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International e-conference on Proteomics Application to Biomedical Research (PABR-2022)

Organized By
Department of Chemistry,
Sangola Taluka Shetkari Shikshan Prasarak Mandal Sangola's, Vidnyan Mahavidyalaya, Sangola
Tal-Sangola, Dist-Solapur, MH-413307, India
Collaboration with
Internal Quality Assurance Cell (IQAC)

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Synthesis, Characterization of Cr^{+3}, Mn^{+2} Metal Ion Chelates with Newly Synthesized Benzothiazolyl Hydrazone Derivatives

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ABSTRACT

The transition Metal ion chelates of Cr+3, Mn+2 is synthesized by using 2-(4′-dimethylamion phenyl)-4-bromo-6-ethoxy benzothiazolyl hydrazones and characterized by different analytical procedure and spectral study. These metal ion chelates are insoluble in common organic solvents. Infrared spectrum showed the bonding through azomethizine N and ring N.

Keywords: - benzothiazolyl hydrazones, Metal ion chelates.

I. INTRODUCTION

Chemistry of ligand:- The coordination chemistry of hydrazones is an intensive area of study and numerous metal complexes of these ligand have been investigated[1]. The development of the field of bioinorganic chemistry has increased the interest in Schiff base complexes, since it has been recognized that many of these complexes may serve as models for biologically important species [2-4]. The hydrazones metal complexes have found application in various process like sensor, medicine, nonlinear optics etc. they are well known for their metal binding ability and exhibit interesting coordinating behavior with transition metal ion [5,6]. Coordination compound derived from aryl hydrazones have been reported because of their anti-tuberculosis, antimicrobial and corrosion inhibitor[7-9]. Hydrazones have been drawing much attention from coordination chemistry to transition metal[10]. In the context of the above application we have tried to the synthesis and characterization of transition metal complexes of 2-(4′-dimethyl amino phenyl)-4-bromo-6-ethoxy benzothiazolyl hydrazones. Prepared complexes were dried and the physical and chemical properties were recorded. analysis of the complexes and different spectral studies like I.R. , Electronic spectra of the complex were used for find out the donor site of the ligand.

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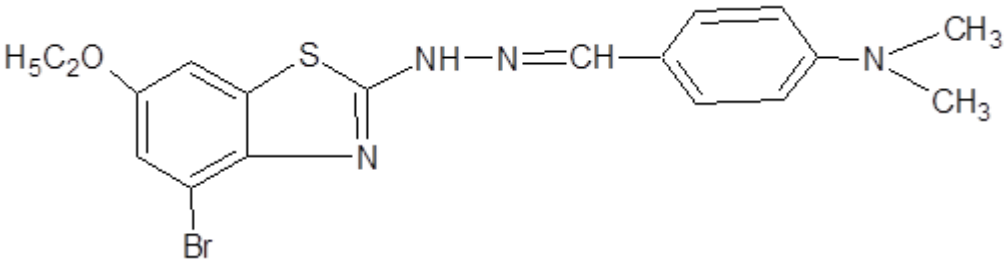
II. SYNTHESIS OF LIGAND

Preparation of 2-(4′-dimethylamion phenyl)-4-bromo-6-ethoxy benzothiazolyl hydrazones from 4-bromo-6-ethoxy benzothiazolyl hydrazones. To the ethanolic solution of 4-bromo-6-ethoxy benzothiazol was added in ethanolic solution of 4-dimethylaminobenzaldehyde. The mixture was refluxed on water bath for two hours. Obtained solid is cooled filtered, washed with ethanol and recrystallized from hot benzene

Structure of ligand.



2-(4′-dimethylamion phenyl)-4-bromo-6-ethoxy benzothiazolyl hydrazones

Physical parameter-

III. SYNTHESIS OF COMPLEXES.

i) Synthesis of Bis 2-(4′-dimethylamion phenyl)-4-bromo-6-ethoxy bemzothiazolyl hydrazones Cr III chloride complex

100 ml 0.1 M $CrCl_3.6H_2O$ were prepared in alcohol and 2-(4′-dimethylamion phenyl)-4-bromo-6-ethoxy bemzothiazolyl hydrazones, 0.2 M solution were prepared in ethyl alcohol. These two solutions were mixed and transfer into 500 ml round bottom flask attached water condenser, 6.5 pH is of the reaction mixture were adjusted by adding basic buffer solution pH-10. Reaction mixture were fefluxed for one hour in water bath. The precipitate was obtained . it is digested, after cooling it is filtered through buckner funnel , the precipitate of complex were furified by washing with ethyl alcohol, the complex were dried by keeping it in oven. The product was packed into sample bottle.

ii) Synthesis of Bis 2-(4′-dimethylamion phenyl)-4-bromo-6-ethoxy bemzothiazolyl hydrazones Mn II chloride complex

100 ml 0.1M alcoholic solution of $MnCl_2.4H_2O$ were treated with 100 ml of alcoholic ,0.2 M 2-(4′-dimethylamion phenyl)-4-bromo-6-ethoxy bemzothiazolyl hydrazones in 500 ml flask. The Ph of reaction mixture were kept 6-8 by adding alcoholic solution of basic buffer solution drop by drop. The precipitate was further digested and cooled and the precipitate was filtered through Buckner funnel, the precipitate was washed with alcohol and dried it by keeping in oven.

IV. PHYSICAL PARAMETER AND ELEMENTAL ANALYSIS

Decomposition point was determined with the help of melting point apparatus by open capillary methos. M:L ratio was determined by heating known weight of complex in platinum crucible .Metal ion percentage in a complex is determined by E.D.T.A. titration method. Chloride is estimated by Mohr's method.
Physical parameter and analytical data of the Cr(III), Mn(II), complexes and ligand 2-(4′-dimethylamion phenyl)-4-bromo-6-ethoxy bemzothiazolyl hydrazones (MAPBEBTH). Are given in table no. 5.1. metal ligand ratio and empirical formula were assigned on the basis of T.G.A. measurement and elemental analysis is given in table no.5.2.

V. CHARACTERIZATION OF COMPLEXES

U.V. and visible spectra of complexes and ligand recorded on U.V. SHIMADZU UV3600 spectrophotometer at range 200-800 nm by using D.M.S.O. solvent at P.G. department of chemistry Shivaji University Kolhapur. I.R. spectra of ligand were recorded at Yeshwant Mahavidyala Nanded and I.R. spectra of complexes are recorded at PERKIN ELMER spectrum-100/79720 by KBr platelate method at Shivaji University Kolhapur. Thermo gravimetric analysis (T.G./D.T.A.) measurement are recorded on thermo gravimetric analyzer on TA model S.T.D-2960 at Shivaji University Kolhapur in Nitrogen atmosphere .XRD pattern of the complexes recorded on PW-3719/1710 Philips –Holland spectrometer at Shivaji University Kolhapur and E.S.R. is recorded at IIT, pawai, Mumbai.

VI. RESULT AND DISCUSSION

The complexes of Cr(III), Mn(II). are prepared with the ligand 2-(4′-dimethylamion phenyl)-4-bromo-6-ethoxy bemzothiazolyl hydrazones (MAPBEBTH). This complexes are coloured. These complexes are soluble in D.M.S.O. but insoluble in water, alcohol, chloroform, and D.M.F. Decomposition point of complexes are in the range of 240-300°C . It suggest that they have good thermal stability at room temperature
Table.5.1: physical property of (MAPBEBTH) metal complexes.

Complex	color	D.P.	Yield%	%Cl
[Cr (MAPBEBTH)$_2$Cl $_2$]H$_2$O Cl	Light blue	272-276	70	10.492
[Mn (MAPBEBTH)$_2$ (H$_2$O) $_2$] Cl$_2$.	Creamy	270-278	63	7.097

Table.2.2: Percent C,H,N and metal ion in HMPBMBTH metal *complex*

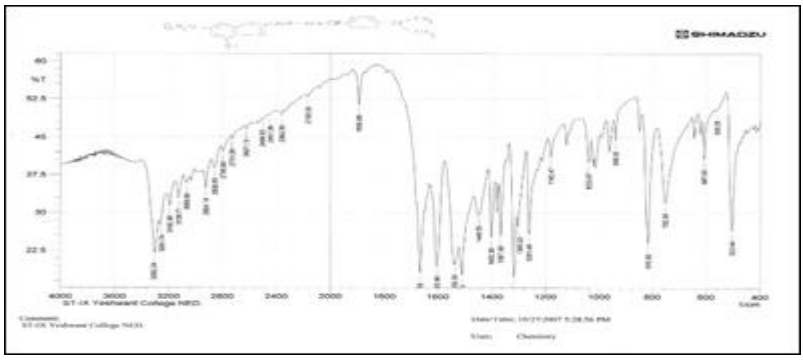
compond	M.wt	Empirical formula	%C	%H	%N	%M
MAPBEBTH	419.20	$C_{18}H_{19}N_4BrSO$	51.576	4.532	13.365	-
[Cr (MAPBEBTH)$_2$Cl $_2$]H$_2$O Cl	1015	$C_{36}H_{40}Cl_3CrN_8S_2Br_2O_3$	42.602	3.940	11.034	5.124
[Mn (MAPBEBTH)$_2$ (H$_2$O) $_2$] Cl$_2$	1000.3	$C_{36}H_{42}Cl_2MnN_8S_2Br_2O_4$	43.228	4.198	11.196	5.488

U.V.

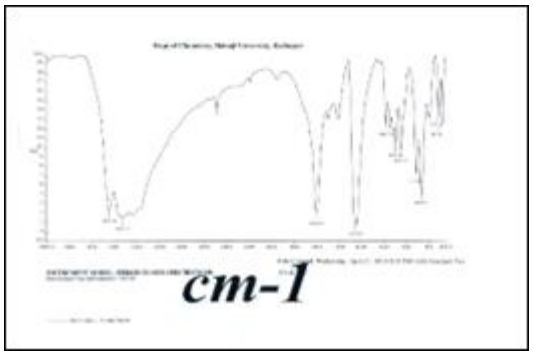
U.V. and visible spectra of complexes and ligand recorded on U.V. SHIMADZU UV3600 spectrophotometer at range 200-800 nm by using D.M.S.O. solvent at P.G. department of chemistry Shivaji University Kolhapur. Theligand 2-(4′-dimethylamion phenyl)-4-bromo-6-ethoxy bemzothiazolyl hydrazones has exhibited one characteristic maxima in U.V. region at 246 nm where in [Cr (MAPBEBTH)$_2$Cl$_2$]H$_2$O Cl complex it is shifted at 258 nm and in complex [Mn (MAPBEBTH)$_2$ (H$_2$O)$_2$] Cl$_2$. Band is observed at 266 nm this shifteing of band is due the complex formation.

I.R. spectra-

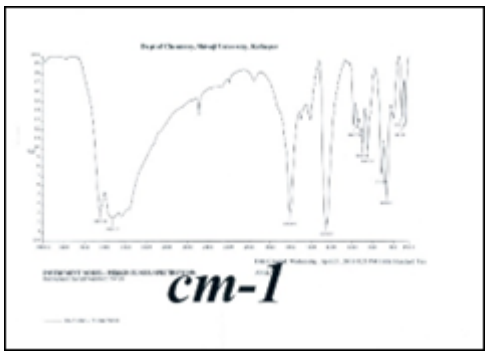
A sharp strong band is observed in I.R. spectra of ligand at 1665 in ligand it is due to the C=N of thiazole ring nitrogen. This band is shifted in Cr^{+3} complex as well as in Mn^{+2} complex. In Cr^{+3} complex it is observed at 1645 and in Mn^{+2} complex it is observed at 1606 this shifting of band in both complexes it indicate that the Nitrogen of thiazole ring is involve in the complex formation. Another band is observed at 1602 in ligand. This band is support to the presence of C=N (azomethazine) group in ligand. This band is shifted in Cr^{+3} and Mn^{+2} complexes. The band is observed in Cr^{+3} complex at 1590 where in Mn^{+2} complex it is observed at 1510. This shifting of band indicate that the azomethazine nitrogen involve in the complex formation. One band is observed at 3302 in ligand it may be due to the presence of N-H group. This band is not observed in Cr^{+3} and Mn^{+2} complexes it is evidence that the N-H group is involve in the complex formation. One more band is observed at 481 where as in Mn^{+2} complex it is observed at 468 but not in ligand it indicate that there is a formation of M-L bond.Thus the ligand act as a bidentate. It coordinate through azomethazine, Nitrogen of thiazole ring .



I.R.of (MAPBEBTH



I.R. of [Cr (MAPBEBTH)$_2$Cl$_2$]H$_2$O Cl



I.R. of [Mn (MAPBEBTH)$_2$ (H$_2$O)$_2$] Cl$_2$.

Thermal analysis.:-

Results of TG analysis were used to determine the nature of water molecules present and decomposition pattern of the complexes. Lattice water molecules were lost in the 70-110 °C temperature range while coordinate water molecules were eliminated at relatively high temperature range of 150-240 °C. complet decomposition of ligand occur at about 800 °C and observed residue corresponds to respective metaloxide.
Present losses of material as obtained from TGA curve are good agreement with calculated percent loss in mass. Thermo gravimetric results coincide well with DTA peaks. TGA/DTA scans are depicted in fig.

TGA/DTA of [Cr (MAPBEBTH)$_2$Cl $_2$] H_2O Cl

TGA/DTA plot of [Cr (MAPBEBTH)$_2$Cl $_2$] H_2O Cl shows five peak of decomposition. The first peak is observed at the temperature range 50-130°C and 9.023% loss of mass is observed . This loss of mass is due to the elimination of lattice chloride and water molecule from the compound. In second peak 18.047% loss is observed in the temperature range 130-280°C. The loss of mass is due to the elimination of two molecule of $N(CH_3)$ and ethoxy group form the complex. Third peak is observed in the temperature range 280-430°C and 15.411% mass is lost . This loss in mass is due to the elimination of two benzene ring from the molecule. In the fourth peak 31.228% mass is lost in the temperature range 430-570°C.The loss of mass is due to the elimination of two bromobenzene rings from the complex. Last peak is observed in the temperature range 570-760°C . In this peak 20.277% mass is lost. This loss in weight is due to the elimination of thiazole ring part and its substituent chain NH-N=CH. From the temperature 760°C curve of graph show constant value. It indicate that remaining mass is of metal oxide. Calculated value are coincide with observed value.

TGA/DTA [Mn (MAPBEBTH)$_2$ (H_2O) $_2$] Cl_2. complex

TGA/DTA plot of [Mn (MAPBEBTH)$_2$ (H_2O) $_2$] Cl_2 Complex Shows five peaks of decomposition. First peak is observed at temperature range 50-110°C and 6.208% mass is lost. This loss in mass is due to the elimination of lattice chloride from the complex. In second peak 9.356% mass is lost in the temperature range110-260°C. This loss in weight is due to the burning of coordinate chloride and water molecule. Observed values are in good agreement with calculated values. Third peak is observed at the temperature range 260-490°C . In this temperature range 15.564% weight is lost form the complex compound . this loss of mass is due to the elimination of $N(CH_3)_2$ and OC_2H_5 group from complex. Fourth peak is observed at temperature range 490-620°C and 40.622% weight is lost. This loss in weight is due to the elimination of bromobenzen ring. In last fifth peak 17.488% mass is lost in the temperature range 620-770°C this loss in mass is due to the elimination of thiazole ring part and its substituent chain NH-N=CH. Form the temperature range 770°C curve of the graph show constant value of weight of complex it indicate that remaining mass is of metal oxide. Observed figures and calculated figures are approximately equal.

Temp. range °C	% loss	Nature of decomposition
50-130	9.023(9.087)	Lattice chloride &water molecule
130-280	18.047(18.022)	$N(CH_3)_2$ & OC_2H_5

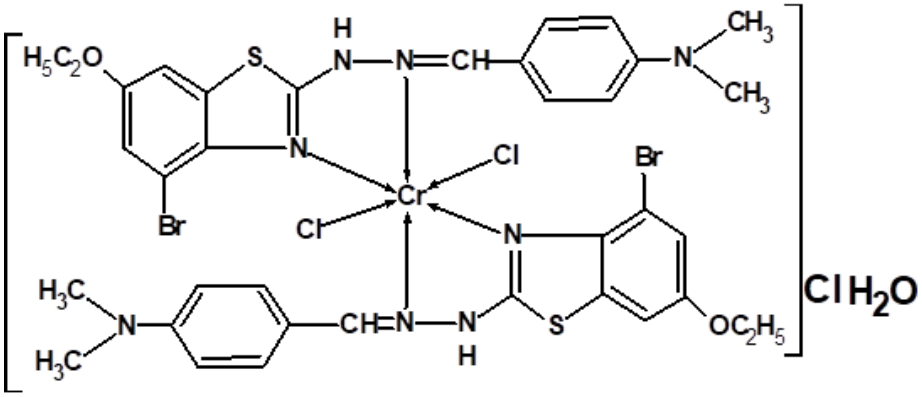
280-430	15.411(15.241)	Two benzene ring
430-570	31.228(31.385)	Two bromo Benzene ring
5570-760	20.277 (20.262)	Thiazole ring part and substituted chain.

