to haif. That's why this are economically important reactions by using Nano-catalyst**(Scheme2).**



Scheme 2. Synthesis of tetrahydropyrazolopyridine**(8a-l)**

III. RESULTS AND DISCUSSION

3.1 Characterization of Powdered ZnO Catalyst

a. X-Ray Diffraction Studies

The precipitated fine particles (ZnO) were characterized by XRD as shown in fig 1.5 The structure and their crystallite size were evaluated. The crystallite size of the non- crystalline samples was measured using Debye-Scherer formula,

$$DXRD = \frac{0.98\lambda}{\beta \cos \theta}$$

Where λ is the wavelength of X- ray used in A°, β is the full width at half maximum (FWHM) in radians in 2θ secale, θ is the bragg angle, D_{XRD} is the crystallite size in nm.

The major diffraction peaks are present between 20 and 70 (2u) corresponding to the

Hexagonal Zn-O crystal structure. The diffraction peaks at 2u values of 31.65, 34.3, 36.14, 47.45, 56.43, 62.65,67.96 and 69.09 corresponded to the (100), (002), (101),(102), (110), (103), (112) and (201) planes of hexagonal Zn-O nanoparticles respectively (JCPDS 36-1451). 18).The average size of the ZnO nanoparticles determined from the XRD is found within32 nm.

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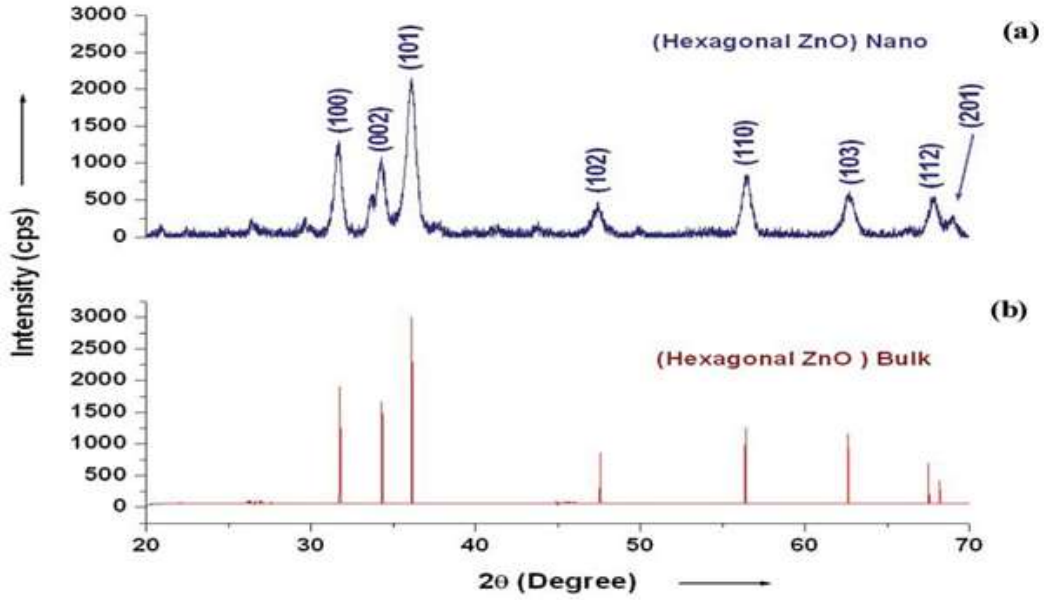

Fig. 1:XRD pattern of the ZnO nanoparticles.

b. FTIR Spectrum of Zn-O

FTIR spectral studies shown in following Figure give information regarding the chemical bonding between Zn and O. The spectrum showed a broad peak around 457 cm^{-1} andshoulders around 545 cm^{-1}, which corresponds to Zn-ONanoparticles. The remaining spectrum was relativelysmooth with a few peaks of CO_2.

