CHAPTER II

Results and Discussion

2. General Discussion

2.1. Introduction

Solvent-free protocols for many a name reaction like the Aldol, Stobbe, Cannizzaro, etc and various other reaction types like condensations, rearrangements, and oxidative coupling have been successfully developed over the last decade and reported from all across the world. In such solvent free protocols mechanochemistry has no doubt, been an inseparable part and has helped in strengthening and advancing the methodology further, either by involving mechanochemical or thermochemical activation. Furthermore, as shown in the introduction part of this work, Multicomponent reactions have taken the scope of solvent-free protocol to newer heights, and have added a fresh dimension to solventless reactions. They are being successfully used as versatile routes to biologically active motifs and have in recent years attracted considerable attention for Diversity Oriented Synthesis (DOS). Thus, we still find ample scope and opportunity to expand the horizon in developing similar methods to synthesize a diverse range of compounds.

This chapter highlights recent advances in solvent-free synthesis with respect to Schiff base synthesis, reactions between metal salts and these Schiff base ligands to give coordination complexes, in particular, and solventless reactions in heterocyclic synthesis and their coordination compounds. We have tried to stick to a non-catalytic solvent-free approach using simple heating. It concentrates on the use of grinding to promote reactions between solid reactants and subsequent heating of the mixtures to form a melt. Despite the fact that mechanochemistry has been efficiently used for synthesis of a large number of compounds, it was found that some reactions do not go to completion on simple mechanochemical activation, or even if it does, it usually takes a longer time. We found that providing additional heat to the mechanochemically agitated mixture gave promising results. The products were formed in much less time, comparable to microwave assisted reactions. And according to arguments put forward in the literature, they could also be regarded as being efficient (less time consuming), and therefore as

being green. It has been pointed out that a fast reaction performed at a high temperature regime (Arrhenius equation) is likely to require less energy compared to a transformation that requires significantly longer reaction times at lower temperatures.[1] However, since it is known that excess heat has a tendency of charring the reaction mixture and also since there are possibilities of runaway reactions it was imperative that the agitated mixtures were heated to an optimum temperature to get the best results. This was accomplished by carrying out thermal analysis of the powdered mixture of the reactants. Thus, initially the optimization of reaction conditions of representatives reactions were done using Thermal analysis techniques like TGA and DSC. Next the reaction optimization for heterocyclic synthesis was done by the use of HPLC where the thermal reactions under solvent-free conditions were monitored and optimized by running HPLC of the reaction mixtures at different temperatures. The HPLC analysis of the reaction mixtures at different time intervals also led to the determination of the reaction kinetics.

2.2. Schiff Bases and their Metal Complexes

Schiff bases[2] - bimolecular condensation products of primary amines with aldehydes – represent valuable intermediates in organic synthesis[3] and, at the same time, Schiff bases derived from aromatic amines and aromatic aldehydes have a wide variety of applications in many fields like inorganic and analytical chemistry.[4] Literature survey shows that many Schiff's bases exhibit biological activities[5] such as antifungal, antibacterial, antitumor, anti inflammatory, and antipyretic.[6] In addition, some of them have been used as complexing agents and powerful corrosion inhibitors.[7] In organic synthesis, Schiff base reactions are useful in making carbon-nitrogen bonds. Certain polymeric Schiff bases have been reported which possess anticancer activity.[8]

While Schiff bases derived from the salicylaldehydes are well known as polydentate ligands coordinating in neutral forms[9] the metal complexes containing nitrogen donor ligands have been known for a long time and are pivotal in coordination chemistry. This class of ligands and their metal complexes are generally used in preparing catalysts because of their facile preparations.[10] Moreover, metal complexes

have been shown to have improved bioactivity as compared to the free ligand.[11] This illustrates the need for easy availability of such Schiff's bases and their metal complexes, and therefore, the demand of synthetic methodologies for obtaining them by faster, cheaper and environmentally safer routes. A handful of other functional groups that deviate slightly from the definition of a Schiff's base and hence display analogous reactivity have also been included in our discussion: they include hydrazones, semicarbazones, oximes and nitrones. A few metal complexes of these ligands have been taken up for our study and discussed subsequently.

2.2.1. Optimization of reaction conditions for Schiff Bases and their Metal Complex syntheses with Thermal Analysis

To our understanding and from a brief survey of the literature it is revealed that thermal analysis techniques have been availed of in studying a reaction profile only in a very few cases. In the majority of its usage, the technique has been used post-reaction to study the decomposition pattern of a synthesized co-ordination complex. The very few cases that have incorporated the use of thermal analysis techniques like the TGA and the DSC have been very simple two component condensation reactions like the synthesis of azomethines in the solid state or for planning a thermolytical reaction.

It was more than a decade ago that Kappe and Stadlbauer had shown that DSC could well provide useful information in organic synthesis in the stage of planning thermolytical reactions.[12] The information could be obtained before the reaction itself was performed and included the temperature range of the planned reaction, hints on subsequent rearrangement and decomposition reactions, choice of suitable solvents and safety precautions in exothermic processes. They had shown that by employing DSC the thermolytical decomposition of azido-hetarenes with an ester group in the ortho position, gave two exothermic reaction steps. The same was proved by synthesis. Two years later, while investigating the mechanism for the solid-solid synthesis of azomethines by AFM, Toda and Kaupp were of the opinion that with four component systems initial phase

diagrams were rather complicated and could not be studied in great detail because of rapid chemical reaction.[13] However they found out that DSC measurement of the reactants showed the melting peaks of the reactants and the product along with some other minor peaks.

These studies on organic synthesis employing DSC as a valuable tool to chalk out or plan different steps for a reaction throws light on how other reactions in organic chemistry could be planned on a similar fashion for better results. We felt that the techniques are very helpful to predict the feasibility and optimization of reactions in the solid-state or under solventless conditions. Initially we ventured towards the study of a similar synthesis and then extended and applied it to the study of a multicomponent system and then further to heterocyclic synthesis. A pertinent example for each system is presented under respective subsections.

Thus, initially a DSC run for a similar system, the synthesis of a biologically and synthetically important Schiff base type compound viz. a nitrone was conducted as shown below (Figure 1). The DSC run was carried out with an equimolar mixture of Vanillin and N-cyclohexylhydroxylamine, finely grinded in a mortar and pestle.

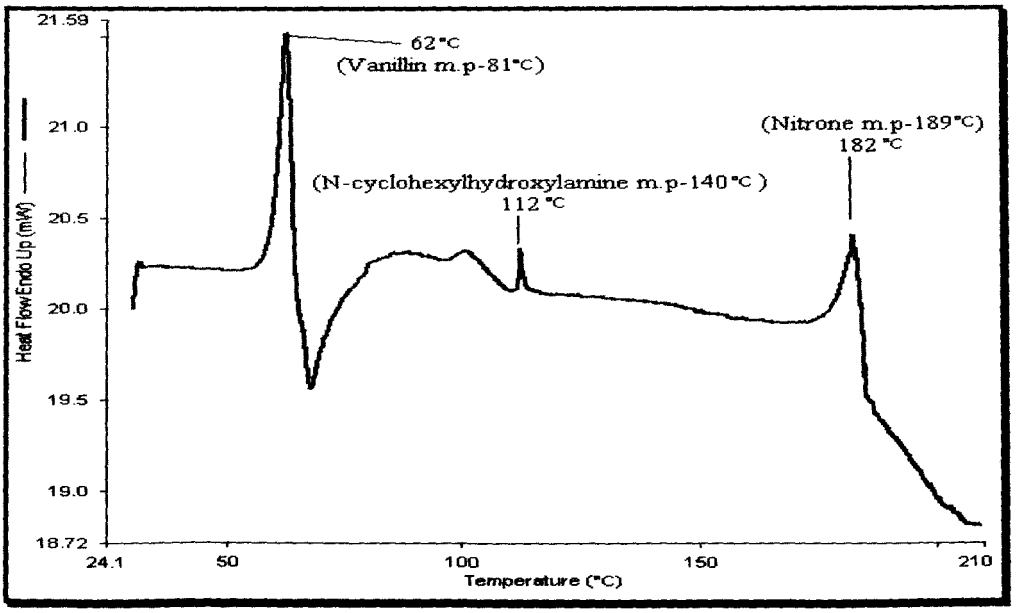
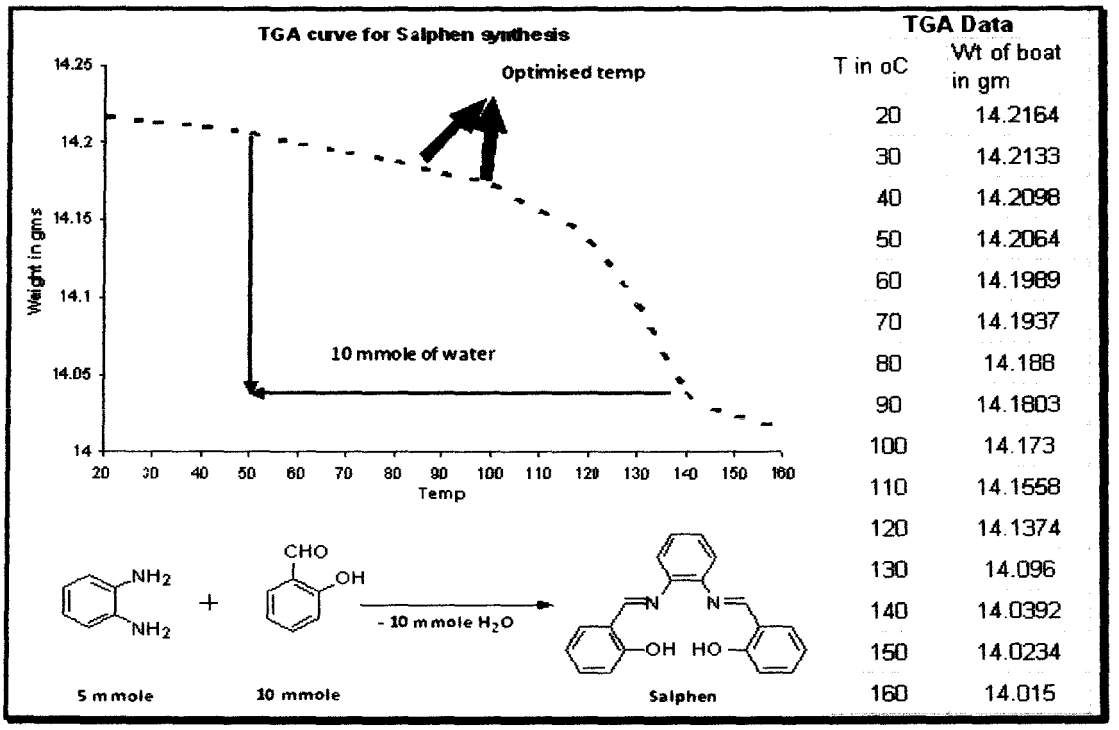


Figure 1 DSC curve of a powdered mixture of Vanillin and N-cyclohexyl hydroxylamine.

The DSC curve clearly predicts the formation of the product, α-(4-hydroxy-3-methoxyphenyl)-N-cyclohexyl nitrone, **[9]** with a melting point peak at 182°C (Litt. m.p. 189°C). The depression of melting point of the reactants in the mixture is also evident from the appearance of their peaks at 62°C and 112°C as against the melting peaks of the pure compounds at 81°C and 140°C. The endotherm starting at around 70°C clearly shows the onset temperature for the reaction. The optimum temperature for the reaction was thus set at 70-80°C. With the interesting results obtained from the DSC run on the mixture leading to the nitrone, subsequent work was planned for optimizing green chemical reaction conditions to generate a rationale, which would help to design a predictive way of planning efficacy of the chemical transformations both in respect to time and money in addition to the greener aspects.

It was further observed that the study of a TGA analysis of different systems before going for the actual reaction maybe of good help in designing the reaction conditions. The basic principle of TGA is well known and simple. It measures mass of a sample as a function of temperature and the technique is commonly utilized in solid state chemistry and material science. Since the temperature raise is fixed with time, idea about the required time of a reaction can also be roughly estimated along with the stoichiometry of the change. It was also observed that if a TGA analysis is carried out with the reaction mixture or carefully designed reactants other than the targeted reactants some idea about the thermal effect on the reaction can be derived. Based on this derived idea optimized green chemical procedure for the desired synthesis may be planned. Apart from predicting the outcome and the onset of the reaction, the importance of these techniques is that only a very small quantity (usually 2-5 mg) of the samples for study is required. Once a thermal analysis of a representative reaction mixture (all solid components) is available, many similar reactions are easily performed. Since the reactions are solventless and multi-component, the products are obtained in high yields and in shorter time.

For illustrating the efficacy of the procedure, few classes of compounds were synthesized. To start with, we conducted the TGA analysis of the appropriate reaction mixture for the salophen formation reaction and found the reaction was stoichiometric and occurred within the range of 50 to 130°C as shown in Figure 2.



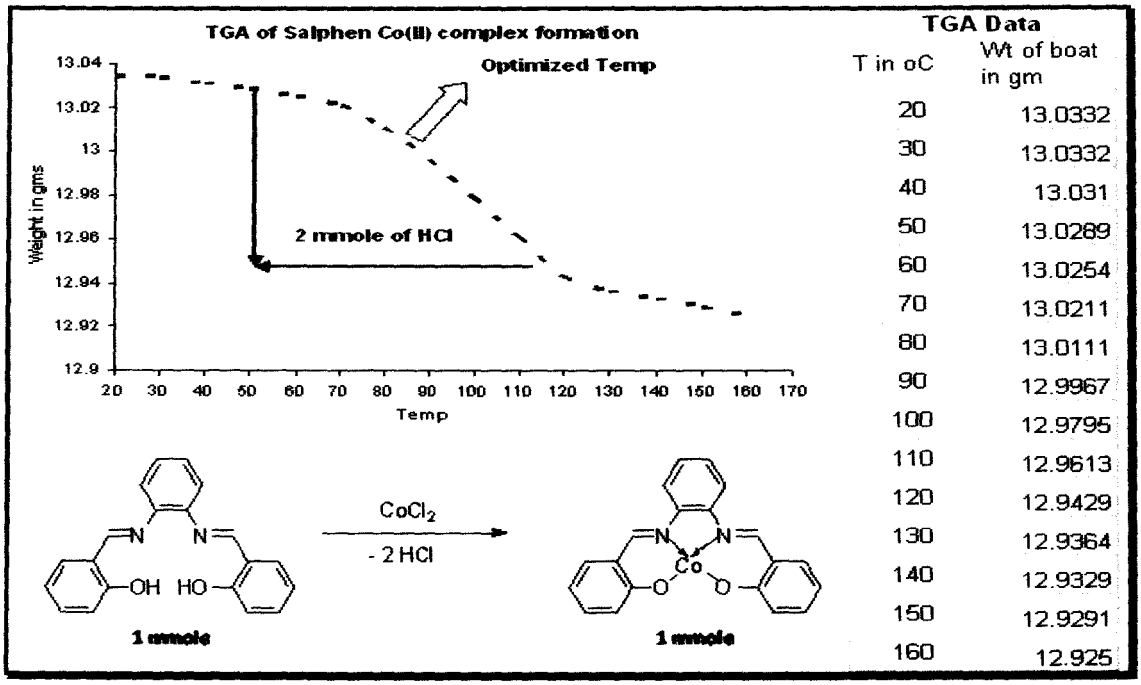
TGA Data	
T in oC	Wt of boat in gm
20	14.2164
30	14.2133
40	14.2098
50	14.2064
60	14.1989
70	14.1937
80	14.188
90	14.1803
100	14.173
110	14.1558
120	14.1374
130	14.096
140	14.0392
150	14.0234
160	14.015

Figure 2 TGA curve for Salphen synthesis

Careful examination of the TGA curve indicates the reaction to be very fast at the temperature in the vicinity of 125°C. In TGA no information is available about the Heat of the reaction and since in our opinion these reactions should be slightly exothermic the idealized reaction condition would be around 90°C to 110°C. We carried out the reaction in solvent less thermal condition and found the quantitative production of salophen which was sufficiently pure for further application. Thus, we developed a rational strategy of the synthesis in which highly pure product was obtained within 10 minutes. Moreover the reaction was carried out using as simple an apparatus as a test tube, oil bath and a thermometer. Another novel aspect of this rationale is that a complete library of other similar ligands viz., different salen type compounds can be synthesized simultaneously

with high purity. It was observed that the solventless condition was superior with respect to the reaction time, yield, product purity and simplicity of required apparatus and above all the convenience of product handling.

It is observed that for stoichiometric-mix of the reactants the deflection temperature in the TGA curve is a characteristic property of the nature of the reaction. In order to investigate whether a solvent is necessary for the formation of metal complexes of Schiff's bases like the salophen we carried out the TGA analysis of a cobalt salt with salophen.



TGA Data

T in oC	Wt of boat in gm
20	13.0332
30	13.0332
40	13.031
50	13.0289
60	13.0254
70	13.0211
80	13.0111
90	12.9967
100	12.9795
110	12.9613
120	12.9429
130	12.9364
140	12.9329
150	12.9291
160	12.925

Figure 3 TGA curve for Salphen Co (II) complex formation

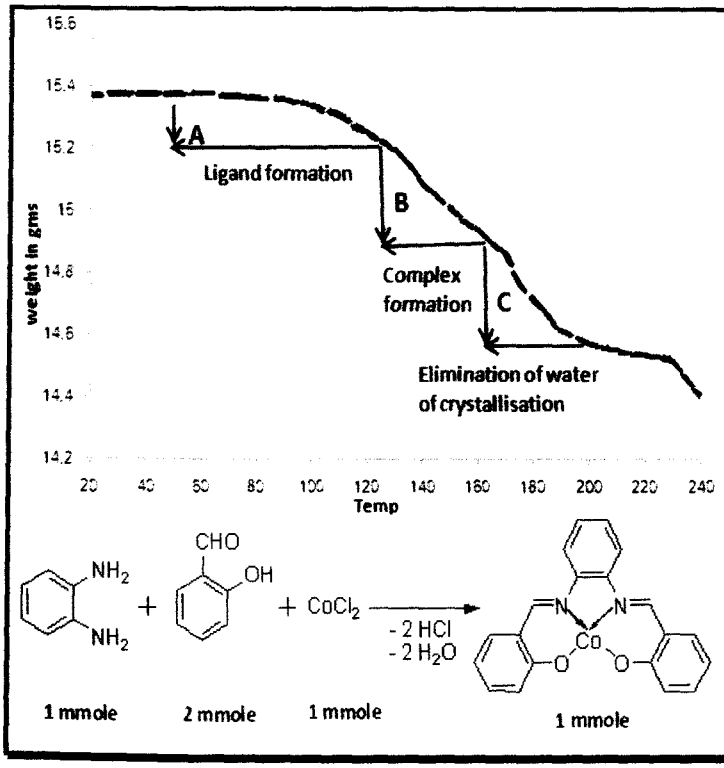
The TGA results (Figure 3) showed that even the complex formation reaction needs no solvent and the reaction is also quantitative. Laden with this idea a method was developed to synthesize the Co (II)-salophen complex in solventless thermal condition and observed that the reaction could be conveniently carried out within 15 minutes in stoichiometric yield. The same principle was successfully applied for the development of green methods of synthesis of different compounds which are not normal Schiff bases.

In Schiff base formation reactions it is envisaged that the dipole-dipole and dipole induced dipole interactions should be dominant in approaching the T.S. while the steric effect of the tetrahedral geometry should govern the stability of the intermediate. Elimination of a small molecule should be the major driving force to reach the thermodynamically unfavorable state of the product; the process may be assisted by the relief of steric strain of the intermediate. On going from the substrate to the intermediate formation, the process should be endothermic. From the intermediate to the product the process consequently is exothermic. Thus a little bit of thermal assistance might be needed to initiate the reaction. In microwave heating the electromagnetic wave agitates the molecular dipoles and the excess energy from the dipoles is released in the form of heat. Thus microwave would partly assist and partly disturb the approaching dipoles of the reactants and this should happen due to sinusoidal nature of electromagnetic wave. This explanation conforms to our observation.

The major advantage of solventless reaction condition is explainable in the same logic. It is common practice to dissolve the reactants in a suitable solvent as it provides a medium for a chemical reaction. Hence, for dissolving polar compound polar solvents is generally used. In such situation for statistical reasons, solvent dipoles would greatly reduce the concentration of the substrate (A)-substrate (B) dipole associations. Since only this association would lead to product formation, incorporation of any other dipole (solvent) interactions should produce negative effect on the reaction rate. Thus solvent does play a major role for getting non-quantitative and slow reactions. A solvent would assist reactions in which a single substrate would generate the product or in such cases where the ionic interactions are dominant. The TGA curve provides the real picture of substrate (A)-substrate (B) interaction in a solvent free environment. But a priori study of TGA in the required system may not be always possible. In such situations TGA of a model reaction may be studied. Schiff's base synthesis is just an example of reactions in which a dipole-dipole orientation is a prerequisite dominant factor for achieving T.S. geometry. In other dipolar interaction initiated reactions similar phenomenon should happen and in fact it has been observed in such other cases. On the other hand

microwaves will greatly assist such reactions where this dipole orientation is not as much important.

To study whether the Co-complex formation could be carried out in three component reactions, a TGA of a molar proportionate mixture of salicylaldehyde, ortho phenylenediamine and cobalt chloride was run. Surprisingly it was found that the TGA curve was a combination of three deflections (Figure 4). This signified that the ligand formation, complex formation and elimination of water molecules (participitated in complex formation) from the complex occurred in tandem. A cursory glance at the TGA curve revealed that the first deflection pattern is similar to that observed during ligand formation (Figure 2) and the second one is similar to the metal-ligand binding reaction (Figure 3). The third deflection is due to the loss of water molecules associated with the complex.



TGA Data			
T in oC	Wt of boat in gm	T in oC	Wt of boat in gm
20	15.3714	140	15.0893
30	15.3714	145	15.047
40	15.3714	150	15.0088
50	15.3714	155	14.9655
60	15.3714	160	14.935
70	15.3677	170	14.8555
80	15.3634	175	14.7667
90	15.3588	180	14.7109
100	15.3308	185	14.6626
110	15.3119	190	14.6126
115	15.2735	200	14.5718
120	15.2539	210	14.547
125	15.2272	220	14.537
130	15.1971	230	14.5121
135	15.148	240	14.3975

Figure 4 TGA curve for three-component Co (II) Salphen complex

The reaction was then carried out in a three component solvent-free thermal condition and it was found that the reaction occurred quantitatively within about 20 minutes. Complexes with other metals like Cu (II), Ni (II) and Zn (II) etc were also successfully prepared in three component solvent free thermal condition. Most advantageously and practically multicomponent reactions (MCR) can often be extended into combinatorial and solid phase syntheses promising manifold opportunities for developing novel lead structures of active agents, catalysts and even novel molecule based materials. Thus, we advocate that a priori miniature reaction in TGA, DTA or DSC boats should be the common practice in laboratories.

2.2.2. Synthesis of Salphen and Metallo-Salphen complexes

One of the oldest and most popular Schiff's bases are the Salen and Salphens, which are diimino tetradentate Schiff bases derived from the condensation of ethylenediamine (Salen) or 1, 2-phenylenediamine, or of its derivatives (Salphen), with two equivalents of salicylaldehyde. The salen and salphen class of Schiff's bases have proved to be the source of versatile ligands for many transition metals.[14] Alkynylated salphen moieties were utilized to establish shape-persistent conjugated macrocycles with tunable pore diameters in the nanometer regime.[15] These macrocycles can bind multiple metals, forming soluble, luminescent complexes.[16]

There is extensive literature on transition metal complexes with the tetradentate Schiff base ligands, Salen and Salphen [17] and, in particular, on the dioxygen affinity of Co (salen) and Co (Salphen). [18] These ligands give complexes which in addition to alkene epoxidation also hold promise in enantioselective cyclopropanation of styrenes, asymmetric aziridination of olefins, asymmetric Diels–Alder cycloaddition, and enantioselective ring opening of epoxides.[19] The most popular complexes of this type are the so-called Jacobsen catalysts which have become commercially available. These metal complexes are biologically important as well since, complexes of salen and its substituted derivatives have been found to mediate the cleavage of right-handed double-helical DNA in the presence of terminal oxidants. [20] Salen metal complexes in conjunction with

suitable co-catalysts represent some of the most robust metal catalysts for the selective coupling of CO_2 and epoxides to provide either polycarbonates or cyclic carbonates (Figure 5).[21]

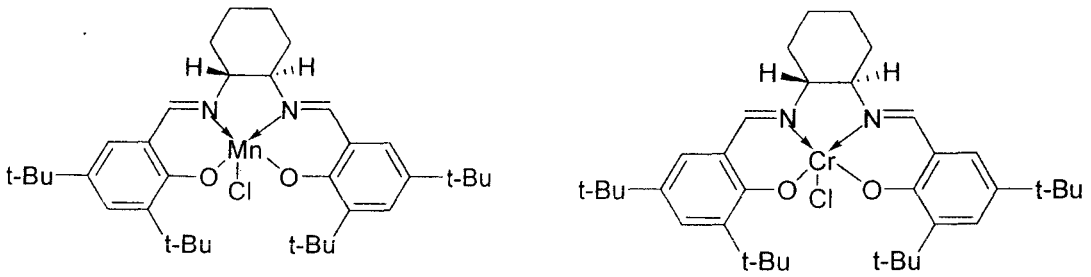


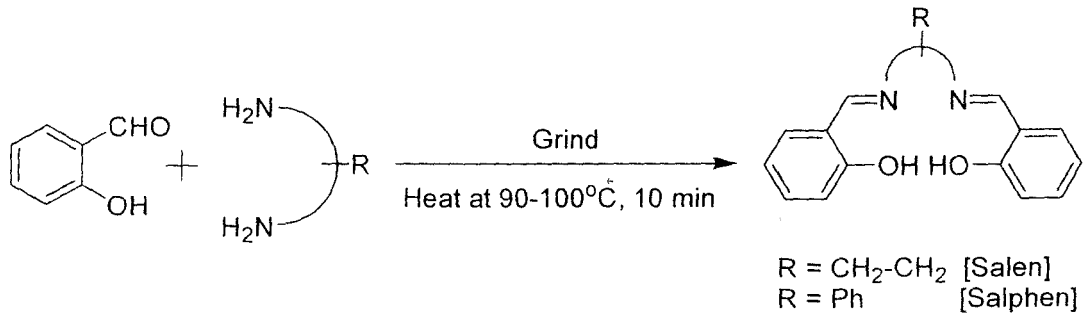
Figure 5 The most reactive and enantioselective (Salen)$M^{III}X$ catalysts for epoxides ring opening

Although the formation of Schiff bases is generally an equilibrium reaction, the Schiff bases of salicylaldehyde are relatively stable towards hydrolysis and dissociation [22] probably because of hydrogen bonding between the arylimine nitrogen and the phenolic hydrogen, making these compounds more stable towards hydrolysis then "normal" imines. Thus, the salen and salphen Schiff bases have been conventionally prepared by stirring a methanolic or ethanolic solution of the diamine with salicylaldehyde for two to three hours and allowing them to stand overnight at room temperature. [Salen: 92% yield; Salophen: 67% yield). The ligands are recrystallized from methanol.[23]

For metal complexation, there are basically five different synthetic pathways and the method preferred depends on the metal. In four of the methods, the starting material is metal alkoxide, metal amide, metal alkyl or aryl compound, or metal acetate or halide. In one of the methods, a sodium or potassium salt of the ligand is prepared first which is then reacted with metal halide. In a conventional synthesis, a solution of salicylaldehyde, the appropriate 1, 2-diaminoarene and hydrated metal salt in MeOH (2.5 mL) is refluxed for 1 hour. The mixture is cooled to room temperature and filtered.[24] Over the past decade, in deviating from conventional tradition, many stalwarts in solid state synthetic chemistry have also come up with benign methods for the synthesis of Schiff's bases. In a first study of its kind, twenty preparatively useful azomethines had been quantitatively

obtained as hydrates by grinding together solid amines with solid aromatic aldehydes without passing through the liquid phases.[25]

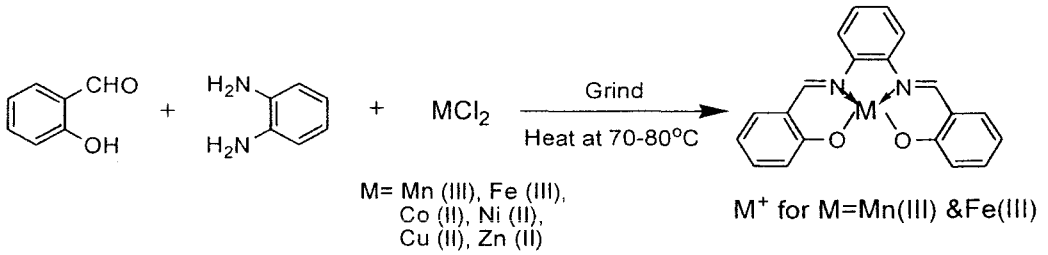
In our present work, Salen and Salphen ligands were quantitatively obtained under the solventless conditions, in much lesser time (Scheme 39). The TGA studies revealed an onset temperature at 90°C, so stoichiometric amount of the diamine was mechanochemically mixed with salicylaldehyde in an agate mortar and pestle followed by thermal heating of the reaction mixture in a oil bath at 90-100°C for 10 minutes. The reaction mixture first transforms into a melt and then solidifies subsequently into a hard yellow or orange solid. The TLC of the product from the test tube, after cooling, indicated it to be sufficiently pure and no further purification was required. Recrystallization, if desired can be done in ethanol.