Thermal decomposition value of [Cr (MAPBEBTH)$_2$Cl $_2$]H$_2$O Cl complex

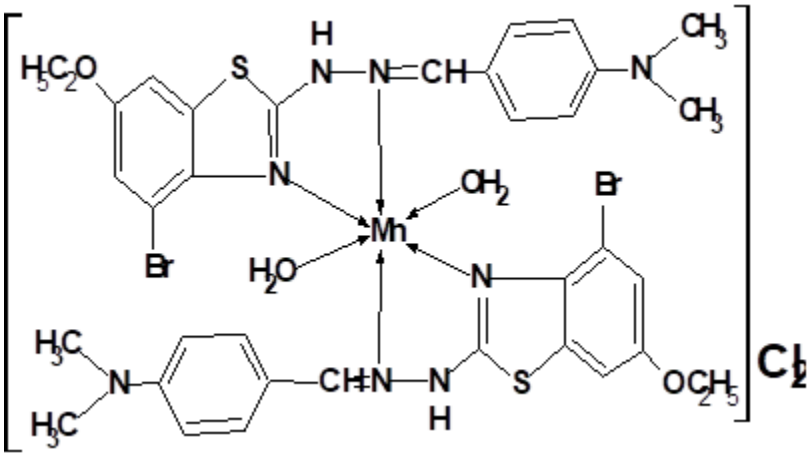
Temp. range °C	% loss	Nature of decomposition
50-130	9.023(9.087)	Lattice chloride &water molecule
130-280	18.047(18.022)	N(CH$_3$)$_2$ & OC$_2$H$_5$
280-430	15.411(15.241)	Two benzene ring
430-570	31.228(31.385)	Two bromo Benzene ring
5570-760	20.277 (20.262)	Thiazole ring part and substituted chain.

Thermal decomposition value of [Mn (MAPBEBTH)$_2$ (H$_2$O) $_2$] Cl$_2$metal

Proposed structure of complexes

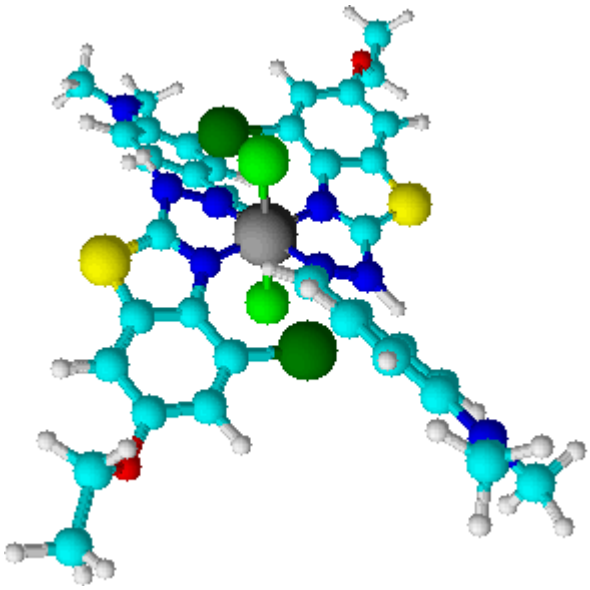


Proposed structure of [Cr (MAPBEBTH)$_2$Cl$_2$] Cl H$_2$O

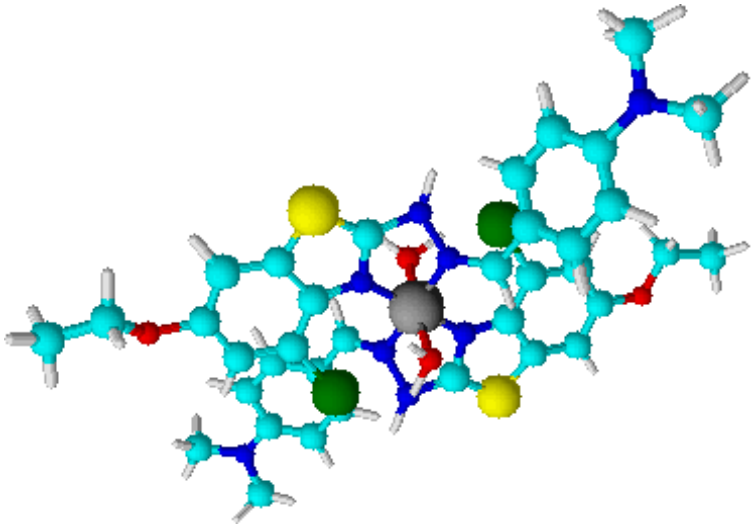


Proposed structure of [Mn(MAPBEBTH)$_2$ (H$_2$O) $_2$] Cl$_2$H$_2$O

Proposed 3D structure metal complexes



$[Cr(MAPBEBTH)_2Cl_2]$ Cl H_2O



$[\ Mn(MAPBEBTH)_2\ (H_2O)_2]\ Cl_2H_2O$

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An Efficient One Pot Synthesis of Polyhydroquinolines Using TS1 Catalyst Under Solvent Free Conditions

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ABSTRACT

The synthesis of polyhydroquinoline derivatives via Hantzsch condensation is excellent route by using four component coupling reaction of aldehydes, dimedone, ethyl acetoacetate and ammonium acetate in the presence of heterogeneous catalyst TS1 under solvent free condition.

Keywords: Aldehyde; Dimedone; TS1 catalyst; Hantzsch reaction.

I. INTRODUCTION

4 Substituted 1,4 dihydropyridine (1,4-DHP) nucleus is a fertile source of biologically important molecules possessing various important pharmacological properties such as vasodilator, antihypertensive, bronchodilator antitherosclerotic, hepto-protective, antitumor, antimutagenic , geroprotective and antidiabetic agents[1-4]. From recent studies 1-4 DHP shows several medicinal applications which include neuroprotectant and platelet anti-aggregatory activity, in addition cerebral antiischemic activity in the treatment in the of Alzheimer's disease [5-7]. An efficient Hantzsch condensation polyhydroquinoline derivatives via a four component coupling reaction of aldehydes, dimedone, ethyl acetoacetate and ammonium acetate in the presence of $HClO_4$-SiO_2 under solvent free conditions at 90°C temperature[8]. $Yb(OTf)_3$ promoted one pot synthesis of polyhydroquinoline derivatives via Hantzsch reaction of aldehydes, dimedone, ethyl acetoacetate and ammonium acetate at ambient temperature in excellent yield[9]. Photocatalytic oxidation of 1,4 dihydropyridine to pyridine has been extensively investigated[10]. Here in the present work, developed new efficient method for synthesis of polyhydroquinoline using TS1 catalyst under solvent free conditions.

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II. MATERIAL AND METHODS:

A mixture of aldehyde (1mmol), dimedone (1mmol), ethyl acetoacetate (1mmol), ammonium acetate (1.5mmol),TS1 (50mg) were refluxed under solvent free conditions. The reaction was confirmed by thin layer chromatography, the resulting solid product was treated with EtOAc followed by water and a brine solution and dried with anhydrous Na_2SO_4. The solution was concentrated in vaccum to afford the crude product. The pure product was obtained by further recrystallization using absolute alcohol.

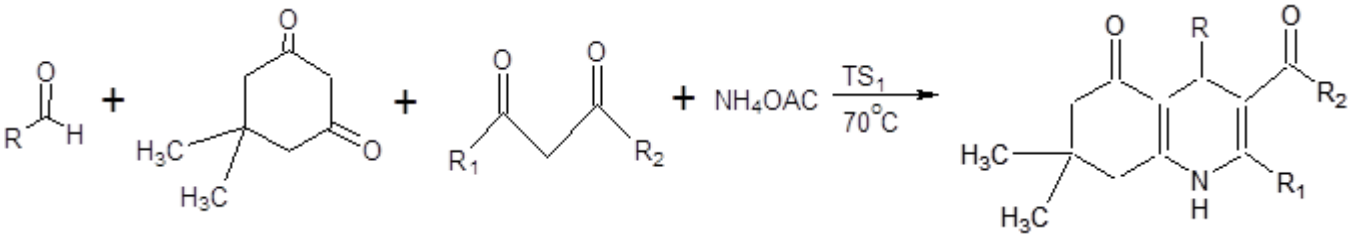

Table: TS1 catalyzed Hantzsch condensation for synthesis of polyhydroquinolines derivatives under solvent free conditions.

Entry	R	R1	R2	Time (min.)	Product	Yield	Melting point (°C) Observed	Melting point (°C) Reported
1	C_6H_5	CH_3	OEt	20	2a	85	203-204	202-204[9]
2	4-F-C_6H_4	CH_3	OEt	22	2b	82	185-186	184-186[9]
3	4-OCH_3-C_6H_4	CH_3	OEt	24	2c	84	256-257	257-259[9]
4	4-CH_3-C_6H_4	CH_3	OEt	21	2d	80	261-262	260-261[9]
5	3-NO_2-C_6H_4	CH_3	OEt	22	2e	82	178-179	177-178[10]

The structure of the product were determined from their spectroscopic (UV, IR, NMR, Mass) data.

III. SPECTROSCOPIC DATA

Ethyl-1,4,7,8-tetrahydro-2,7,7-trimethyl-4-(4-fluorophenyl)-5(6*H*)-oxoquinolin-3-carboxylate (2b). Yellow solid, mp 185-186 °C. IR (KBr): 3292, 2959, 1696, 1649, 1608, 1487, 1380, 1219, 1025, 764 cm-1. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 1.18 (t, J = 7.3 Hz, 3H, CH_3), 2.13-2.25 (m, 4H, 2 ×CH_2), 2.38 (s, 3H, CH_3), 4.05 (q, J = 7.33 Hz, 2H, CH_2), 5.02 (s, 1H, CH), 5.8 (s, 1H, NH), 6.85-6.89 (m, 2H, ArH), 7.23-7.27 (m, 2H, ArH). 13C NMR (75 MHz, $CDCl_3$) δ 14.1, 18.2, 26.4, 29.0, 32.1, 35.2, 50.1, 50.3, 59.0, 103.4, 110.0, 114.2, 114.3, 114.4, 129.0, 129.1, 144.1, 145.1, 149.4, 169.8, 194.2. LCMS: m/z = 356 (M-H)-. Anal. Calcd for $C_{21}H_{24}NO_3F$: C, 70.58; H, 6.72; N, 3.92; F, 5.32. Found: C, 70.52; H, 6.79; N, 3.87; F, 5.28.

Ethyl-1,4,7,8-tetrahydro-2,7,7-trimethyl-4-(4-methoxylphenyl)-5(6*H*)-oxoquinolin-3-carboxylate (2c). Yellow solid, mp 256-257 °C. IR (KBr): 3276, 2956, 1703, 1648, 1606, 1496, 1381, 1215, 1031, 765 cm-1. 1H NMR (200 MHz, $CDCl_3$ + DMSO-d_6): δ = 0.95 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.21 (t, J = 7.2 Hz, 3H, CH_3), 2.01-2.10 (m, 4H, 2 ×CH_2), 2.30 (s, 3H, CH_3), 3.70 (s, 3H OCH_3), 4.00 (q, J = 7.2 Hz, 2H, CH_2), 4.80 (s, 1H, CH), 6.65 (d, J = 7.3 Hz, 2H, ArH), 7.10 (d, J = 7.3 Hz, 2H, ArH), 8.65 (s, 1H, NH). 13C NMR (75 MHz, DMSO-d6)

δ 14.1, 18.2, 26.4, 29.1, 32.1, 34.7, 50.2, 50.5, 54.8, 58.9, 103.2, 110.1, 113.0, 113.1, 128.2, 128.3, 139.8, 144.6, 149.1, 157.2, 166.9, 194.2. LCMS: m/z = 368 (M-H)-. Anal. Calcd for $C_{22}H_{27}NO_4$:C, 71.54; H, 7.31; N, 3.79; Found: C, 71.59; H, 7.35; N, 3.84.

IV. RESULT AND DISCUSSION

The classical method for the preparation of polyhydroquinoline derivatives involves the reaction of aldehyde with ethyl acetoacetate and ammonia, in acetic acid or in refluxing in alcohol. However, this method suffers from several drawbacks such as long reaction time, excess of organic solvent and lower product yield[11]. All the starting materials in the ratio of 1:1:1:1 mixture of aldehyde, dimedone, ethyl acetoacetate and ammonium acetate catalyzed by TS1 catalyst is a green reaction in solvent free condition.

V. CONCLUSION

In conclusion, we reported TS1 recyclable and reused green catalyst for Hantzsch reaction. Some of the efficient feature for this method such as simplicity of the experiment, mild reaction condition, high yield, short reaction time and easy work up. Hence such simple and lucidness makes this method attractive for the synthesis of polyhydroquinoline derivatives.

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One Pot Three Component Eco-Friendly Synthesis of Quinoline-3-Carbonitrile Derivatives

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ABSTRACT

New derivatives of quinoline-3-carbonitrile have synthesized with a direct one pot three component eco-friendly protocol. The present protocol displays a mild and easy access for the Knovenagle condensation utilizing heterocyclic aldehyde, 2-cyanoacetohydrazide, and substituted anilines. The method includes use of recyclable catalyst Bleaching earth clay (PH12.5) incorporated with the PEG-400 as a green solvent. All the synthesized compounds were characterized for their spectral analysis.

Keyword: Bleaching earth clay (BEC), PEG-400, Heterocyclic aldehyde, recyclability.

I. INTRODUCTION

The predominant occurrence of the quinoline-3-carbonitrile derivative in various natural products and established medicinal compounds[1-3] had proven to be a versatile scaffold in organic and medicinal chemistry. quinoline-3-carbonitrile have recognized to acquire varied biological activities such as antibacterial[4], antiviral[5], anticancer[6], antifungal[7], antimalarial[8], anti H.I.V[9], anti-inflammatory[10]. Quinoline-3-carbonitrile derivative are acknowledged medicinal compounds known to be present in the bioactive natural products[11]. Heterocyclic aldehydes are proven to contain varied biological activities[12]. By interpretating these points we combine the heterocyclic aldehydes with anilines and 2-cyanoacetohydrazide assuming that the present combination may lead to formation of improved biological hybrid.

There is always been quest for advancement of the synthetic rout for the conversion of readily available reagent in to widely used organic compounds. For accomplishing this multicomponent reaction (MCR) are recognized as an important tool from economic as well as environmental point of view[13]. Along with the MCR method, use of green solvent is also considered to be an environmental benign access. Amongst the green solvents used for MCR strategy PEG-400 is considered to be well known green solvent[14].

In the previous literature there are abundant synthetic strategies for the synthesis of quinoline-3-carbonitrile derivatives[15]. Development of an heterogenous catalyst for the synthesis of numerous important organic

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motifs was always been a center of interest for organic chemistry students[16-17]. Ease of handling, reusability, easy extraction are some peculiar advantages of heterogenous catalysts. Amongst those heterogeneous catalysts Bleaching earth clay (BEC) is considered as a remarkable heterogenous catalyst for various organic transformations[18]. Taking in account these facts we represent an MCR protocol for synthesis of by Consolidation of heterocyclic aldehydes with anilines and 2-cyanoacetohydrazide Manipulating Bleaching earth clay as catalyst and PEG-400 as green solvent.

II. RESULT AND DISCUSSION

A facile one pot three component protocol for the synthesis of new quinoline-3-carbonitrile derivative **4a-j** is reported by utilizing equimolar heterocyclic aldehydes **2a-j**, anilines **3a-c** and 2-cyanoacetohydrazide **1 Scheme 1**. The synthetic protocol commences with sequential addition of 2-cyanoacetohydrazide and heterocyclic aldehydes in round bottom flask previously filled with catalytic amount of BEC and PEG-400 as green solvent, after completion of reaction as indicated by TLC the anilines was added in the same pot and the reaction mixture was further stirred at 80°C for the formation of product. the first attempt was made using the Triethylamine as a catalyst which results in formation of the product with 50% yield and time required for completion of reaction was 65 minutes Entry1 Table1. Observing these results, we moved for other catalysts piperidine and morpholine Entry 2and 3 Table 1 respectively which the outcomes of 40 and 30% yield with the time of 70 and 60 minutes. When we moved for using BEC as a catalyst 1 Wt% resulting in production of improved 60% yield Entry 4 table1. Enthused with these results we further investigate different wt% compositions of BEC (pH 12.5). We came to investigation that satisfactory yield was obtained when we utilized 15wt% of BEC. The yield was found to hampered when 10 wt% and 20wt% BEC were used Entry 5 and 7 Table 1. However, there was no formation of product when reaction was carried out in absence of catalyst when stirred at RT Entry 8. Even though when reaction mixture was stirred at 80°C without catalyst the formation of product was not observed Entry 9 Table 1. The optimized reaction conditions were found when 15wt% of BEC was used.