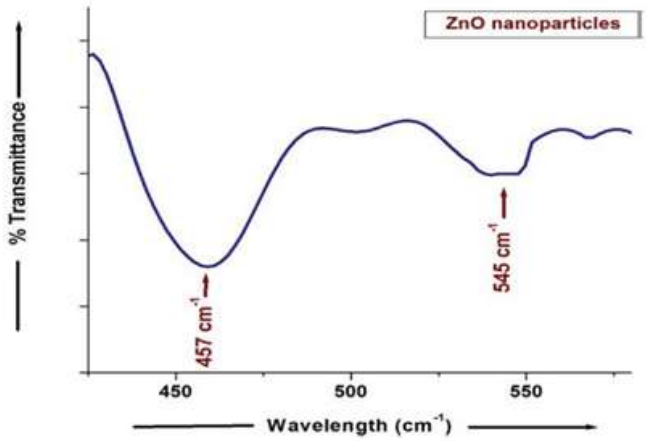

Fig.2: FTIR spectrum of ZnO Nanoparticles.

The thermal study of as-synthesized zinc oxalate was carried out using Thermo Gravinetric Analyser (TGA-DTA,Metler-Toledo Star System) up to 1000^{o}C in air at the heating rate of 10 ^{o}C /min. Powder X-ray Diffract grams (XRD) were recorded on X-ray diffract meter (Riguka-D8/Max-2200V) using CuK-Radiation with Ni-filter. The surface morphology and particle size were determined using a field emission scanning electron microscope (FESEM HITACHI S-4800).

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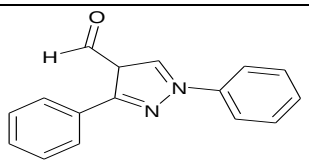
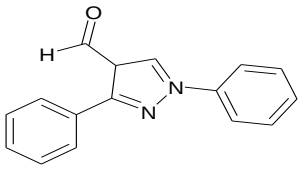
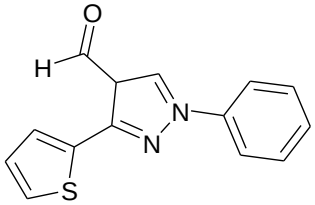
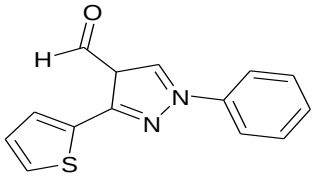
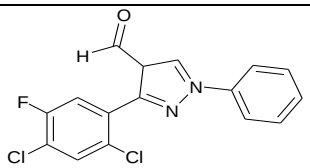
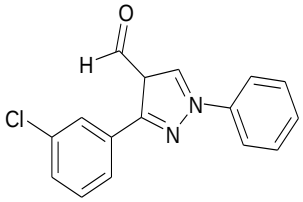
c. Recycling study of ZnO catalyst

The most important property of every catalyst is that it can be reuse or recycled .I can find that the Zn-O Nano-catalyst is regenerated after doing the reaction. In this work, we examined the possibility of recovery and reuse of these catalysts by use of the one-pot reactions by using Zn-Oas nanocatalyst. After completion of reaction catalyst is recovered from reaction mixture by pouring reaction mixture in ethyl acetate or catalyst is recovered during reaction. Then catalyst is washed and dried. Now the catalyst is ready to reuse.

Table 1: Synthesized Substituted Aromatic Aldehydes

Entry	Comp.	Substituted Aromatic Aldehydes	Molecular Formula	Molecular Weight	Melting Point (^{0}C)	Yield (%)
1	4a		$C_{16}H_{13}N_2O$	249.31	120	88
2	4b		$C_{16}H_{13}N_2O$	249.31	120	91
3	4c		$C_{14}H_{11}N_2SO$	255.31	122	78
4	4d		$C_{14}H_{11}N_2SO$	255.31	122	90
5	4e		$C_{16}H_{10}Cl_2N_2FO$	4336.17	180	80
6	4f		$C_{16}H_{12}ClN_2O$	286.06	140	86