Scheme 39 Solventless synthesis of Salen and Salphen Schiff bases

Bearing in mind, the diverse application of metal complexes and the escalating need to develop greener preparative methods, we envisioned that a three-component reaction of the aldehyde, the diamine and the metal salt, under the same reaction conditions as above would provide a convenient route to the Salphen metal complex. Literature survey reveals that almost all metal complexation under solvent-free conditions have been two-component reactions of the ligand with the metal salts.[26] Our TGA studies, as discussed above, revealed that three-component metal complexation are as feasible and the product formation did occur at an optimum temperature of 70-80°C. In a typical experiment, the metal imine Schiff base complex is formed in near quantitative yield by grinding one molar equivalent each of the diamine and the metal acetate or chloride and two molar equivalents of the aldehyde using a pestle and mortar over a

period of ca. 10 minutes. Heating the reaction mixture in an oil bath for further 20 minutes is followed by formation of the product as a colored solid. The products are recrystallised from methanol. Synthetic details of Salphen complexes are summarized in Scheme 40.



Scheme 40 An efficient One-Pot Synthesis of Metal Salphen Complexes under solvent free conditions.

Six salphen metal complexes were conveniently prepared by this methodology. All compounds are stable at room temperature and insoluble in water. The results of the conductivity measurements carried in DMSO show that all metal complexes are non-electrolytes.[27] A typical cyclic voltammogram of Co (II)-salphen in DMSO under an inert atmosphere was also obtained (Figure 6). The voltammetric characteristics of Co (II)-salphen was found to be in good agreement with the literature data.[17, 18]

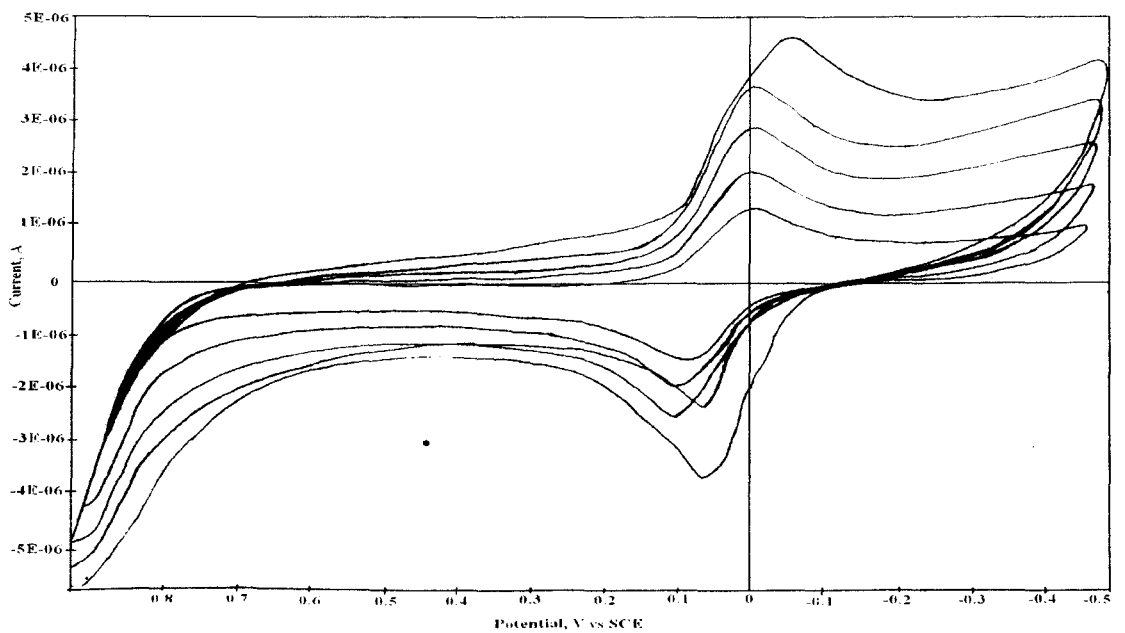


Figure 6 Cyclic voltammogram recorded at 50 mV/s in DMSO solution containing 1.10 mM Co(Salphen)

All synthesized compounds were characterized by IR, ^{1}HNMR, ^{13}CNMR and Mass Spectra. The data were found to be in good agreement with literature data. Moreover, some metal complexes were also synthesized via methods available from the literature in the presence of solvents. Mass and IR data for a few representatives were found to match perfectly. Some physical properties, analytical and spectral data of the compounds are summarized in Table 1.

Table 1 Analytical and spectral data of Salen, Salphen and Salphen metal complexes

Entry	Compound	Compound Colour	M.P (°C)	Λ_M ($\Omega^{-1}cm^2mol^{-1}$)	μ_{eff} BM	U.V. λ_{max} (nm)
1	Salen **[1]**	Yellow	124-126	-	-	257, 318
2	Salphen **[2]**	Orange	163-165	-	-	272, 334
3	Mn(III)Salphen **[3]**	Brown	264-265	13.54	4.89	292, 396
4	Fe(III)Salphen **[4]**	Brown	>300	19.82	5.81	300, 376
5	Co(II)Salphen **[5]**	Brown	>300	16.40	2.56	340, 465
6	Ni(II)Salphen **[6]**	Red	>300	3.85	-	377, 475
7	Cu(II)Salphen **[7]**	Green	257-260	14.90	1.84	309, 422
8	Zn(II)Salphen **[8]**	Yellow	>300	3.71	-	298, 400

A more concrete confirmation was apparent from the powder-XRD data (Figure 7). The powder XRD data of the Ni-Salophen complexes prepared via the solventless and the solvent method were done. As is apparent, there is a perfect match between the plotted data obtained for complexes from the two methods.

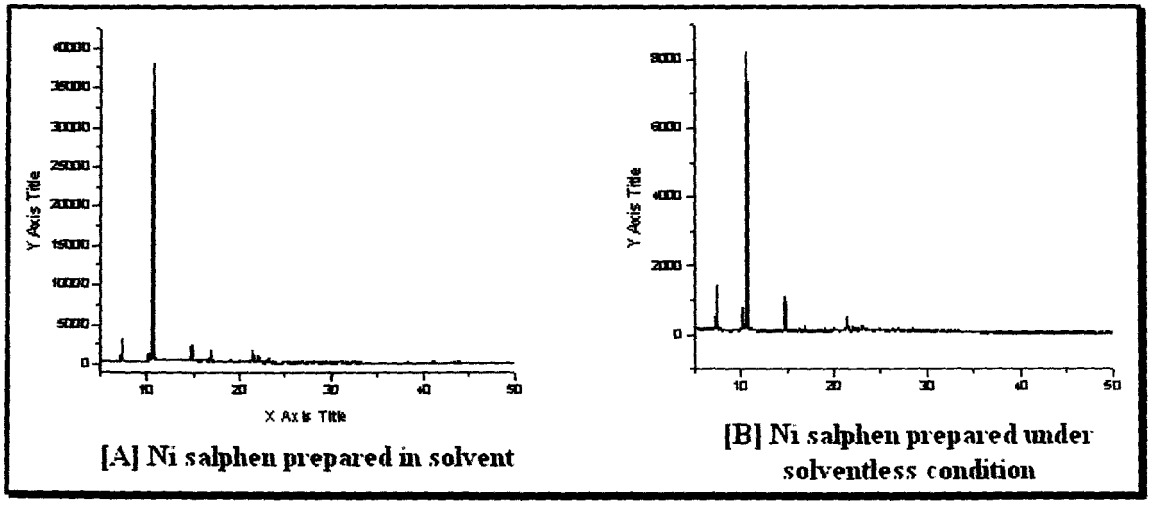


Figure 7 Powder-XRD data for Ni (II) Salphen prepared in [A] Solvent and [B] under solventless condition

A clearer representation is presented for the Zn (II) Salphen complex where the powder XRD data of the complexes synthesized by both the solvent-free and solvent method have been superimposed. There is also a perfect match of the XRD data of the Zn salophen metal complex prepared via the solventless protocol and that synthesized in solvent as shown in Figure 8.

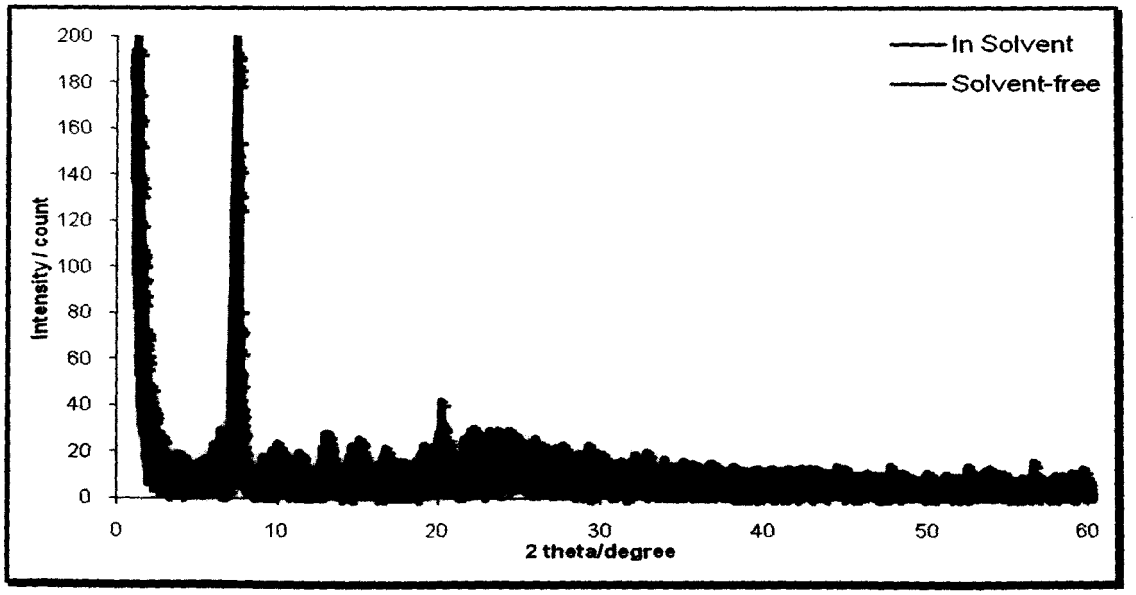
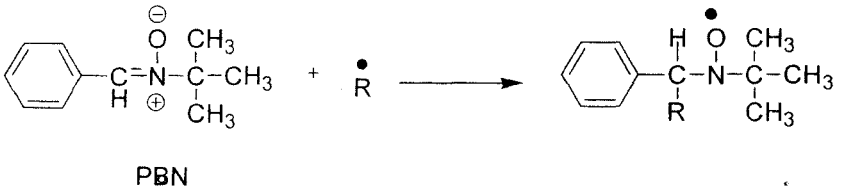


Figure 8 Comparison of Zn (II) salphen synthesized in solvent and under solvent-free condition using Powder X-ray diffraction

2.2.3. Synthesis of Nitrones and Metallo-Nitrone complexes

Nitrones are N-oxides of imines with 1, 3-dipoles and have been known for some time as quite versatile intermediates in organic synthesis since the addition of C—nucleophiles or dipolarophiles occur with ease and may be used to assemble complex structures.[28] Thus the most common application of nitrones in synthesis involves their 1, 3-cycloaddition with alkenes resulting in the formation of synthetically useful isoxazolidines,[29] or as imines in nucleophilic additions, that allows the straightforward synthesis of biologically important heterocycles and structurally complex molecules with a high degree of selectivity.[30] They are well known for their free radical-trapping ability and the wide-spread use as spin traps in the EPR spin trapping technique (Scheme 41).[31]



Scheme 41 Phenyl-*N-tert-* butyl nitrone as a spin trap for free radicals

It was during the 1980's that the pharmacological potential of the nitrones was first noted. Nitrone-based free radical spin traps such as phenyl-*N-tert-* butyl nitrone (PBN) and 5, 5-dimethyl -1- pyrroline N-oxide (DMPO) have been developed as antioxidants.[32] Because nitrones react with highly reactive free radicals, to render them less reactive, this represents a potential means of controlling free radical processes. Several studies indicate that nitrones like PBN and CPI-1429 has life span – enhancing properties (Figure 9).[33]

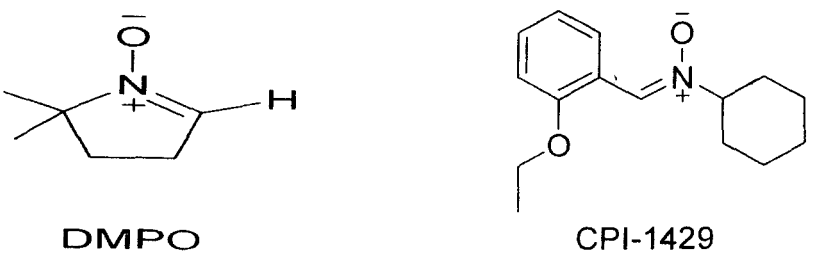


Figure 9 Some pharmacologically potential nitrones

Over the decades several methods for the synthesis of nitrones have been developed. The first synthesis of a nitrone was accomplished by alkylating an oxime.[34] The most widely employed methods for the synthesis of nitrones are the condensation between an aldehyde or a ketone and an alkyl (or aryl) hydroxylamines[35] and the oxidation of secondary amines or N, N-disubstituted hydroxylamines. Many methods have been employed for the oxidation of *N*, *N*-dialkylhydroxylamines into the corresponding nitrones. Various metal (copper, silver, lead and ruthenium) salts, yellow HgO and MnO_2,[36] as well as organic oxidants and (salen) Mn (III) complexes proved useful for this oxidation.[37] Nitrones have also been prepared by the in-situ reductions of nitro-compounds to hydroxylamines followed by their condensation with aldehydes/ketones.[38]

Though the chemistry of nitrones attracts steady interest due to their wide application as intermediates in organic synthesis, less is known about properties of the nitrones as ligands in coordination chemistry. In all these applications metal ions may play an important role, as catalysts in synthesis schemes and in biochemical and radical-generating systems, or by providing desired material science properties.[39] Surprisingly, only a few complexes of metals with simple nitrones have been reported though heterocyclic N-oxide complexes with transition and non-transition metals have elicited much interest.[40] Of late, because of the growing interest on metallo-nitrone complexes, they are now being synthesized and few X-ray crystallographic structures are available.[41] The X-ray structure determinations have also involved unusual nitrones such as the nitrone function as part of a porphyrin ring (Figure 10).[42]

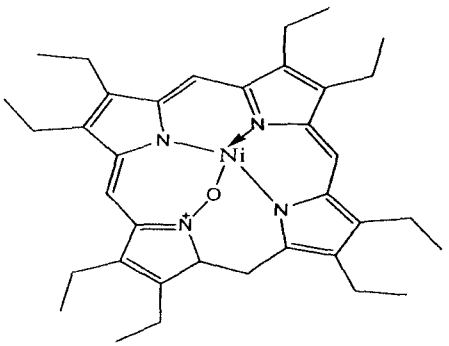
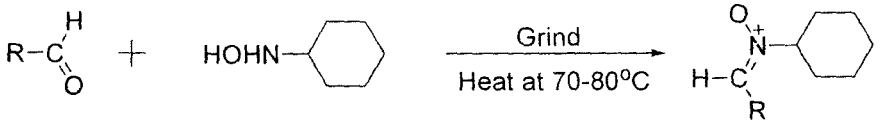


Figure 10 Ni complex with a nitrone function as part of a porphyrin system

We envisaged that a solvent-free strategy for the synthesis of nitrones would be appropriate and challenging. Appropriate, because the nitrones are also Schiff base type of compounds and challenging, because they are well-known for their instability. The synthesis of α-(4-hydroxy-3-methoxyphenyl)-N-cyclohexyl nitrone **[9]**, was investigated under three different reaction conditions. It took 48 hours to get good yield under refluxing conditions using ethanol as solvent. The solventless microwave irradiation process needed only one hour but subsequent chromatographic purification was necessary. Disadvantages here are the constraints in scaling up and the need for elaborate work-up at times. Thus, the attention was turned to classical heating with prior mechanochemical activation where we got the pure nitrone in quantitative yield under optimized solventless thermal condition and that too in only 30 minutes (Scheme 42). Pure crystals of the product can be obtained by directly adding hexane or a 50:50 mixture of hexane and ethyl acetate to the product from in the test tube after completion of the reaction. Thus a theory was framed-

- Formation of Schiff-bases and Schiff-base type of compounds are quantitative in nature. Use of reactants in stoichiometric proportion would avoid the product purification step.
- Use of solvent retards the reaction rate and hence prolongs the reaction time.
- Optimized temperature (70-80°C) affords good quality products. Super heating leads to charring of the products both in case of the thermal and under microwave conditions.



Scheme 42 Solventless synthesis of nitrones

Ultra-sound or microwave assistance is not necessitated. In terms of yield, no effect, positive nor negative, was observed with microwave irradiation. The findings also corroborate Kappe and Stadler's comparison between microwave heating and thermal heating under almost identical conditions which revealed that there was no appreciable difference in the reaction rates between reactions carried out under thermal heating or

microwave heating at identical temperatures.[43] The differences in rates and yields observed between thermal and microwave heating was fully attributed to higher reaction temperatures in the microwave methods. The advantages of the microwave method are thus based only on a conventional thermal effect. Moreover, it has also been concluded that all speculation of special and nonthermal effects in microwave heating had no basis. The reported increased reaction rates and yields could be rationalized by taking into account increased temperatures caused by superheating or concentration effects.[44]

Apart from UV, IR and Mass, the 2D NMR COSY spectra shown below (Figure 11), undoubtedly confirmed the structure of the synthesized α-(4-hydroxy-3-methoxyphenyl)-N-cyclohexyl nitrone **[9]**.

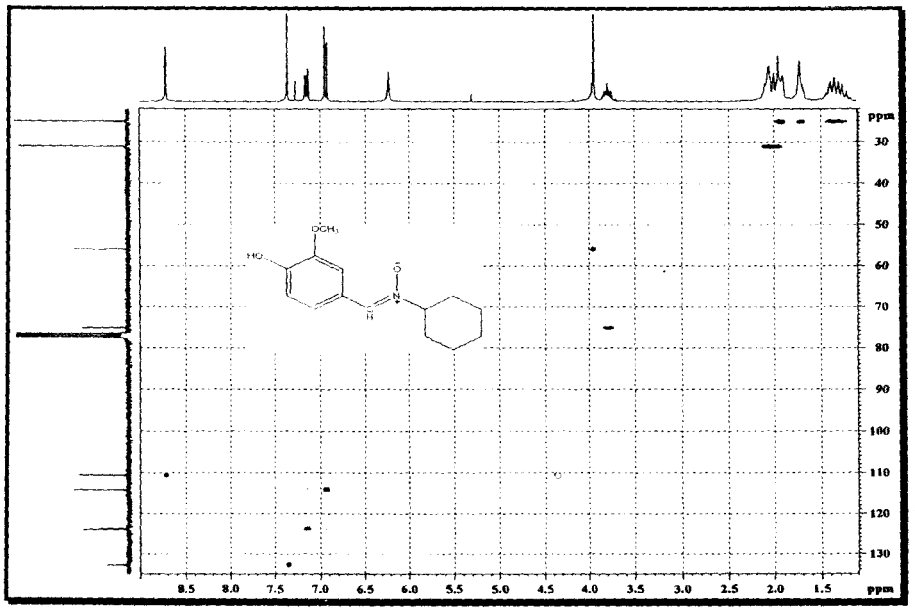
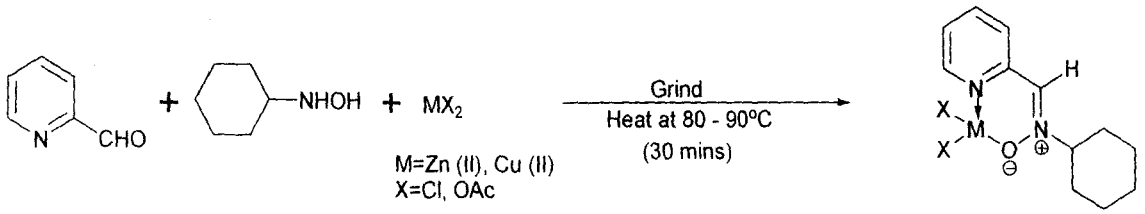


Figure 11 COSY spectra of α-(4-hydroxy-3-methoxyphenyl)-N-cyclohexyl nitrone

Considering that the nitrone function, incorporated unto various backbones is being increasingly studied, a facile access to this class of compounds was needed. The simplest existing route to a metal nitrone complex requires the following two steps. The first step is the synthesis of the nitrone ligand. It involves the addition of N-substituted hydroxylamine and magnesium sulfate to a well stirred solution of aldehyde in DCM. The resulting mixture is stirred for 4 hours at which time the reaction mixture is filtered

and the filtrate evaporated under reduced pressure. The residue is purified by column chromatography (Et_2O) to give the nitrone. Subsequently, in the second step a solution of the nitrone in acetone is treated with metal halide under an inert atmosphere and the resulting mixture is stirred for 6 hours. After this time diethyl ether is added until no more precipitation of a solid is observed. The resulting precipitate is filtered, washed with cold acetone and dried to give essentially pure complex.[41]

Since only a few complexes of metals with simple nitrones have been reported, the versatility of our solventless method was also demonstrated by the facile formation of metal nitrone complexes. In a representative reaction, taking pyridine-2-carbaldehyde, an aliphatic hydroxylamine and $ZnCl_2$ as the metal salt, the metallo-nitrone complex was synthesized in a one-pot reaction, without the need for separation and purification of the nitrone (Scheme 43). The time is drastically shortened from 10 hours to 30 minutes. While using metal acetate (Cu (II) acetate) it was found that acetic acid vapor was released during grinding the mixture; as was evidenced from its strong pungent odour. The formation of the desired products and completion of the reaction was checked with TLC and IR spectroscopy in KBr. Simple washing with a little amount of ethanol is all that is required for product purification. The normal workup procedure for the reaction consists of a tedious chromatographic separation in order to get the pure product. The conventional solvent-based method involves a two-step process which considerably prolongs the reaction time. Due to the thermo chemical activation, it was possible not only to eliminate altogether the use of halogenated solvents, but in many cases to avoid the need of a tedious extraction sequence and column chromatography as the products were immediately isolated in analytically pure form.



Scheme 43 An efficient one-pot Solvent-free synthesis of metallo-nitrone complex

Keeping adhered to the prudence of developing a unified general approach of Schiff-base synthesis and their metal complexes we synthesized six nitrones and the Zn(II) and Cu(II) complexes of α-pyridyl-N-cyclohexyl nitrone **[10]** very conveniently in solventless optimized thermal condition. Some physical properties, analytical and spectral data of the compounds are summarized in Table 2. The compounds have also been characterized by Mass, 1H NMR, 13C NMR, and IR spectra.

Table 2 Analytical and spectral data of some nitrones and its metal complexes

Entry	Compound	Compound Colour	M.P (°C)	Λ_M ($\Omega^{-1}cm^2mol^{-1}$)	μ_{eff} BM	U.V. λ_{max} (nm)
1	α-(4-hydroxy-3-methoxyphenyl)-N-cyclohexyl nitrone **[9]**	White	186-188	-	-	246, 351
2	α-pyridyl-N-cyclohexyl nitrone **[10]**	White	75-77	-	-	301
3	α-phenyl-N-cyclohexyl nitrone **[11]**	White	95-97	-	-	292
4	α-styryl-N-cyclohexyl nitrone **[12]**	Yellow	118-120	-	-	328
5	α-furyl-N-cyclohexyl nitrone **[13]**	Brown	89-91	-	-	206, 304
6	α-(4-fluorophenyl)-N-cyclohexyl nitrone **[14]**	White	85-88	-	-	205, 291
7	Zn(II) N Cyclohexyl-C-(2-pyridyl) Nitrone **[15]**	White	233-235	5.05	-	301
8	Cu(II) N-Cyclohexyl-C-(2-pyridyl) Nitrone **[16]**	Green	180-181	18.46	1.47	261

2.2.4. Synthesis of Hydroxy benzylidene Glycine and its Metal complex

The Schiff bases derived from amino acids and hydroxy aldehydes and ketones are not only pharmacologically important but also act as valuable ligands for metal complexes. The tridentate dianionic amino acid Schiff base ligand binds through phenolate and carboxylate oxygen and imine nitrogen atoms. Studies on the effect of the Schiff base derived from *L*-glycine on the activity of total (ACP), prostatic (PAP) and non prostatic (NPA) acid phosphatase enzymes have been reported. They have been found to have some inhibition effect on the ACP and NPA activities and activation effect on PAP activity.[45]

Metal complexes of the Schiff base of hydroxyaldehydes / ketones with amino acids serve to be very useful for model studies on spectra-structure correlations for the protein metal sites.[46] In spite of their apparent usefulness as models for the more complicated metal-pyridoxal-amino acid systems, which are the intermediates in biologically important transamination reactions,[47] the metal complexes of Schiff bases derived from salicylaldehyde and amino acids,[48] have received comparatively little attention. Since the complexes of amino acid Schiff base with transition elements possess some antibacterial (Figure 12)[49] and anticarcinogenic activities[50] the coordination chemistry of amino acid Schiff bases is of considerable interest.