Table1: Optimized reaction conditions

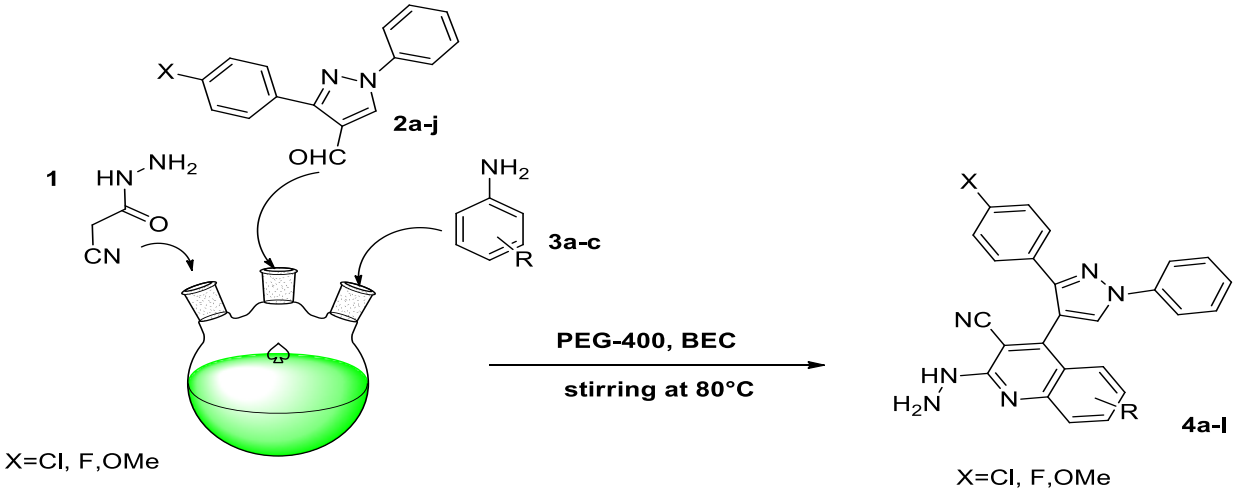
Entry	Catalyst (Mol/wt%)	Temp (°C)	Time (Min)	Yield of 4a (%)
1	Triethylamine (Mol%)	70	65	50
2	Piperidine (Mol%)	80	70	40
3	Morpholine (Mol%)	80	60	30
4	Bleaching earth Clay 1 wt%	80	50	60
5	Bleaching earth Clay 10 wt%	80	40	70
6	Bleaching earth Clay 15 wt%	80	35	90
7	Bleaching earth Clay 20 wt%	80	20	70
8	No catalyst	**RT**	70	0
9	No catalyst	80	80	0

[a] Reaction progress was monitored by thin layer chromatography (TLC)

[b] Yield refers to isolated yield

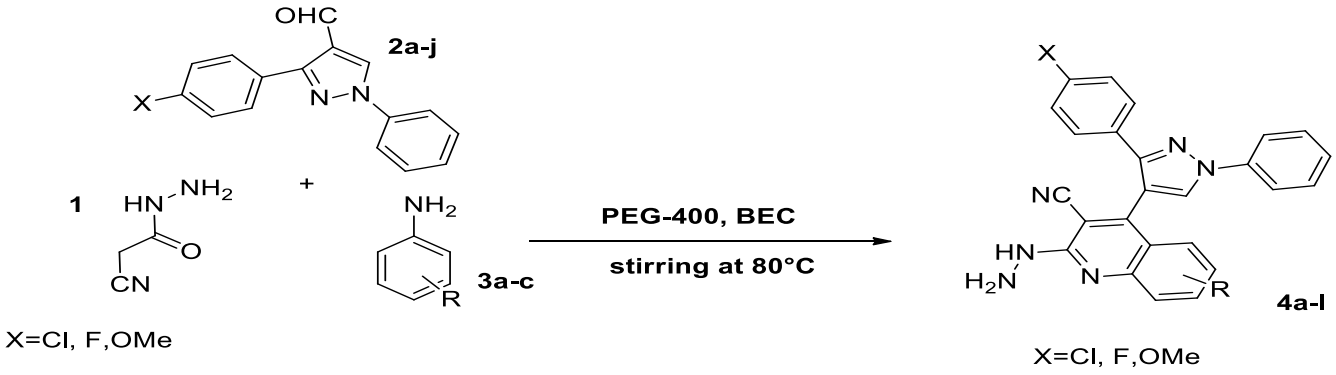
With these optimized conditions we initiated to find the substrate scope the reaction condition was found to operate for varied substrate scope Table 2.

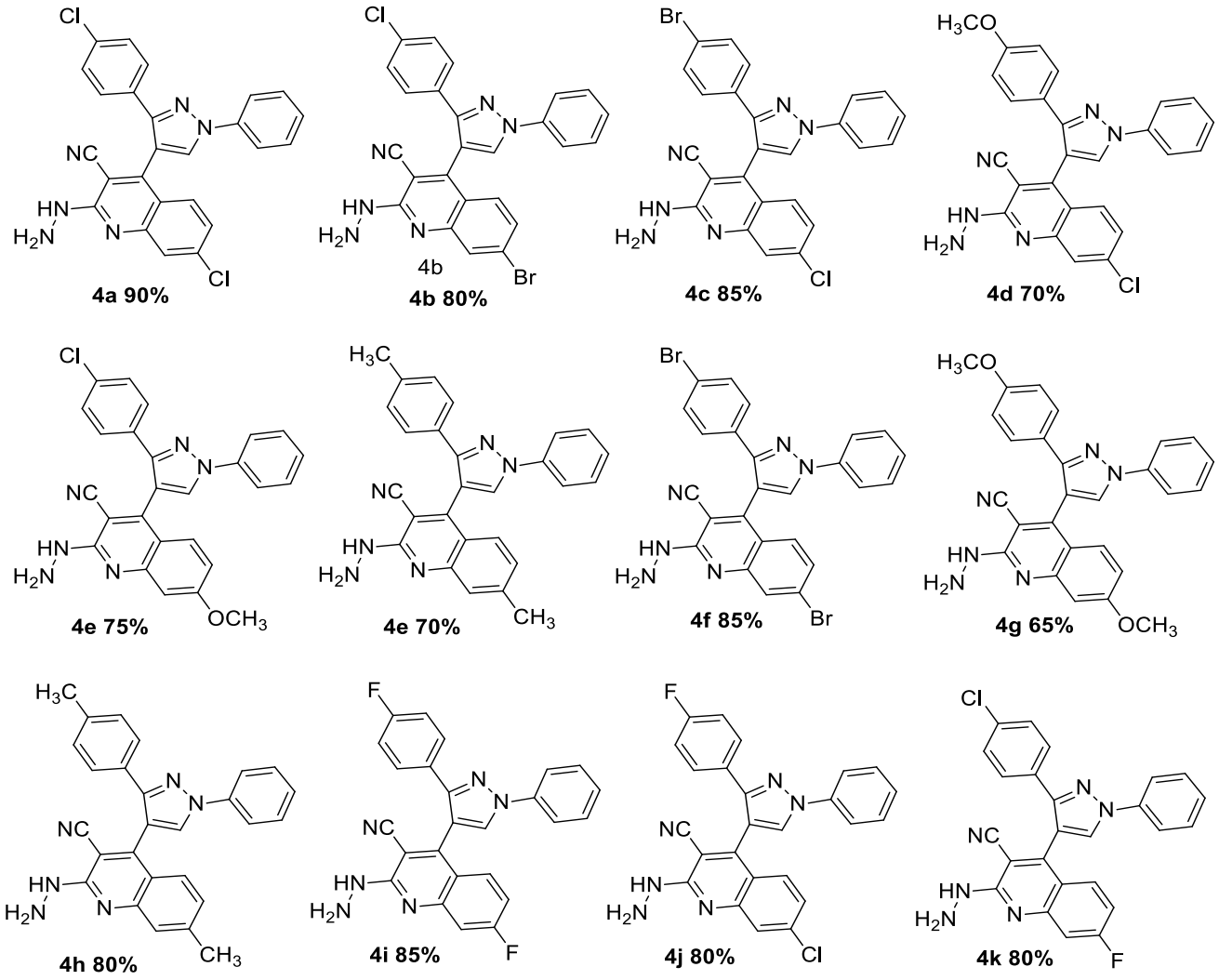
Scheme 1



The finding of the substrate scope indicates that the MCR strategy allows variety of substrate to undergo smoothly with formation of product with satisfactory yield. Interpretation of the yield of the substrate scope indicate that the reactant with electron donating group either on aldehyde 2a-j or on the anilines 3a-c renders the product yield. The substrates with electron withdrawing groups on the aldehydes or on the anilines are providing the products with good yield.

Table 2 Substrate Scope

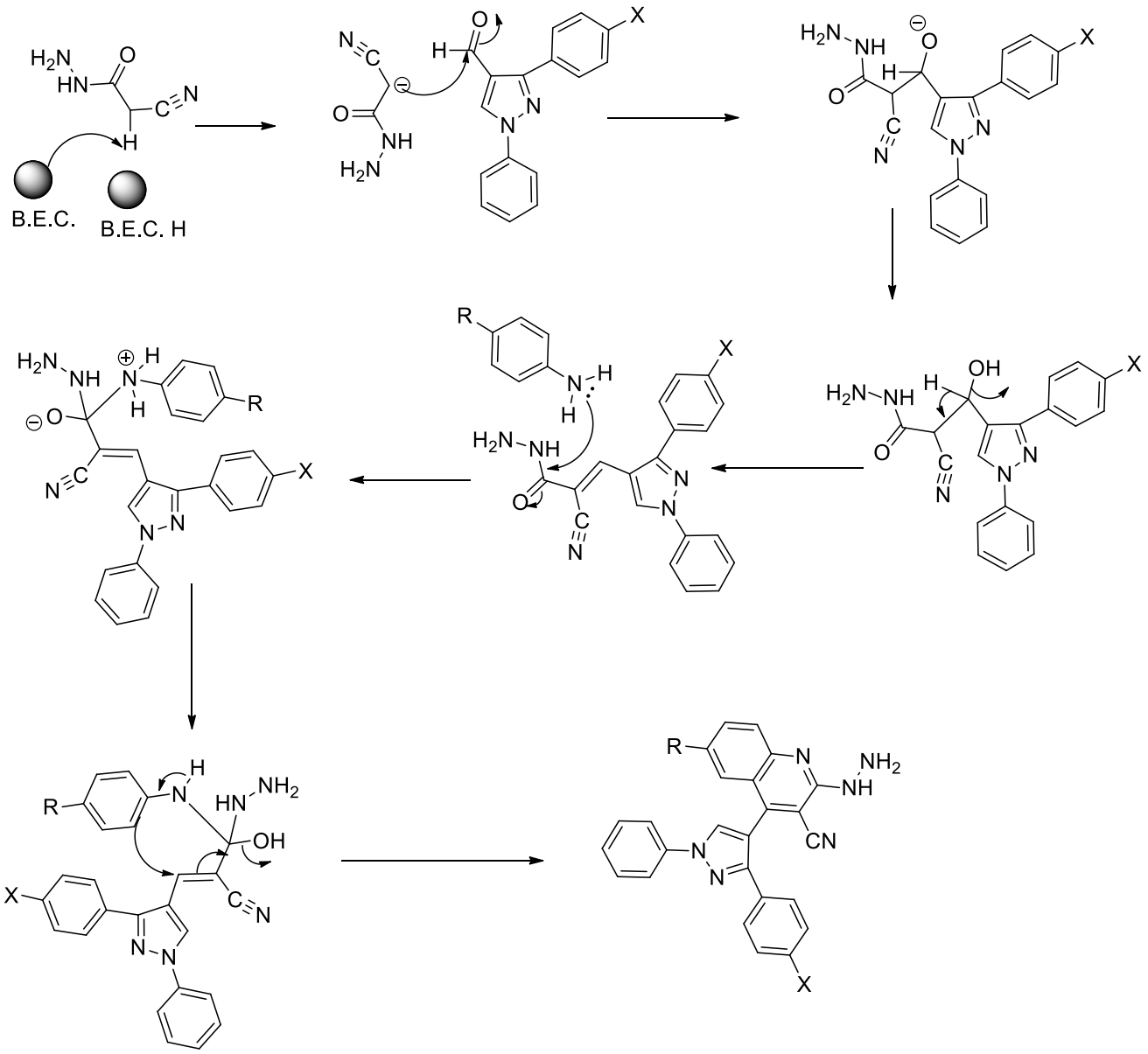




[a]Yield refers to the isolated product after column chromatography

The plausible mechanistic path was proposed in Scheme 2. The mechanism indicate reaction was proceed through abstraction of proton from 2-cyanoacetohydrazide by BEC then the anion attack on the carbonyl of heterocyclic aldehyde. Furthermore addition of substituted anilines leads to formation of final product.

Scheme 2 Plausible mechanism



III. CONCLUSION

The proposed protocol provides an easy access for the synthesis of quinoline-3-carbonitrile derivatives. the MCR strategy for the synthesis is woven with the environmental benign approach through the use of BEC as a catalyst and PEG-400 as a solvent. The protocol delivers an efficient access for the formation of new hybrid product with coupling of easily available reactants which may lead to improved biological activities.

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Highly Proficient Extractive Studies on The Behaviour of Neodymium (III) Assisted By 2-Octylaminopyridine from Weak Succinate Media

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ABSTRACT

The extraction behaviour studies of neodymium(III) from sodium succinate medium at pH 7.5 with 2-octylaminopyridine in xylene. The extracted neodymium(III) was stripped with 0.1 M HCl from the organic phase and determined by arsenazo. Physicochemical parameters like diluents study, phase ratio, and loading capacity to name a few were optimized for the quantitative extraction of neodymium(III). Neodymium(III) was selectively extracted and separated from binary and ternary mixtures.

Keywords: - Extraction, Neodymium (III), 2-octylaminopyridine, Succinate media.

I. INTRODUCTION

Neodymium is one most abundant element in earth crust but never occur in nature as a native element, its main source is ores of Monazite, Xenotime and Bastnaesite [1]. Neodymium is used as a permanent magnet, neodymium, boron, and iron tetragonal alloy ($Nd_2Fe_{14}B$) have been used in a wide range of applications requiring high coercive force and high energy product (e.g. Hybrid electric vehicles and miniature high capacity hard disk drives) [2,3]. Neodymium is rare and valuable therefore their recycling and extraction are mandatory for technical, environmental, economic, and resource conservation reasons.

Separation of neodymium from natural resources by environmentally friendly approaches is most significant. Therefore, man strategies for the isolation of neodymium have been developed. Among which solvent extraction is the most often used technique. Different extractants have been used for the extraction of neodymium such as 8-hydroxyquinoline [4], Cyanex 921 [5], trioctylphosphine oxide (TOPO) and trialkylphosphine oxide [6], 2-ethylhexylphosphoric acid [7]. Tributylposphate in supercritical carbon dioxide solvent has been successfully used for the quantitative recovery of neodymium [8]. Mono-2-ethylhexyl ester [9]. The extractantdialkylphospate in the ionic liquid has been studied for the extraction of neodymium [10].

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Long-chain crown ethers such as poly[dibenzo-18-crown-6] [11], dicycloheano-18-crown-6 [12], and TODGA [13] were used.

As per as the robustness of the work is concerned. In earlier work, Nd(III) was extracted with different extractants. However those required either mineral acid media, the high time of extraction, high concentration of extractant, etc. Whereas in the present method, the extraction was carried out in 0.005 M sodium succinate at pH – 7.5, and extractant concentration was 0.05 M indicating the method is relatively eco-friendly and a step ahead towards green Chemistry.

The proposed study aimed to develop a more greener and precise method for the extraction of Nd(III). Efforts have been made to optimize the extraction system. The novelty of the system lies in the minimum use of concentration of extractant and use of greener weak acid media. The method has a good recovery of solvent and does not require too much of instrumentation.

II. EXPERIMENTAL

Apparatus

Digital spectrophotometer optimized α was used for the absorption measurement using 1 cm quartz cells. An Elico digital pH meter model LI-127 was used to measure the pH. METLER TOLEDO was used for weighing operations model ML-204/-01 having accuracy 1×10^{-4} g.

Reagents

Standard Neodymium(III) 500 µg/ml stock solution

The stock solution of neodymium (III) was prepared to dissolve 1.165 g. of neodymium oxide in 40 ml of perchloric acid and the final volume was brought to 1000 ml with double distilled water.

2-Octylaminopyridine (2-OAP)

2-OAP was synthesized by Borsch and Petrukhin [14] and the working extractant solution having molarity (0.05M) was prepared in xylene.

Arsenazo-I

Arsenazo-I **(0.05**% w/v) was prepared by dissolving 0.05 g. of arsenazo-I (s. d. Fine-chem limited) in water.

Triethanolamine buffer

Added 200 ml 15% triethanolamine in 160 ml of 1M HNO_3 and 40 ml of water. Adjust the pH of the solution to 7.2 with dilute NH_3 or HNO_3.

All reagents and metal salts used are of analytical grade and their solutions were prepared in water and mineral acid.

Recommended Procedure

A solution containing 75 µg neodymium(III), was made to 0.005 M w/v with sodium succinate, and pH was brought to 7.5 with dilute mineral acid and base by maintaining total dilution volume to 25 ml and then transferred to 125 ml separatory funnel to this added 10 ml 0.05 M 2-OAP in xylene as an extractant and shaken for 5 min, two phases were allowed to disengage. The neodymium(III) extracted in the organic phase was stripped with 0.1 M HCl (3 × 10) ml as a strippant solution.

The stripped solution containing neodymium(III) was evaporated to moist dryness. To this added 5% sulphosalicyclic acid. After two minutes added 5 ml of the Arsenazo-I [15] (0.05% w/v) solution, 10 ml of triehanolamine buffer, water to 40 ml, and ammonia till the pH was 7.2. Transfer the solution to a 50 ml volumetric flask, diluted up to the mark with water, and measured the absorbance at 580 nm using reagent solution as a reference.