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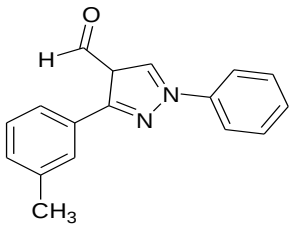
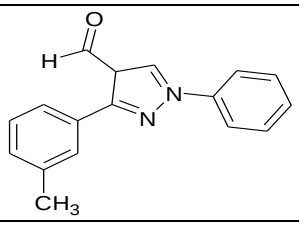
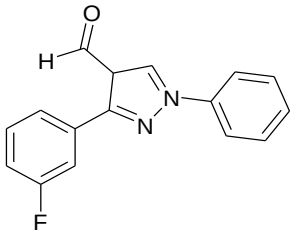
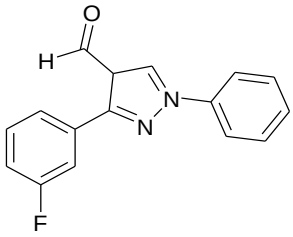
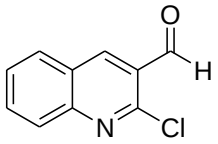
7	4g		$C_{17}H_{15}N_2O$	263.31	152	85
8	4h		$C_{17}H_{15}N_2O$	263.31	152	89
9	4i		$C_{16}H_{12}FN_2O$	267.09	138	86
10	4j		$C_{16}H_{12}FN_2O$	267.09	138	86
11	4k		$C_{10}H_6ClNO$	191.61	148	88

Table 2:- Synthesis of tetrahydropyrazolopyridine derivatives (**8a-l**).

Aldehydes	**Product**	**Molecular Formula**	**Molecular Weight**	**M.P. (^{0}C)**	**Yield (%)**
4a	8a	$C_{24}H_{21}N_7$	407.47	238	80
4b	8b	$C_{36}H_{29}N_7$	559.66	218	70
4c	8c	$C_{34}H_{27}N_7S$	565.2	140	78
4d	8d	$C_{15}H_{15}N_5$	265.31	188	74
4e	8e	$C_{22}H_{19}N_7S$	413.5	192	82
4f	8f	$C_{24}H_{19}ClFN_7$	459.14	284	75
4g	8g	$C_{36}H_{28}ClN_7$	594.11	210	71

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4h	8h	$C_{25}H_{23}N_7$	421.5	216	79
4i	8i	$C_{37}H_{31}N_7$	573.69	222	81
4j	8j	$C_{24}H_{20}FN_7$	425.18	242	71
4k	8k	$C_{36}H_{28}FN_7$	577.65	242	74
4l	8l	$C_{18}H_{15}ClN_6$	350.8	248	78

3.2 Spectral analysis of synthesized Tetrahydropyrazolopyridine derivatives

Compound 8a:- (Table 5, entry 1): M.F. $C_{24}H_{21}N_7$; M.P. 238°C; IR: 3160.1,3150, 3100, 1592.2, 1500, 1026.02 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 2.0 (s, 6H), 7.3-8 (m, 10H), 8.7 (s, 1H), 9.2 (s.1H), 10.2 (s, 1); MS: m/z (%): 407.1.

Compound 8b:- (Table 5, entry 2): M.F. $C_{36}H_{29}N_7$; M.P. 218°C;IR: 3125.01,3138, 1502.2, 1500, 995.1 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 3.1 (s, 6H), 7.1-7.9 (m, 21H), 7.8 (s, 1H), 10.2 (s.1H), 10.8 (s, 1H); MS: m/z (%): 559.25.

Compound 8C:- (Table 5, entry 3): M.F.$C_{34}H_{27}N_7S$; M.P. 140°C; IR: 3200, 1550, 1598, 992.01
^1H NMR (400 MHz, DMSO-d_6) δ: 3.4 (s, 6H), 7.2-8.0 (m, 19H), 7.2 (s, 1H), 9.8 (s.1H), 10.2 (s, 1H); MS: m/z (%): 565.20.

Compound 8d:- (Table 5, entry 4): M.F. $C_{15}H_{15}N_5$; M.P. 188°C;IR: 3248, 1532, 1400, 965 cm^{-1}
^1H NMR (400 MHz, DMSO-d_6) δ: 3.3 (s , 6H), 7.3-8.0 (m,5H), 7.7 (s,1H), 8.7 (s.1H), 10.3 (s,1H); MS: m/z (%): 265.13.