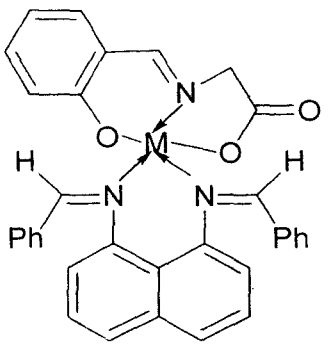
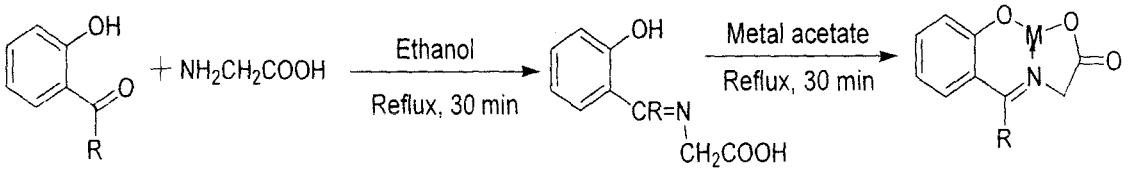


Figure 12 Metallo-salicylidene glycine complex possessing antibacterial activity

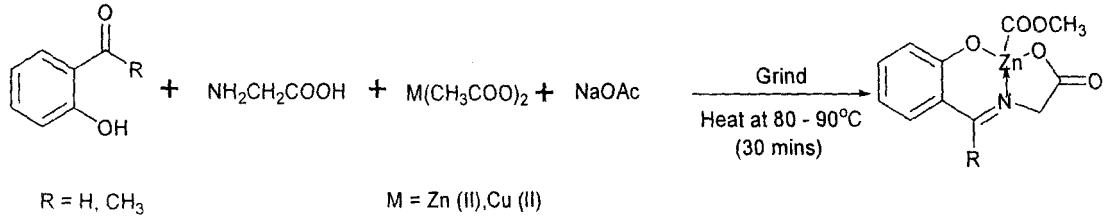
Conventionally, the ligand salicylidene glycine is prepared as its potassium salt by adding an ethanolic solution of salicylaldehyde to an ethanolic–KOH solution of glycine and stirring at 50°C for an hour. The product is crystallized by diffusion of excess absolute diethyl ether into the solution.[51] The synthesis of metal complexes of salicylidene Schiff bases of the α-amino acids often results in low yields of the desired compounds.[52] The approach to these complexes so far has been condensations between the o-hydroxy aldehyde or ketone and glycine with subsequent additions of the metal acetates under refluxing conditions in ethanol (Scheme 44).[53]



Scheme 44 A typical two-step synthesis of metal complexes of hydroxybenzylidene glycine

The salicylidene glycine ligand was prepared in a very short time by our solventless method. In a typical reaction, equimolar amount of glycine is finely grinded with sodium acetate and to it was added salicylaldehyde and heated further for 15 minutes. The completion of the reaction is indicated by a single spot in the TLC. The product was crystallized by dissolving the contents of the test tube in alcohol and adding ether to the alcoholic solution.

To further expand the scope, our method stated herein was also applied to the synthesis of the Zinc and Copper salicylidene glycine complexes. In addition to the stoichiometric amounts of the hydroxy aldehyde/ketone, glycine and the metal acetate, equimolar amount of sodium acetate was used (Scheme 45). On grinding the reactants together in an agate mortar and pestle, a colored melt is obtained. The reaction is found to go to completion only after heating it to 80-90°C for another 20 minutes. Pure product is obtained by simply washing with water and a little amount of ethanol. The procedure is superior to the often-used reflux method in that it is a one-step multi-component solvent-free route to these compounds.



Scheme 45 An efficient one-pot solvent-free synthesis of metal complexes of hydroxybenzylidene glycine

The products have been characterized by IR, HNMR, CNMR and Mass spectra. Table 3 summarizes some physical, spectral and analytical analysis.

Table 3 Analytical and spectral data of hydroxy benzylidene amino acetic acid and its metal complexes

Entry	Compound	Compound Colour	M.P (°C)	Λ_M ($\Omega^{-1}cm^2mol^{-1}$)	μ_{eff} BM	U.V. λ_{max} (nm)
1	Sodium salt of Hydroxy benzylidene amino acetic acid **[17]**	Yellow	205-207	-	-	314, 408
2	Sodium salt of Hydroxy acetophenone amino acetic acid **[18]**	Yellow	236-238	-	-	347, 423
3	Zn(II) N-(2-Salicylaldehyde) glycinate **[19]**	White	>300	4.65	-	271, 367
4	Cu(II) N-(2-Salicylaldehyde) glycinate **[20]**	White	>300	12.68	1.23	267, 369
5	Zn (II) N-(2-hydroxyacetophenone) glycinate **[21]**	White	>300	4.34	-	390

The 2D NMR COSY spectra of Zn (II) N-(2-hydroxyacetophenone) glycinate, as shown below (Figure 13) indicates the presence of one acetate molecule coordinated to the metal ion as is also evidenced from the mass spectra.

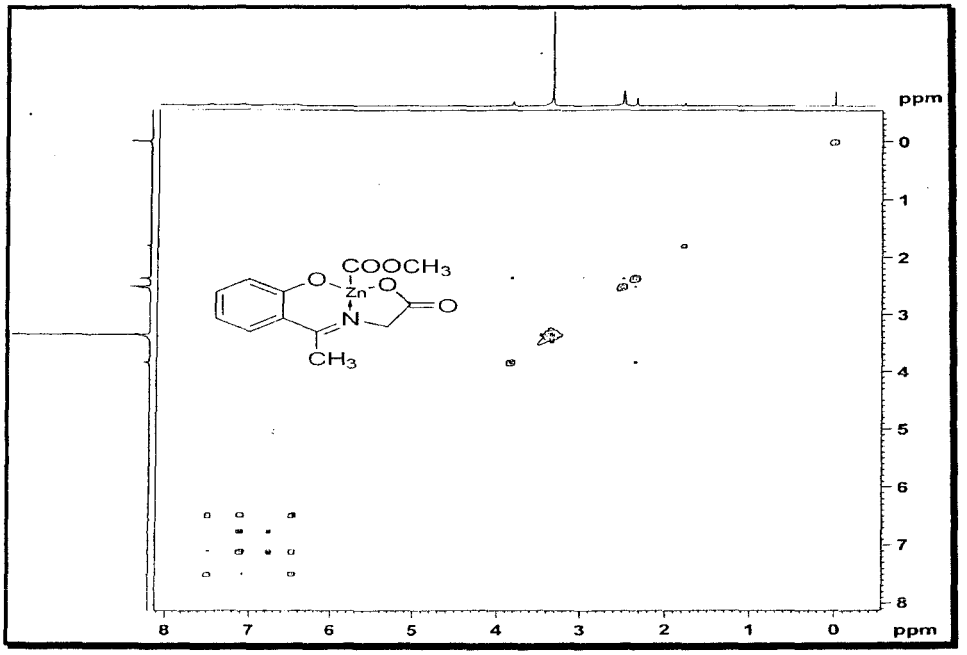


Figure 13 COSY spectra of Zn (II) N-(2-hydroxyacetophenone) glycinate

2.2.5. Synthesis of Hydrazones and Metallo-hydrazone complexes

Phenyl hydrazones, exhibit a wide spectrum of physiological activity. It is known that phenyl hydrazones (PHs) of some ketones exhibit antitubercular and antiviral activity.[54] It is believed that the pharmacological effect, especially the antioxidant and the antiradical activity,[55] of phenylhydrazone compounds is associated, directly or indirectly, with their effect on the free-radical processes occurring in a living body. Apart from the significant activity of phenyl hydrazones arising because of their complexation with metal ions, their use as an indicator for the titration of organometallic reagents is unparalleled among others.[56]

In the last two decades, much interest has been focused on compounds containing hydrazide and hydrazone moieties and their complexes with first row transition metals.[57] Such interest has been growing due to their use in medicine[58] (for treatment of tuberculosis), biological systems[59] and analytical chemistry.[60] In analytical chemistry hydrazones find application by acting as multidentate ligands [61] with metals (usually from

the transition group). Hydrazone complexes of Cu (II), Ni (II), Pd (II) and Co (II) and benzoyl hydrazone complexes of copper (II), vanadium, and ruthenium (II) have found to be potent bactericides and fungicides (Figure 14).[62]

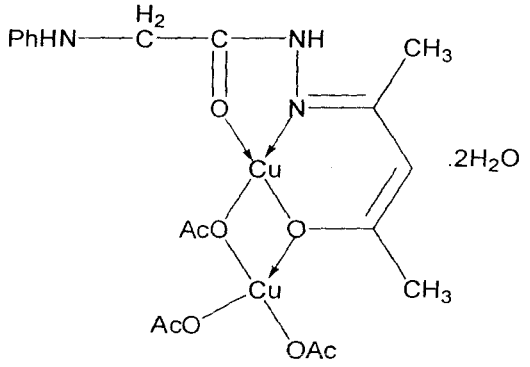
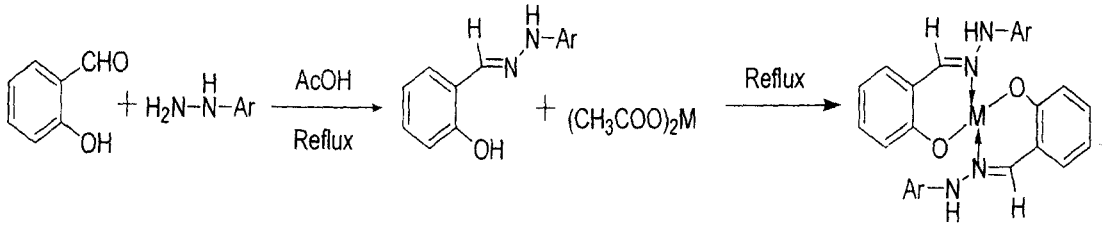


Figure 14 Cu complex of 4-methylphenylamino acetoacetylacetone hydrazone – a potent bactericide and fungicide

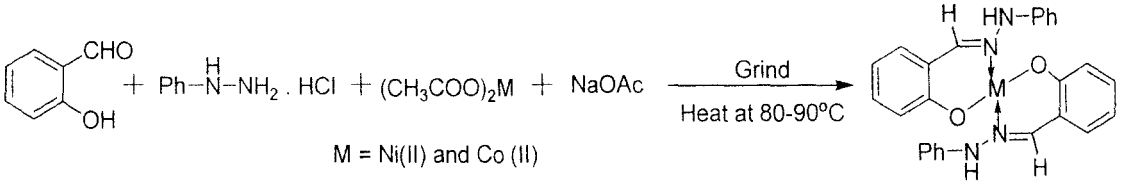
According to the literature procedure the preparation of phenyl hydrazone ligand involves room temperature stirring of phenyl hydrazine with salicylaldehyde in ethanol for 30 minutes and cooling to -15 °C.[56] It can also be alternatively prepared by adding a few drops of acetic acid to an ethanolic solution of the appropriate aryl/acylhydrazine and salicylaldehyde. The mixture is heated at reflux for 1 hour, and then cooled to room temperature (Scheme 46). The crystalline solid is collected by filtration, washed with cold ethanol, and dried in air. For metal complexation, a mixture of metal acetate and the corresponding hydrazone in ethanol is then heated at reflux for 1 hour with stirring. After cooling, the mixture is filtered, the solid washed with ethanol and dried in air, and finally recrystallised from THF/DMF.[58]



Scheme 46 A typical two-step synthesis of metal hydrazone complexes under reflux

The versatility of our solventless method was also demonstrated by the facile formation of the Salicylaldehyde phenylhydrazone ligand and its metal complexes with a dramatic increase in yields from 50-60% to almost quantitative. The ligand was prepared by grinding 1 mmole of phenyl hydrazine hydrochloride and sodium acetate and subsequently adding salicylaldehyde when a brown paste is formed. Further heating for 10 minutes results in the product, which crystallizes from alcohol.

The metal complex of salicylaldehyde phenylhydrazone is prepared by the solvent-free multicomponent method in a single-pot reaction in a similar approach employing the metal salt as the third component. As a general approach, one molar equivalent of the metal salt, two molar equivalents each of sodium acetate and the hydrochloride salt of phenyl hydrazine were mixed with a mortar and pestle for ca. 10 minutes. Aldehyde is then added to the reaction mixture. Heating the mixture for another 20 minutes gave a single spot in the TLC (Scheme 47). Subsequent washing with water and a little amount of hot ethanol was sufficient to obtain pure products.



Scheme 47 An efficient one-pot solvent-free synthesis of metal hydrazone complexes

The micro-crystalline solids are stable at room temperatures and non-hygroscopic. They are insoluble in water, sparingly soluble in common organic solvents but completely soluble in coordinating solvents like DMF and DMSO. By this time-saving multi-component protocol the Ni (II) and Co (II) complexes have been conveniently prepared. The experimentally obtained μ_{eff} value of 2.47 for the Co (II) complex suggests a square-planar geometry for the complex. Analytical and spectral data of the compounds are presented in Table 4.

Table 4 Analytical and spectral data of Salicylaldehyde phenyl hydrazone and its metal complexes

Entry	Compound	Compound Colour	M.P (°C)	Λ_M ($\Omega^{-1}cm^2mol^{-1}$)	μ_{eff} BM	U.V. λ_{max} (nm)
1	Salicylaldehyde phenyl hydrazone **[22]**	Cream	140-142	-	-	299, 347
2	Ni(II) complex of Salicylaldehyde hydrazone **[23]**	White	248-250	5.82	-	308, 356
3	Co(II) complex of Salicylaldehyde hydrazone **[24]**	Brown	254-256	20.42	2.47	307, 357

2.2.6. Synthesis of Semicarbazones and Metallo-semicarbazone complexes

Like hydrazones, Semicarbazones have demonstrated a wide range of biological activities.[63] Semicarbazones are reported to possess versatile structural features[64] and very good antifungal and antibacterial properties.[65] They are also versatile ligands for metal complexation.[66]

Metal complexes of semicarbazones have been the subject of extensive investigations because of their potential pharmacological properties and a wide variation in their modes of bonding and stereochemistry. Research on the coordination chemistry,[67] analytical applications[68] and biological activities[69] of these complexes is now increasing steadily over the years. For instance, Ni (II) and Cu (II) complexes with semicarbazone ligands have displayed biological properties.[70] Very recently, studies on their Cu (II) complexes has revealed the antitumor potential of this class of compounds.[71] Only a few years back, a group of vanadium complexes of salicylaldehyde semicarbazone derivatives

were reported for their selective potency on human kidney TK 10 tumour cells (Figure 15).[72]

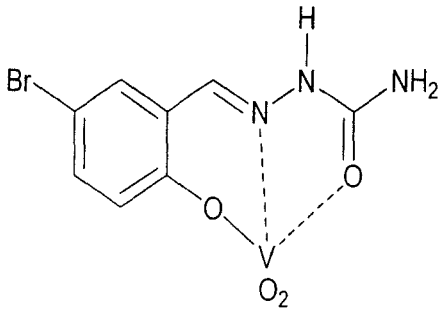


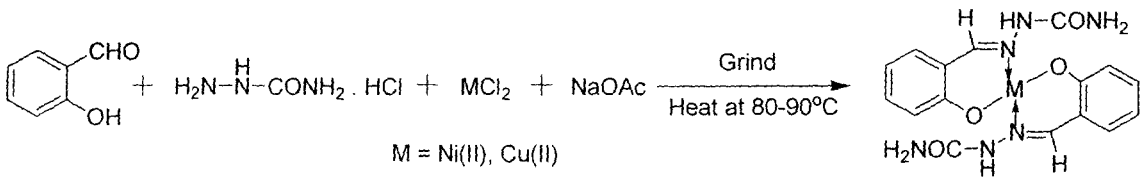
Figure 15 Dioxovanadium (V) semicarbazone complex

Conventionally, salicylaldehyde semicarbazone and its metal salt are prepared by first mixing semicarbazide and salicylaldehyde in ethanol to yield the semicarbazone. The complex is then subsequently prepared by adding drop wise a solution of metal salt in methanol to the solution of the salicylaldehyde semicarbazone in DCM with vigorous stirring.[63]

After having successfully tested almost all Schiff base type compounds for the transformations, the attention was turned to the remaining few. The semicarbazone ligand was prepared by simple grinding of the hydrochloride salt of semicarbazide with salicylaldehyde in equimolar amounts and an excess of sodium acetate. Quantitative yield are obtained on further heating the product mixture for 10 minutes at 80-90°C. Purification by crystallization from ethanol gives the products as crystals.

For preparing Semicarbazone metal complexes, the reaction was run under similar conditions with the metal salt as the additional component. In a typical reaction, 2 mmole each of salicylaldehyde and semicarbazide hydrochloride is grinded with one mmole of metal salt along with an excess of sodium (Scheme 48). The colored mixtures after heating for 20 minutes and subsequent washing with hot water and a little amount of hot ethanol gave sufficiently pure products. Even then, the products were further

recrystallized from 1:1 methanol /ethanol mixture, but it did not bring about a change in the melting point of the product. The products were isolated in excellent yields.



Scheme 48 An efficient one-pot solvent-free synthesis of metal semicarbazone complexes

Furthermore when 5 mmole and 10 mmole quantities of the reactants are taken for scaling up the reaction, there was no loss in the yield. The analytical data of the Ni (II) and Cu (II) complexes prepared quantitatively by this method are given below (Table 5).

Table 5 Analytical and spectral data of Salicylaldehyde semicarbazone and its metal complexes

Entry	Compound	Compound Colour	M.P (°C)	Λ_M ($\Omega^{-1}cm^2mol^{-1}$)	μ_{eff} BM	U.V. λ_{max} (nm)
1	Salicylaldehyde semicarbazone **[25]**	White	224-226	-	-	281, 358
2	Ni(II) complex of Salicylaldehyde semicarbazone **[26]**	White	212-214	3.62	-	281, 359
3	Cu(II) complex of Salicylaldehyde semicarbazone **[27]**	Green	>300	12.36	1.11	282, 402

This solvent-free method scores over other reported methods for preparation of these metal complexes as it does not require extensive work-up and it does not necessitate the use of halogenated solvents during work-up. Additionally, since it is a single pot method, it is time-saving and cost effective.

2.2.7. Synthesis of Oximes and Metallo-oxime complexes

Oximes and azo dyes have often been used as chelating ligands in the field of coordination chemistry and their metal complexes have been of great interest for many years. The biological importance of oximes and their complexes is very well known.[73] Different oximes and their metal complexes have shown notable bioactivity as chelating therapeutics, as drugs, as inhibitors of enzymes and as intermediates in the biosynthesis of nitrogen oxides.[74]

Dioximes being bidentate form stable complexes with various metal salts. On the other hand, very few monoximes have been reported to form complexes with nickel, iron and cobalt salts which are stable.[75] The formation of stable monoxime complexes of cyclohexanone with Ni, Pt and Pd has been briefly reported.[76] The chemistry of these oximes is important in view of their possible application as biochemical models.[77] Only recently some oxime based Nickel complexes have been found to be effective in selective ethylene oligomerization (Figure 16).[78]

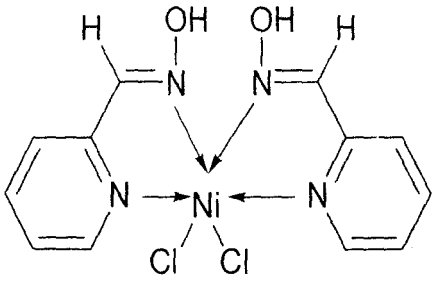
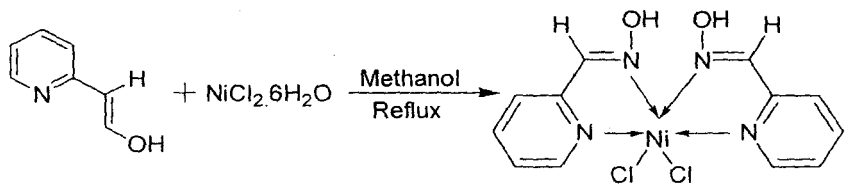


Figure 16 Moderately active Ni complex for ethylene oligomerization

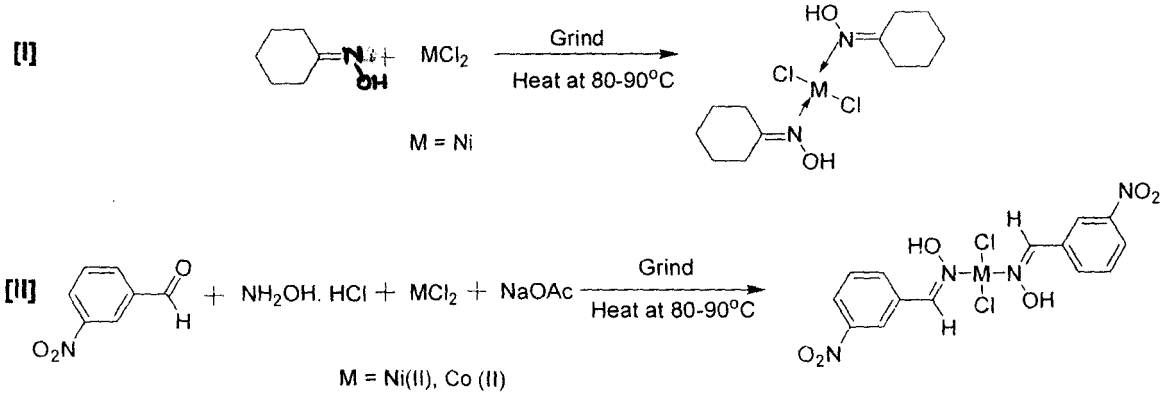
Synthesis of various oximes and their complexes with different transition metals are reported in the literature[79] and found to be active as anti-bacterial, anti-tubercular, anti-lepral, anti-viral, anti-malarial and active against certain kinds of tumours.[80] The synthesis of oxime complexes usually involves refluxing of the reaction mixture containing the oxime and metal salt in alcohol for about 3 hours in a hot water bath (Scheme 49).[81]



Scheme 49 Synthesis of oxime metal complexes under refluxing conditions

In our quest for the development of more easier and quicker methods for the synthesis of metal complexes, the substrate scope for our methodology was also extended to metal complexes of this Schiff base type compound. Interestingly, in the case of the oximes it was found that a sequential addition reaction gave quantitative results in some cases rather than the multicomponent synthesis. While with m-nitrobenzaldehyde oxime metal complexes, a multicomponent reaction gave better results, the cyclohexanone oxime metal complex was best obtained from a sequential addition of the oxime with the metal salt.

The cyclohexanone oxime is easily prepared by taking 1 mmole of cyclohexanone with 1.5 mmole of hydroxylamine hydrochloride and 2.5 mmole of sodium acetate in water. The mixture in the conical flask gives white crystalline cyclohexanone oxime after warming in a water bath for 10 minutes with constant agitation. For metal complexation, 2 mmole of the cyclohexanone oxime is mixed with 1 mmole of the metal chloride and finely grinded in an agate mortar and pestle for 10 minutes. Heating the intimate mixture for another 20 minutes gives a red colored product which is washed with alcohol and dried in vacuum (Scheme 50 [I]).



Scheme 50 An efficient one-pot solvent-free multicomponent synthesis of metal oxime complexes

On the other hand, the m-nitrobenzaldehyde oxime metal complex is synthesized in a typical multicomponent strategy (Scheme 50 [II]) where two molar equivalents each of the aldehyde, hydroxylamine hydrochloride and sodium acetate were finely grinded along with one molar equivalent of the metal salt and heated to 80-90°C. The product formation is also completed after 20 minutes of reaction, indicated by TLC. After washing with a small volume of ether and alcohol, the products are isolated in quantitative yields.

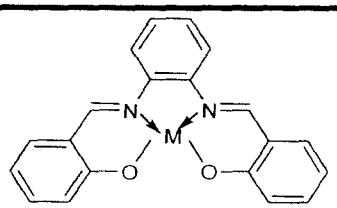
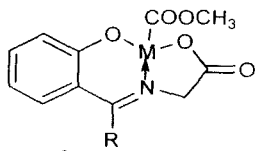
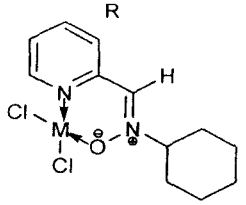
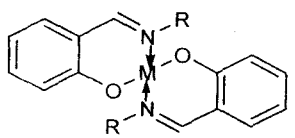
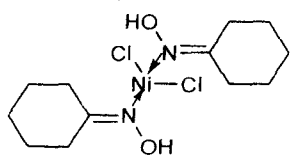
Interestingly, in a solvent-free multi-component one-pot synthesis, equimolar amounts of the reactants could be used without any loss in yield. This is probably due to a more effective mixing of the reactants or to the fact that the concentration of reactants is simple higher and the reactants are at a close proximity to each other. Ni (II) and Co (II) metal oxime complexes have been prepared and their spectral and analytical data are presented in Table 6.

Table 6 Analytical and spectral data of Oxime metal complexes

Entry	Compound	Compound Colour	M.P (°C)	Λ_M ($\Omega^{-1}cm^2mol^{-1}$)	μ_{eff} BM	U.V. λ_{max} (nm)
1	m-nitrobenzaldehyde oxime **[28]**	Yellow	122-123	-	-	264
2	N-cyclohexanone oxime **[29]**	White	89-91	-	-	-
3	Ni(II) complex of N-cyclohexanone oxime **[30]**	Red	>300	6.25	-	-
4	Ni (II) m-nitrobenzaldehyde oxime **[31]**	Brown	>300	4.65	-	257
5	Co (II) m-nitrobenzaldehyde oxime **[32]**	Green	225-226	14.56	2.33	251

Typically the solution-phase synthesis of these compounds employs the use of organic solvents such as toluene or methanol, refluxing for over an hour, followed by extensive recrystallization and/or chromatography. Moderate yields are recorded in such processes. With the optimized conditions form the TGA and DSC runs and via the solventless multi-component method, salphen and other Schiff's base derived metal complexes have been synthesized in significantly higher yields in a shorter time as shown in Table 7. Comparisons of both approaches viz., the solventless method and the conventional method using solvents, has been done in terms of yield and the reaction time and listed in the table to highlight the significance and superiority of the solvent-free method,

Table 7 Comparison of reaction time and percentage yield of metal complexes synthesized (a) in solvent and (b) under solvent-free condition

Entry	Metal Complex	Reaction Time (a)	(b)	Reported Yield (%)
1		1 hr[24]	20 mins	70-90
2		1 hr[53]	20 mins	75
3		6 hrs[40]	30 mins	90
4		4 hrs[79]	30 mins	50-60
5		2 hrs[79]	30 mins	60-70

2.3. Imidazoles: tri- and tetra- substituted and their derivatives

After having successfully tried and tested our methodology, the attention was turned to other transformations that could be easily performed via the solvent-free multi-component protocol. Considering that suitably substituted heterocycles containing an imidazole backbone have very frequently been found to have interesting biological activities, an interest arose for the corresponding 1-Hydroxy Imidazole-3-oxides with the hydroxy function at the N-1 and oxide functionality at the N-3 positions.