III. RESULTS AND DISCUSSION

Effect of pH

The formation of a complex of metal with a particular extractant and the subsequent extraction was greatly influenced by the pH of the solution. The influence of the pH on the extraction of neodymium(III), was studied in the range from 1-10 (Fig. 1). The required H^+ ion concentration at various pH was reached by adding dil. HCl or NaOH. The extraction of ion-pair complex of neodymium(III) was increased with pH and became quantitative in the pH range 7.0 - 8.2, above this optimum pH range neodymium(III) extraction decreases. Therefore 7.5pH was selected throughout the experiment.

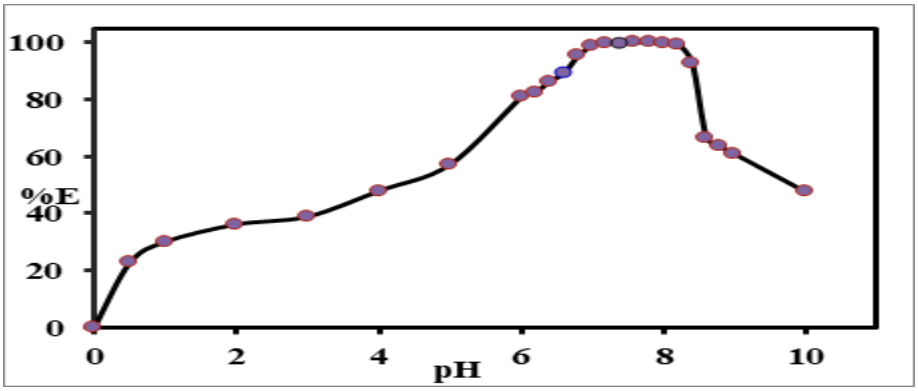

Fig. 1 Effect of pH on extraction of Nd(III) - 2-OAP complex.

Influence of 2-OAP concentration on extraction of neodymium(III)

The concentration of extractant is one of the most important factors for the extraction of any metal. Hence extraction performance of neodymium(III) greatly depended on the concentration of 2-OAP. To elucidate the effect of 2-OAP concentration on the neodymium(III) extraction, the experiment was carried out at a various concentration of 2-OAP from 0.001- 0.10 M (Fig. 2), and other parameters such as pH 7.5, 0.005 M sodium succinate, phase ratio 2.5:1 were kept constant and extraction was carried out. The results illustrate that the extraction commences at 0.001 M 2-OAP concentration and becomes quantitative in the range of 0.04-0.06 M,

further increase in concentration beyond 0.06 M there was a decrease in the extraction of neodymium(III). For the further study, 10 ml of 0.05 M 2-OAP was adopted as an optimum concentration of extractant for the quantitative extraction of neodymium(III). The recycling capacity of the reagent for quantitative extraction of neodymium(III) was observed to be three times.

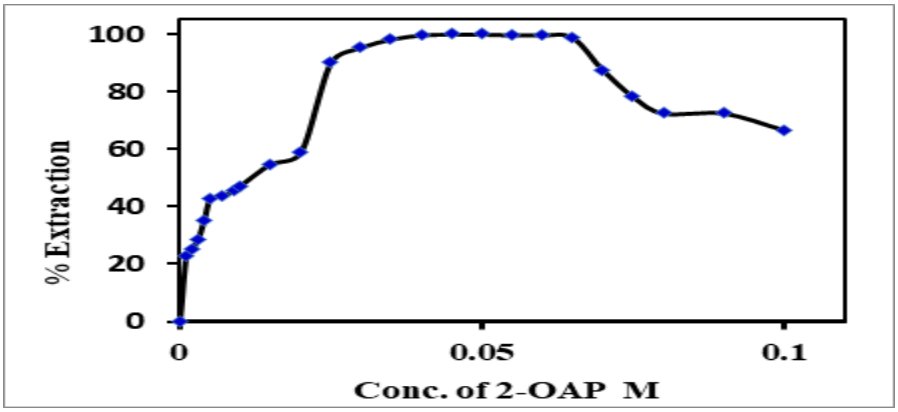

Fig. 2 Impact of conc. of 2- OAP on extraction of Nd(III)

Impact of weak organic acid concentration

The extraction of neodymium(III) was investigated at pH 7.5 with 10 ml of 0.05 M 2-OAP in xylene in the presence of a varying concentration of different weak organic anions like acetate, succinate, malonate and citrate. Quantitative extraction of neodymium(III) was found from succinate media. The weak acid curve of sodium succinate indicates that quantitative extraction was taking place in the concentration range of 0.003 to 0.010 M. In general procedure 0.005 M sodium succinate was recommended throughout the experiment (Fig. 3). The salicylate, malonate, citrate, and ascorbate do not give quantitative extraction of neodymium(III) as there was no formation of stable ion-pair complexes.

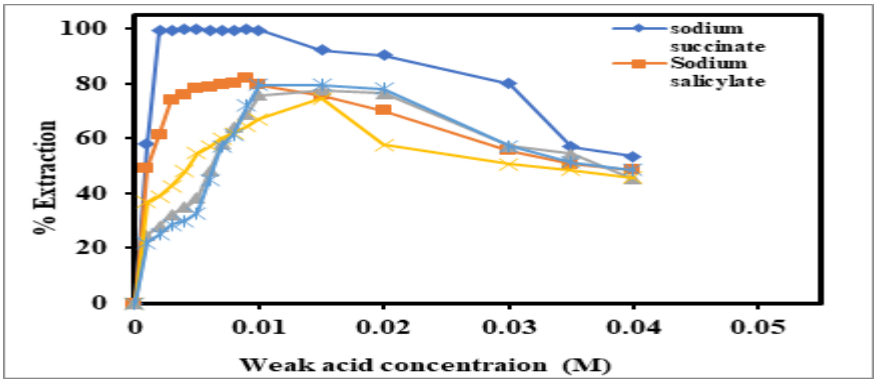

Fig. 3 Impact of weak organic acid concentration

Metal Loading Capacity

The extraction behaviour of neodymium(III) was studied concerning the metal loading capacity was demonstrated at a varying concentration of neodymium(III) in the range 25 µg to 900 µg. The analysis elucidates that the nearly hundred percent extractions take place in the range of 25 to 700 µg. It means up to 700 µg of neodymium(III) 10 ml of 0.05 M 2-OAP is sufficient and after 700 µg neodymium(III) decrease in

extraction demonstrates that there might be a deficiency of 2-OAP. Thus this study indicates that 700 µg of neodymium(III) is a maximum capacity for 10 ml 0.05 M 2-OAP.

Impact of stripping reagents on the extraction of neodymium(III)

Stripping is a back extraction and is reverse to that of extraction. If the extraction took place in a basic medium, usually the acidic strippants become more efficient and vice versa. The loaded organic phase of 2-OAP, was back-extracted with various stripping reagents as shown in Fig. 4. The results demonstrate that, the extraction efficiency of the different stripping reagents like ammonia buffer, water, ammonia, HCl, H_2SO_4 and HNO_3. The study illustrates that neodymium(III) was extracted with 2-OAP in xylene and stripped out completely with HCl, while other reagents showed incomplete stripping of neodymium(III) from the loaded organic phase. Therefore, the stripping of neodymium(III) from the loaded organic phase was carried out with 0.1 M HCl (3 × 10 ml) solution. The stripping mechanism-

[2-OAPH+Nd (succinate)$^{-}{}_2$ $_+$3 HCl⇌ 2-OAP +$NdCl_3$ +2 succinic acid

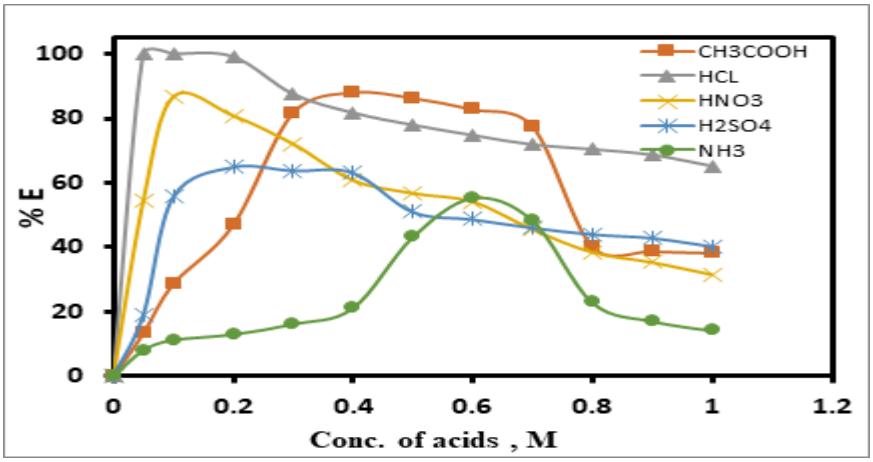

Fig. 4 Impact of strippants on extraction of Nd(III)

Solvent Study

The use of suitable solvents is very important in solvent extraction. The different solvents were studied such as amyl alcohol, 1,2-dichloroethane, xylene, n-butanol, kerosene, methyl *iso*butylketone, chloroform, toluene, benzene, carbon tetrachloride (Fig. 5). The extraction of neodymium(III) was found to be quantitative in xylene and toluene with 0.05 M 2-OAP. It was found that there was no significant relationship between dielectric constant and percentage extraction. Hence xylene was selected as a solvent for extraction of neodymium(III) which has low cost and showed clear phase separation.

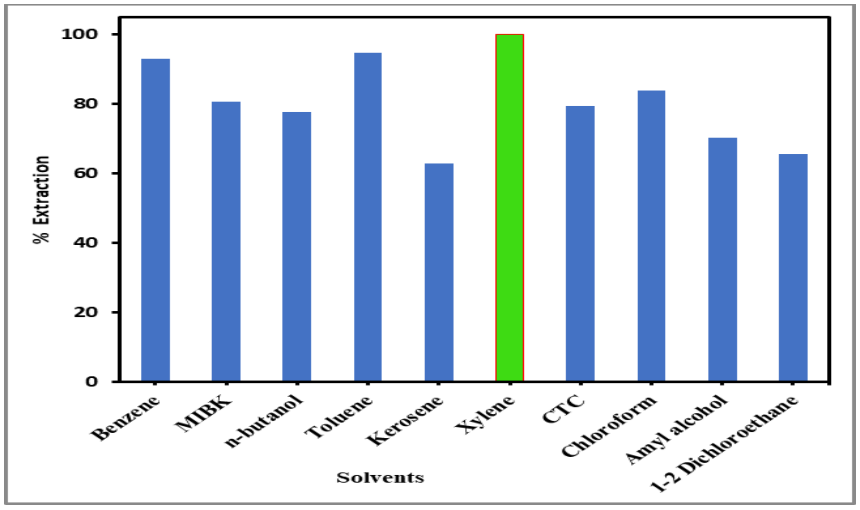

Fig. 5 Effect of solvents

Effect of organic to aqueous volume ratio

The different volume of aqueous phase to non-aqueous phase was examined by keeping organic phase volume fixed. The analysis was carried out in the range of 1:1 to 1:30. The study reveals that 1:1 to 1:6 ratios give quantitative extraction of neodymium(III). Beyond 1:6 ratio the distribution ratio decreases because of lack of 2-OAP extractant due to an increase in volume (Fig. 6). Therefore 1:2.5 ratio of organic to aqueous was recommended for the proposed method for practical suitability and to avoid the losses of chemicals.

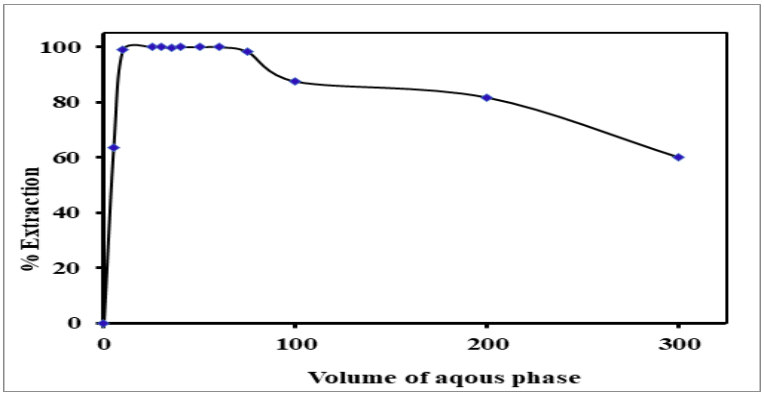

Fig. 6 Effect of organic to aqueous volume ratio

Stoichiometry of extracted species

The mechanism of extraction of neodymium(III) was proposed by evaluating the experimental information and based on slope ratio study. The plot of log $D_{[Nd(III)]}$ Vs log $C_{[\text{succinate}]}$ at fixed pH 5.5 and 9.5 was linear with slopes 2.02 and 2.03 respectively. This illustrates that two succinate ions react with one Nd(III) species (Fig. 7). The plot of log $D_{[Nd(III)]}$ Vs log $C_{[2\text{-OAP}]}$ at fixed pH 5.5 and 9.5 showed a slope of 1.18 and 1.09 respectively. This illustrates that one mole of 2-OAP takes part in reaction with one mole of neodymium(III) (Fig. 8). Therefore the slope ratio method proposes the possible combination of species as 1:2:1 (Metal: succinate: 2-OAP). The probable mechanism of extraction based on the slope ratio analysis method was as follows

$$Nd(III) + 2\ succinate^{2-} \rightleftharpoons [Nd(succinate)_2]^-_{aq} \quad (1)$$

$H^+ + 2\text{-}OAP_{org.} \rightleftharpoons 2\text{-}OAPH^+_{org.}$ (2)

$2\text{-}OAPH^+_{org} + [Nd(succinate)_2]^-_{aq} \rightleftharpoons [2\text{-}OAPH{+}Nd(succinate)^{-2}]$ (3)

$[2\text{-}OAPH{+}Nd(succinate)^{-2}] + 3HCl \rightleftharpoons 2\text{-}OAP + NdCl_3 + 2$ succinic acid (4)

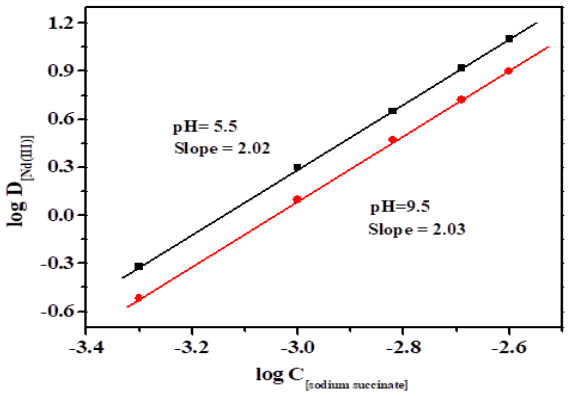

Fig.7 Plot $\log D_{[Nd(III)]}$ Vs $\log C_{[succinate]}$

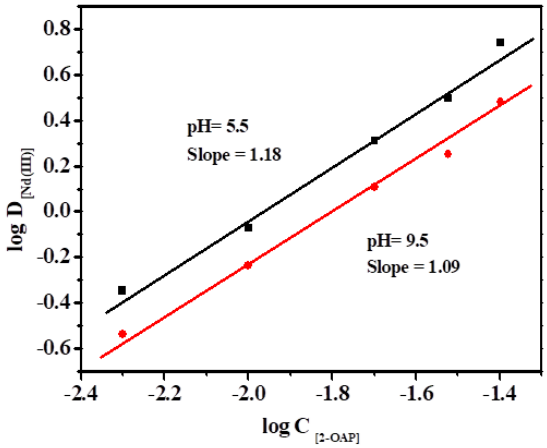

Fig. 8 Plot of log D [Nd(III)] Vs $\log C_{[2\text{-}OAP]}$

IV. APPLICATIONS

Separation of neodymium(III) from associated metal ions

The influence of commonly associating ions in the ore samples on the extraction recovery of neodymium(III) was studied. Various salts and metal ions were added individually to a solution containing 75 µg of neodymium(III) in 25 ml aqueous volume and an extraction procedure was employed. The tolerance limit of the associating ions, defined as the largest amount making the recovery of neodymium(III) less than 95 %. Most of the metal ions and anions do not interfere in the extraction of the neodymium(III) even at the milligram level. The versatility of the proposed method was checked by carrying out extraction of neodymium(III) with various associated metal ions such as Zr(IV), Ce(IV), Y(III),Th(IV), La(III),Gd(III), Sm(III), Cd(II), Pb(II), Ba(II), Ru(III), Se(IV), Mg(II), Sr(II), Mo(VI), U(VI), V(V), Zn(II), Ca(II), Cr(VI),

W(VI), Ti(IV), Nb(V), Co(II), Mn(II), Fe(II), Ta(V), Ni(II), Eu(III), Pd(II), As(III), Cu(II), Bi(III), Te(IV) and Sb(III) with 10 ml of 0.05 M 2-OAP in xylene from 0.005 M succinate medium (Table 1). Added metal ion was estimated by a classical method using a selective reagent spectrophotometrically whereas neodymium (III) was determined spectrophotometrically by the Aresnazo-I method.