Compound 8e:- (Table 5, entry 5): M.F. $C_{22}H_{19}N_7S$; M.P. 192°C; IR: 3120.03, 1596.09, 1500, 1211.95, 1053.17, 685.48 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 2.3 (s, 6H), 7.1-8.0 (m, 9H), 8.0 (s, 1H), 8.9 (s.1H), 10.2 (s, 1H); MS: m/z (%): 413.14.

Compound 8f:- (Table 5, entry 6): M.F. $C_{24}H_{19}ClFN_7$; M.P. 284°C; IR: 3108.01, 3008, 1582.02, 1500, 920 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 3.09 (s, 6H), 6.1-9.0 (m, 9H), 7.2 (s, 1H), 8.3 (s.1H), 10.1 (s, 1H); MS: m/z (%): 459.14.

Compound 8g:- (Table 5, entry 7): M.F. $C_{36}H_{28}ClN_7$; M.P. 210°C; IR: 3192.2, 3038.1, 1590, 1520, 994 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 2.3 (s, 6H), 7.2-7.9 (m, 10H), 7.9 (s, 1H), 7.9 (s.1H), 10.2 (s, 1H); MS: m/z (%): 593.21.

Compound 8h:- (Table 5, entry 8): M.F. $C_{25}H_{23}N_7$; M.P. 216°C; IR: 3092, 3030.20, 1584.21, 1518.2, 981.20 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 3.9 (s, 6H), 7.3-8.3 (m, 10H), 6.10 (s, 1H), 8.3 (s.1H), 10.1 (s, 1H); MS: m/z (%): 421.20.

Compound 8i:- (Table 5, entry 9): M.F. $C_{37}H_{31}N_7$; M.P. 222°C; IR: 3145, 3059.24, 1595.34, 1495.62, 750 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 2.4 (s, 6H), 2.3 (s, 3H), 7.1-7.8 (m, 10H), 7.9 (s, 1H), 8.0 (s.1H), 10.21 (s, 1H); MS: m/z (%): 573.26.

Compound 8j:- (Table 5, entry 10): M.F. $C_{24}H_{20}FN_7$; M.P. 242°C; IR: 3185.1, 1536.96, 1218.22, 837.54 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 2.0 (s, 6H), 7.3-8 (m, 10H), 8.7 (s, 1H), 9.2 (s.1H), 10.2 (s, 1H); MS: m/z (%): 525.18.

Compound 8k:- (Table 5, entry 11): M.F. $C_{37}H_{28}FN_7$; M.P. 242°C; IR: 3120.21, 2902, 1568, 1533.33, 890.99 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 3.9 (s, 6H), 6.9-8.0 (m, 10H), 7.7 (s, 1H), 8.9 (s.1H), 10.9 (s, 1H); MS: m/z (%): 577.24.

IV. CONCLUSION

The procedure and techniques employed for characterization of different Tetrahydropyrazolo pyridine derivative by elemental analysis, IR, and ^1H-NMR spectroscopy. We were successfully accomplished 'Green' synthesis of tetrahydropyrazolo pyridine derivatives. Use of nano catalyst Zn-O nanocrystales was found to be an efficient catalyst for heterogeneous this Multicomponent reaction. The catalyst used was environmentally free and yield of product was also increased. Finaly catalyst is recycled.

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REFERENCES

[1]. Domling, A.; Ugi, I. Anew,(1993),Multicomponentreaction, Chem. Intl. Ed. 32, 563.

[2]. Mustelin, T.; Tasken, K., Positive and negative regulation of T-cell activation

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Volume 10, Issue 6 Nov - Dec 2025, pp: 343-350 www.ijprajournal.com ISSN: 2456-4494

through kinases and phosphatases.Biochem J 2003, 371, (Pt 1), 15-27.

[3]. Park, H. J.; Lee, K.; Park, S. J.; Ahn, B.; Lee, J. C.; Cho, H. Y.; Lee, K. I (2005). Design, Synthesis, and Biological Activities of Novel Pyrazole Oximes CompoundsBioorg. Med. Chem. Lett., 15, 3307.