As a starting point for this study a facile access to Imidazole, substituted Imidazoles and their derivatives thereof was needed. Some preliminary synthesis were done on Imidazole, both tri- and tetra-substituted for a few reasons; firstly because they were deemed easy to investigate without a need to synthesize complex starting materials (easily available simple starting materials like benzil, glyoxal etc can be used); secondly, even though surplus literature is available for them, it was thought to be very challenging to come up with a new protocol (as simple as thermo-chemical activation) which could compete with the latest technologies, in terms of yield, reaction time, scalability and greenness of the reaction; and thirdly, since the Imidazoles and compounds with the imidazole ring system have many pharmacological properties and play significant roles in biochemical processes,[82] a Diversity Oriented Synthesis (DOS) to this class of compounds and their metal complexes would be extremely helpful.

Imidazoles are heterocycles that are part of a large number of highly significant biomolecules such as the essential amino acid histidine and related compounds, biotin and the imidazole alkaloids.[83] Synthetic imidazoles are present in many fungicides and herbicides[84] and also in antifungal, antiprotozoal, and antihypertensive medications.[85] Insertion of the imidazole nucleus is an important synthetic strategy in drug discovery. Imidazole drugs have broad applications in many areas of clinical medicine.[86] The imidazole moiety is also contained in many histaminergic ligands for histamine H1, H2 and H3 receptors as well as in several FTase inhibitors.[87] The important therapeutic properties of imidazole drugs have encouraged the medicinal chemists to synthesize and

test a large number of novel molecules. Several 5-lipoxygenase, 'P38' MAP and B-Raf Kinase inhibitors containing the imidazole moiety have been synthesized.[88] Some substituted triarylimidazoles are selective antagonists of the glucagon receptor[89] and inhibitors of Tie2 and IL-1 biosynthesis.[90] The potency and wide applicability of the imidazole pharmacophore can be attributed to its hydrogen bond donor–acceptor capability as well as its high affinity for metals, which are present in many protein active sites (e.g., Zn, Fe, and Mg). Thus, the synthesis, reactions, and biological properties of substituted imidazole constitute a significant part of modern heterocyclic chemistry. Recent advances in green chemistry and organometallic chemistry have extended the boundary of imidazoles to the synthesis and application of a large class of imidazoles as ionic liquids[91] and imidazole related N-heterocyclic carbenes.[92] In industry, imidazoles have been used extensively as a corrosion inhibitor on certain transition metals, such as copper.[93]

2.3.1. Synthesis of Tri- and Tetra-substituted Imidazoles

The development of efficient approaches to chemically and biologically important products from readily available inexpensive starting materials has been an active topic in modern organic chemistry.[94] The synthetic approach to the Imidazoles has been constantly redesigned over the years. The first synthesis of the imidazole core, starting from 1, 2-dicarbonyl compounds, aldehydes and ammonia, was first reported by Debus in 1858, and then fully developed by Radziszewski and Japp in 1882.[95] Although classical methods were derived from this early success, the reaction suffered from low yields, mixtures of products and longer reaction times. Despite this, the development in synthesis of such compounds did not wear out down the years. Since then, the imidazole nucleus has over the years prompted the development of new improved methodologies.

A number of methods have been developed for the synthesis of 2, 4, 5-trisubstituted and 1, 2, 4, 5-tetrasubstituted imidazoles. Generally 2, 4, 5-trisubstituted imidazoles are synthesized by three component cyclocondensation of 1, 2-diketone, α-hydroxyketone or α -ketomonoxime with aldehyde and ammonium acetate. On the other

hand, the synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles have been carried out by four-component condensation of a 1, 2-diketone, α -hydroxyketone or α -ketomonoxime with an aldehyde, primary amine and ammonium acetate. Tri-and tetra-substituted imidazoles have been synthesized by using zeolites HY/silica gel,[96] NaHSO3,[97] sulphanilic acid,[98] iodine,[99] ceric ammonium nitrate,[100] silica sulphuric acid,[101] L-proline[102] and some common Lewis acids such as $Yb(OTf)_3$, $NbCl_3$, $LaCl_3$, $FeCl_3$, $AlCl_3$[103] or by classically refluxing in acetic acid.[104]

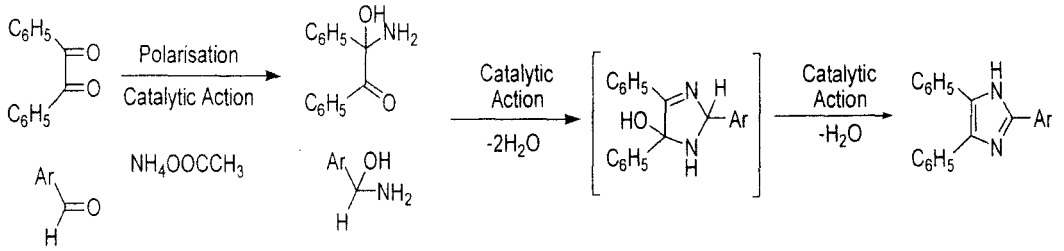
Recent modifications on the synthesis route have focused on the usage of microwave irradiation. Several microwave (MW) assisted syntheses of imidazoles from 1, 2- diketones and aldehydes in the absence of any solvent[105] or in the presence of a variety of catalysts such as silica-gel, silica-gel/HY, Al_2O_3,[106] DMF, acetic acid,[107] $ZrCl_4$,[108] $NiCl_2.6H_2O$,[109] and ionic liquid,[110] has been reported. Kidwai *et al* reported that during the MAOS of tri- and tetra substituted derivatives they got sticky solid which indicated that, it was not a cleaner approach[111] Other non-classical methods include an ultrasound-promoted synthesis of imidazoles catalyzed by $Zr(acac)_4$,[112] and another using a continuous flow micro reactor system under pressure.[113]

Each of the above methods for this reaction has its own merits, while some of the methods are plagued by the limitations of poor yield, longer reaction time, laborious work-up and effluent pollution, other synthetic methods suffer from one or more drawbacks such as harsh reaction conditions, use of hazardous and often expensive acid catalysts and tedious purifications, etc. Moreover, the synthesis of these heterocycles has been usually carried out in polar solvents such as ethanol, methanol, acetic acid, DMF and DMSO leading to complex isolation and recovery procedures. The preparations of some catalysts require relatively expensive reagents, harsh reaction conditions, and sometimes tedious workup using toxic reagents or solvents. These processes generate waste containing catalyst and solvent, which have to be recovered, treated and disposed off. Therefore, the development of a new non catalytic method with an efficient and environmentally benign protocol is necessary to overcome their shortcomings, and fulfill mild conditions for the synthesis of multi-substituted imidazoles.

A microwave reaction system can no doubt, provide an environment in which the reaction mixture can be rapidly dielectrically heated in sealed vessels at temperatures far above the boiling point of the solvent under pressure. However, it is difficult to scale up due to the limited penetration depth of microwave irradiation into absorbing media.[114] Consequently, exploring a simpler, greener, and easy to scale-up method for the efficient synthesis of tri- and tetra-substituted imidazoles is still desirable.

2.3.1.1. Optimization of reaction conditions for Imidazole synthesis with HPLC studies

To begin with, a representative substituted imidazole, 2-(4-methoxyphenyl)-, 4,5-diphenylimidazole **[34]** was initially prepared by a three-component reaction using the inputs anisaldehyde, benzil and ammonium acetate via a catalyst-free solvent-free procedure according to Scheme 51.



Scheme 51 A plausible solvent-free mechanism for the synthesis of Tri-substituted Imidazoles

We initially envisaged that the multicomponent reaction of aldehydes with ammonium acetate and benzil under thermochemical activation might not give quantitative results because it is well known that aldehydes have been frequently reacted with ammonium acetate in a bid to prepare 1, 2-diaminoethanes.[115] The reaction conditions favored for such reactions are continuous stirring for 3 hours at 120°C resulting into 1, 2-diaryl-*N*-arylmethylene-*N'*-aroyl-1, 2-diaminoethanes. Under the conditions, it has been revealed that in the reaction hydrobenzamide is formed in the first stage which in turn is transformed into amarine (*cis*-triphenylimidazoline). The compound further reacted with another aldehyde molecule and through a series of

intermediates formed the benzylidenebenzoyl derivative. But in the case of our protocol, though both ammonium acetate and an aldehyde are present in the reaction mixture, the products that have been reported above have not been found. As has been generally the case with several reported methods like ultrasonication, microwave and catalytic methods, we too exclusively obtained the Imidazoles. A possible reasoning might be that the presence of benzil hinders the formation of the said intermediates.

To obtain mechanistic insights we sought to look for the intermediate ammonia addition product with the help of HPLC. Initially, HPLC (at 259 nm with methanol as eluent, a C-18 column and flow rate of 0.5ml/min) of pure benzil and the imidazole **[34]** were recorded to locate the retention time of each of the substrates. While pure benzil gives a peak with retention time of 5.872 minutes (Figure 17), the pure recrystallised product, previously prepared, gives a peak with retention time of 6.092 minutes (Figure 18).

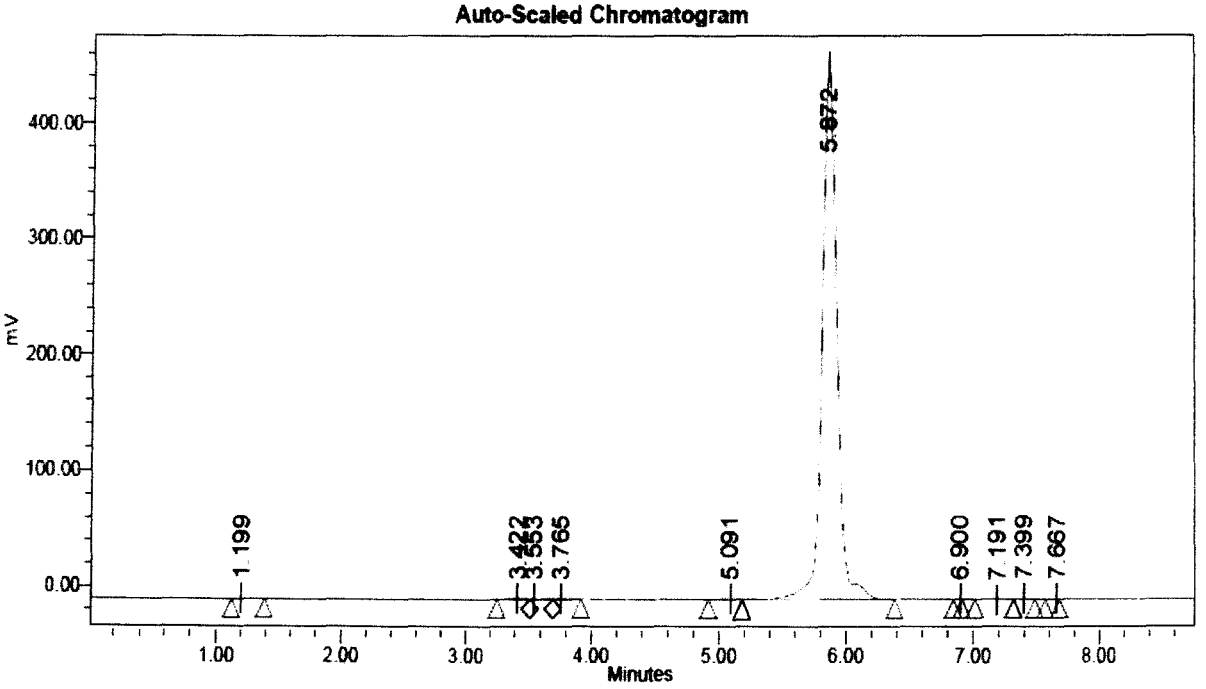


Figure 17 HPLC chromatogram of pure benzil

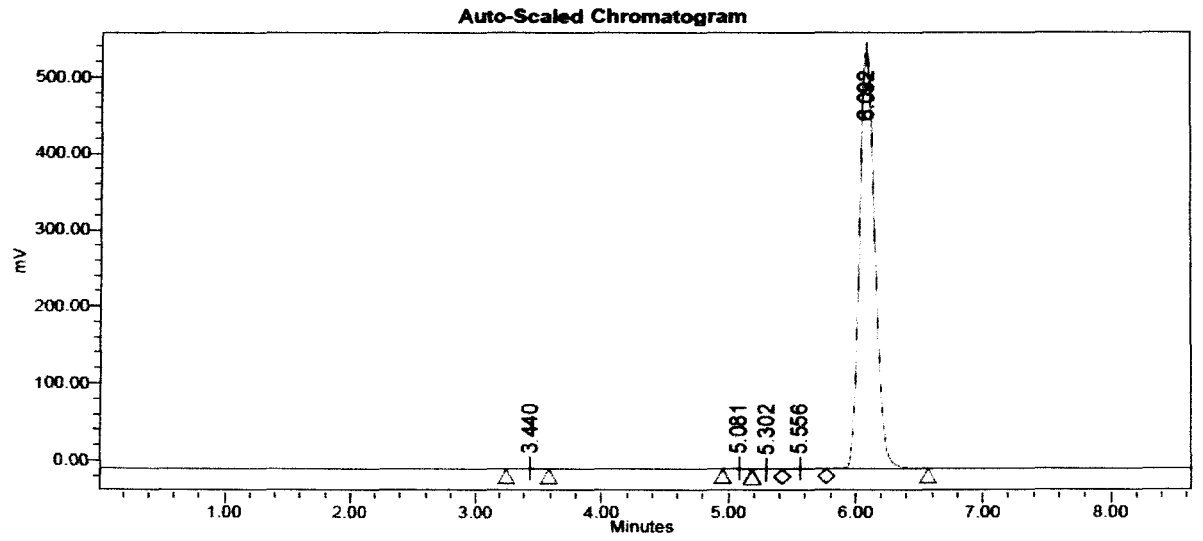


Figure 18 HPLC chromatogram of the pure product 2-(4-methoxyphenyl)-4,5-diphenylimidazole **[34]**

For further HPLC studies, 5 mmole of NH_4OAc was mixed thoroughly with 1 mmole of benzil and heated to 120°C and kept for 5 minutes. The HPLC chromatograms obtained for benzil and NH_3 mixture shows a major peak at 5.801 which is attributed to benzil (Figure 19). A new peak was observable at retention time of 8.075 indicating maybe the benzil-ammonia addition product.

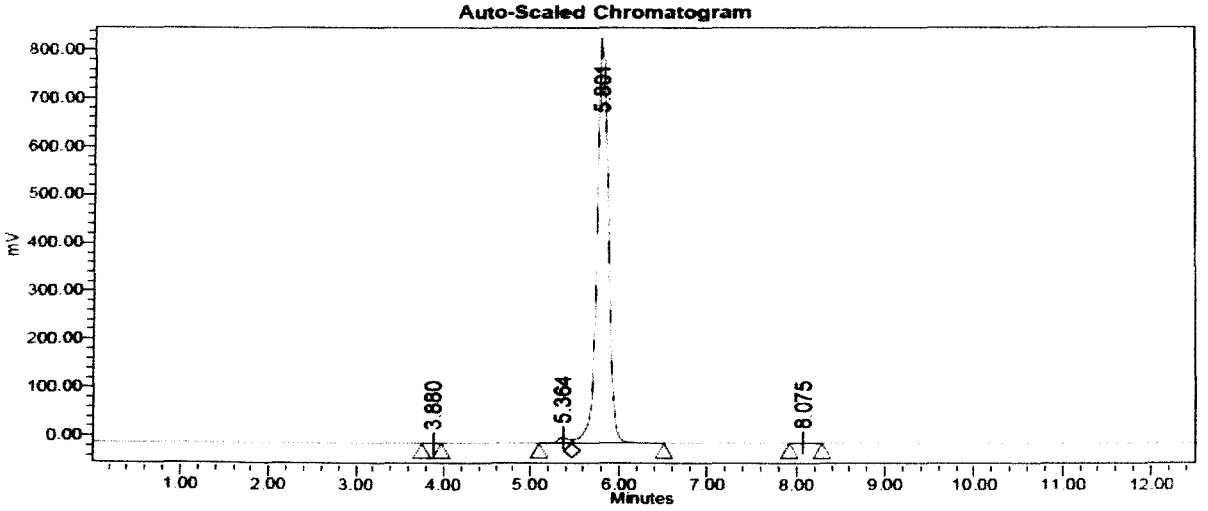


Figure 19 HPLC chromatogram of benzil and ammonium acetate

It is also significant to note that the peak at 8.075 is not observed in the HPLC chromatogram of pure benzil (Figure 17) whereas it is observable in the chromatogram

obtained from the HPLC run of the reaction mixture leading to the Imidazole, **[34]** (Figure 20). The chromatogram of the complete reaction mixture indicates the presence of the intermediates at 8.045 along with the presence of the Imidazole, **[34]** peak at 5.926, anisaldehyde peak at 5.543and the peak for benzil at 5.789.

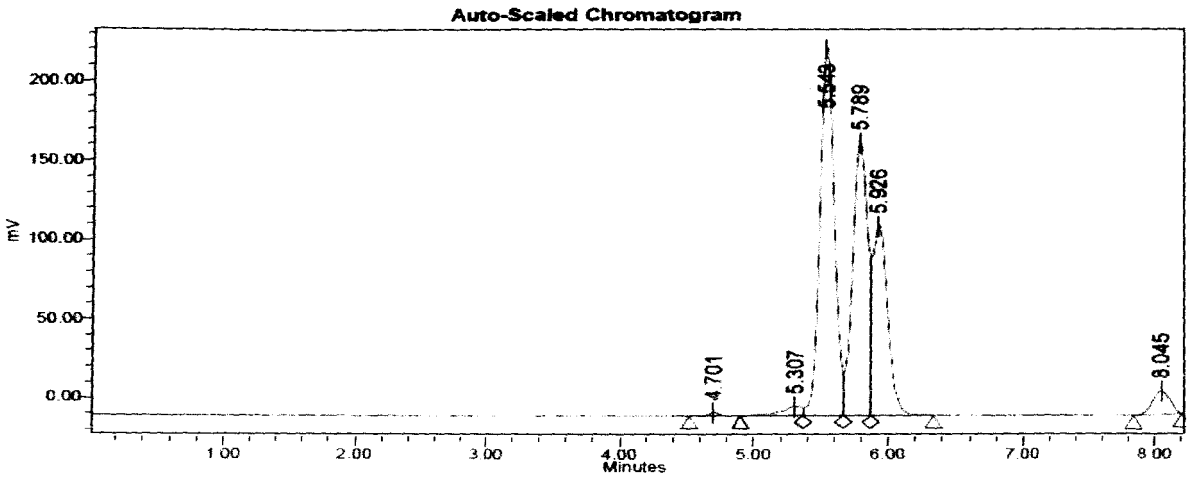


Figure 20 HPLC chromatogram of reaction mixture of benzil, anisaldehyde and ammonium acetate after 15 minutes at 120°C

On the other hand, the HPLC chromatogram of the aldehyde (anisaldehyde) treated with ammonia under similar conditions showed no peak at a higher retention time than the aldehyde itself which shows a peak at retention time of 5.549 (Figure 21). The peak at R.T. 5.310 may be for the aldehyde-ammonia addition product

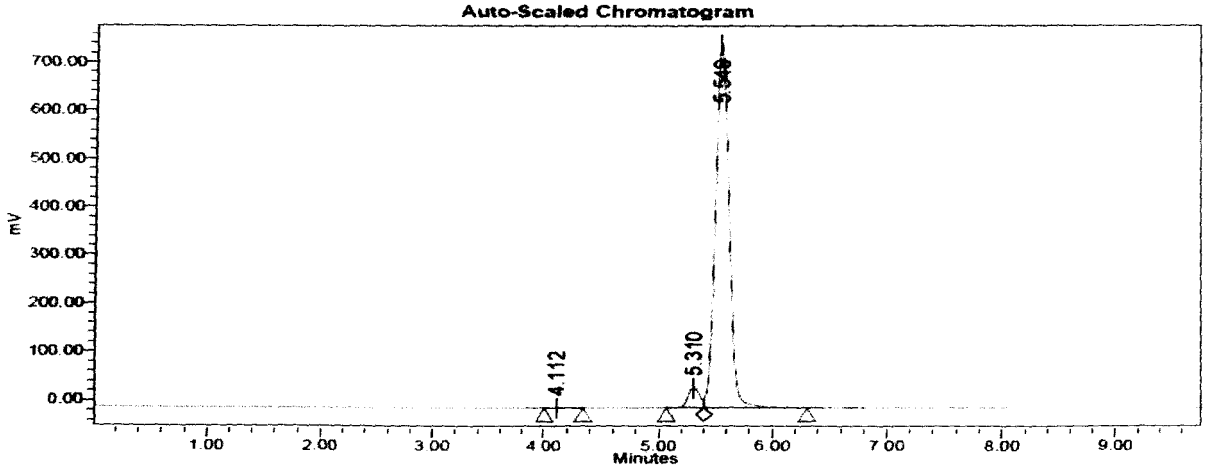


Figure 21 HPLC chromatogram of Anisaldehyde and ammonium acetate

Initial optimization of the reaction temperature and reaction time was done by conducting the reaction for 20 minutes at different temperatures and the peak areas obtained from HPLC were plotted against temperature (^{0}C). From the plot (Figure 22), it was found that in initial steps ammonia addition begins at comparatively lower temperature, but the product (imidazole) formation starts at a later stage and was quite sensitive to temperature variation; optimum temperature being 125-135°C.

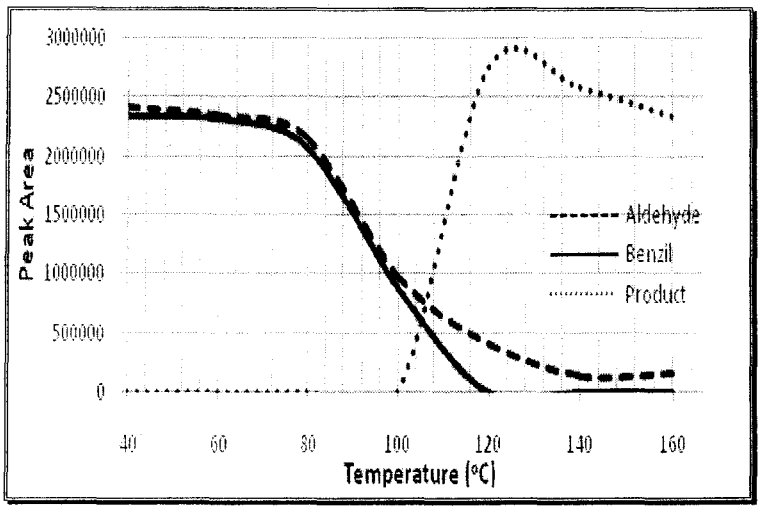


Figure 22 HPLC Peak Area vs Temp. after 20 mins of reaction (Compound **[34]** via Scheme 51)

2.3.1.2. Solventless multi-component synthesis of Tri- and tetra-substituted Imidazoles

In the light of our previous discussions and understanding, it was essential to verify other similar reactions to investigate the reason behind the phenomenon of an apparent catalytic effect in such solvent-free reaction medium, which, hitherto has not been done. Therefore, it was felt that the multicomponent Imidazole synthesis would serve as a good model to investigate the catalytic effect of solvent free condition since the study of the reaction in solvent-free condition from a kinetic perspective has not been done earlier. In fact, our intuition drove us to hypothesize that the solvent-free condition itself might have produced some catalytic effect on these types of reactions.

Existing literature reveals that the Debus-Radziszewski imidazole synthesis in solution state takes around 24 hrs to achieve moderate to good yield.[116] Heather to, the two most efficient syntheses reported are under microwave irradiation conditions where the reactants are irradiated at 180°C in acetic acid for 5 minutes[107] (Wolkenberg et al) and at 120°C for 3-5 minutes[105] (Zhou et al) in absence of a catalyst. In both cases the yields are almost quantitative. The acetic acid catalyzed the reaction in the first case and focused microwave heating in solvent-free condition worked well in the second case. From our present study it is revealed that the solvent-free condition is mostly responsible for self-catalytic effect. The basic chemistry remains same in all the cases; only changes in electrophilicity and polarizability of the carbonyl group has an effect on the rate of the reaction. Quantitative yields under less than four minutes are obtained even under solvent free thermal conditions and that too without the aid of a catalyst. Moreover, reactions based on thermal heating may be significantly more practical to use in scaled up syntheses.

The novelty of this study lies in its simplistic approach towards investigation of a reaction in condensed phase and its pertinence in comparison to other systems. To verify the role of catalysts and their essentiality in this present reaction sequence, catalytic screening was done by monitoring the kinetics of such reactions with the help of HPLC. The synthesis of imidazole **[34]** was then carried out in the presence of various catalysts at the optimized temperature of 125-135°C. Since the reaction was found to be first order with respect to benzil, aldehyde and the imidazole, natural logarithm values (-ve for the reactants and +ve for the products) of peak area against time was recorded. A good linearity was observed in each case. From the slope of these curves the first order rate constants and half lives ($t_{1/2}$) were determined using the first order rate equation;

$$\begin{aligned} dC/dt &= (+/-)\, kC \\ C &\alpha I \\ C &= I*X \\ \pm \ln I &= (+/-)\ kt + \text{integration constant} \end{aligned}$$

The advantage of the procedure is that it gives simultaneously a clear idea about the benzil or aldehyde consumption rates along with the rate of product formation. This

information helps to understand more about the sequences of reactions which manifest together as a multi-component reaction. The observed dependence of reactant concentration (logarithm) and product formation with the variation of time (at reaction temperature 125^{0}C) is shown in Figure 23. The product peak in HPLC was not much prominent within first 10 minutes.