Table 1 The influence of foreign ions on extraction of neodymium(III)

Tolerance limit in mg	Foreign ions added
0.5	Gd(III) [f]
1	U(VI)[a], V(V) [a], Fe(II), Ta(v)[a], Ce (IV) [a], Pb(II) [b], Al(III) [d], Ni(II) [c]
2	La(III), Y(III), Mo(II), Zr(IV)[a] , Zn (II), Ba(II), Mn(II), Sb(II), Ru(III), Th(IV)[a]
3	Se(IV), Bi(III), Te(IV), Co(II), Eu(III)
4	Mg(II)
5	Cd(II), Ti(IV), Nb(V), Cu(II)
7	Pd(II)
10	Sr(II), Cr(VI), Sm(III) [e], W(VI), Fluoride, Nitrite, phosphate, EDTA
15	Ascorbate, Tartarate, Iodide, Thiourea, Chloride, Salicylate, Thiocyanate
25	Acetate, Nitrate, Thiosulphate, Citrate, Ca(II), Sulphate, Succinate
50	Bromide , Oxalate ,

a = Fluoride, b = thiosulphate, c = thiocyanate, d = oxalate, e = ascorbate ,
f = thiourea

Separation of neodymium(III)from ternary mixture

A ternary mixture of neodymium (III) with Th(IV) Zr(IV):La(III) Ce(IV): Cd(II), Fe(II): Th(IV), Fe(II): Th(IV), Y(III) :Y(III), La(III) : Sm(III), U (VI): Zr(IV), Mo(VI): Eu(III), U(VI):BI(III), La(III):U(VI), Ce(IV) and U(VI) Th(IV) were prepared and analyzed by general procedure (Table 2).

Table 2 Separation of neodymium(III) from synthetic mixtures.

Metal ions	Amount taken in μg	% Recovery of Nd(III)*	RSD, %
Nd(III)	75	99.75	0.07
Th(IV)	40		
Zr(IV)	400		
Nd(III)	75	99.72	0.15
La(II)	250		
Ce(IV)	300		
Nd(III)	75	99.68	0.07
Bi(III)	300		

La(III)	250		
Nd(III)	75	99.75	0.17
Th(IV)	40		
Ce(IV)	300		
Nd(III)	75	99.78	0.10
Y(III)	75		
La(III)	250		
Nd(III)	75	99.62	0.19
Eu(III)	150		
U(VI)	200		
Nd(III)	75	99.78	0.16
Sm(III)	200		
U(VI)	200		
Nd(III)	75	99.48	0.13
Zr(IV)	400		
Mo(VI)	150		
Nd(III)	75	99.58	0.09
Fe(III)	400		
Cd(II)	40		
Nd(III)	75	99.62	0.11
Y(III)	75		
Th(IV)	40		
Nd(III)	75	99.72	0.15
U(VI)	200		
Ce(IV)	300		
Nd(III)	75	99.70	0.17
U(VI)	200		
Th(IV)	40		

* Average five determinations

Added metal ions remained in a non-organic phase whereas from loaded non-aqueous phase containing neodymium(III) was back-extracted with 0.1 M HCl (3 × 10) ml and determined spectrophotometrically by arsenazo-I. To check and confirm the accuracy of the method average three determinations were carried out.

V. CONCLUSION

I]. The ion-pair complex of neodymium(III) succinate with the 2-OAP in xylene was good enough for separating the various binary, ternary mixtures which are commonly associated with it.

II]. During extraction of neodymium(III) there was no need for the addition of any surfactant or modifier for quantitative extraction in a single step from weak acid media at 7.5 pH and at room temperature.

III]. The neodymium(III) from the loaded organic phase of 2-OAP was back-extracted by stripping the non-aqueous phase with 0.1 M HCl (3 × 10 ml) solution.

IV]. The extractant 2-OAP was extended for separating the neodymium(III) from binary and ternary mixtures.

V]. The strippants used for the separation are simple.

VI]. The probable composition of the proposed method was 1:2:1 (metal: succinate: 2-OAP extractant).

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Ammonium Chloride in PEG As an Efficient Catalyst for Synthesis Dihydropyrano [3,2-C] Chromene-3-Carbonitrile Derivatives

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ABSTRACT

The present paper reports a green, efficient, and rapid method for the synthesis of 2-amino-5-oxo-4-phenyl-4, 5-dihydropyrano[3,2-c]chromene-3-carbonitrile derivatives by one-pot condensation of 4-hydroxy-2H-chromen-2-one, aldehyde, and malononitrile in the presence of ammonium chloride in PEG-400. The method has the advantages of operational simplicity, mild reaction conditions, short reaction time, and no environmental impact.

Keywords: Ammonium chloride, Green chemistry, PEG-400.

I. INTRODUCTION

Advances in organic synthesis enable chemists to prepare most natural product targets. Even with state of the art methods, however, syntheses often require many synthetic manipulations and purifications, resulting in low overall yields and generation of large amounts of chemical waste. To address these issues, increasing synthetic efficiency and reducing E-factors (defined as the ratio of the mass of waste produced to the mass of product) are becoming more important in designing synthetic routes [1]. One approach to streamline organic synthesis is through tandem and sequential reactions that accomplish multiple steps in a single flask and minimize isolations, purifications, and solvent use. Recently, we have reported several MCRs on the synthesis of Pyrano-[2,3- c]-pyrazoles [2-4].It is well known that pyrans are important core units in a number of natural products [4] and photochromic materials [5]. Compounds with pyran ring system have many pharmacological properties and play important roles in biochemical process [5]. Moreover, 4H-pyrans are useful intermediates for the synthesis of various compounds, such as pyranopyridine derivatives [6], polyazanaphthalenes [7], pyrano[2]pyrimidines [8], and pyridin-2-ones [9]. Therefore, preparation of this heterocyclic nucleus has gained great importance in organic synthesis. There are many sound reports expressing that pyrano[3,2- c]chromene is a class of vital heterocycles with a wide range of biological effects [10] such as spasmolytic, diuretic, anticoagulant, anti-cancer and anti-anaphylactic activity [11]. Moreover fused chromene derivatives have a relatively broad spectrum with high activity profile against various bacteria and fungi [12][26] along with antiproliferative [13], sexpheromonal [14], mutagenicitical [15],

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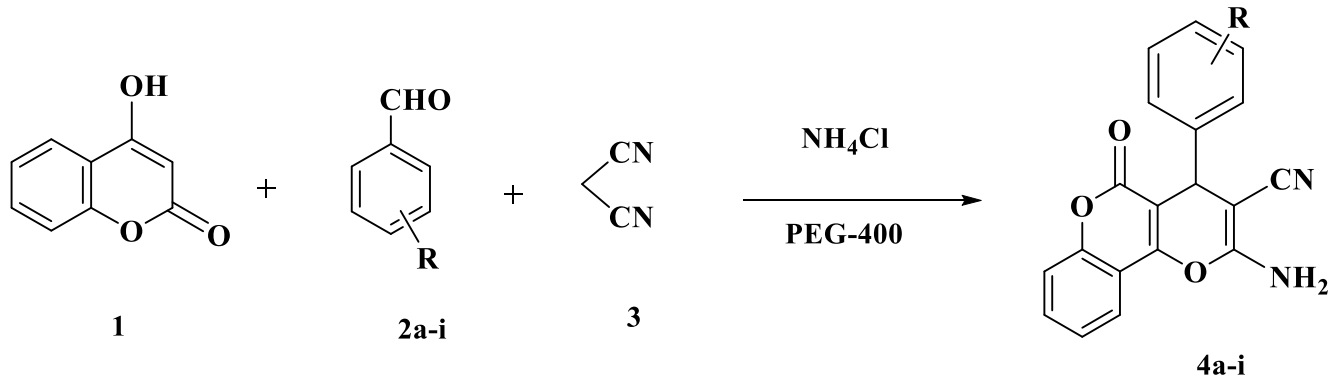
antitumor [16], anti-viral [17,18] and central nervous system activities [19]. Recently, several methods have been reported for the synthesis of pyran derivatives via a three-component condensation of b-dicarbonyl compounds with aldehydes and malononitrile [20].

As there is increasing environmental consciousness in chemical research and industry, the challenge for a sustainable environment calls for clean procedures that can avoid using volatile organic solvents and heavy metal ions as catalysts. Together with the volatile character and very poor environmental and toxicological profiles of the most commonly used compounds, there is a need for alternative solvents that may replace the present ones [1, 21, 22] Several approaches within the green chemistry framework have been proposed in the last few years; supercritical fluids and ionic liquids being the most promising and extended ones among academia. In spite of the promising characteristics of these alternative fluids, their extension to large scale industrial applications is very scarce nowadays, especially for ionic liquids. Among these alternative organic solvents with adequate properties, polyethylene glycol-400 (PEG-400) [22] is one of the most promising ones.

II. RESULT AND DISCUSSION

As part of a continuing effort in our laboratory toward the development of new multi-component condensation reactions, we became interested in the possibility of developing environmental friendly methodologies for the preparation of 2-amino-5-oxo-4-phenyl-4, 5-dihydropyrano[3,2-c]chromene-3-carbonitrile derivatives through a three-component condensation reaction of 4-hydroxyquinolin-2(1H)-one, aldehydes, and malononitrile. By a preliminary experiment, we found that this three-component condensation reaction in PEG-400 using ammonium chloride as a promoter worked very well. Therefore, we herein report a green, efficient, and rapid procedure for the one-pot synthesis of 2-amino-5-oxo-4-phenyl-4, 5-dihydropyrano[3,2-c]chromene-3-carbonitrile derivatives by using ammonium chloride as the catalyst in excellent yields (Scheme 1).



Scheme1. Synthetic route of 2-amino-5-oxo-4-phenyl-4, 5-dihydropyrano[3,2-c]chromene-3-carbonitrile derivatives

Initially, we investigated the three-component condensation reaction of 4-hydroxy-2H-chromen-2-one **1**, benzaldehyde **2a**, and malononitrile **3** in PEG-400 as green solvent in the presence of different catalysts and the results are summarized in Table 1.

Table 1. Comparison of Catalytic Activity of Various Catalysts for synthesis of pyrano[3,2-c]chromene-3-carbonitrile derivatives

Entry	Catalyst (mol/wt %)	Time (min)	Yield of 4a[a] (%)
1	PTSA (20)	>60	70
2	NH_2SO_3H (20)	>60	58
3	SiO_2–$NaHSO_3H$ (10)	>60	60
4	$ZnCl_2$ (20)	>60	52
5	$MgCl_2$ (20)	>60	62
6	TEA (20)	30	70
7	Piperidine (20)	20	78
8	MgO (20)	20	60
9	Ammonium chloride (1)	25	75
10	Ammonium chloride (5)	22	89
11	Ammonium chloride (10)	20	94
12	Ammonium chloride (20)	25	91
13	KF–Al_2O_3 (0.3 g)	120	78

[a]Isolated yields.

In this three-component reaction, we found that catalysts had significant effects on the reaction time and yields (Table 1). The results indicated that in the presence of proton acids and classical Lewis acids as catalysts the yields at lower side in EtOH under reflux conditions for 60 min, such as TsOH, NH_2SO_3H, SiO_2–$NaHSO_3$, $ZnCl_2$, and $MgCl_2$ (Table 1, entries 1–5). The model reaction was carried out using ammonium chloride in PEG, to our delight, the desired condensation product 4a was obtained in moderate to excellent yields (50–94%), which meant that this three-component condensation reaction of 4-hydroxy-2H-chromen-2-one 1, benzaldehyde 2a, and malononitrile 3 could proceed smoothly catalyzed by mild acidic condition. As shown in Table 1, ammonium chloride was found to be the most effective catalyst in terms of reaction time and yields (Table 1, entries 9–12). Further-more, we found that the yields of 4a were improved as the amount of ammonium chloride increased from 5% to 10%, and the yields plateaued when the amount of ammonium chloride was further in-creased from 20% to 50% (Table 1, entries 11–14). However, only 78% yield of the desired product was obtained in the presence of KF–Al_2O_3 as catalyst for 5 h (Table 1, entry 13). Therefore, 10 wt % of ammonium chloride was considered to be the most suitable.

As shown in Table 2, only a trace amount of the target product 4a was observed when the mixture was heated for 60 min in the presence of 10 wt % of ammonium chloride in ethanol, methanol, DMF as well as under a solvent-free condition (Table 2, entries 1-4). The increasing interest of organic chemists in the use of PEG (Table 2, entries 5-8) as a solvent of choice and its unique properties [2-4] attracted our attention to its use as a green solvent in the present study. The reaction using PEG-400 (94%) as the solvents gave the corresponding product 4a in high yields and in short reaction time (Table 2, entries 7 and 12). From the economic and environmental point of view, PEG-400 was chosen as the reaction medium for all further

reactions. Therefore, the best reaction conditions were obtained by using 10 wt % of ammonium chloride as the catalyst in PEG-400.

Table 2. Study of effect of solvent on synthesis of pyrano[3,2-c]chromene-3-carbonitrile derivatives.

Entry	Solvent	Temp ◦C	Time (Min)	Yield[a] (%)
1	None	100	120	Traces
2	Ethanol	60	60	50
3	Methanol	60	60	46
4	DMF	100	30	80
5	PEG-200	60	30	82
6	PEG-400	Rt	25	89
7	PEG-400	60	20	94
8	PEG-600	60	30	88

[a] Isolated Yields.

Having established the optimized reaction conditions, we then successfully synthesized a variety of 2-amino-5-oxo-4-phenyl-4, 5-dihydropyrano[3,2-c]chromene-3-carbonitrile derivatives 4 and the results were summarized in Table 3.

Table 3. Physical data of ammonium chloride catalyzed synthesis of pyrano[3,2-c]chromene-3-carbonitrile derivatives.

Product	Ar	Yield[a] (%)	MP◦C Found(Reported)
2a	C_6H_5 **2a**	94	255-257 (256-258)[23]
2b	4-$CH_3C_6H_4$ **2b**	92	252-254 (250-252)[23]
2c	4-CH_3O-C_6H_4 **2c**	90	241-244 (240-242)[23]
2d	4-F-C_6H_4 **2d**	89	210-212
2e	4-Cl-C_6H_4 **2e**	92	264-267 (263-265)[23]
2f	4-Br-C_6H_4 **2f**	91	247-250 (249-251)[23]
2g	3-CH_3O-4-HOC_6H_3 **2g**	94	228-230
2h	4-OH-C_6H_4 **2h**	87	258-260
2i	3-OH-C_6H_4 **2i**	89	263-265
2j	4-NO_2-C_6H_4 **2j**	90	259-261 (258-260)[23]
2k	3-NO_2-C_6H_4 **2k**	87	261-263 (262-264) [23]
2l	2-Cl-C_6H_4 **2l**	93	275-277
2m	2,4-$Cl_2C_6H_3$ **2m**	90	256-258 (257-259)[23]
2n	2-OH-C_6H_4 **2i**	88	280-282

[a]Isolated yields.

A series of aromatic, heterocyclic, and aliphatic aldehydes were selected to undergo the condensation in the presence of ammonium chloride. As shown in Table 3, aromatic aldehydes 2 carrying either electron-donating or electron-withdrawing substituent reacted efficiently giving excellent yields (Table 3, entries 1–14). Hence, the effect of the nature of the substituent on the aromatic ring showed no obvious effect on this

conversion. The experimental procedure is an efficient, green, convenient, rapid and has the ability to tolerate a variety of other functional groups, such as methoxyl, nitro, hydroxyl, and halides under these reaction conditions.

III. CONCLUSIONS

In summary, the present method discloses a new and simple modification of the condensation of 4-hydroxyquinolin-2(1H)-one **1**, aldehyde **2**, malononitrile **3** to the synthesis of 2-amino-5-oxo-4-phenyl-4, 5-dihydropyrano[3,2-c]chromene-3-carbonitrile derivatives **4** by using ammonium chloride as a catalyst in PEG-400. The present method has the advantages of operational simplicity, mild reaction conditions, short reaction time, improved yields of the products and characteristic recyclable ability of catalyst, thus making it a useful and important addition to the existing methods. Undoubtedly, this reaction should be useful to design a simple work up procedure for the synthesis of 2-amino-5-oxo-4-phenyl-4, 5-dihydropyrano[3,2-c]chromene-3-carbonitrile derivatives **4**.

IV. EXPERIMENTAL

All the melting points were uncorrected and determined in an open capillary tube. The chemicals and solvents used were of laboratory grade and were purified. Completion of the reaction was monitored by thin layer chromatography on precoated sheets of silica gel-G (Merck, Germany) using iodine vapour for detection. IR spectra were recorded in KBr pellets on a FTIR Schimadzu spectrophotometer. ^{1}H NMR (300MHz) and ^{13}C NMR (75 MHz) spectra were recorded in DMSO-*d6* with an Avance spectrometer (Bruker, Germany) at a 300-MHz frequency using TMS as an internal standard. Mass spectra were recorded on an EI-Shimadzu QP 2010 PLUS GC-MS system (Shimadzu, Japan). Elemental analyses were performed on a Carlo Erba 106 Perkin-Elmer model 240 analyzer (Perkin-Elmer, USA).