[4]. Clark, M. P.; Laughlin, S. K.; Laufersweiler, M. J.; Bookland, R. G.; Brugel, T. A.; (2004).Development of orally bioavailable bicyclic pyrazolones as inhibitors of tumor necrosis factor-alpha production. J. Med. Chem, 11, 2724.

[5]. Yasutaka, K.; Narie, S.; Mieko, S. M.; Hiromu, M.; Kimiko, M. M.; Biochem. Biophys. (2004) Synthesis and Antimicrobial Activity of 2-(1H-Pyrazol-4-yl)-1H-Benzo [D] Imidazole DerivativesRes. Commun.4, 1351.

[6]. Clark, M. P.; Bookland, R. G. (2005) Synthesis and Conjoint Experimental-DFT Characterization of Some Pyrazolone Functionalized Dioxovanadium (V) Schiff Base Complexes, Expert Opin. Ther. Pat., 11, 1617.

[7]. Takeishi, H.; Kitatsuji, Y.; Kimura, T.; Meguro, Y.; Yoshida, Z.; Kihara, S. (2001) A clean and highly efficient synthesis of 4,40-(aryl ethylene)bis(3-methyl-1-phenyl-1H-pyrazol- 5-ols) using Ce(SO4)2.4H2O as heterogeneous catalyst, Anal. Chim. Acta.1, 69**.**

[8]. Abdel-Latif, S. A. ;(2001) Synthesis of some novel heterocyclic dyes derived from pyrazole derivatives, Synth. React. Inorg. Metal-organic Chem., 8, 1355.

[9]. Yu, G.; Mason, H.; Wu, X.; Wang, J.; Chong, S.; Dorough, G.; Henwood, A.; Pongrac, R.; Seliger, L.; He, B.; Norman din, D.; Adam, L.; Krupinski, J.; Macor, J. (2001), Substituted Pyrazolopyridopyridazines as Orally Bioavailable Poten**t,** J. Med. Chem., 44, 1025.

[10]. Liu, C.; Li, Z.; Zhao, L.; Shen, L. (2009) An efficient synthesis of tetrahydropyrazolopyridine derivatives by a one-pot tandem multi-component reaction in a green media Arkivoc, , 258.

[11]. Chen, Y. L. WO Pat. 9534563 A1, (1995) An efficient synthesis of tetrahydropyrazolopyridine derivatives by a one-pot tandem multi-component reaction Chem. Abstr., 124, 232447.

[12]. Tao, Y. T.; Balasubramaniam, E.; Danel, A.; Tomasik, P.(2000),Theoretical Investigation of Pyrazolo[3,4-b]quinoline Derivatives as Emitting Materials, Appl. Phys. Lett., 77, 933.

[13]. Tao, Y. T.; Chuen, C. H.; Ko, C. W.; Peng, J. W. (2002), Efficient Blue Light-Emitting Diodes Based on Triarylamine-Substituted Dipyrazolopyridine Derivatives, Chem. Mater., 14, 4256.

[14]. Kappe, C. O (2000), biologically active dihydropyrimidones of the Biginelli-type a literature survey Eur. J. Med. Chem., 35, 1043.

[15]. Varache-Lembewge, M.; Nuhrich, A.; Zemb, V.; Devaux, G.; Vacher, P.; Vacher, A. M.; Dufy, B. (1996), Novel Derivatives of 2-Pyridinemethylamine as Selective, Potent, and Orally Active Agonists at 5-HT_{1A} Receptors, Eur. J. Med. Chem., 31, 547.

[16]. Hantzsch, A. Ber. (1881), recent advances in 1-4 Dihydropyridines, Dtsch. Chem. Ges., 14, 1637.

[17]. Ghosh, S.; Saikh, F.; Das, J.; Pramanik, A. K. (2013), Efficient One Pot Synthesis of 1,4-Dihydropyridines Under Solvent Free Conditions Using Carbonaceous Solid Acid Catalyst, Tetrahedron Lett. 54, 58.