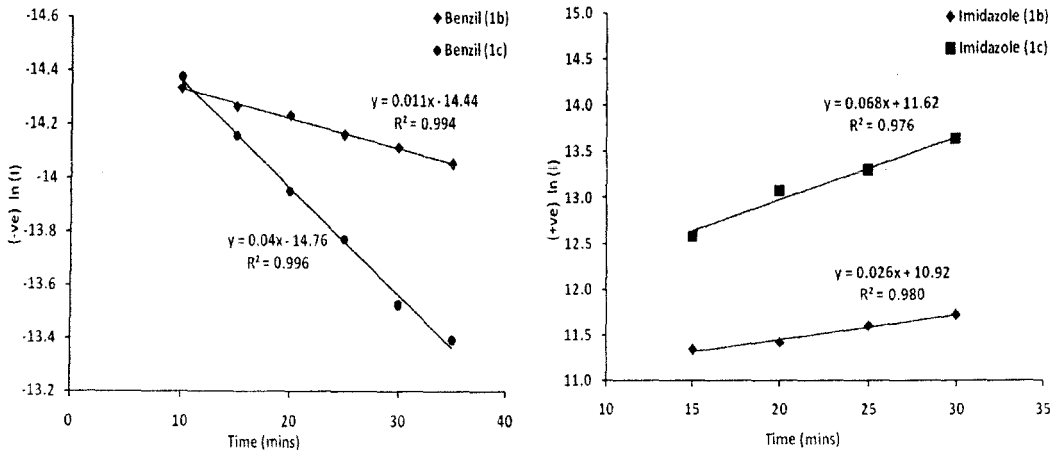


Figure 23 (–ve)/(+ve) ln(I) vs time(mins) of [i] benzil during formation of imidazoles **[34]** and **[35]**; [ii] rate curve of the product imidazoles **[34]** and **[35]** formation; I = Peak A.

The catalytic effect of some metal salts (5 mole %) at the same reaction temperature (125°C) was also compared. The corresponding rate constant and half life values are shown in Table 8.

Table 8 Rate constants and half lives of reactant consumption and product formation at 125°C under solvent-free conditions.

Catalyst	Rate of benzil consumption ($t_{1/2}$)[a]	Rate of aldehyde consumption ($t_{1/2}$)	Rate of product formation ($t_{1/2}$)
Solvent-free (no catalyst)	0.011 (63.01)	0.008 (86.64)	0.026 (26.66)
$Sm(NO_3)_3.6H_2O$	0.012 (57.76)	0.008 (86.64)	0.023 (30.13)
$Yb(SO_3CF_3)_3$	0.033 (21.00)	0.009 (77.02)	0.115 (6.03)
$ZrO(NO_3)_2$	0.058 (11.95)	0.017 (40.77)	0.034 (20.38)
$(NH_4)_2Ce(NO_3)_6$	0.035 (19.80)	0.024 (28.88)	0.112 (6.19)
$NiCl_2.6H_2O$	0.032 (21.66)	0.021 (33.00)	0.041 (16.90)

[a] Note: Half-life ($t_{1/2}$) in minutes

To cite a representative case of Ytterbium triflate, a threefold increase in the rate of benzil consumption and fivefold increase in imidazole formation as against the catalyst free reaction was observed. Employing a catalyst, no doubt facilitates reaction conditions and in many cases, it aids in lowering the temperature for a reaction by lowering the activation energy while in other cases the reaction time is dramatically shortened. The compiled results indicate that the catalysts did act at different stages of the reaction sequences of the multicomponent reaction but overall the reaction rate is augmented only five times than that of a catalyst-free process.

For further validation of our hypothesis and the above assumption, it was thought worthwhile to carry out the reaction at a more elevated temperature and under catalyst-free condition to see if the rise in temperature would increase the reaction rate considerably as compared to the increase brought about by the use of a catalyst. Hence, the kinetics of the imidazole **[34]** formation was studied at 140°C and 160°C. Surprisingly, the product formation starts after as early as 3 minutes at 140°C and reaction rates are increased almost 12-14 times in each stage. Increasing the bath temperature to 160°C yielded the products in quantitative yields (94-99 %) within 2-4 minutes (Figure 24). The reaction rates are increased almost 20 times. A quantitative yield of around 94.2% in two minutes at the said temperature suggests that the reactants are self-activated, even in the absence of catalysts or solvents.

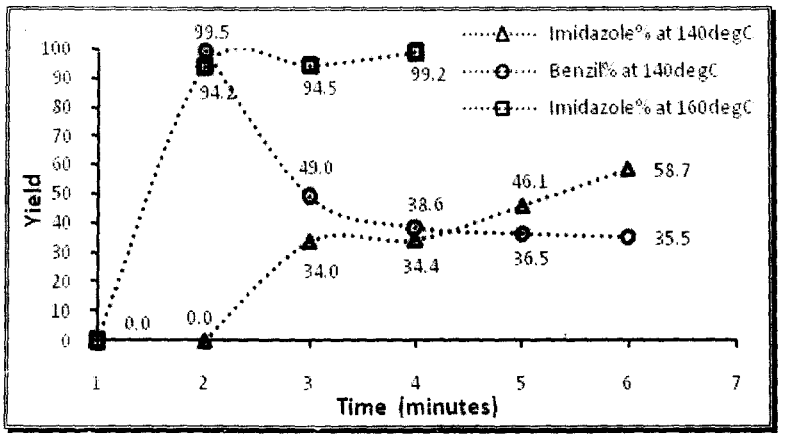
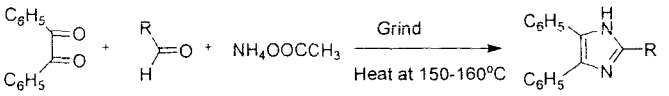
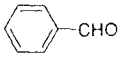
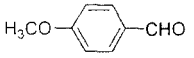
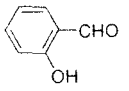
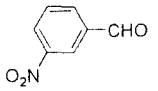
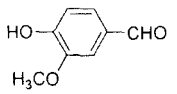
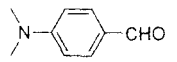
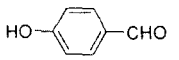
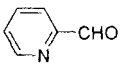


Figure 24 Comparison of percentage yield of Imidazole, **[34]** at 140°C, 160°C and benzil consumption at 140°C versus time (mins)

We next examined a wide variety of aldehydes (both aromatic and aliphatic) with various substituents to establish the solvent-free catalyst-free protocol for this reaction. A wide range of *ortho*-, *meta*-, and *para*-substituted aromatic aldehydes undergo this one-pot multi-component synthesis with 1, 2-diketones and ammonium acetate to afford 2, 4, 5-trisubstituted imidazoles in quantitative yields (Table 9). In all cases, we observed almost the same performance towards this cyclocondensation to give the desired products. Reaction profile is very clean and no side-products are formed. All the synthesized imidazoles have been characterized on the basis of elemental and spectral studies.

Table 9 Solvent free synthesis of 2,4,5-trisubstituted Imidazoles

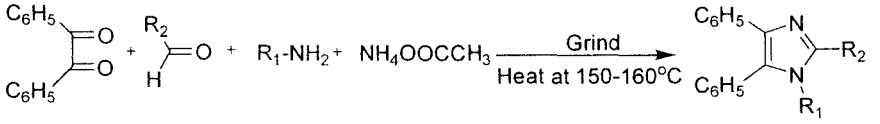


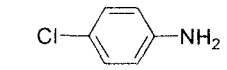
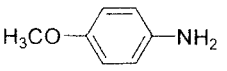
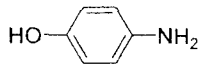
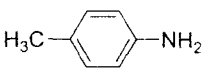
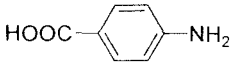
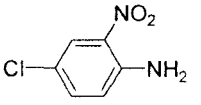
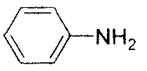
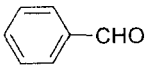
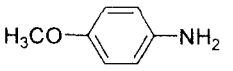
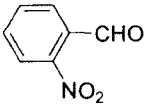
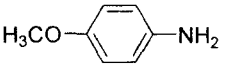
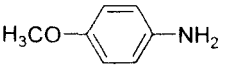
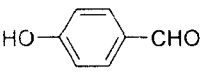
Entry	Aldehyde (R-CHO)	Product	Melting Point / °C	Reaction Time	Reported Time [a]
1		**[33]**	274-276	4 min	8.3 h[110]
2		**[34]**	226-228	4 min	9 h[110]
3		**[35]**	202-203	4 min	9.1 h[110]
4		**[36]**	> 300	4 min	8.5 h[110]
5		**[37]**	165-168	4 min	
6		**[38]**	256-258	4 min	10 h[114]
7		**[39]**	260-261	4 min	8.4 h[110]
8		**[40]**	240-242	4 min	
9		**[41]**	225-226	4 min	12 h[110]

Near Quantitative yields of above 98% was obtained in all cases. [a]Time reported in presence of catalyst and in solvents. In absence of any catalyst the reaction time is 24 hours to get 10% yield.[110]

In order to explore the applicability of this method, the same reaction conditions were applied for the synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles (Table 10) via a one-pot, four-component condensation of benzil (1mmol), an aldehyde (1mmol), a primary amine (1mmol) and ammonium acetate (5mmol).

Table 10 Solvent free synthesis of 1,2,4,5-tetrasubstituted Imidazoles



Entry	Amine (R_1-NH_2)	Aldehyde (R_2-CHO)	Product	Melting Point / °C	Reaction Time
1	$CH_3CH_2CH_2CH_2NH_2$		**[42]**	78-80	4 min
2			**[43]**	209-211	4 min
3			**[44]**	180-182	4 min
4			**[45]**	218-220	4 min
5			**[46]**	170-172	4 min
6			**[47]**	>270	4 min
7	NH_2CH_2COOH		**[48]**	173-175	4 min
8			**[49]**	206-208	4 min
9			**[50]**	78-80	4 min
10			**[51]**	209-211	4 min
11			**[52]**	180-182	4 min
12			**[53]**	218-220	4 min

Near Quantitative yields of above 98% was obtained in all cases.

To our delight, the tetra substituted imidazoles were obtained in high yields and both aromatic and aliphatic amines as well as aromatic and aliphatic aldehydes have been successfully subjected to this protocol. In each case, the reaction profile is clean and one of the major advantages of this protocol is the isolation and purification of the products, which have been achieved by simple washing and crystallization of the crude products.

The reaction protocol, being as good as any catalytic synthetic procedure cited till date, was substantiated by the rationale of self-activation of carbonyls in the condensed phase. For this, semi-empirical PM3 calculation for the monomer, a dimeric association and on a set of only twenty formaldehyde molecules was carried out. It has been reported that the PM3 semi-empirical quantum-mechanical method successfully predicts intermolecular hydrogen bonding between neutral molecules. The geometries of the PM3 hydrogen bonded complexes agree with high-resolution spectroscopy and gas electron diffraction data, as well as with high level *ab initio* calculations. Accurate *ab initio* calculations replicating hydrogen bonding systems are expensive, and the correct kind of *ab initio* calculation is not obvious. Because *ab initio* methods give quantitative results only for relatively small molecules, semi-empirical procedures have been used to study larger organic systems.[117] From the PM3 calculations, a minimum energy supra-molecular conformation in which the carbonyl groups were arranged like a trail of ants with the unidirectional dipole arrangement was obtained (Figure 25).

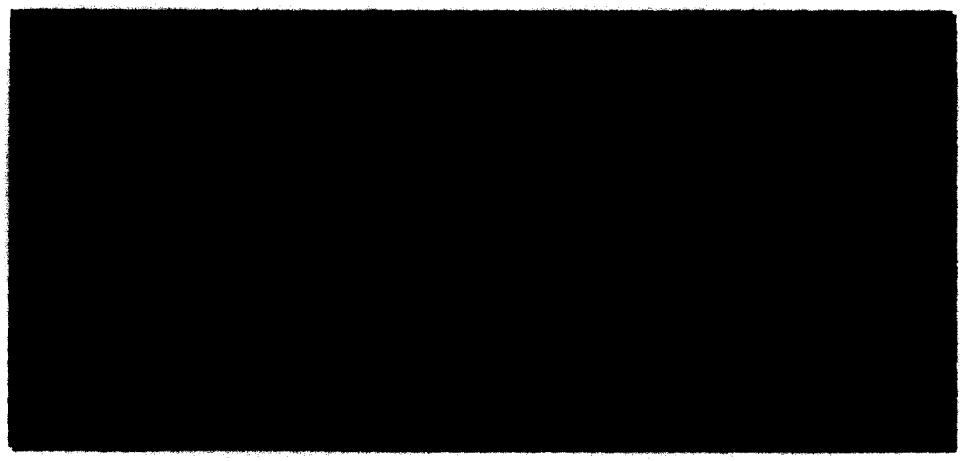


Figure 25 Minimum energy conformation for twenty formaldehyde molecules

In these conformations the partial charge on each atom, polarizability per carbonyl group and dipole moment were found to increase whereas the heat of formation and ionization potential were found to be slightly less than the calculated value for a free formaldehyde molecule (Table 11).

Table 11 Summary of the results of the semi-empirical calculation for the formaldehyde clusters.

	Monomer	**Dimer cluster**	**Cluster of 20 molecules**
Mulliken charge at C	0.296601	0.301379 (av. value)	0.312 (av. value)
Mulliken charge at O	-0.310644	-0.324707 (av. value)	-0.348 (av. value)
Mulliken charge at H	0.007039	0.009 (av. value)	0.018 (av. value)
Dipole moment	2.170D	4.542D (2.271D av. value)	48.217 (2.41D av. value) 2.32D[a]
C-O bond length	1.20318A	1.20318A	1.205A (av. value)
Heat of formation	-34.09985 KCal/mole	-34.54486 KCal/mole (av. value)	-35.2638 KCal/mole (av. value)
Ionization potential	10.63361EV	10.27820EV	10.02919EV
Symmetry	C2v	C2	C1
Polarizability (alpha) isotropic average	9.91817AU	10.08859AU (av. value)	10.3854AU (av. value)

[a] Experimental in solvent-free state.[118]

This supra-molecular arrangement is also supported by *a priori* work wherein it was stated that little or no H-bond occurs in formaldehyde itself and the intermolecular interaction is of dipole-dipole type.[119] The decrease in the heat of formation of about 1 kcal/mol suggests that the dipole cluster is stabilized to the extent of Van der Waal's complex. The carbonyl groups were found to be polarized to the maximum feasible

extent in their environment as the partial charges increased in each atom. Polarizability (alpha) was also increased. Apart from the steric factor, an increase in the polarizability and partial charge might be responsible for the observed self-catalysis. As a result of the cooperative effect of very weak forces a bulk amount of carbonyl groups got activated and considerable catalytic action became viable in condensed phase. In addition to this self-activating effect, if some oxiphilic substance were present in catalytic amount it bonded to the terminal carbonyl oxygen affecting further activation of the trail of carbonyls and thereby resulting in further enhancement of the catalytic effect. The theoretical ab initio calculation of conformationally similar formaldehyde dimer was done by Dayle et al,[120] whereby they have shown that an excess electron can attach to the system forming a dipole bound anion. This work indirectly supports our proposition as well, to the cause of enhancement in electrophilic behavior of the carbonyl group under solvent-free condition.

In a non-polar solvent a strong tendency for anti-parallel molecular association is suggested for benzaldehyde cluster,[121] wherein the dipole quenching effect would expectedly reduce electrophilicity of the carbonyl group. In polar solvents, the weak but favorable conformation of the carbonyl cluster expectedly breaks due to stronger solute-solvent interactions. Thus solvents act adversely to the self-catalytic effect.

When the PM3 semi empirical calculations were further extended to the aromatic systems, the results corroborated our findings for the formaldehyde clusters. Aromatic aldehydes in condensed phase by probability can be H-bonded and non H-bonded type and the different stacking pattern of the aromatic ring makes the system more complicated. As the displaced-stacked conformer is prevalent,[122] comparisons were made only on two models, one H-bonded and the other dipole-dipole type, as laminar and stacked models separately (Figures 26-28). The summary of results of the semi-empirical calculation for the three types of conformations of the benzaldehyde clusters is also presented which clearly indicates the increase in the polarizability and the dipole moments of the clusters with respect to the monomer as is apparent from Tables (12-14).

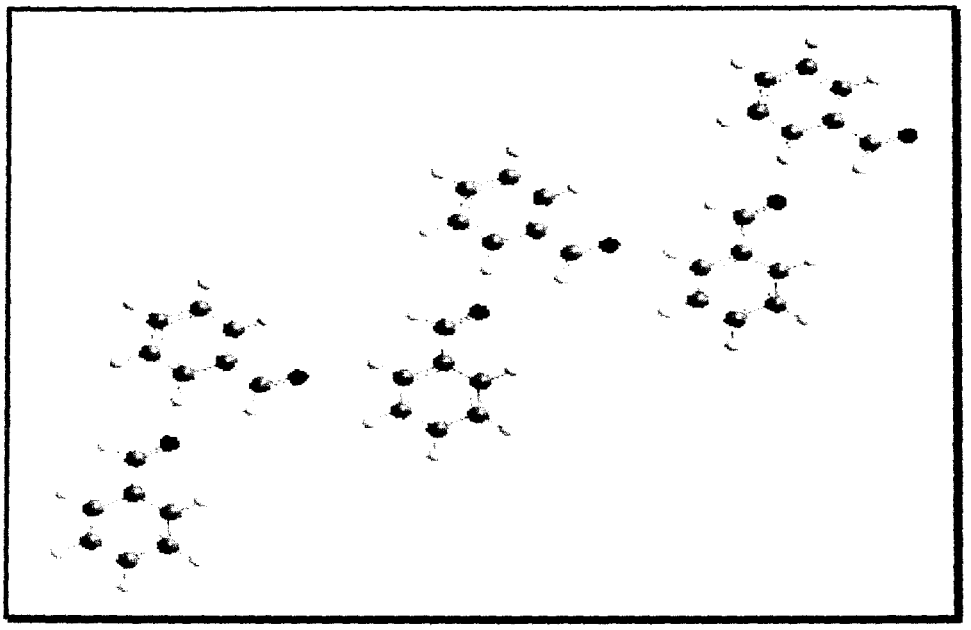


Figure 26 Cluster of 6 benzaldehyde molecules, H-bonded laminar

Table 12 Summary of the results of the semi-empirical calculation for the benzaldehyde clusters (H-bonded- laminar)

	Benzaldehyde Monomer	**Benzaldehyde Dimer**	**Cluster of 6 benzaldehyde molecules**
Heat of formation	-10.73605 KCal/mole	-11.05173KCal/mole (av. value)	-11.41256KCal/mole (av. value)
Dipole moment	-2.690 D	5.686 D (2.843 D av. value)	18.351 D (3.1 D av. value)
Mulliken charge at C	0.28035	0.27590 (av. value)	0.22104 (av. value)
Mulliken charge at O	-0.32969	-0.34229 (av. value)	-0.35179 (av. value)
Polarizability(alpha) isotropic average	58 A.U	30.5AU (av. value)	108.78 (av. value)

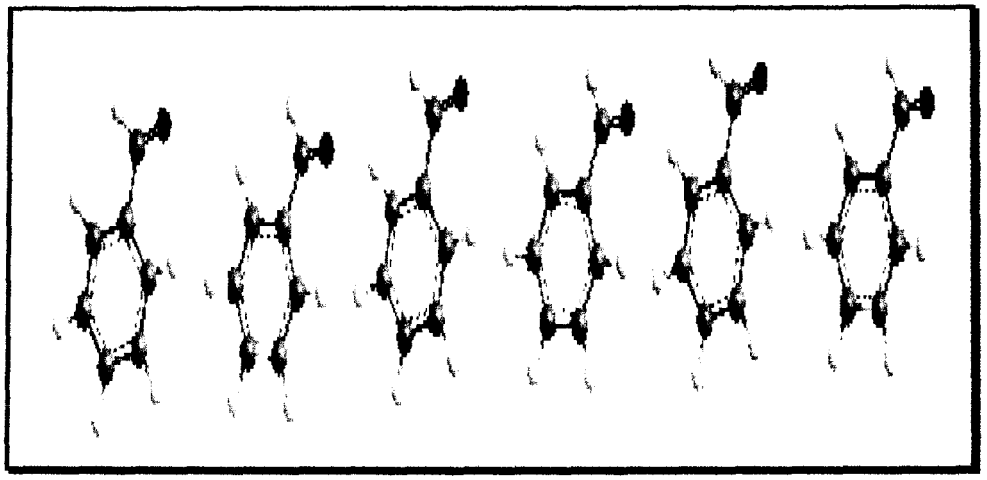


Figure 27 Cluster of 6 benzaldehyde molecules, non H-bonded, dipole-dipole - laminar

Table 13 Summary of the results of the semi-empirical calculation for the benzaldehyde clusters (non H-bonded, dipole-dipole - laminar).

	Benzaldehyde Monomer	**Benzaldehyde Dimer**	**Cluster of 6 benzaldehyde molecules**
Heat of formation	*-10.73605* KCal/mole	-11.683 KCal/mole (av. value)	-11.823 KCal/mole (av. value)
Dipole moment	-2.690 D	5.322 D (2.661 D av. value)	16.51 D (2.75 D av. value)
Mulliken charge at C	0.28035	0.2820 (av. value)	0.2854 (av. value)
Mulliken charge at O	-0.32969	-0.33229 (av. value)	-0.34517 (av. value)
Polarizability(alpha) isotropic average	58 A.U	31.15AU (av. value)	62.88AU (av. value)

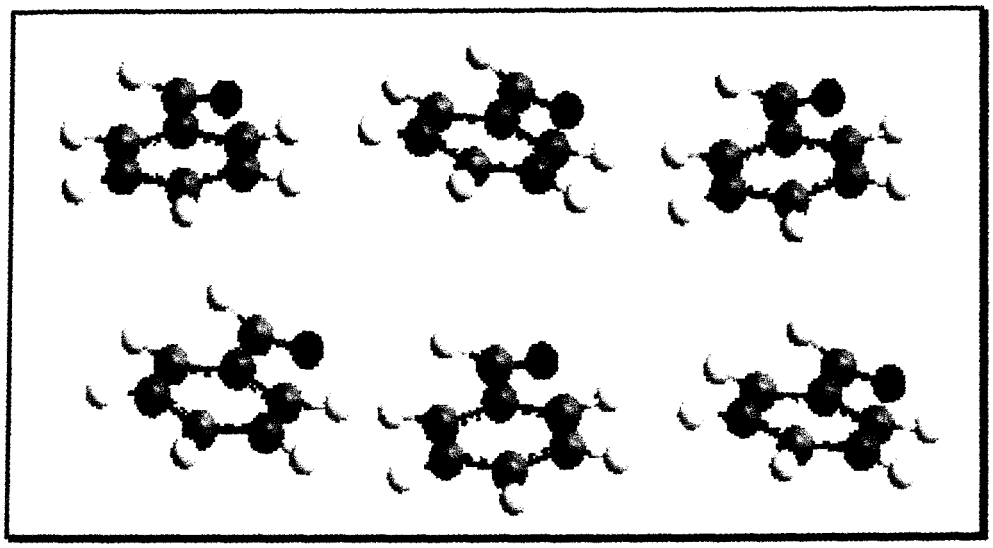


Figure 28 Cluster of 6 benzaldehyde molecules, non H-bonded, dipole-dipole – laminar-stacking

Table 14 Summary of the results of the semi-empirical calculation for the benzaldehyde clusters (non H-bonded, dipole-dipole – laminar-stacking).

	Benzaldehyde Monomer	**Benzaldehyde Bi-planar Cluster of 6 benzaldehyde molecules**
Heat of formation	-10.73605 KCal/mole	-11.70KCal/mole (av. value)
Dipole moment	-2.690 D	16.374 D (2.729 D av. value)
Mulliken charge at C	0.28035	0.2853 (av. value)
Mulliken charge at O	-0.32969	-0.3369 (av. value)
Polarizability(alpha) isotropic average	58 A.U	60.20AU (av. value)

As against the theoretical evidence for self-activation of carbonyls, IR spectroscopic investigations too provided evidences in support to our present hypothesis for bulk polarization and the activation of carbonyls by metal catalysts. It is reported[123] that C=O stretching band of benzil appears at 1676 cm^{-1} in crystal and 1685 cm^{-1} in solution. The difference in stretching frequency (9 cm^{-1}) indicates a greater degree of single bond character in the C=O bond in crystalline state. Similar shift of carbonyl stretching frequency for benzophenone in TiO_2 surface is reported.[124]

The extent of the shift caused by the presence of trace amount of zirconyl nitrate and ytterbium triflate on benzil carbonyl stretching frequency in hexane solution was studied. The IR spectra in the carbonyl range are presented in Figure 29. It was found that in the solution spectra, the free carbonyl peak at 1685 cm^{-1} and all other associated peaks showed a little amount of red-shift in the presence of a catalyst. In addition to this, there was concomitant diminishing of the intensity of the free carbonyl peak with increasing intensities of some other peaks at lower frequencies (particularly the peak at 1680 cm^{-1}) in the presence of traces of catalyst. It is also apparent (Figure 29) that the catalyst, zirconyl nitrate, caused a little bit more polarization than that with ytterbium triflate.

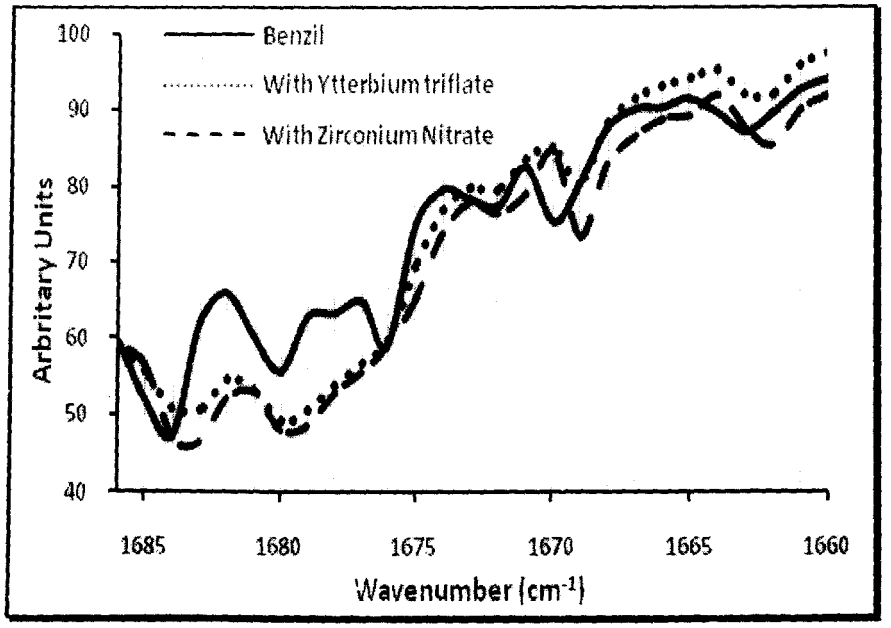


Figure 29 Solution IR spectra in the carbonyl range of benzil in hexane (%T vs wave number).

Notably it was found that the catalytic effect of zirconyl nitrate was comparatively more pronounced in terms of benzil consumption rate (Table 8). The characteristic rise of the band near 1680 cm^{-1} in presence of the catalyst suggested the dual effect of the catalyst in polarizing the carbonyl as well as influencing the conformation of benzil. Another significant observation was the appearance of a less intense peak near 1676 cm^{-1} compared to the peak at 1685 cm^{-1} in solution state. These observations suggested that the catalyst bonded to the carbonyl oxygen and activated it with the enhancement of polarization.