4.1. General procedure for the synthesis of 2-amino-5-oxo-4-phenyl-4, 5-dihydropyrano[3,2-c]chromene-3-carbonitrile derivatives 4: A mixture of 4-hydroxy-2H-chromen-2-one 1 (1 mol), aldehyde (2a–2l) (1.1 mol), malononitrile 3 (1.1 mmol), and ammonium chloride (10 wt %) in PEG-400 (10 mL) was heated to 60^{o}C under stirring for the given time (Table 3). After completion (by TLC), the reaction mixture was filtered to separate catalyst then cooled to room temperature, then ice cold water (50 mL) was added to the mixture and stirred magnetically for 5-10 min. The solid was filtered and recrystallized from EtOH to afford the pure products **4 a-i.**

4.1.1.Product 4a: Pale yellow powder; Yield: 294 mg, 93 %; m.p. 255-257 °C (recrystallized from EtOH); IR (KBr) cm^{-1}: 3323, 3204, 2195, 1720, 1668, 1601, 1519, 1381, 1264, 1143, 1048, 761, 481; ^{1}H NMR (300 MHz, DMSO-d6 TMS) δ ppm; 4.41 (1H, s, CH), 7.21-7.30 (5H, m, arom.), 7.36 (2H, s, NH_2), 7.40-7.48 (2H, m, arom.), 7.69 (1H, t, J = 7.2 Hz, arom.), 7.86 (1H, d, J = 7.2 Hz, arom); ^{13}C NMR(75 MHz, DMSO-d6, TMS) δ ppm; 37.1, 58.1, 104.1, 113.0, 116.6, 119.3, 122.6, 124.7, 127.2, 127.7, 128.6, 133.0, 143.4, 152.2, 153.5, 158.1, 159.6; Anal. Calcd for $C_{19}H_{12}N_2O_3$: C, 72.15; H, 3.82; N, 8.86 %. Found: C, 72.11; H, 3.81; N, 8.84 %.

4.1.2. Product 4b: Grayish solid; Yield: 304 mg, 92 %; m.p. 252-254 °C (recrystallized from EtOH); IR (KBr) cm^{-1}: 3319, 3310, 3195, 2196, 1718, 1676, 1608, 1377, 1057, 954, 757, 506; ^{1}H NMR (300 MHz, DMSO-d6 TMS) δ ppm; 2.21 (3H, s, CH_3), 4.36 (1H, s, CH), 7.05-7.11 (4H, m, arom.), 7.34 (2H, s, NH_2), 7.39-7.47 (2H, m, arom.), 7.66 (1H, t, J = 9.0 Hz, arom.), 7.86 (1H, d, J = 9.0 Hz, arom.); ^{13}C NMR(75 MHz, DMSO-d6, TMS) δ ppm; 20.7, 36.7, 58.2, 104.2, 113.1, 116.6, 117.8, 119.3, 122.5, 124.7, 127.6, 129.1, 132.9, 136.3, 140.5, 152.2, 153.3, 158.0, 159.6. Anal. Calcd for $C_{20}H_{14}N_2O_3$: C, 72.72; H, 4.27; N, 8.48 %. Found: C, 72.74; H, 4.27; N, 8.47 %.

4.1.3. Product 4c: White solid; Yield: 304 mg, 88 %; m.p. 221-223 °C (recrystallized from EtOH); IR (KBr) cm^{-1}: 3370, 3290, 3182, 2191, 1709, 1671, 1605, 1571, 1507, 1459, 1379, 1319, 1251, 1178, 1111, 1052, 1026, 951, 834, 756, 564, 529; ; ^{1}H NMR (300 MHz, DMSO-d6 TMS) δ ppm; 3.68 (3H, s, OCH_3), 4.35 (1H, s, CH), 6.82 (2H, d, J = 8.4 Hz, arom.), 7.13 (2H, d, J = 8.4 Hz, arom.), 7.33 (2H, s, NH_2), 7.38-7.47 (1H, m, arom.),7.63-7.69 (1H, m, arom.), 7.84 (1H, dd, J = 7.5 Hz, J = 1.2 Hz, arom.), 7.93 (1H, d, J = 9.0 Hz, arom.); ^{13}C NMR(75 MHz, DMSO-d6, TMS) δ ppm; 36.2, 55.1, 58.4, 104.3, 114.0, 115.3, 116.6, 119.4, 122.5, 124.8, 128.8, 132.9, 133.5, 135.5, 152.2, 153.1, 158.0, 159.6, 160.5; Anal. Calcd for $C_{20}H_{14}N_2O_4$: C, 69.36; H, 4.07; N, 8.09 %. Found: C, 69.38; H, 4.06; N, 8.10 %.

4.1.4. Product 4e: Light yellow colored solid; Yield: 315 mg, 90 %; m.p. 265-267 °C (recrystallized from EtOH); IR (KBr) cm^{-1}: 3402, 3323, 3204, 2197, 1714, 1670, 1604, 1509, 1379, 1264, 1143, 1047, 761, 481; ; ^{1}H NMR (300 MHz, DMSO-d6 TMS) δ ppm ; 4.46 (1H, s, CH), 7.23 (2H, d, J = 8.4 Hz, arom.), 7.43-7.50 (6H, m, NH_2+arom.), 7.68-7.72 (1H, m, arom.), 7.88 (1H, d, J = 7.2 Hz, arom.); ^{13}C NMR(75 MHz, DMSO-d6, TMS) δ ppm; 36.4, 57.7, 103.6, 113.1, 116.6, 119.1, 122.6, 124.8,128.6, 129.6, 131.7, 133.1, 142.4, 152.3, 153.6, 158.1, 159.7; Anal. Calcd for $C_{19}H_{11}ClN_2O_3$: C, 65.06; H, 3.16; N, 7.99 %. Found: C, 65.11; H, 3.19; N, 8.02 %.

4.1.5. Product 4f: Yellow colored solid; Yield: 367 mg, 93 %; m.p. 220-222 °C (recrystallized from EtOH); IR (KBr) cm^{-1}: 3385, 3305, 3188, 2191, 1712, 1674, 1606, 1375, 1060, 759, 510; ; ^{1}H NMR (300 MHz, DMSO-d6 TMS) δ ppm; 5.12 (1H, s, CH), 7.17-7.23 (3H, m, NH_2+arom.), 7.34 (3H, t, J = 8.7 Hz, arom.), 7.46 (4H, t, J = 10.1 Hz, arom); ^{13}C NMR(75 MHz, DMSO-d6, TMS) δ ppm; 37.0, 56.6, 116.5, 116.9, 119.5, 120.7, 124.8, 125.1, 125.8, 129.8, 130.4, 131.9, 134.5, 142.5, 150.3, 154.1, 159.0; Anal. Calcd for $C_{19}H_{11}BrN_2O_3$: C, 57.74; H, 2.81; N, 7.09 %. Found: C, 57.77; H, 2.82; N, 7.08 %.

4.1.6. Product 4j: Yellow colored solid; Yield: 336 mg, 93 %; m.p. 251-253 °C (recrystallized from EtOH); IR (KBr) cm^{-1}: 3390, 3212, 3179, 2197, 1662, 1575, 1465, 1409, 1260, 1227, 746, 548; ^{1}H NMR (300 MHz, DMSO-d6 TMS) δ ppm: 4.64 (1H, s, CH), 7.44 (2H, t, J = 7.5 Hz, arom.), 7.49-7.54 (2H, m, arom.), 7.57 (2H, s, NH_2), 7.69 (1H, t, J = 7.5 Hz, arom.), 7.87 (1H, d, J = 7.5 Hz, arom.), 8.14 (2H, d, J = 8.4 Hz, arom.); ^{13}C NMR(75 MHz, DMSO-d6, TMS) δ ppm; 22.3, 36.9, 43.9, 56.9, 102.9, 113.0, 116.7, 118.9, 122.7, 123.8, 124.8, 129.2, 133.2, 146.7, 150.8, 152.4, 154.0, 158.1, 159.6. Anal. Calcd for $C_{19}H_{11}N_3O_5$: C, 63.16; H, 3.07; N, 11.63 %. Found: C, 63.17; H, 3.08; N, 11.65 %.

4.1.7. Product 4k: Yellow colored solid; Yield: 332 mg, 92 %; m.p. 257-258 °C (recrystallized from EtOH); IR (KBr) cm^{-1}; 3382, 3235,3179, 2193, 1728, 1663, 1600, 1416, 1298, 1173, 1119, 1010, 753, 472; ^{1}H NMR (300 MHz, DMSO-d6 TMS) δ ppm: 4.69 (1H, s, CH), 7.42 (1H, d, J = 8.7 Hz, arom.), 7.48 (1H, d, J = 7.8 Hz, arom.), 7.52 (2H, s, NH2), 7.59 (1H, t, J = 7.8 Hz, arom.), 7.68 (1H, dt, J = 8.0 Hz, J = 8.0 Hz, J = 1.4 Hz, arom.), 7.76

(1H, t, J = 7.8 Hz, arom.), 7.87 (1H, d, J =7.2 Hz, arom.), 8.08 (2H, d, J = 7.8 Hz, arom.),; ^{13}C NMR(75 MHz, DMSO-d6, TMS) δ ppm; 22.3, 36.8, 43.9, 57.1, 103.0, 113.0, 116.7, 119.0, 122.5, 124.8, 130.2, 133.2, 134.8, 145.6, 148.0, 152.4, 154.0, 158.3, 159.7. Anal. Calcd for $C_{19}H_{11}N_3O_5$: C, 63.16; H, 3.07; N, 11.63 %. Found: C, 63.19; H, 3.06; N, 11.66 %.

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Synthesis of Spiro-fused Heterocycles under Aerobic Conditions by using Polymer Gel Entrapped Catalyst

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ABSTRACT

Spiro-fused heterocycles were synthesized in good to excellent yields by a pseudo three-component reaction of an aldehyde, urea and Meldrum's acid or barbituric acid at ambient temperature.

Keyword: Aldehydes, Gel Entrapped-ZnCl2, modified Biginelli reaction, recyclability.

I. INTRODUCTION

Multi-component reactions (MCRs) have recently emerged as valuable tools in the preparation of structurally diverse chemical libraries of drug-like heterocyclic compounds [1]. The Biginelli reaction is a well-known multi-component reaction involving a one-pot cyclocondensation of an aldehyde, active methylene compounds like Meldrum's acid or barbituric acid and urea [2-4]. Multi-component reactions (MCRs) have recently gained tremendous importance in organic and medicinal chemistry. The main contributing factors are the high atom economy, wide application in combinatorial chemistry and diversity-oriented synthesis [5-11]. Typical examples of the various homogeneous catalysts employed are polyphosphate ester [12], $LaCl_3 \cdot 7H_2O$ [13] and $LiClO_4$ [14]. Recently Lewis acid catalyzed Biginelli reactions have been extensively reported in the literature.

The use of Lewis acids in organic synthesis, especially in catalysis is one of most rapidly developing fields in synthetic organic chemistry [15]. While various kinds of Lewis acids catalyzed reactions have been developed and many of them applied in industries, these reactions must be carried out strictly under moisture-free conditions [16, 17]. After the completion of reaction, the only viable alternative for separating them is by a destructive water quench. This fact makes the use of Lewis acids as a prime source of the huge quantities of inorganic waste produced within chemical industries. An intriguing line of development in this regard is to replace stoichiometries technologies involving hazardous reagents like Lewis acids with cleaner alternatives.

In this regard, we envisioned that the entrapment of Lewis acids in matrix of agar-agar, the concept acronymed as gel entrapped Lewis acids (GELAs), can prove to be highly attractive strategy to alleviate the problems associated with Lewis acids. The agar-agar is natural hydrosoluble carbohydrate polymer composed

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of linear chains of repeating agarobiose units alternating between 3-linked–β-D-galactopyransoyl (G) and 4-linked 3,6-anhydro-α-L-galactopyransoyl(LA) units **(Fig. 1)**. The bioavailability and potent biocompatibility of agar-agar explains the interest taken by us for entrapment. We hypothesized that concept of GELA can combine the properties of Lewis acids with that of solid support thus facilitating significant advances in selectivity and activity. Additionally, we envisioned the intact network structure of GELAs will allow for a robust recycling with excellent activity.

Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione isopropylidene malonate) is an active methylene compound having rigid cyclic structure with high acidity (pKa=4.97) which undergoes hydrolysis very easily. Barbituric acid or malonylurea or 6-hydroxyuracil is an organic compound based on a pyrimidine heterocyclic skeleton. It is an odorless powder soluble in water. Barbituric acid is the parent compound of barbiturate drugs, although barbituric acid itself is not pharmacologically active. Knowing the chemical and pharmacological importance the spiro-fused heterocycles and as a part of our continuing efforts towards the development of sustainable routes for preparation of biologically active compounds, we report herein an efficient multi-component synthesis of spiro-fused heterocycles by using GELAs.

II. RESULTS AND DISCUSSION

Initially, we focused our attention towards the preparation of GELAs. The $ZnCl_2$ and $AlCl_3$ were used as the prototype Lewis acid in these studies. A series of experiments were under taken in which different concentrations of selected Lewis acids (5-25 %) were dissolved in a varying amount of agar-agar in water. After a substantial experimentation, we found that 20 % *w/w* of agar-agar aqua gel containing 10 % Lewis acids resulted in the formation of soft gel that served as GELAs in the present work. The GELAs are white jelly like substance that could be cut into pieces. The changes in physical nature of GELAs were studied in different solvents like ethanol, dichloromethane, toluene, acetone, dichloromethane and isopropanol. We found that gel remained intact in these organic solvents. On the contrary, the GELAs swelled in water and became soft.

Thermal behaviour of GELAs was investigated by thermogravimetric analysis (TGA) and differential thermal analysis (DTA) **(Fig. 2)**. The thermograms displayed an initial weigh loss upto 225 °C accompanied by an endotherm corresponding to loss of water molecules accumulated in the GELAs. A second weight loss which occurs between 225 °C to 520 °C can be attributed to thermal decomposition polymeric matrix of agar-agar. This is followed by small weight loss (~ 4%) which can be attributed to the decomposition of metal halide resulting in the formation metallic species. These results revealed that the entrapment of Lewis acids into matrix of agar-agar does not affect the thermal stability of polymer.

Our next task was to demonstrate the catalytic activity of GELA in the synthesis of Spiro-fused heterocycles. A model reaction between the Meldrum's acid/ barbituric acid (5 mmol), urea (5 mmol) and benzaldehyde (5x3 mmol) was carried out. Typically, the reactions were carried out at ambient temperature in open air using 1 gm of GELAs with 5 mmol of substrates in ethanol. The reaction proceeded efficiently yielding the Spiro-fused heterocycles in excellent yield within very short time. In order to delineate the role of GELAs, a control experiment was carried out in which the model reaction was performed without gel catalyst. No reaction was

observed even after prolonged reaction time. We further examined the effect of different atmospheres on the model reaction. We observed that the reaction carried out under aerobic conditions.

As better results were obtained for $ZnCl_2$-GELA as compaired to $AlCl_3$, we employed this particular catalyst for further studies. The generality of the protocol was validated by reacting commercially available Meldrum's acid (pKa=4.97) / barbituric acid (pKa=4.01) (5 mmol), urea (5 mmol) and benzaldehyde (5x3 mmol) (Scheme 1) under aerobic conditions. In general the corresponding Spiro-fused heterocycles were obtained in good to excellent yields. No significant effects were observed for the substituents on benzaldehyds. The striking feature of all the reactions was the isolation of products. During the course of the reaction the product precipitates out and can be isolated simply by filtration. The product obtained after sufficient washing with ethanol was found to be practically pure. The identity of all the compounds was ascertained on the basis of IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy data. The physical and spectroscopic data are in consistent with the proposed structures.

It has been well established that in case of the gel entrapped catalysts, the reagent trapped in the gel may leach into the solvent. Atomic absorption spectroscopy was used for assessing the stability of $ZnCl_2$-GELA towards leaching. The analysis revealed that only 65.5 mg/L is leached from 1 gm of catalyst. These results confirm that $ZnCl_2$-GELA is stable under the operating conditions used in experiment. Using the amount of $ZnCl_2$ same as that leached out, the reaction between Meldrum's acid/ barbituric acid (5 mmol), urea (5 mmol) and benzaldehyde (5x3 mmol) did not gave quantitative yield of the corresponding product. This clearly demonstrated that catalysis was solely due to intact gel rather than leached $ZnCl_2$. Moreover, hot filtration experiments proved that these catalysts are truly heterogeneous.

Applications of green chemistry and for industrial point of view, the recovery and reusability of catalyst is an important factor. To investigate the possibility of catalyst recycling, the model reaction using $ZnCl_2$-GELA in ethanol was carried out. After completion of the reaction, the $ZnCl_2$-GELA was recovered by simple filtration, washed with ethanol and subsequently reused in another catalytic cycle with identical substrates. We were delighted to find that the catalyst could be reused for seven runs with excellent yield of product **(Fig. 3)**. In addition, the catalyst can be stored and handled in air without deterioration. It was interesting to note that the rates and yields of the reactions were almost same when the catalyst was used after one month of storage on the bench top in air at room temperature.