In a thin film, the peak at 1685 cm^{-1} which was assumed for free carbonyl stretching is remarkably less intense. The carbonyl region in IR spectra of benzil in thin film is presented in Figure 30. Very thin film preparation was difficult because benzil when grounded spatter on handling; however, it is clear that the free carbonyl band at 1685 cm^{-1} is apparently diminished in intensity compared to the band near 1680 cm^{-1} with concomitant increase in intensity of the band at 1676 cm^{-1}. Addition of a catalyst to the solvent-free state also produced red-shift as observed in the solution spectra of benzil.

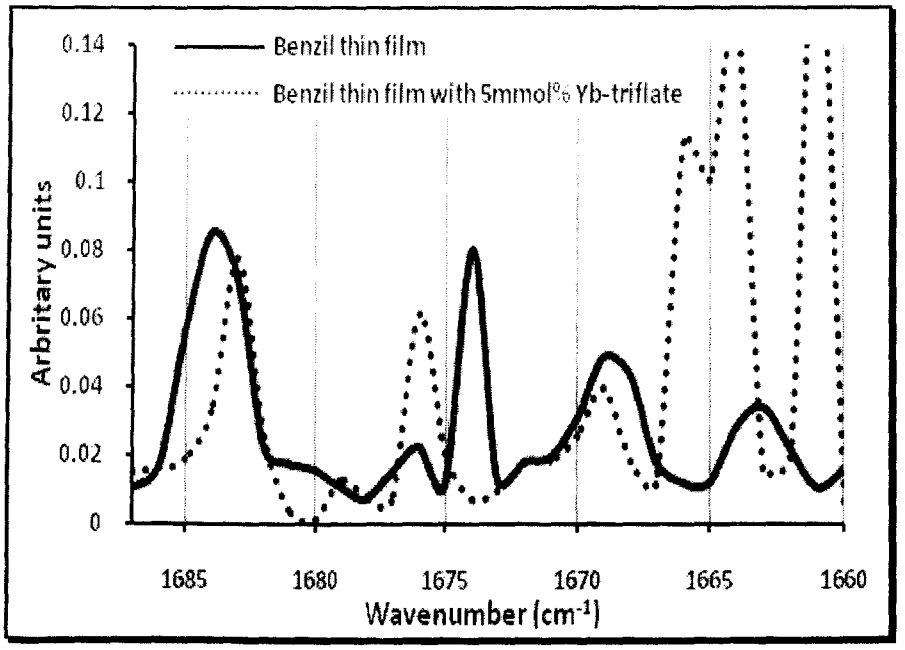


Figure 30 IR spectra of Benzil in thin film (%T vs wave number).

The conspicuous enhancement of the band at 1680 cm^{-1} in the presence of a catalyst in both the solution and the solid state is observed. The peak at 1680 cm^{-1} was described[125] as another C=O stretching band associated with a different symmetry of the molecule. This may happen due to probable conformational changes in the presence of a catalyst. Hence, these findings strongly support our hypothesis that in the condensed phase electrophilicity of carbonyl carbon enhances due to bulk polarization. The real strength of co-operative interactions of very weak forces to impart various properties of molecules as well as supra-molecules has gained considerable recognition in the present time. A supramolecular catalyst that operates by a novel mechanism involving substrate activation by hydrogen bonding was proposed by Lehn and others.[126] This study conforms to the suggestion that similar effect could occur in the absence of added catalyst, when experimented in condensed phase.

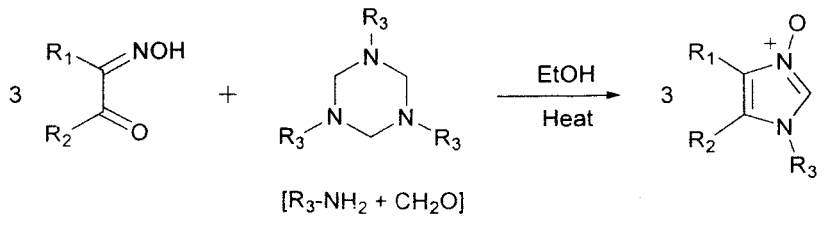
2.3.2. Synthesis of Imidazole N-Oxides and 1-hydroxy Imidazole 3-oxide

As we have seen in the preceding section, the bioactive heterocycles with an imidazole ring system, being part of a large number of highly significant biomolecules, have many pharmacological properties and also play significant roles in biochemical processes. Another noteworthy observation in the chemistry of heterocyclic compounds is that there is a well-known *N*-oxide group effect which leads to a substantial change in reactivity of heteroaromatic *N*-oxides, as compared to their unoxidized analogues, activating them to electrophilic, nucleophilic and radical agents.[127] The presence of an N-oxide group or an N- hydroxy functionality in the ring system of an imidazole is liable to alter the properties of the diazole compound.

The synthesis and reactivity of imidazole N-oxides and 1-hydroxy imidazole-3-oxides are of current interest as they are useful building blocks for the selected transformations of diverse imidazole derivatives, including enantiomerically pure compounds.[128] More importantly, they have also been found to possess diverse biological activities.[129] In general, heterocyclic aromatic N-oxides, or dioxides in particular have

been found to be an interesting class of antitumor agents exhibiting DNA-damaging properties.[130] Furthermore, the presence of a supplementary hydroxyl substituent on the imidazole framework in imidazole N-oxides has been frequently used to prepare 1-hydroxy imidazoles by selective reduction,[131] since 1-hydroxyimidazoles[132] are useful intermediates for the preparation of pharmaceuticals and agricultural chemicals. Currently these heterocycles are among the most widely developed compounds in the toolbox of modern chemistry for the synthesis of a class of versatile alternative media,[133] where *N*-bulky substituted imidazole 3-oxides serve as potentially attractive starting materials for the synthesis of new, stable nucleophilic carbenes (NHC) *via* three step deoxygenation-quaternization-elimination procedure.[134] Apart from the synthetic and pharmacological utility, 1-hydroxyimidazole-3-*N*-oxides have also been found to be effective aluminum corrosion inhibitors.[135]

In general, imidazole *N*-oxides are not available by direct oxidation of the parent compound. However, a recent paper describes the preparation of 1-methylimidazole N^3-oxide by treatment of 1-methyl-1*H*-imidazole in THF with H_2O_2 at room temperature.[136] Convenient syntheses of 2-unsubstituted imidazole *N*-oxides are condensations of *a*-(hydroxyimino) ketones with *in situ* generated formimides,[137] of *a*-amino oximes with orthoformates,[138] and of diimines with formaldoxime.[139] The condensation of α-(hydroxyimino) ketones with aldehyde and a corresponding primary amine under various conditions (either refluxing in alcohol or in presence of acetic acid) has remained the method of choice for their preparation (Scheme 52). The amines are converted into formaldimines (monomeric forms) or hexahydro-1, 3, 5-triazine using either paraformaldehyde or formalin.



Scheme 52 Conventional synthesis of Imidazole n-oxides

Likewise, 3-hydroxyimidazole-1-oxides can be prepared by the condensation of either α-(hydroxyimino) ketones and aldehyde monoximes or by the condensation of dioximes with aldehydes or else by a three-component cyclization of a 1, 2-diketone, an aldehyde, and hydroxylamine which has been the method of choice.[131] While the first two procedures are time consuming, the third involves an elaborate process extended over more than 24 hours.

In view of the general utility of the N-oxides and the 1-hydroxy imidazole-3-oxides in synthetic organic chemistry and biology, a one-pot solvent free pathway for the synthesis of imidazole derivatives would provide a simple and environmentally friendly complement to the reported methods. In the published papers dealing with the preparation of Imidazole N-oxides and 1-hydroxy imidazole-3-oxides, solvent free procedures have not been explored so far and the mechanistic investigations on the same have not been dealt with. While, the elaboration of simple and efficient methods for their synthesis is a challenging task, it becomes all the more interesting and significant when the scope of the study extends positively with newer findings. A benign, simple and versatile route to Imidazole N-oxides and 1-hydroxyimidazole-3-oxides in good yield has been demonstrated in this part of the work. The study investigates the synthesis and characterization of these compounds (some of which are previously unpublished) by a solvent-free multi-component method. To date there have been no published report on a solvent-free method for the synthesis of such heterocycles.

2.3.2.1. Optimization of reaction conditions for the synthesis of Imidazole derivatives with Thermal Analysis

In order to obtain the most efficient reaction conditions, a Differential Scanning Calorimetry (DSC) study was done using diacetyl monoxime, p-hydroxy benzaldehyde and p-amino benzoic acid as a model reaction for N-oxide formation. A DSC run of a powdered mixture of equimolar amounts of each reactant for the synthesis of 1-substituted Imidazole N-oxides shows that the reaction is exothermic and an exotherm at

112°C indicates the onset of reaction and product formation should start at this temperature (Figure 31)

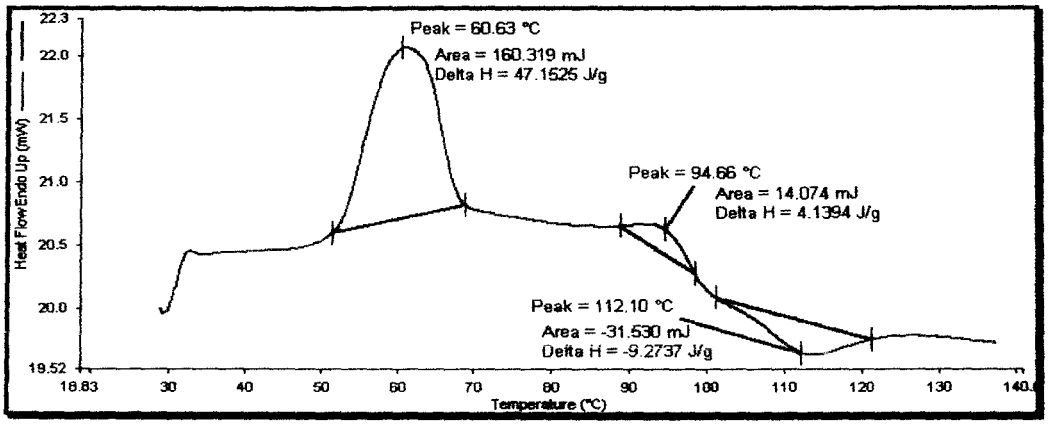


Figure 31 DSC plot of a mixture of diacetyl monoxime, p-hydroxy benzaldehyde and p-amino benzoic acid

With the 1-hydroxy 2, 4, 5-trisubstituted imidazole-3-oxides synthesis the DSC and TGA results gave even more interesting inputs to the study. For refinement of the present study, the DSC plot of three systems was compared. A DSC trace of an intimate mixture of diacetyl monoxime and m-nitrobenzaldehyde monoxime (Figure 32) shows two significant peaks at 60°C (sharp) and 222 °C corresponding to the m.p of the diacetyl monoxime and the product m.p. respectively, and two broader humps at around 97°C and 125°C corresponding to the m.p. of m-nitrobenzaldehyde monoxime (Litt. M.p.122-123°C) and sublimation of diacetyl monoxime.

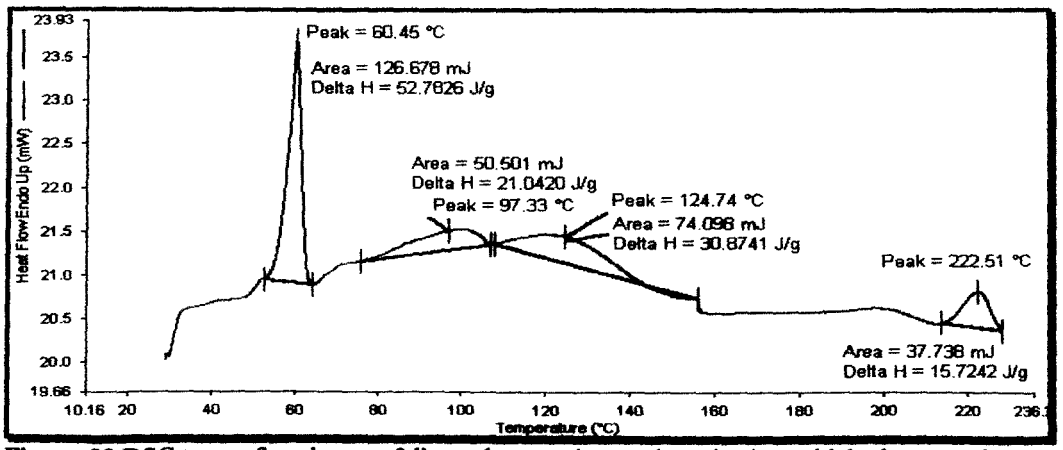


Figure 32 DSC trace of a mixture of diacetyl monoxime and m-nitrobenzaldehyde monoxime

The help of Simultaneous Thermal Analysis (STA) was also taken to get a much clearer picture on the reaction profile. But as it could be carried out only in an open sample holder, and since one of the reactants, the diacetyl monoxime underwent sublimation; a correct picture of the loss of water molecule could not be obtained. Despite this, the TGA trace from the STA of the mixture of diacetyl monoxime and m-nitrobenzaldehyde oxime indicated the onset temperature at around 90°C while the m.p. peak of the product at 222-225°C could be observed in the DSC trace (Figure 33).

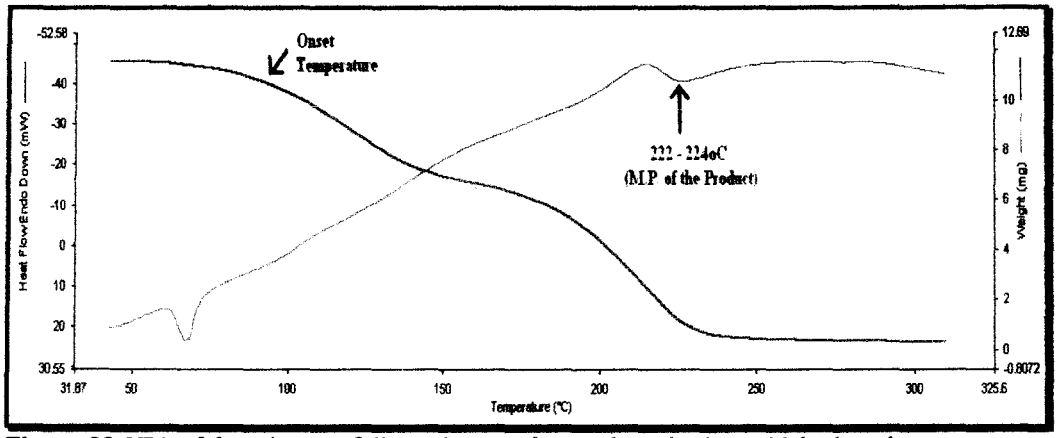


Figure 33 STA of the mixture of diacetyl monoxime and m-nitrobenzaldehyde oxime

A second DSC trace of a mixture of dimethyl glyoxime and m-nitrobenzaldehyde (Figure 34) shows three peaks at 58°C, 60°C and 202°C corresponding to the m.p. of the m-nitrobenzaldehyde (Litt. m.p. 55-58°C), diacetyl monoxime (Litt. m.p. 75-78°C) and the product (Observed m.p. 225-227°C).

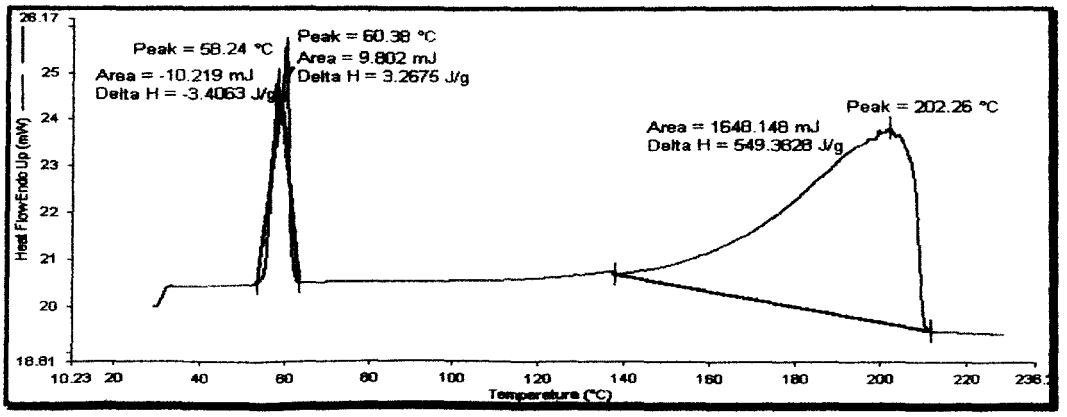


Figure 34 DSC trace of a mixture of dimethyl glyoxime and m-nitrobenzaldehyde

The appearance of a peak at 60°C for the melting point of diacetyl monoxime in the second DSC trace, even in its absence as a reactant, suggests that there might be some mechanism involved whereby the dioxime first gets converted to the monoxime by the exchange of the oxime grouping between the aldehyde and the dioxime, a mechanism earlier proposed by John B. Wright[139] but not yet verified. The reaction then proceeds via the monoxime to yield the products. A DSC trace for pure dimethyl glyoxime for comparison was obtained (Figure 35). No peak was seen at the m.p. of diacetyl monoxime or at 60°C as was observed earlier, when it was mixed with m-nitrobenzaldehyde. It maybe safely concluded that the peak at 60°C arises, only in the presence of the aldehyde and that the peak is because of the diacetyl monoxime which always tends to melt at that temperature in a mixture.

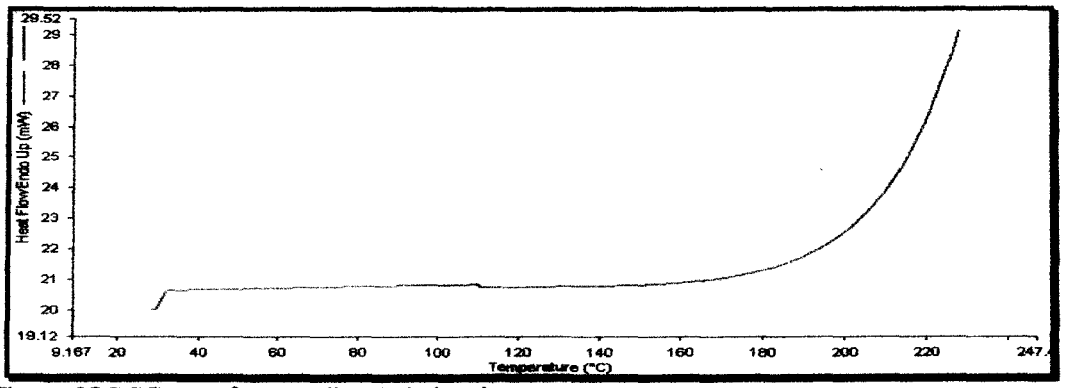


Figure 35 DSC trace for pure dimethyl glyoxime

The DSC trace of pure diacetyl monoxime confirmed the appearance of an endotherm for sublimation of diacetyl monoxime (Figure 36).

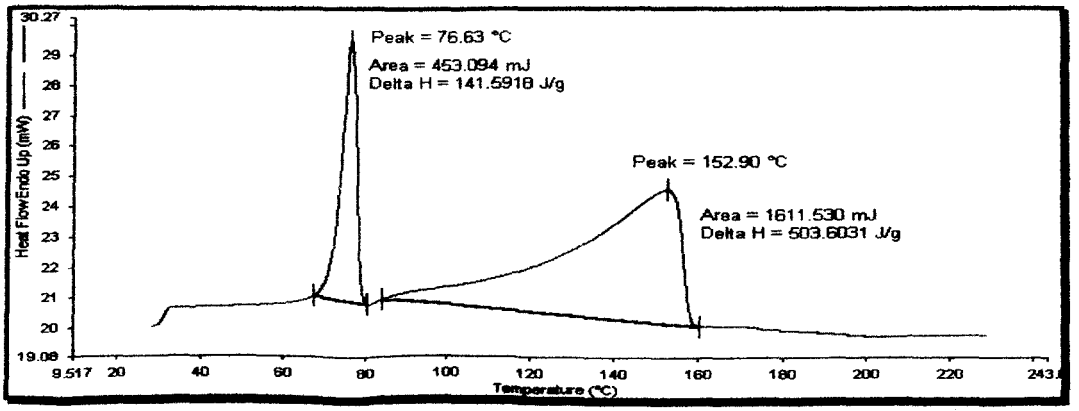
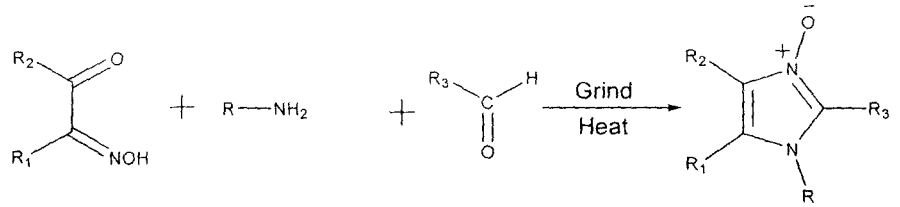


Figure 36 DSC trace of pure diacetyl monoxime

The peak at 153°C in the above DSC trace corresponds to the sublimation of pure diacetyl monoxime, which in this case is at a higher temperature compared to the peak at 125°C, attributed for the same in the case of the reaction mixture as shown in Figure 32. This depression of 28°C maybe due to the presence of other compounds in the reaction mixture, quite similar to the observed depression of melting point of diacetyl monoxime from 76°C in the pure form to 60°C in the reaction mixture. Overall, it may be said that the reaction proceeds via the monoxime in all three cases. Whatever the substrate functionality, the major input in all the three reactions was found to be α-(hydroxyimino) ketones.

2.3.2.2. Solventless multicomponent synthesis of Imidazole oxides and 1-hydroxyimidazole-3-oxides

Based on the DSC study, an initial one-pot reaction of α-(hydroxyimino) ketones with a wide range of aliphatic/aromatic aldehydes and aliphatic/aromatic amines gave N-substituted imidazole N-oxides at the optimized temperature of 115-120°C within 10 minutes. The yield of the product was not affected by the structure of the amine. An overview of the synthetic details is summarized in Scheme 53.



$R_1 = R_2 = CH_3$ (Monoxime A)

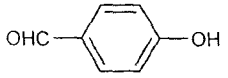
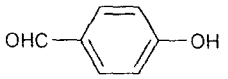
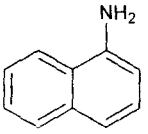
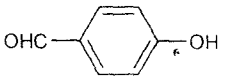
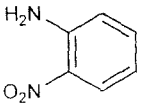
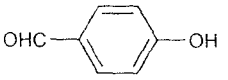
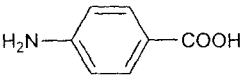
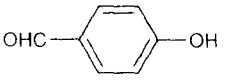
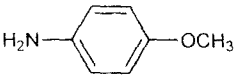
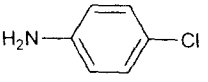
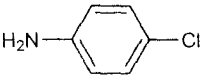
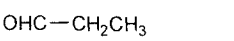
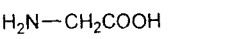
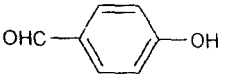
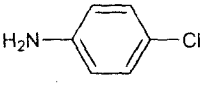
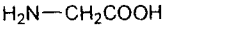
$R_1 = R_2 = Ph$ (Monoxime B)

Scheme 53 One-pot solvent free method for synthesis of N-substituted Imidazole N-oxides

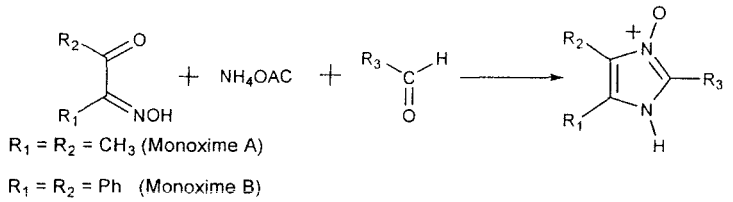
In a typical reaction, 1 mmole each of the monoxime and the aldehyde was grinded with 1.5 mmole of the amine and subsequently heated. The completion of the reaction was indicated by TLC and the product so formed was washed with a little amount of ether and further by hot ethyl acetate. A little excess of the amine was used since a stoichiometric amount resulted in only 75% yield and the reactant spots were also

visible in the TLC after 10 minutes of reaction. While when 1.5 mmole of the amine was used, within 10 minutes, a single spot of the product was observed and the reactant spots disappeared. With this approach ten imidazole N-oxides were prepared in quantitative yields and characterized by IR, ^{1}H NMR, ^{13}C NMR and Mass spectra.

Table 15 Synthesis of N-substituted Imidazole N-oxides under catalyst-free and solvent-free conditions

Entry	Monoxime	Aldehyde	Primary amine	Product	Melting Point
1	A		$CH_3CH_2CH_2CH_2NH_2$	**[54]**	128-130
2	A			**[55]**	232-235
3	A			**[56]**	272-273
4	A			**[57]**	210-213
5	A			**[58]**	205-207
6	A			**[59]**	238-240
7	B			**[60]**	170-172
8	B			**[61]**	>260
9	B			**[62]**	182-184
10	B			**[63]**	248-250

The approach also implies a sizeable reduction in the reaction time for N-oxide formation as compared to 3-6 hours under refluxing conditions via conventional methods. From the above-described results a variety of Imidazole N-oxides were further explored under the optimized reaction conditions using a wide range of aliphatic/aromatic aldehydes and ammonium acetate instead of the amine component according to Scheme 54.

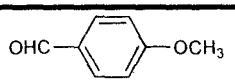
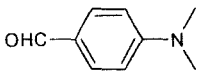
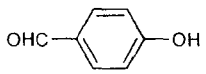
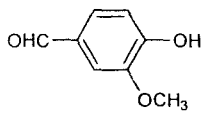
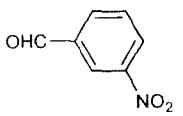
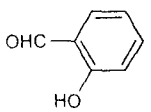
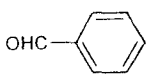
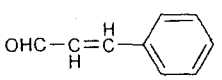
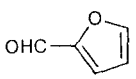
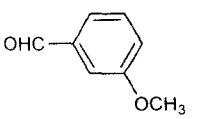
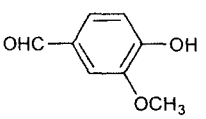
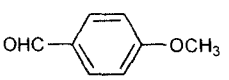
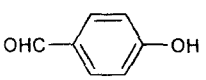
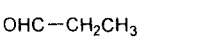


Scheme 54 One-pot solvent free method for synthesis of Imidazole N-oxides

In a typical reaction 1 mmole each of the monoxime and the aldehyde was finely grinded with 5 mmole of ammonium acetate. The intimate mixture was then heated to 115-120°C and then cooled when a black sticky precipitate resulted. To the black precipitate was then added a small volume of diethyl ether when a brown precipitate separated. The precipitate was thoroughly washed with ethyl acetate to yield pure products. The work up leading to the products resulting from benzil monoxime was slightly different. The black precipitates were dissolved in ethanol and then water was added drop wise till a hazy solution resulted. On warming the solution, the milkiness disappears and on cooling further, creamy colored precipitates are obtained.

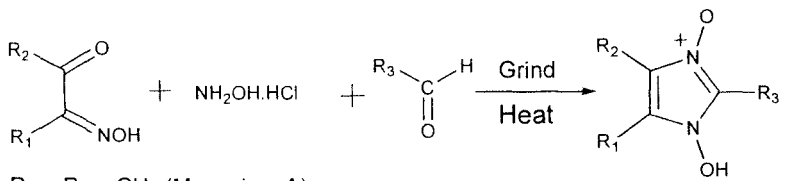
A wide range of aromatic and aliphatic aldehydes have been effectively employed to give a variety of Imidazole oxides. The reaction proceeded smoothly to give quantitative yield of the products and the results are summarized in Table 16. The synthesis can be diversified by taking different monoximes, the methodology working well with all kinds of substitution on the monoxime.

Table 16 Synthesis of Imidazole N-oxides under catalyst-free and solvent-free conditions

Entry	Monoxime	Aldehyde	Product	Melting Point (°C)
1	A		**[64]**	138-140
2	A		**[65]**	233-235
3	A		**[66]**	>260-270
4	A		**[67]**	258-259
5	A		**[68]**	172-174
6	A		**[69]**	233-235
7	A		**[70]**	125-127
8	A		**[71]**	116-118
9	A		**[72]**	95-97
10	A		**[73]**	118-120
11	B		**[74]**	197-199
12	B		**[75]**	95-96
13	B		**[76]**	230-232
14	B		**[77]**	72-74
15	B		**[78]**	88-90

This solventless approach based on grinding together macroscopic particles typically involves the formation of a eutectic melt and requires subsequent heating for completion of the reaction. The cost effective approach, when extended to the synthesis of 1-hydroxy Imidazole-3-oxides, is even more rewarding as it reduces the reaction time from 24 hours to 10 minutes. Accordingly the DSC and TGA results prompted us to choose the easily available α-(hydroxyimino) ketones as the substrates for the synthesis of 1-hydroxy 2,4,5-trisubstituted imidazole-3-oxides via our solventless approach.

Typically in the optimized solvent-free preparation of 1-hydroxyimidazole-3-oxides, the products are formed in near-quantitative yield by low intensity grinding of equimolar amounts of the monoxime and the aldehyde and an excess of hydroxylamine hydrochloride using a pestle and mortar over a period of ca. 3 min, associated with constant agitation of the mixture and subsequent heating for another 7 min at 110-120°C (Scheme 55). The products remain as a eutectic melt on cooling and immediately precipitate out on adding ether. It is further washed with water and ethyl acetate.



$R_1 = R_2 = CH_3$ (Monoxime A)

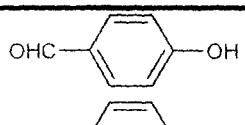
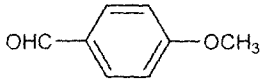
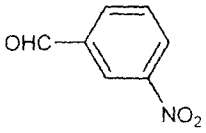
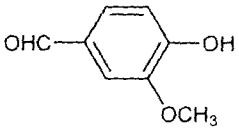
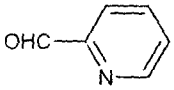
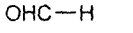
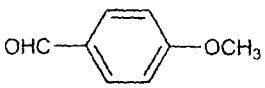
$R_1 = R_2 = Ph$ (Monoxime B)

Scheme 55 One-pot solvent free method for synthesis of 1-hydroxylmidazole-3-oxides

In the case of compounds **[80]**, **[83]** and **[84]**, they are found to be soluble in water. **[80]** was obtained as fine white crystals by simply warming in water and allowing it to cool. The workup for compound **[84]** was similar to that of **[80]** while since compound **[83]** was highly hygroscopic, it was obtained by dissolving in a minimum volume of ethanol and subsequent addition of ethyl acetate. On scratching the walls of the test tube, a yellow precipitate starts to separate.

A significant observation that deserves mentioning is that involving only the mechanochemical process of grinding a representative reaction involving benzil monoxime, anisaldehyde and an excess of hydroxylamine hydrochloride at room temperature took 8 days to yield the product which precipitated from water and could be recrystallised to get pure crystals. The solvent-free method yielded the product in 10 minutes. Analysis of the product by ^{1}H and ^{13}C NMR shows only the pure products. As shown in Table 17, 1-hydroxy 2,4,5-trisubstituted imidazole-3-oxides were prepared at the optimized temperature in excellent yield without any extensive workup or purification and that too in a very short time. Apart from the lower reaction times (energy saving), other advantages in using this solventless approach are that the product purity is very high.

Table 17 Synthesis of 1-hydroxyImidazole-3-oxides under catalyst-free and solvent-free conditions

Entry	Monoxime	Aldehyde	Product	Melting Point
1	A		[79]	165-168
2	A		[80]	196-198
3	A		[81]	209-211
4	A		[82]	201-203
5	A		[83]	hygroscopic
6	A		[84]	136-137
7	B		[85]	233-235

Overall the synthetic strategy is facile, leading to higher yields and is amenable to up-scaling. More importantly, an operationally simple, efficient and green route to the synthetically and biologically important imidazole N-oxides and 1-hydroxyimidazole-3-oxides has been developed. The high yields and overall low waste generation of this approach gives it attractive green chemistry metrics, along with remarkable versatility. As against the previous reported methods, this approach avoids the use of organic solvents and extensive work-up and hence makes it quite attractive and practical for library synthesis of such compounds.

The convenient synthesis of N-substituted imidazole N-oxides and 1-hydroxyimidazole-3-oxides within 10 minutes of reaction was also based on the same synthetic methodology as the Imidazoles. This undoubtedly proves that the increase in the reaction rates of the reactions in condensed phase is not just because of the presence of ammonium acetate, which furnishes acetic acid that is said to catalyze the reaction. The synthesis of N-substituted Imidazole N-oxide warrants the use of an amine compound instead of ammonium acetate while hydroxylamine hydrochloride is used during the preparation of the 1-hydroxyImidazole-3-oxide. Thus the higher reaction rates in such reactions may possibly be due to self-activation of the carbonyl group in the condensed phase. This novel approach might help to devise a convenient protocol for the synthesis of similar pharmaceutically important molecules with the proper understanding of the origin of catalytic effect in condensed-phase reactions.

2.3.3. Synthesis of Imidazole Metal complexes

While, on the one hand the development of small molecular weight scaffolds that contain privileged heterocyclic cores with a high degree of diversity is a leading focus in medicinal chemistry; metal template-based multi-component reactions on the other hand have not been explored as tools of drug discovery-oriented synthetic organic chemistry though heterocyclic cores containing metal ions have been found to exhibit profound pharmacological properties as can be evidenced from the extensive literature available. We have recently also reported one such scaffold adding to the large volume of literature

already present.[141] In view of the enormous literature highlighting the significance of the presence of the metal ions in these scaffolds, we envisage that a metal template based MCR would allow synthesizing library of diverse small molecules incorporating metal ions in simple one-pot procedures for biological screening.

Though the chemistry of Imidazole and its derivatives attract steady interest due to their wide range of applicability, there is comparatively very less literature related to their metal complexes and their activity. Imidazole is of considerable interest as a ligand and its presence in many biological systems provides a potential binding site for metal ions.[142] The Imidazole-metal complexes are biologically important since they have been found to interact with DNA by intercalation.[143] Another series of novel complexes of transition metal (Co, Fe and Mn) with imidazole display DNA binding ability. [144] Apart from bio-activity, they have some catalytic effects too. Imidazole-containing cyclophosphazene metal complexes have been found to show high catalytic specificity in phosphoester hydrolysis.[145] Ni-Imidazole complexes, upon activation with methylaluminoxane, have been reported to show good activity towards norbornene polymerization.[146]

So far, the available literature on Imidazoles deals mainly with the varied synthetic approaches to this heterocycle. The metal complexes of imidazoles on the other hand, have conventionally been prepared by a general two step process involving the initial first step preparation of the imidazole ligand and the final second step metallation with metal salts. The ligand is prepared by refluxing the reactants in glacial acetic acid for a few hours. Metallation is then carried out by refluxing the ligands with the metal salts in alcohol for another two hours.[147]

A one-pot or sequential multi-component solvent-free synthesis has till date, not been extended to the preparation of the Imidazole metal complexes. The solvent free synthesis of metal complexes has recently been reviewed focusing various reasons to ponder the diverse aspects of the protocol.[26] According to the review, a wide range of complexes can be accessed using solvent-free techniques, featuring diverse structures,

metal ions, ligand types and dimensionalities but none have reported a multicomponent synthetic strategy under solvent-free conditions for their synthesis.

2.3.3.1. Optimization of Metallo-Imidazole synthesis using HPLC

As with the solventless imidazole synthesis we sought to optimize the reaction conditions for metal complexation with the imidazole **[35]**, i.e., 2-(4,5-diphenyl 1H-imidazol-2-yl) phenol. First, the optimal temperature and reaction time for the four component reaction were determined by HPLC using the inputs benzil, salicylaldehyde, Ni (II) chloride hexahydrate and ammonium acetate to produce the nickel complex of Imidazole.

For comparison, an initial run involving the three components benzil, salicylaldehyde and ammonium acetate yielded the 2-(4,5-diphenyl 1H-imidazol-2-yl) phenol, **[35]** with retention time 7.203. A representative trace of the reaction mixture after 20 minutes is shown in Figure 37.

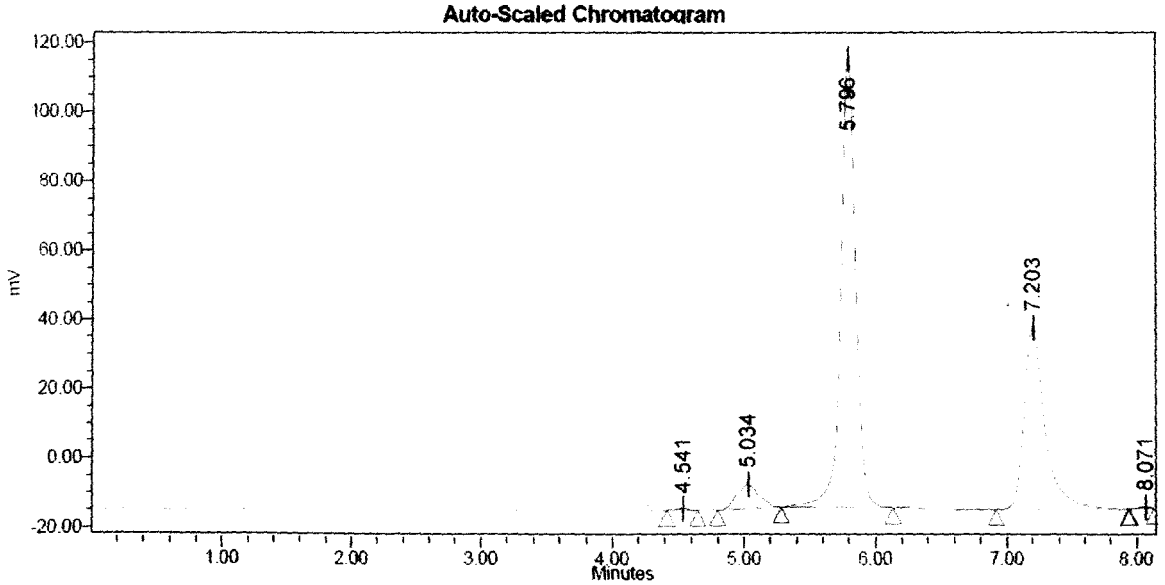


Figure 37 HPLC trace for formation of 2-(4, 5-diphenyl 1H-imidazol-2-yl) phenol, **[35]**

The multi-component one-pot metal complexation reaction was then monitored at 100°C and HPLC was done. It was found that at 100°C, the product peak with retention

time 6.242 appeared only after 10 minutes of reaction as shown in Figure 38. Another comparable peak is observed at 7.151 which if for the Imidazole **[35]** ligand.

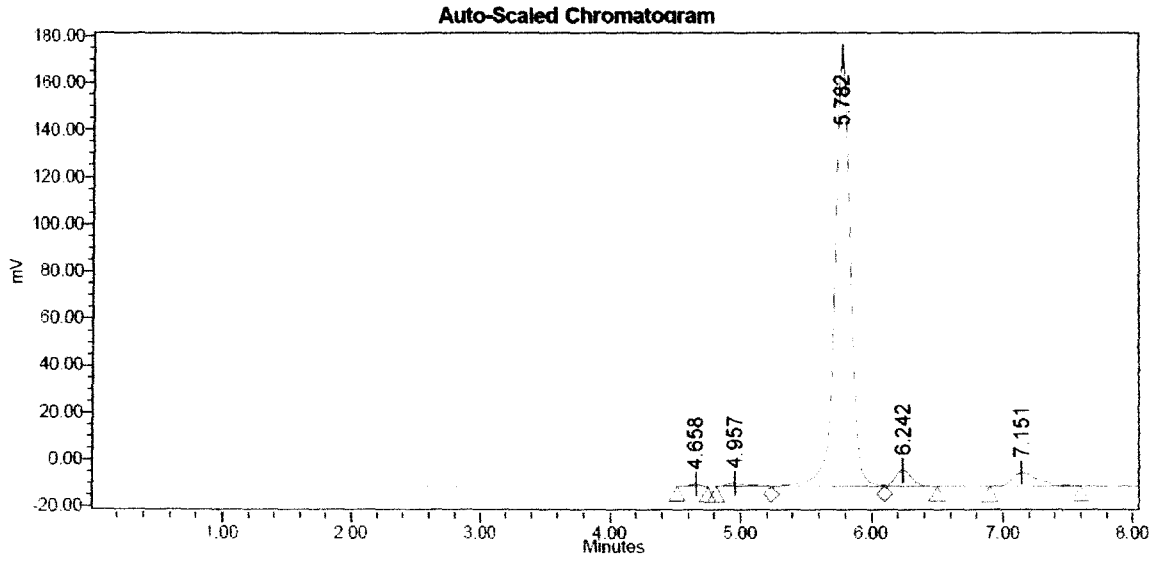


Figure 38 HPLC trace for formation of 2-(4, 5-diphenyl 1H-imidazol-2-yl) phenol, **[35]** at 100 °C

At 120°C, the product peak appeared with retention time of 6.238 after 5 minutes of reaction. The peak area is also larger, indicating the formation of the product at a faster rate with increase in temperature (Figure 39). The Imidazole ligand peak is also seen at 7.147.

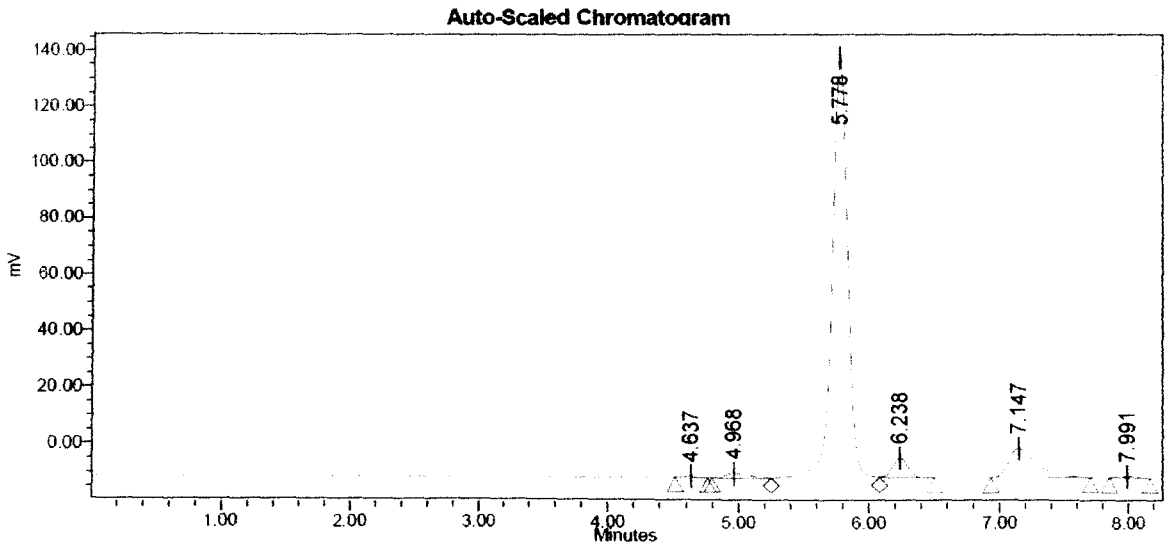


Figure 39 HPLC trace for formation of 2-(4, 5-diphenyl 1H-imidazol-2-yl) phenol, **[35]** at 120 °C

When the temperature of the reaction is further increased to 140°C, interestingly within 5 minutes, the imidazole peak was found to disappear. The product peak is now much larger and appears with retention time of 6.285 (Figure 40).

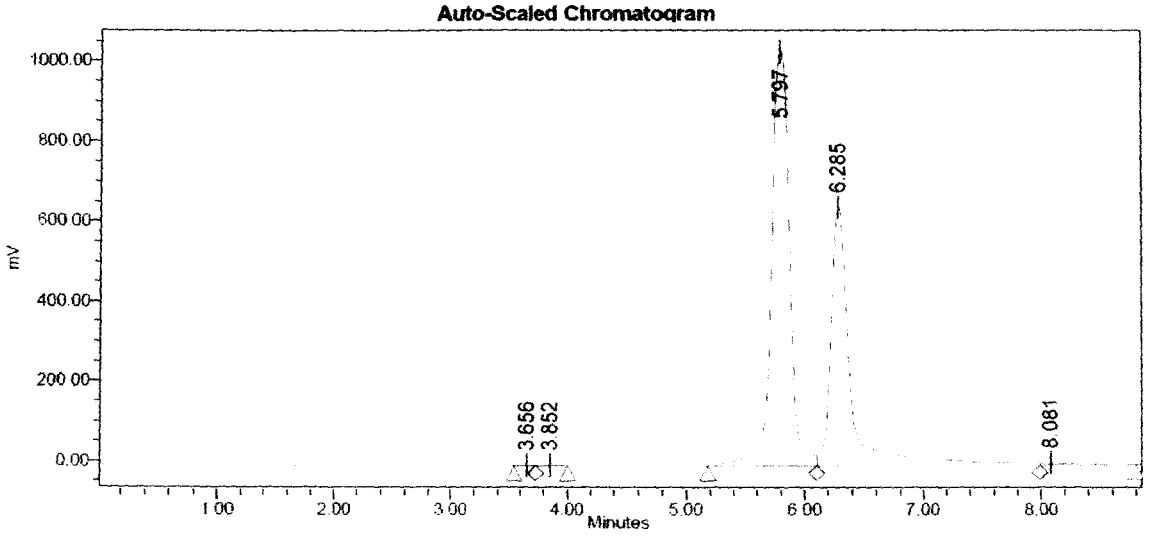


Figure 40 HPLC trace for formation of 2-(4, 5-diphenyl 1H-imidazol-2-yl) phenol, **[35]** at 140 °C

The HPLC traces indicated start of the product formation as early as 5 minutes. In a representative reaction in which Ni (II), benzil, and salicyldehyde were used in molar proportions to monitor the kinetics, more than 90% yield (at 140°C) was observed in the first 5 minutes (Figure 41) but to obtain quantitative yield the reaction took another 20 minutes.

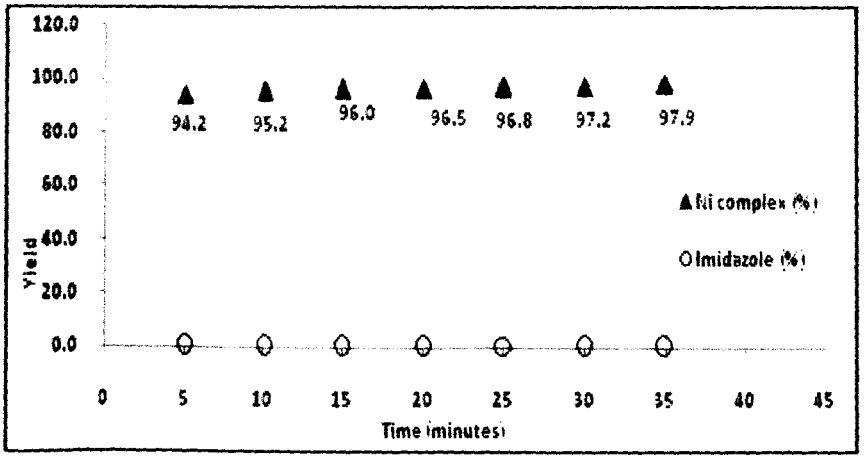
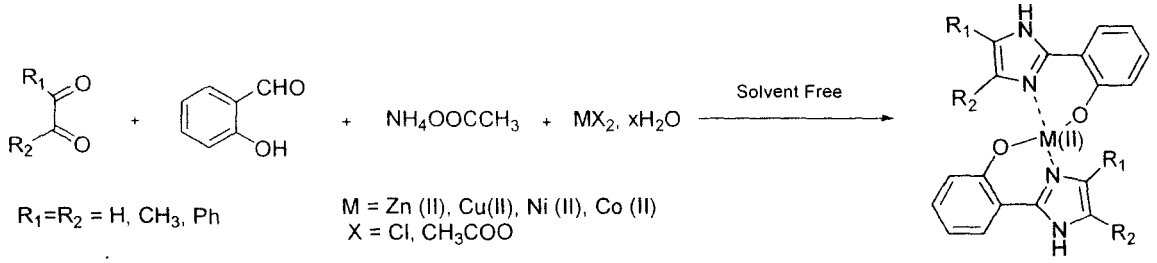


Figure 41 Yield (%) of the nickel imidazole complex and Imidazole **[35]** vs time (mins).

From the peak areas of the HPLC trace a straightforward reliable quantitative analysis of conversions was obtained. After performing the test reaction at three different temperatures (100, 120 and 140°C), the highest conversions were obtained at 140°C. The Zn (II), Co (II) and the Cu (II) complexes are also formed in comparable rate. The synthesis of the Ni-complex is not reported earlier. However, the synthesis of the complexes (Cu-II, Zn-II) in solvent medium is reported,[147] where, in a two stage preparation, duration of 2 hrs was required for the synthesis of the imidazole ligand and 1hr for the complex formation. Our observations suggested a two stage acceleration of the reactions. One due to the effect of solvent-free process, and the other was the further augmentation of the catalytic process in the presence of metal ions. In a suitable environment the metal ion may participate in complex formation.

2.3.3.2. Solventless synthesis of Metallo-Imidazole complexes

In extension to our previous studies on metal complexation,[148] the chosen synthetic procedure was also applied to gain access to various Imidazole metal complexes via the solventless mechanochemical activation, which hitherto has not been done. A four-component one-pot strategy for preparing these complexes (Scheme 56) was found to be immensely successful and met three basic criteria: it was cheaper and greener; and was applicable in large scale and yielded the products in quantitative yields.



Scheme 56 An efficient one-pot synthesis of metal Imidazole complexes under solvent-free conditions

In a typical experiment, the metal imidazole complex is formed in near quantitative yield by grinding two molar equivalents each of the diketone and salicyldehyde and one molar equivalent of the metal acetate or chloride along with an excess of ammonium acetate (20 mmole) using a pestle and mortar over a period of ca. 5

minutes. Heating the reaction mixture in an oil bath for further 20 minutes is followed by formation of the product as colored solids. After this simple functional synthetic route to the metal complexes was found, several possible diversifications were possible. Using the optimized conditions, a library synthesis was set up combining three different diketones and four different metal salts. Thus eleven metal complexes were prepared in a very short time (Table 18).

Table 18 Analytical and spectral data of Imidazole Metal complexes

Entry	Compound	Compound Colour	M.P (°C)	Λ_M ($\Omega^{-1}cm^2mol^{-1}$)	μ_{eff} BM	U.V. λ_{max} (nm)(DMSO)
1	**Bis{2-(4,5-diphenyl-1H-imidazol-2-yl) phenoxy}Zn**	Yellow	>300°C	3.57	-	208,231, 295
2	**Bis{2-(4,5-diphenyl-1H-imidazol-2-yl) phenoxy}Ni**	Orange	>300°C	6.25	-	321, 400
3	**Bis{2-(4,5-diphenyl-1H-imidazol-2-yl) phenoxy}Co**	Pink	>300°C	4.65	2.69	330, 415
4	**Bis{2-(4,5-diphenyl-1H-imidazol-2-yl) phenoxy}Cu**	Violet	>300°C	14.56	2.09	264, 342
5	**Bis{2-(4,5-dimethyl-1H-imidazol-2-yl) phenoxy}Ni**	Brown		7.15	-	322, 400
6	**Bis{2-(4,5-dimethyl-1H-imidazol-2-yl) phenoxy}Zn**	Yellow		4.03	-	270, 327
7	**Bis{2-(4,5-dimethyl-1H-imidazol-2-yl) phenoxy}Cu**	Green		11.56	1.48	267, 334
8	**Bis{2-(4,5-dimethyl-1H-imidazol-2-yl) phenoxy}Co**	Brown		5.62	2.2	
9	**Bis{1H-imidazol-2-yl)phenoxy}Ni**	Brown		5.86	-	322, 399
10	**Bis{1H-imidazol-2-yl)phenoxy}Cu**	Green	255-257	13.58	1.41	353
11	**Bis{1H-imidazol-2-yl)phenoxy}Co**	Brown	285-286	4.69	2.49	355

When the protocol was extended further to involve a five–component reaction of the diketone, salicylaldehyde, primary amine, ammonium acetate and the metal salt to give a tetra-aryl imidazole metal complex, the one-pot synthesis predominantly yielded the metal complex of the triaryl imidazole and the metal complex of the Schiff base rather than the tetra-aryl imidazole metal complex. The results did confirm reports that alkylation of 1H-imidazoles did not necessarily produce the anticipated push of electron density to the donor nitrogen, rather the substituent on the 4, 5-carbon of the imidazole rings is more important for tuning the donor attributes of the imidazole base. Otherwise, the expected N-alkyl substituted metal complex (tetra-aryl imidazole metal complex) would have been selectively and predominantly formed rather than the tri-aryl imidazole metal complex.[149]

In an MCR, a product is said to be assembled according to a cascade of elementary chemical reactions. Thus, there is a network of reaction equilibria, which all finally flow into an irreversible step yielding the product.[150] The challenge is to conduct an MCR in such a way that the network of pre-equilibrated reactions channel into the main product and do not yield side products. The result is clearly dependent on the reaction conditions: solvent, temperature, catalyst, concentration, the kind of starting materials and functional groups. Such considerations are of particular importance while designing for a DOS. Hence, we envisaged that employing a number of appropriate metal salts and different diketones instead of N-alkylations using different amines would be better and a large number of metal complexes could be added to the library.