III. EXPERIMENTAL SECTION

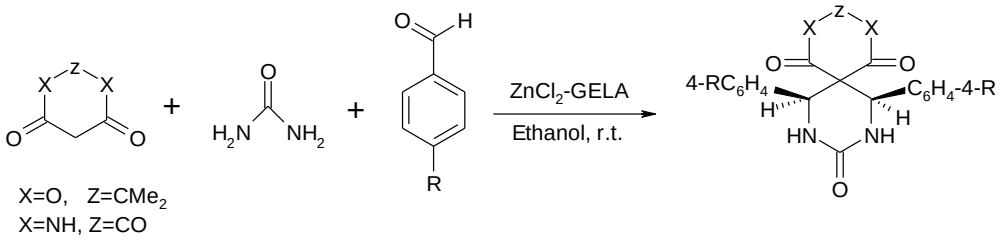
Melting points were determined in an open capillary and are uncorrected. Infrared spectra were recorded on a PerkinElmer FT-IR spectrometer. The samples were examined as KBr discs ~5 % *w/w*. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avon 300 spectrometer using DMSO-d_6 as solvent and TMS as internal reference. The mass spectrum was recorded on Thermo, LCQ Tune spectrometer. TGA-DTA analysis was recorded on SDS Q600 N20.9 in nitrogen. All the chemicals were obtained from s. d. FiNE CHEM, SPECTROCHEM and used without further purification.

Preparation of Gel Entrapped $ZnCl_2$ (GELA)

A mixture of agar-agar (20 g) in water (140 mL) was prepared first and then added the solution of $ZnCl_2$ (10 g) in water (10 mL). The resultant solution was boiled with stirring for few minutes and cooled in ice bath to yield the desired GELAs. The GELA is a milky jelly like substance that can be cut into small cubes.

Synthesis of Spirofused Heterocyclic Compound

A mixture of Meldrum's acid/ barbituric acid (5 mmol), urea (5 mmol) and benzaldehyde (5x3 mmol) was stirred in the presence of GELA (1 g) in 5 mL of ethanol at ambient temperature till the completion of the reaction as monitored by TLC. The resulting crude product was filtered and recrystallized from ethanol to yield the desired product.



Scheme 1: GELA catalyzed multi-component synthesis of spirofused heterocyclic compound

IV. CONCLUSION

In conclusion, the present method is an operationally simple and environmental friendly procedure for the synthesis of spirofused heterocyclic compounds using $ZnCl_2$-GELA at ambient temperature. In addition recyclability, cost effective, short reaction time, easy handling, clean reaction profile, excellent yields of products without any use of more purification and no energy consumption make this methodology a valid contribution to existing processes in the field of spirofused heterocyclic compounds synthesis. To the best of our knowledge, this procedure provides the first example of $ZnCl_2$-GELA catalyzed efficient synthetic method for spirofused heterocyclic derivatives.

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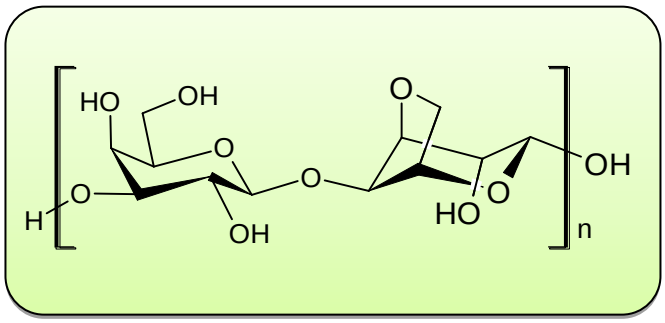
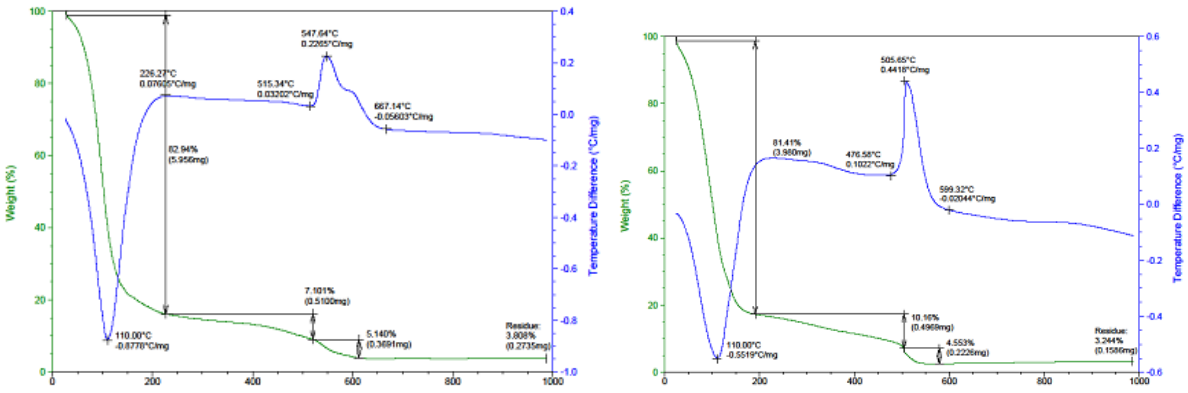


Fig.1 Stucture of agarose



(a) (b)

Fig.2 DSC-TGA graph of (a) $ZnCl_2$-GELA and (b) $AlCl_3$-GELA

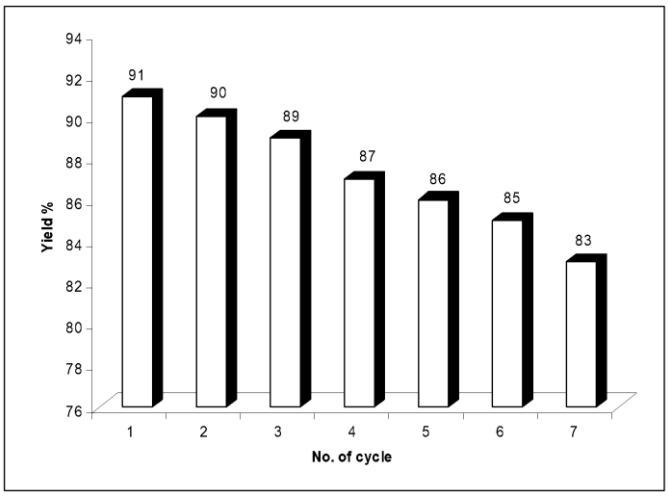


Fig. 3 Recyclic use of GELA in spirofused heterocyclic compound

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DBU Catalyzed One Pot Four-Component Synthesis of Pyrano Pyrazole Derivatives with their Antioxidant Activity

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ABSTRACT

A green, efficient and simple procedure has been developed for the synthesis of Pyrano [2,3-*c*] Pyrazoles from a one pot four component condensation of Ethylacetoacetate, Malononitrile, Hydrazine hydrate and different substituted aromatic Aldehydes using 1,8-diazabicyclo [*5.4.0*] undec-7-ene (DBU) as catalyst in ethanol-water. The synthesized Pyrano [2,3-*c*] Pyrazoles were screened for their Antioxidant activity. These newly synthesized compounds were evaluated by their using various spectroscopic techniques and also elemental analysis.

Keywords : Pyrano pyrazoles, MCRs, DBU

I. INTRODUCTION

Multicomponent Reactions (MCRs) are very proficient in the synthesis of organic molecule[1-3]. In this protocol single step reaction gives magnificent yield without any isolation of intermediate and intimately associated with the principals of green chemistry.[4]

Pyrano pyrazole derivatives has vital role in the class of organic compounds because of their broad spectrum of biological as well as pharmacological importance. The Pyrano pyrazole moieties of the drug with wide medicinal application such as antimicrobial[5-6], antitumor[7], antipyretic[8], anti-inflammatory[9], antidepressant[10], antihypertensive[11], and peptide deformylase inhibitor[12]. Moreover, Dihydro pyrano [2,3-*c*] pyrazole showed hypotensive and hypoglycemic agents[13], mollusicidal activity[14] and as well as a screening hit for Chkl kinase inhibitor[15].

Chemists have reported various methods for the synthesis of Pyrano pyrazole derivatives. Various method of four component synthesis by using Thiamine hydrochloride (VB_1)[16], CsF[17], ZnO nanoparticle[18], CAPB[19], $NaHSO_3$ using ultrasound mediated,[20] TBAHS,[21] and molecular iodine non recoverable[22] also have

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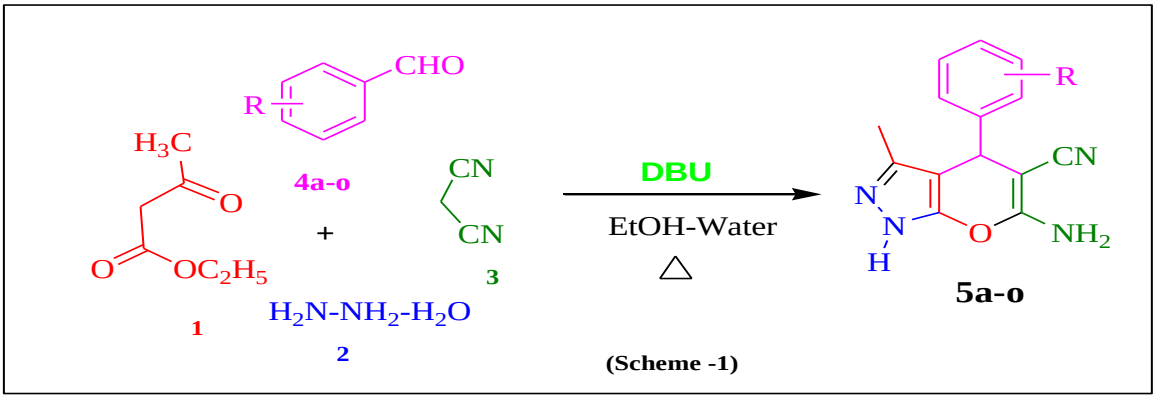
been reported. Overall, all these reported methods are effective but requires long time, expensive catalyst. So in order to overcome these problems, keeping green approach in mind, in this present investigation we have reported synthesis of the Pyrano pyrazole derivatives by simple, efficient and eco-friendly method. We have synthesized Pyrano pyrazoles derivatives by using as a catalyst.

We decisive to investigate DBU as an homogeneous catalyst for the synthesis of dihydropyrano [3,2-*c*]chromene derivatives in aquous ethanol. Catalyst used (DBU) 1,8-diazabicyclo[*5.4.0*]undec-7-ene acts as homogeneous catalyst and it execute much organic transformation under placid condition. As a part of our constant efforts toward the development of well-organized, cost-effective and novel methods using green catalysts and solvents, we investigated the activity of the readily available and environmentally benign DBU as catalyst for the synthesis of pyrano pyrazole derivatives.

RESULT AND DISCUSSION:



(Scheme -1)

As a Initial steps, we have focused on model reaction (**Scheme 1**) by refluxing equimolar amount of Ethylacetoacetate **(1)** (3.0 mmol), Hydrazine hydrate (80%) **(2)** (3.0 mmol),Malononitrile **(3)** (3.0 mmol), and different substituted aromatic aldehydes **(4)** (3.0 mmol) in ethanol-water (1:1) buy using DBU (1,8-diazabicyclo[*5.4.0*]undec-7-ene) (10 mol%) for three hour at 60^{0}C which results in the formation of compound **5b** with 80% yield (Table 1, entry 7). The investigating the effectiveness of different polar and non polar solvent using catalytic amount of DBU (10 mol%). Solvent optimization clearly suggested that ethanol-water is the best solvent for the desired transformation due to fast reaction rate and high yield (Table1, entry 7). The other polar protic solvents gives moderate yield (Table1, entry 6).while other a protic solvent like DCM, THF, Acetonitrile, and Toluene displayed slow reaction rates leading lower yield (Table1, entry 1-4). Also,carried out the model reaction using different stoichiometric amount of DBU catalyst. The catalyst screening result are summarized in Table 2. It was observed that the excellent yield was achieved by using 10 mol% of DBU (1,8-diazabicyclo[*5.4.0*]undec-7-ene) (Table 2, entry 6).

After optimization the reaction condition, the scope of the method was investigated with a series of substituted aromatic aldehydes and the result are summarized in Table 3.

These synthesized products (5a-o) were completely characterized from IR, 1H-NMR, Mass and 13C-NMR spectroscopic technique and also elemental analysis. We proposed tentative plausible mechanism for

the formation of Pyrano [2,3-c] pyrazoles (5a-o) in the presence of DBU as a catalyst. The overall, mechanism takes place according to Knoevenagels-Micheal reaction (Scheme-II).

Table 1. Optimization of the reaction conditions using different solvents.[a]

Entry	Solvent	Reaction Time (h)	Yield (%)[b]
1	DCM	7.0	30
2	THF	6.5	35
3	Acetonitrile	6.0	40
4	Toluene	5.5	45
5	Ethanol	3.0	65
6	Water	3.0	70
7	Ethanol-Water	3.0	80

[a] ***Reaction conditions:*** Ethylacetoacetate **(1)** (3.0 mmol), hydrazine hydrate (80%) **(2)** (3.0 mmol), malononitrile **(3)** (3.0 mmol), and different substituted aromatic aldehydes **(4)** (3.0 mmol) in Ethanol-Water and DBU (1,8-diazabicyclo[*5.4.0*]undec-7-ene) were refluxed at 60°.

[b] Isolated yields.

Table 2: Optimization Study for the amount of DBU (1,8-diazabicyclo[*5.4.0*]undec-7-ene) (.[a]

Entry	Catalyst (mole %)	Temperature (°C)	Reaction Time (h)	Yield %[b]
1	01	60	3.0	30
2	02	60	3.0	50
3	05	60	3.0	60
4	06	60	3.0	60
5	08	60	3.0	70
6	10	60	3.0	80
7	15	60	3.0	80

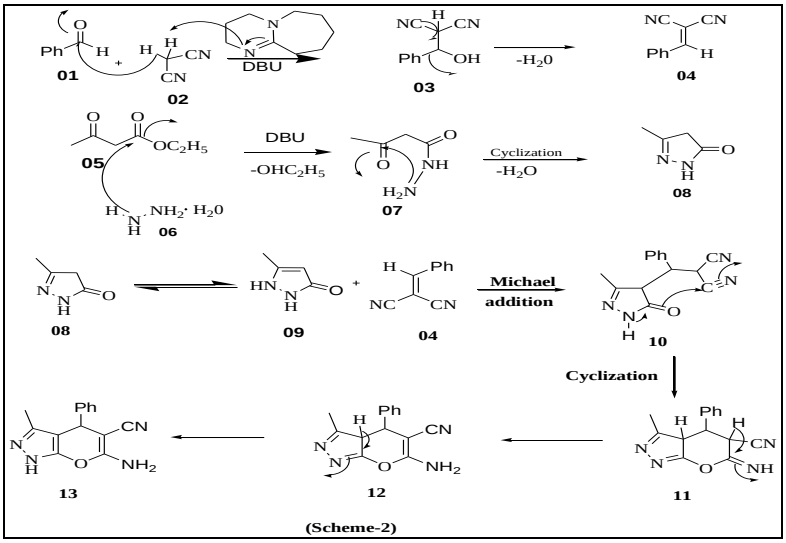
[a] ***Reaction conditions:*** Ethylacetoacetate **(1)** (3.0 mmol), Hydrazine hydrate (80%) **(2)** (3.0 mmol), Malononitrile **(3)** (3.0 mmol), and different substituted Aromatic aldehydes **(4)** (3.0 mmol) in Ethanol-Water and DBU (1,8-diazabicyclo[*5.4.0*]undec-7-ene) as a catalyst were refluxed for three hours at 60°C. [b] Isolated yields.

Table 3. Synthesis of pyrano [2,3-*c*] pyrazoles derivatives .[a]

Entry	Ar	Time (Hrs)	Yield%[a]	M.P. (⁰C)	
				Found	Lit.[Ref]
5a	C_6H_5	3.5	68	245-246	244-245[22]
5b	4'-OCH_3 -C_6H_4	3.0	80	209-210	209-211[22]
5c	4'-CH_3 -C_6H_4	3.0	78	205-207	205-207[23]
5d	4'-Br -C_6H_4	3.0	70	179-181	177-179[24]
5e	4'-Cl -C_6H_4	3.5	70	233-235	234-235[23]
5f	4'-NO_2 -C_6H_4	4.0	60	248-250	251-252[23]
5g	4'-OH -C_6H_4	3.0	75	221-223	223-225[25]
5h	4'-F -C_6H_4	3.5	65	172-174	170-171[23]
5i	4'-OCH_3, 3'-OCH_3-C_6H_3	3.0	80	310-312	311-313[23]
5j	4'- OCH_3 ,3'-OH-C_6H_3	3.0	80	242-244	244-246[22]
5k	3'- Br -C_6H_4	3.5	66	223-224	223-225[23]
5l	3'- NO_2 -C_6H_4	3.5	56	193-195	190-192[26]
5m	3'- OH -C_6H_4	3.0	72	223-225	221-223[27]
5n	2'- OH -C_6H_4	3.0	65	207-208	207-209[28]
5o	2'- Cl -C_6H_4	3.5	68	143-144	143-145[28]

[a] ***Reaction conditions:*** Ethylacetoacetate **(1) (3.0 mmol),** Hydrazine hydrate(80%) **(2) (3.0 mmol),** Malononitrile **(3) (3.0 mmol),** and different substituted Aromatic aldehydes **(4) (3.0 mmol)** in Ethanol-Water and DBU (1,8-diazabicyclo[*5.4.0*]undec-7-ene) as a catalyst were refluxed for three hours at 60⁰C.[b] Isolated yields.

Probable Mechanism:



Experimental:

Melting points were determined on electro-thermal melting point apparatus and are uncorrected. IR (KBr) spectra were recorded using Perkin-Elmer FTIR spectrophotometer. Mass spectral data were recorded on liquid chromatography mass spectrometer (Shimadzu 2010Ev) using ESI probe. The ^{1}H and ^{13}C NMR spectra were recorded on spectrometer at 300MHz using TMS as an internal standard. All the reactions were monitored by thin layer chromatography, carried out on 0.25 mm thick silica gel-G plate using iodine vapour for detection.

General procedure for the synthesis of 4-substituted derivatives of 4- phenyl Pyrano [2,3-c] pyrazoles (5a-5o):

A mixture of Ethylacetoacetate **(1)** (3.0 mmol), Hydrazine hydrate (80%) **(2)** (3.0 mmol), Malononitrile **(3)** (3.0 mmol), was refluxed independently with different substituted Aromatic aldehydes **(4)** (3.0 mmol) in presence of DBU (1,8-diazabicyclo[*5.4.0*]undec-7-ene) (10 mol%) as catalyst in ethanol-water as solvent for three hours at 60^{0}C.The progress of reaction were monitored by TLC, the product obtained was filtered, and recrystallized from ethanol (5ml) to give the pure products of **5(a-o),** (Table **3**).

Spectral Characterization of Representative Compounds.

6-amino-1,4-dihydro-3-methyl-4-phenylpyrano[2,3-c]pyrazole-5-carbonitrile (5a):

Yellow solid, IR (KBr / cm^{-1}) 3410,3340 (-NH_2), 3120(-NH) , 2220 (–C≡N) , 1665 (C=N), 1270(-C-O-C-) ; ^{1}H NMR (300MHz, DMSO-d_6 / ppm) δ 1.72(s,3H); 4.5 (s,1H,-CH); 6.70(s, 2H); 7.10-7.40 (m,5H, Ar-H); 12.06(s,1H,-NH); EI-MS (m/z: RA %): 253 ($M^{+\cdot}$ +1, 100%). Elemental analysis calculated data for $C_{14}H_{12}N_4O$; C, 66.65; N, 22.11. Found: C, 66.63; N, 22.09.

6-amino-1,4-dihydro-4-(4-methoxyphenyl)-3-methylpyrano[2,3-c]pyrazole-5-carbonitrile (5b):

Yellow solid, IR (KBr/ cm^{-1}) 3400 , 3250 (-NH_2), 3110 (-NH) , 2192 (–C≡N), 1655 (C=N), 1250 (-C-O-C-) ; ^{1}H NMR (300MHz, DMSO-d_6 / ppm) δ 1.70 (s,3H); 3.7 (s,3H, Ar–OCH_3); 4.5(s,1H,-CH); 7.0 (s,2H); 7.2 -6.7 (m,4H, Ar-H); 12.0(s,1H,-NH); EI-MS (m/z: RA %): 283 ($M^{+\cdot}$ +1, 100%). ^{13}C NMR (300 MHz, DMSO–d6 / ppm) δ: 36.8, 55.5, 99.2, 114.0, 120.1,127.2, 129.6, 144.2, 159.0. Elemental analysis calculated data for $C_{15}H_{14}N_4O_2$; C, 63.82 ; N, 19.82. Found: C, 63.79; N, 19.80.

6-amino-1,4-dihydro-3-methyl-4-p-tolylpyrano[2,3-c]pyrazole-5-carbonitrile(5c):

Yellow solid, IR (KBr/ cm^{-1}) 3317 , 3409 (-NH_2), 3190 (-NH) , 2190 (–C≡N) 1647 (C=N), 1157 (-C-O-C-) ; ^{1}H NMR (300MHz, DMSO-d_6 / ppm) δ 1.77 (s,3H); 2.26 (s,3H, Ar–OCH_3); 4.54(s,1H,-CH); 6.8 (s,2H); 7.02 -7.12 (m,4H, Ar-H); 12.07 (s,1H,-NH); EI-MS (m/z: RA %): 267 ($M^{+\cdot}$ +1, 100%). Elemental analysis calculated data for $C_{15}H_{14}N_4O$; C, 67.65 ; N, 21.40. Found: C, 67.63; N, 21.38.

6-amino-4-(4-bromophenyl)-1,4-dihydro-3-methylpyrano[2,3-c]pyrazole-5-carbonitrile(5d):

White solid, IR (KBr/ cm^{-1}) 3474 , 3325 (-NH_2), 3190 (-NH) , 2192 (–C≡N) 1658 (C=N), 1157 (-C-O-C-) ; ^{1}H NMR (300MHz, DMSO-d_6 / ppm) δ 1.7 (s,3H); 4.6 (s,1H,-CH); 6.93 (s,2H); 7.12 -7.52 (m,4H, Ar-H); 12.14 (s,1H,-NH); EI-MS (m/z: RA %): 330($M^{+\cdot}$) 332 ($M^{+\cdot}$ +1, 100%). ^{13}C NMR (300 MHz, DMSO–d6 / ppm) δ: 35.0, 56.0, 97.2, 119.0, 120.1, 131.0, 143.0, 154.0, 160.0. Elemental analysis calculated data for $C_{15}H_{14}BrN_4O$; C, 50.77 ; N, 16.92. Found: C, 50.75; N, 16.90.

6-amino-4-(4-chlorophenyl)-1,4-dihydro-3-methylpyrano[2,3-c]pyrazole-5-carbonitrile(5e):

White solid, IR (KBr / cm^{-1}) 3425 , 3325 (-NH_2), 3174 (-NH) , 2200 (–C≡N) 1647 (C=N), 1184 (-C-O-C-) ; ^{1}H NMR (300MHz, DMSO-d_6 / ppm) δ 1.79 (s,3H); 4.63 (s,1H,-CH); 6.93 (s,2H); 7.18 -7.20 (m,4H, Ar-H); 12.00 (s,1H,-NH); EI-MS (m/z: RA %): 287($M^{+\cdot}$) 288 ($M^{+\cdot}$ +1, 100%). Elemental analysis calculated data for $C_{15}H_{14}ClN_4O$; C, 58.65 ; N, 19.54. Found: C, 58.63; N, 19.54.

Biological Evaluation:

Antioxidant Activity:

a) **DPPH (1,1-diphenyl-2-picrylhydrazyl) radical scavenging assay** :

DPPH (1, 1-diphenyl-2-picrylhydrazyl) radical scavenging assay was proceed by reported method. Take 1 ml (1 mM) of the test sample is added to equimolar quantity of 0.1 mM solution of DPPH in ethanol. After incubation at room temperature for 25 min, then the DPPH reduction was takes places and measured by Reading the absorbance at 517 nm. Ascorbic acid (1mM) used as reference compound.

The compound **5(d, f, k, l & o),** (Table 4) showed remarkable antioxidant activity against DDPH radical scavenging activity with reference of ascorbic acid**.**

b) **OH radical scavenging assay:**

Hydroxy radicals scavenging activity was measured with Fenton's reaction (Rollet –Labelle et al., 1998). The reaction mixture contained 60 µl of $FeCl_2$ (1mM), 90 µl of 1,10-phenanthroline(1mM), 2.4 ml of phosphate buffer (pH 7.8),150 µl of 0.17M H_2O_2 and 1.5 ml of individual newly synthesized organic compounds (1mM). The reaction mixture was kept at room temperature for 5 minutes incubation and the absorbance was recorded at 560 nm using UV-Visible spectrophotometer. Ascorbic acid (1mM) was used as the reference compound. The OH radical scavenging activity, the OH radical in which oxygen species are most reactive. The effective OH radical stabilizing potential observed strong absorption maximum at 560 nm using standard Ascorbic acid (89.5 ± 0.021) drug.

The compound **5(d, f, k & l),** (Table 4) showed remarkable antioxidant activity against OH radical scavenging activity with reference of ascorbic acid.

Table 4 : Antioxidant activity of tested compounds (5a-5o.)

Entry	Compound Code	% Radical scavenging activity	
		DPPH radical scavenging	OH radical scavenging
01	**5a**	55.7 ± 1.03	53.2 ± 1.39
02	**5b**	68.5 ± 0.79	60.3 ± 2.20
03	**5c**	60.2 ± 0.54	65.2 ± 1.30
04	**5d**	81.1 ± 1.50	80.2 ± 1.28
05	**5e**	79.1 ± 0.72	73.6 ± 0.69
06	**5f**	**88.5 ± 1.68**	**84.2 ± 1.40**

07	**5g**	50.2 ± 0.32	55.2 ± 1.66
08	**5h**	60.4 ± 0.66	65.2 ± 2.00
09	**5i**	58.2 ± 1.44	49.2 ± 0.80
10	**5j**	61.2 ± 0.08	45.2 ± 2.10
11	**5k**	**89.5 ± 2.68**	**86.2 ± 0.28**
12	**5l**	**82.8 ± 1.04**	**86.2 ± 0.10**
13	**5m**	44.0 ± 0.30	55.8 ± 2.11
14	**5n**	58.1 ± 1.60	59.2 ± 1.80
15	**5o**	82.7 ± 1.70	78.2 ± 2.60
16	**Ascorbic Acid (Standard)**	**91.4 ± 0.021**	**89.5 ± 0.021**

Conclusion:

The method we used for the synthesis of 4-substituted derivatives of Pyrano [2,3-c] pyrazoles derivatives by using DBU (1,8-diazabicyclo[*5.4.0*]undec-7-ene) is efficient catalyst. The product can be easily isolated by simple workup technique, requires ambient reaction condition, short time, less expensive and give excellent yield. Among these synthesized compounds few compounds shows potent antioxidant activity.

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Nanoparticles and Nanotechnology Research and Applications in Science

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ABSTRACT

Nanoparticles are seen either as agents of changeof various phenomena and processes, or as buildingblocks of materials and devices with tailored characteristics.Use of nanoparticles aims to take advantage of properties that are caused by the confinement effects, larger surface area, interactions at length scales where wave phenomena have comparable features to the structural features, and the possibility of generating new atomic and macromolecular structures. Important applications of nanoparticles are in dispersionsand coatings, functional nanostructures, consolidated materials, biological systems and environment. Research programs on nanoparticles and nanotechnology around the world suggest different strengths have developed in various countries

Keywords: Droplets, Bubbles Nanoparticles ,Technical communications

I. INTRODUCTION

Nanoparticles have been empirically synthesized for thousands of years, for example, the generation of carbon black. A fourth century Roman masterpiece, known as the Lycurgus Cup, exhibits the unusual property of dichronism, appearing to be green in the reflected light and red in transmitted light, because of nanometer particles suspended in the glass (Lambert, 1997). It is noticeable that very few nanoparticle synthesis processes areas have emerged. One finds in this category the pyrolysis process for carbon black and the flame reactionfor pigments, particle polymerization techniques, selfassembling of micelles in colloidal suspensions, and chemistry selfassembling. Several kinds of nanoparticles are routinely produced for commercial use via aerosol and ronic properties, information recording layers, bio-detectors, advanced drug delivery systems, chemical–mechanical polishing,a new generation of lasers, chemical catalysts, have developed their scientific base decades ago, long before other nanotechnology nanoparticle reinforced matericolloid reactors in the US, Japan and Europe. The wide range of powder prices is a function of market size, from $0.5/kg for carbon black and Alumina (each with over 5 Mt/year worldwide market) to about $1,000/kg for superconductors (about 2 t/year) and Silicon Carbite whiskers (about 1 t/year). Important areas of relevance for nanoparticles and nanotechnology are advanced materials, electronics, biotechnology, pharmaceutics and sensors. Emerging technologies that have been introduced in the last few years already impact tens of billions of dollars production in the 1998 high tech US industries alone. These include hard

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disks in computers, photographic systems, dispersions with novel optoelectals, ink jet systems, colorants,and nanosystems on a chip, to name some of the most important.

Different Types Of Nanoparticles:

Nanoparticles can be classified into different types according to the size, morphology, physical and chemical properties. Some of them are carbon-based nanoparticles, ceramic nanoparticles, metal nanoparticles, semiconductor nanoparticles, polymeric nanoparticles and lipid-based nanoparticles. Nanoparticles types are commonly divided in two main groups: organic and inorganic. The first group includes micelles, dendrimers, liposomes, hybrid and compact polymeric nanoparticles. The second group includes fullerenes, quantum dots, silica and metal nanoparticles. Another way of classifying nanoparticles is based on their morphology, size and chemical properties. Based on physical and chemical characteristics, some of the important classes of nanoparticles are:

i) Carbon-based – (fullerenes, carbon nanotubes, graphene, carbon dots). These materials are of great interest due to their electrical conductivity, high strength, structure, electron affinity, and versatility.

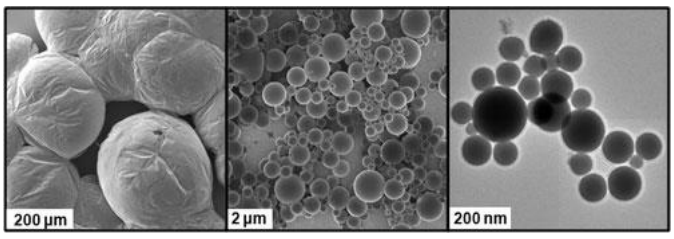
ii) Metal – They are purely made of the metals precursors. Due to well-known localized surface plasmon resonance (LSPR) characteristics, these these possess unique optoelectrical properties.

iii) Ceramic – These inorganic nonmetallic solids are getting great attention of researchers due to their use in applications such as catalysis, photocatalysis, photodegradation of dyes, and imaging applications.

iv) Semiconductor – Semiconductor materials possess properties between metals and non-metals and have wide bandgaps. Bandgap tuning results in significant alteration in their properties. Therefore, they are very important materials in photocatalysis, photo optics and electronic devices.

v) Polymers – Scientists have developed many techniques to synthesize polymeric nanoparticles for a wide range of applications including surface coating, sensor technology, catalysis, and nanomedicine.

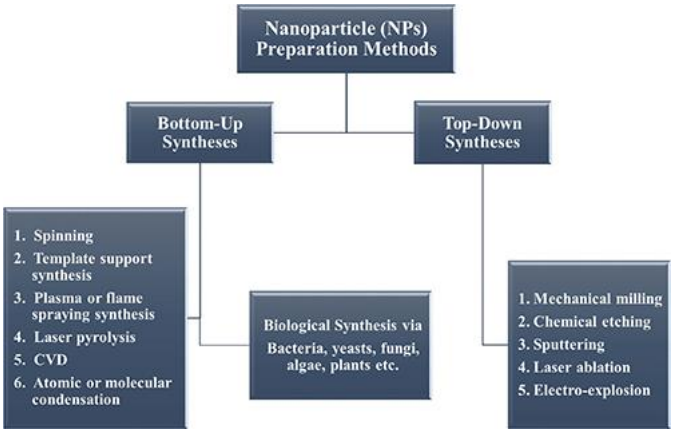
vi) Lipids – These NPs contain lipid moieties and are used in many biomedical applications as drug carriers (the mRNA Covid-19 vaccines are using lipid nanotechnology). Lipid nanoparticles are also regarded as highly promising systems for delivering nucleic acids in gene therapy.



Liquid-phase eutectic gallium–indium (EGaIn) alloy nanoparticles.

Synthesis of Nanoparticles:

Specific synthesis processes are employed to produce the various nanoparticles, coatings, dispersions or composites. Defined production and reaction conditions are crucial in obtaining such size-dependent particle features. Particle size, chemical composition, crystallinity and shape can be controlled by temperature, pH-value, concentration, chemical composition, surface modifications and process control. Two basic strategies are used to produce nanoparticles: top-down and bottom-up. Read all about it in our detailed article on how nanoparticles are made. In general, the term top-down refers here to the mechanical crushing of source material using a milling process. In the bottom-up strategy, structures are built up by chemical and self-assembly processes. The selection of the respective process depends on the chemical composition and the desired features specified for the nanoparticles.



Typical synthetic methods for nanoparticles for the (a) top-down and (b) bottom-up approaches.

Nanoparticle, crystal and nanolayer manufacturing processes and applications :

1) New physical, chemical or biological properties are caused by size scaling. Smaller particle size determines larger interfacial area, an increased number of molecules on the particle interfaces, quantum electromagnetic interactions, increased surface tension, and size confinement effects (from electronic and optic to confined crystallization and flow structures). The wavelike properties of the electrons inside matter are affected by shape and volume variations on the nanometer scale. Quantum effects become significant for organizational structures under 50 nm, and they manifest even at room temperature if their size is under 10 nm.
2) Testing and measurement. There are a wide range of instruments and techniques, from scanning tunneling mapping of surfaces to atomic force chemistry, nuclear chemistry and near-field visualization. Scanning probes and optical and laser-based diagnostic techniques are the most widely applied experimental tools.

3) Information technology, including pattern recognition, molecular organization mechanisms, and nanorobotics. Information on surfaces play a key role in selforganization and selfassembling.
4) Reaction pathways and process control. Such techniques can be used in order to obtain a predetermined structure or function, and integrate the operation of nanosystems with complex architectures.

Conclusion:

Based on the review in this paper, Nanotechnology has the potential to be the key to a brand new world in the fields of food and agriculture, construction materials, mechanical, medicine . Although replication of natural systems is one of the most promising areas of this technology, scientists are still trying to grasp their astonishing complexities. Furthermore, nanotechnology and nanomaterials is a swiftly growing area of research.

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