To summarize we may say that, on performing the MCR via metal template synthesis, good yields of the metal complexes in comparable time was achieved, probably because of the metal ions playing a pivotal role in catalyzing the reactions. The multiple component approach is especially appealing in view of the fact that products are formed in one-pot, and the diversity can be readily achieved simply by varying the reacting components. Additionally, there are distinct advantages of these solvent-free protocols since they provide reduction or elimination of solvents thereby preventing pollution in organic synthesis ''at source''.

References

1. J. D. Moseley and C. O. Kappe, *Green Chem.*, 2011, **13**, 794
2. H. Schiff, *Ann. Chem. Pharm. Suppl.*, 1864, **3**, 343
3. G. Roman and M. Andrei, *Bulletin of the Chemists and Technologists of Macedonia*, 2001, **20**, 131
4. M. N. Ibrahim and S. A. Sharif, *European Journal of Chemistry*, 2007, **4**, 531
5. (a) P. G. More, R. B. Bhalvankar and S. C. Patter, *Journal of the Indian Chemical Society*, 2001, **78**, 474
6. V. Opletalov, J. Hart, A. Patel, A. Palt and V. Buchta, *Farmaco*, 2002, **57**, 135
7. W. Sawodny, M. Riederer and E. Urban, *Inorganica Chimica Acta*, 1978, **29**, 63
8. R. F. Zabinski and M. D. Toney, *J. Am. Chem. Soc.*, 2001, **123**, 193
9. M..Sonmez, and M. Sekerci, *Polish. J. Chem.*, 2002, **76**, 907
10. S. A. Svejda and M. Brookhart, *Organometallics*, 1999, **18**, 65
11. D. Kovala-Demertzi, M. A. Demertzis, J. R. Miller, C. Papadopoulou, C. Dodorou and G. Filousis, *J. Inorg. Biochem.*, 2001, **86**, 555
12. T. Kappe and W. Stadlbauer, *Molecules*, 1996, 225
13. J. Schmeyers, F. Toda, J. Boy and G. Kaupp, *J. Chem. Soc., Perkin Trans. 2*, 1998, 989
14. X. Wang, X. M. Zhang, H. X. Liu, *Polyhedron*, 1995, **14**, 293; (b) X. Zhang, H. Z. You, *Polyhedron*, 1996, **15** 1793; (c) G. A. Kolawole, K. S. Patel, *J. Chem. Soc., Dalton Trans.*, 1981, 1241
15. C. Ma, A. Lo, A. Abdolmaleki and M. J. MacLachlan, *Org. Lett.*, 2004, **6**, 3841
16. Kai-Lun Kuo, Chiung-Cheng Huang and Ying-Chih Lin, *Dalton Trans.*, 2008, 3889
17. (a) M. Hariharan, F. L. Urbach, *Inorganic Chemistry*, 1969, **8 (3),** 556; (b) E. Solari, C. Floriani, D. Cunningham, T. Higgins, P. McArdle, *J. Chem. Soc., Dalton Trans.*, 1991, 3139; (d) P. G. Cozzi, *Chem. Soc. Rev.*, 2004 , **33**, 410
18. (a) D. Chen, A. E. Martell and Y. Sun, *Inorg. Chem.*,1989, **28,** 2647; (b) B. Ortiz and Su-Moon Park, *Bull. Korean Chem. Soc.*, 2000, **21 (4)**, 405
19. (a) M. Tokunage, J. F. Larrow, F. Kakiuchi, E. N. Jacobsen, *Science*, 1997, **277**, 936; (b) D. J. Darensbourg, *Chem. Rev.*, 2007, **107**, 2388

20. D. J. Gravert and J. H. Griffin, *Inorg. Chem.* 1996, **35**, 4837
21. D. J. Darensbourg, *Chem. Rev.*, 2007, **107**, 2388
22. M. Calligaris, L. Randaccio, in *Comprehensive Coordination Chemistry*, Sir, G. Wilkinson Pergamon Press, Oxford, 1987, 717
23. A. Pui, C. Dobrota and J. Mahy, *Journal of Coordination Chemistry*, 2007, **60 (5),** 581
24. A. D. Cort, L. Mandolini, C. Pasquini, K. Rissanen, L. Russo and L. Schiaffino, *New J. Chem.*, 2007, **31**, 1633
25. J. Schmeyers, F. Toda, J. Boy and G. Kaupp, *J. Chem. Soc., Perkin Trans. 2,* 1998, 989
26. A. L. Garay, A. Pichon and S. L. James, *Chem. Soc. Rev.*, 2007, **36**, 846
27. W. J. Geary, *Coord. Chem. Rev.*, 1971, **7**, 81
28. K. B. G. Torssell, *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis.*; VCH: New York, 1988, pp 75.
29. (a) B. N. Norman, Y. Gaeau, A. Padwa, *J. Org. Chem*, 1991, **56**, 2154; (b) B. K. Simonsen, P. Bayo, R. G. Hazell, K. V. Gothelf, and K. A. Jorgensen, *J. Am. Chem. Soc.* 1999, **121**, 3845; (c) P. Merino, S. Anoro, S. Franco, F. L. Merchan, T. Tejero, and V. Tunon, *J. Org. Chem.* 2000, **65**, 1590
30. (a) A. Padwa, K. F. Kohler, A. Rodriguez, *J. Am. Chem. Soc.*, 1981, **103**, 4974; (b) R. Pal, and A. Basak, *Chem. Commun.*, 2006, 2992; (c) M. Lombardo, C. Trombini, *Current Organic Chemistry*, 2002, **6 (8)** 695
31. (a) E. G. Janzen, *Acc. Chem. Res.*, 1971, **4**, 31; (b) G. Barriga, C. Olea-Azar, E. Norambuena, A. Castro, W. Porcal, A. Gerpe, M. Gonzalez, H. Cerecetto, *Bioorganic & Medicinal Chemistry,* 2010, **18**, 795
32. R. A. Floyd, K. Hensley, M. J. Forster, J. A. Kelleher-Andersson, P. L. Wood, *Mech. Aging Dev.* 2002, **123**, 1021
33. R. A. Floyd, K. Hensley, M. J. Forster, J. A. Kelleher-Anderson and P. L. Wood, *Ann. N. Y. Acad. Sci.*, 2002, **959**, 321
34. V. Migrdichian, *Organic Synthesis*, Vol. 2; Reinhold Publishing Co., New York, 1957, pp1634

35. P. H. Morgan and A. H. Beckett, *Tetrahedron*, 1975, **31**, 2595

36. S. Cicchi, M. Marradi, A. Goti and A. Brandi, *Tetrahedron Letters*, 2001, **42**, 6503

37. A. Goti, F. Cardona and G. Soldaini, *Organic Synthesis*, 2005, **81**, 204

38. H. Mallesha, K. R. Ravikumar, B. K. Vishukumar, K. Mantelingu and K. S. Rangappa, *Proc. Indian. Acad. Sci. (Chem. Sci.)*, 2001, **113 (4)**, 291

39. F. A. Villamena and D. R. Crist, *J. Chem. Soc., Dalton Trans.*, 1998, 4055

40. (a) S. Sivasubramaniam, P. Manisankar, M. Palaniandavar, N. Arumugam, *Transition Met. Chem.*, 1982, **7**, 346; (b) P. Merino, S. Anoro, E. Cerrada, M. Laguna, A. Moreno and T. Tejero, *Molecules*, 2001, **6**, 208

41. (a) F. A. Villamena, M. H. Dickman, and D. R. Crist, *Inorg. Chem.*, 1998, **37**, 1446; (b) R. W. Kluiber and W. D. Horrocks, *Inorg. Chim. Acta* 1970, **4**, 183

42. A. Caneschi, D. Gatteschi and P. Rey, *Prog. Inorg. Chem.*, 1991, **39**, 331

43. A. Stadler and C. O. Kappe, *Eur. J. Org. Chem.*, 2001, 919

44. N. Kuhnert, *Angew. Chem. Int. Ed.*, 2002, **41 (11)**, 1863

45. P. K. Panchal and M. N. Patel, *Synth. React. Inorg. Met.-Org. Chem.*, 2004, **34 (7)**, 1277

46. L. Casella, M. Gullotti, A. Pintar, L. Messori, A. Rockenbauer, and M. Gyor, *Inorg. Chem.*, 1987, **26**, 1031

47. D. E. Metzler, M. Ikawa and E. E. Snell, *J. Amer. Chem. Soc.* 1954, **76**, 648

48. G. L. Eichhorn and J. W. Dawes, *J. Am. Chem. Soc.*, 1954, **76**, 5663

49. A. Garcia-Raso, J. J. Fiol, F. Badenas and M. Quiros, *Polyhedron* 1996, **15 (24)**, 1407

50. W. Zishen and G. Ziqi, *Synth React. Inorg. Met. -Org. Chem.*, 1990, **20**, 335

51. Z. S. M. Al-Garawi, I. H. R. Tomi, A. H. R. Al-Daraji, *E-Journal of Chemistry*, 2012, **9 (2)**, 962

52. (a) L. Davis, F. Roddy, D. E. Metzler, *J. Am. Chem. Soc.*, 1961, **83**, 127; (b) D. Heinert, A. E. Martell, *J. Am. Chem. Soc.*, 1963, **85**, 1334.

53. R. K. Ray and G. B. Kauffman, *Journal of Thermal Analysis*, 1989, **35**, 1603

54. A. N. Mirskova, G. G. Levkovskaya, P. V. Medina,.,*et al.*, *Khim.-Farm. Zh.*, 1977, **11 (3)**, 74

55. A. N. Nikolaevskii, T. A. Filipenko, and E. I. Pleskushkina, *Neftekhimiya*, 2000, **40**, 145

56. B. E. Love and E. G. Jones, *J. Org. Chem.* 1999, **64**, 3755

57. (a) V. M. Naik, M. I. Sambrani, N. B. Mallur, *Indian J Chem.*, 2008, **47(A)**, 1793; (b) C. Pelizzi, G. Pelizzi and F. Vitali, *J. Chem. Soc., Dalton Trans.*, 1985, 177

58. W. O. Foye and R. N. Duvall, *J. Am. Pharm. Assoc.*, 1958, **47**, 285

59. (a) La-Mei Wu, Han-Bing Teng, Xian-Bing Ke, Wen-Jin Xu, Jiang-Tao Su, Shu-Cai Liang, and Xian-Ming Hu, *Chemistry & Biodiversity*, 2007, **4**, 2198

60. M. Katyal and Y. Dutt, *Talanta*, 1975, **22**, 151

61. (a) I. H. A. Suez, S. O. Pehkonen, M. R. Hoffmann, *Sci. Technol.*, 1994, **28**, 2080; (b) L. H. Terra, A. M. C. Areias, I. Gaubeur and M. E. V. Suez-Iha, *Spectrosc. Lett.*, 1999, **32** 257

62. (a) R. Dinda, P. Sengupta, S. Ghosh and T. C. W. Mak, *Inorg. Chem.*, 2002, **41**, 1684; (b) R. Raveendran and S. Pal, *Polyhedron*, 2005, **24**, 57

63. D. Gambino et al, *Eur. J. Inorg. Chem.*, 2004, **2**, 322; (b) S. Padhye and G. B. Kauffman, *Coord. Chem. Rev.*,1985, **63**, 127

64. P. F. Lee, C. Yang , D. Fan, J. J. Vittal, J. D. Ranford, *Polyhedron*, 2003, **22**, 2781

65. J. R. Dimmock, R. N. Puthucode, J. M. Smith, M. Hetherington, J. W. Quail and U. Pugazhenthi, *J. Med. Chem.* 1996, **39**, 3984

66. M. Shimada, K. Ishikawa and J. Nomiya, *Inorg. Biochem.*, 2001, **84**, 55

67. J. S. Casas , M. S. Garcia-Tasende and J. Sordo, *Coordination Chemistry Reviews*, 2000, **209**, 197

68. R. B. Singh and H. Ishii, *Crit. Rev. Anal. Chem.*, 1991, **22**, 381 and Refs. therein.

69. S. N. Pandeya and J. R. Dimmock, *Pharmazie*, 1993, **48**, 659 and Refs. therein.

70. (a) N. C. Kasuga, K. Sekino, C. Kuomo, N. Shimada, M. Ishikawa and K. Nomiya, *J. Inorg. Biochem.*, 2001, **84**, 55; (b) J. Patole, S. Dutta, S. Padhey and E. Sinn, *Inorg. Chim. Acta*, 2001, **318**, 207

71. W. Y. Lee, P. P. F. Lee, Y. K. Yana and M. Laub, *Metallomics*, 2010, **2**, 694

72. Gambino et al., *Journal of Inorganic Biochemistry*, 2005, **99**, 443

73. (a) V. V. Ponomareva, N. K. Dalley, K. Xiaolan, N. N. Gerasimchuk and K. V. Domasevich, *J. Chem. Soc. Dalton Trans.*, 1996, 2351; (b) C. J. Milios, T. C. Stamatatos and S. P. Perlepes, *Polyhedron,* 2006, **25,** 134

74. B. K. Singh, U. K Jetley, R. K. Sharma, and B. S. Garg, *Spectrochim. Acta, Part A,* 2007, **68,** 63

75. (a) H. Kuma, K. Motobe and S. Yamada, *Bull. Chem. Soc. Japan,* 1978, **51 (4),** 1101; (b) W. J. Holland and L. Lee, *Canadian Journal of Chemistry*, 1963, **41**, 1657

76. (a) S. Imamura, T. Kajimoto, Y. Kitano and J. Tsuji, *Bull. Chem. Soc. Japan*, 1969, **42**, 805; (b) M. E. Stone and K. E. Johnson, *Can. J. Chem.*, 1973, **51**, 1260

77. G. N. Schrauzer, *Inorg. Chem.* 1975, **14 (5),** 1200

78. S. Mukherjee, B. A. Patel, and S. Bhaduri, *Organometallics,* 2009, **28**, 3074

79. (a) B. K. Rai, *Asian J Chem.*, 2002, **14**, 312; (b) M. M. Hania, *Asian J. Chem.*, 2007, **17**, 439

80. (a) N. E Morrison and F. M. Collins, *Int. J. Leprosy*, 1981, **49**, 180; (b) D. H. Jones, R. Slack and S. Squires, *J. Med. Chem,*, 1965, **2**, 676; (c) D. L. Klayman and F. Joseph, *J. Med. Chem.*, 1979, **22**, 855; (d) H. G. Petering, H. H. Buskik and G. E. Underwood, *Cancer Res.*, 1963, **64**, 367

81. N. A. Patel, J. R. Shah and R. P. Patel, *J. fur Prakt. Chemie*, 1979, **321 (2),** 336

82. J. G. Lambardino and E. H. Wiesman, *J. Med. Chem.*, 1974, **17**, 1182

83. L. De Luca *Current Med. Chem.*, 2006, **13**, 1

84. (a) L. B. Townsend, *Chem. Rev.*, 1967, **67**, 533; (b) T. D. Heightman and A. T. Vasella, *Angew. Chem., Int. Ed.* 1999, **38**, 750

85. N. Sennequier, D. Wolan and D. J. Stuehr, *J. Biol. Chem.*, 1999, **274**, 930

86. J. J. Sheets, J. I. Mason, C. A. Wise and R. W. Estabrook, *Biochem. Pharmacol.*, 1986, **35**, 487

87. H. D. Lim, R. M. Van Rijn, P. Ling, R. A. Bakker, R. L. Thurmond and R. Leurs, *J. Pharmacol. Exp. Ther.*, 2005, **314**, 1310

88. (a) R. N. Swaminathan and D. B. James, *Curr Top Med Chem*, 2005, **5**, 987; (b) J. C. Lee, J. T. Laydon, P. C. McDonnell, T. F. Gallagher, S. Kumar, D. Green,D.

McNulty, et al. *Nature* 1994, **372**, 739; (d) A. K. Takle et al., *Bioorg. Med. Chem. Lett.*, 2006, **16**, 378

89. L. L. Chang, K. L. Sidler, M. A. Cascieri, S. Laszlo, G. Koch, B. Li, M. MacCoss, N. Mantlo, S. O'Keefe, M. Pang, A. Rolando and W. K. Hagmann, *Biorg. Med. Chem. Lett.*, 2001, **11**, 2549
90. N. W. Johnson, M. Semones, J. L. Adams, M. Hansbury and J. Winkler, *Biorg. Med. Chem. Lett.*, 2007, **17**, 5514
91. (a) S. Chowdhury, R. S. Mohan and J. L. Scott, *Tetrahedron*, 2007, **63**, 2363; (b) T. Welton, *Chem. Rev.* 1999, **99**, 2071; (c) P. Wasserscheid and W. Keim, *Angew. Chem., Int. Ed.*, 2000, **39**, 3772
92. (a) D. Bourissou, O. Guerret, F. P. Gabbai and G. Bertrand, *Chem. Rev.* 2000, **100**, 39; (b) P. L. Arnold and S. T. Liddle, *Chem. Commun.*, 2006, 3959; (c) O. Kuhl, *Chem. Soc. Rev.*, 2007, **36**, 592
93. E. S.-Lisac, A. Gazivoda and M. Madzarac, Electrochimica Acta, 2002, **47 (26)**, 4189
94. L. F. Tietze, *Chem. Rev.* 1996, **96**, 115
95. (a) Debus, H., *Ann.*, 1858, **107**, 204; (b) B. Radziszewski, *Chem. Ber.*, 1882, **15**, 1493; (b) F. Japp and H. Robinson, *Chem. Ber.*, 1882, **15**, 1268
96. S. Balalaie, A. Arabanian and M. S. Hashtroudi, *Monat. Chem.*, 2000, **131**, 945
97. J. Sangshetti, N. Kokare and A. Kotharkar, *Monat. Chem.*, 2008, **139**, 125
98. A. Mohammed, N. Lokare and J. Sangshetti, *J. Korean Chem. Soc.*, 2007, **51**, 418
99. M. Kidwai, P. Mothsra and V. Bansal, *Monat. Chem.*, 2006, **137**, 1189
100. S. Ahmad, M. Ali and B. Maryam, *Synth. Commun.*, 2009, **39**, 102
101. A. Shaabani and A. Rahmati, *J. Mol. Catal. A Chem.*, 2006, **249**, 246
102. S. Samai, G. C. Nandi, P. Singh and M. S. Singh, *Tetrahedron*, 2009, **65**, 10155
103. L. M. Wang, Y. H. Wang, H. Tian, Y. F. Yao, J. H. Shao and B. Liu, *J.Fluorine Chem.* 2006, **127**, 1570
104. (a) J. Wang, R. Mason, D. V. Derveer, K. Feng and X. R. Bu, *J. Org. Chem.* 2003, **68**, 5415; (b) E. A. Steck and A. R. Day, *J. Am. Chem. Soc.* 1943, **65**, 452

105. C. Zhang, E. J. Moran, T. F. Woiwade, K. M. Short and A. M. Mjalli, *Tetrahedron Lett.*, 1996, **37**, 751

106. M. V. Chary, N. C. Keerthysri, S. V. N. Vupallapati, N. Lingaiah and S. Kantevari, *Catal. Commun.*, 2008, **9**, 2013

107. S. E. Wolkenberg, D. D. Wisnoski, W. H. Leister, Y. Wang, Z. Zhao and C. W. Lindsley, *Org. Lett.* 2004, **6**, 1453 and references citied therein

108. G. Sharma, Y. Jyothi and P. Lakshmi, *Synth. Commun.*, 2006, **36**, 2991

109. (a) C. Amantini, F. Fringuelli, F. Pizzo, L. Vaccaro, *J. Org. Chem.*, 2001, **66**, 6734; (b) K. Selvakumar, A. Zapt and M. Beller, *Org. Lett.*, 2002, **4**, 3031

110. (a) S. A. Siddiqui, U. C. Narkhede, S. S. Palimkar, T. Daniel, R. J. Lahoti and K. V. Srinivasan, *Tetrahedron,* 2005, **61,** 3539; (b) M. M. Heravi, M. Zakeri, N. Karimi, M. Saeedi, H. A. Oskooie, and N. Tavakoli-Hosieni, *Synthetic Communications*, 2010, **40**, 1998

111. M. Kidwai, S. Saxena, R. Rastogi and S. Rastogi, *Bull. Korean Chem. Soc.*, 2005, **26** (12), 2051

112. A. R. Khosropour, *Ultrason. Sonochem.* 2008, **15**, 659

113. L. Kong, X. Lv, Q. Lin, X. Liu, Y. Zhou, and Y. Jia, *Organic Process Res. Development* 2010, **14**, 902

114. B. Jiang, X. Wang, F. Shi, S. Tu, T. Ai, A. Ballew and G. Li, *J. Org. Chem.*, 2009, **74**, 9486

115. M. V. Proskurnina, N. A. Lozinskaya, S. E. Tkachenko, and N. S. Zefirov, *Russian Journal of Organic Chemistry*, 2002, **38 (8)**, 1149

116. S. D. Sharma, P. Hazarika and D. Konwar, *Tetrahedron Lett.*, 2008, **49**, 2216

117. M. W. Jurema and G. C. Shields, *J. Computational Chemistry*, 1993, **14**, 89

118. K. Kondo and T. Oka, *J. Phys Soc. Jpn.* 1960, **109**, 9671

119. K. Bahrami, M. M. Khodaei and A. Nejati, *Green Chem.* 2010, **12**, 1237

120. (a) T. Bercovici, J. King and R. S. Becker, *J. Chem. Phys.* 1972, **56,** 3956; (b) J. E. D. Bene, *J. Chem. Phys.* 1971, **60**, 3812

121. M. A. Dayle, J. S. Smith, Y. Elkadi and L. Adanokicz, *Chem. Phy. Lett.*, 1999, **305**, 169

122. A. G. Gilani, M. Managhami and L. Anbir, *Journal of Solution Chemistry*, 2003, **32**, 625

123. E. C. Lee, D. Kim, P. Jurecka, P. Tarakeshwar, P. Hobza and K. S. Kim, *J. Phys. Chem. A* 2007, **111**, 3446

124. L. Colombo, D. Kirin, V. Volovsek, N. E. Lindsay, J. F. Sullivan and J. R. Durig, *J. Phys. Chem.* 1989, **93**, 6290

125. L. M. Babkov, T. V. Bezrodnaya, G. A. Puchkovskaya, K. E. Uspenskii and V. V. Shimanovaskaya, *Journal of Structural Chemistry* 2008, **49**, 517

126. V. Volovhkt and L. Colombo, *J. Phys. Chem.* 1993, **97**, 1283

127. (a) J. M. Lehn, *Angew. Chem. Int. Ed.* 1990, **29**, 1304 (b) B. Briet, L. Diab, T. Smejkal, J. Geier, *Angew. Chem. Int. Ed.* 2009, **48**, 8022

128. A. R. Katritzky and J. M. Lagowski, Chemistry of the Heterocyclic N-Oxides, Academic Press: New York-London, 1971.

129. M. Boiani and M. Gonzales, *Mini-Rev. Med. Chem.* 2005, **5**, 409

130. Q. Xia, L. Zhang, J. Zhang, R. Sheng, B. Yang, Q. He, and Y. Hu, *Eur. J. Med. Chem.*, 2011, **46**, 919

131. (a) W. Z. Antkowiak, and W. P. Gessner, *Tetrahedron Lett.*, 1979, **20**, 1931; (e) G. M. Nicholas, J. W. Blunt, and M. H. G. Munro, *J. Nat. Prod.*, 2001, **64**, 341

132. G. Laus, J. Stadlweiser and W. Klotzer, *Synthesis*, 1989, 773

133. (a) H. Lettau, *Z. Chem.* 1970, **10**, 211; (b) M. R. Grimmett, In Comprehensive Heterocyclic Chemistry; A. R. Katritzky, C. W, Rees, Eds.; Pergamon Press: Oxford, 1984; **5**, p 457

134. G. Mloston, J. Romanski, M. Jasinski and H. Heimgartner, *Tetrahedron: Asymmetry*, 2009, **20**, 1073

135. (a) A. J. Arduengo R. L. Harlow, and M Kline, *J. Am. Chem. Soc.* 1991, **113**, 361 (b) W. A. Herrmann, *Angew. Chem. Int. Ed.*, 2002, **41**, 1290; (c) D. Bourissou, O. Guerret, F. P. Gabbai and G. Bertrand, *Chem. Rev.*, 2000, **100**, 39

136. H. Scholl and M. M. D. Jimenez, *Corrosion Science*, 1992, **33 (12)**, 1967

137. Y.-S. Lin, C.-W. Liu and T. Y. R. Tsai, *Tetrahedron Lett.*, **2005**, *46*, 1859

138. (a) G. Mloston, T. Gendek and H. Heimgartner, *Helv. Chim. Acta* 1998, **81**, 1585; (b) I. J. Ferguson and K. Schofield, *J. Chem. Soc., Perkin Trans. 1,* 1975, 275

139. H. Cerecetto, A. Gerpe, H. Gonzales, Y. F. Sainz, O. E. Piro, *Synthesis* 2004, 2678

140. J. B. Wright, *Canadian Journal of Chemistry*, 1964, 1620

141. R. D. Ghosh, S. Das, A. Ganguly, K. Banerjee, P. Chakraborty, A. Sarkar, M. Chatterjee, A. Nanda, K. Pradhan and S. K. Choudhuri, *Dalton Trans.*, 2011, **40**, 10873

142. J. Alcazar, M. Begtrup and A. de la Hoz, *Heterocycles,* 1996, **43**, 1465

143. (a) P. Brooks and N. Davidson, *J. Am. Chem. Soc.* 1960, **82**, 2118; (b) J. Wan, S. J. Ye, Y. H. Wen and S. S. Zhang, *Chin. J. Chem.*, 2003, **21**, 1461

144. S. S. Zhang, S. Y. Niu, G. F. Jie, X. M. Li, H. Xu, X. Shi and K. Jiao, *Chin. J. Chem.*, 2006, **24**, 51

145. J. Wang, X. Liu, Y.Sun, K.Li and S.Zhao, *Advanced Materials Research,* 2011, Vols. 233-235, 175

146. L. Wang, Y. Ye, V. Lykourinou, A. Angerhofer, L. J. Ming and Y. Zhao, *Eur. J. Inorg. Chem.*, 2011, 674

147. (a) A. O. Eseola, M. Zhang, J. F. Xiang, W. Zuo, Y. Li, J. A. O. Woods and W. H. Sun, *Inorganica Chimica Acta*, 2010, **363**, 1970; (b) A. O. Eseola, W. Li, R. Gao, M. Zhang, X. Hao, T. Liang, N. O. Obi-Egbedi, and W.-H. Sun, *Inorganic Chemistry*, 2009, **48** (19), 9133

148. K. Pradhan, K. Selvaraj and A. K. Nanda, *Chem. Lett.* 2010, **39 (10)**, 1078

149. E. Gelens, F. J. J. De Kanter, R. F. Schmitz, L. A. J. M. Sliedregt, B. J. Van Steen, C. G. Kruse, R. Leurs, M. B. Groen and R.V.A. Orru, *Molecular Diversity,* 2006, 10, 17

150. L. Benisvy, A. J. Blake, D. Collison, E. S. Davies, C. D. Garner, J. Eric, L. McInnes, J. McMaster, G. Whittaker and C. Wilson, *Dalton Trans.* **2003**, 1975