CHAPTER-II

(SECTION A)

A mechanistic insight of carbonyl activation under solvent-free strategy: evidence drawn from the synthesis of imidazole derivatives

II.A.A. Introduction

In the past two decades successful solvent-free procedures for various types of reactions like rearrangements, condensations and oxidative couplings have been createdd apart from the various name reactions like the Claisen,[1]aldol,[2] Knoevenagel condensations,[3] Stobbe,[4] Thorpe,[5] Reformatsky, [6] Luche reactions,[7] Baeyer–Villiger oxidation,[8] pinacol rearrangement[9] and Tischenko just to name a few. The use of a solvent-free synthetic procedure for organic compounds that were traditionally synthesized in the presence of a solvent has become common in recent years.[10] Thus a large number of well-known organic reactions have been found to occur in solvent-free conditions and are more efficient than the reactions in solution. Such solvent free procedures serve as a tool to expand the chemistry including Green Chemistry reactions. Green chemistry has turned into the realm of chemistry which is more efficient and sustainable one and it can be been realized in several ways; reactions in aqueous media or ionic liquids and neat reactions, microwave reactions, among others. Mechano-chemistry has no doubt become an integral part of the green chemistry reactions and has helped in advancing and strengthening the solvent-free reaction methods further, either by including mechanochemical or thermochemical excitation. Moreover, metal-template reactions, multi-component reactions, one pot-synthesis and DOS have widened the scope for solvent-free protocol. Solvent-free methods have already been developed for almost all kinds of traditional multi-component reactions like Biginelli,[11] Strecker,[12] Passerini,[13] Hantzsch,[14] Mannich,[15] Petasis,[16] Ugi,[17] Radziwenski synthesis,[18] Gewald,[19] and so on. And to impart a higher reactivity to the reactants and the reagents, these synthetic protocols have been wisely exploited in the use of transition metal catalysts and the various organocatalysts. They are now being successfully used as a versatile route to biologically active motifs and have attracted considerable attention in the recent years. Thus, we can find ample scope and opportunity in the development of similar methods to synthesize a wide range of compounds. Lewis acids and many organocatalysts have also been shown to be efficient catalysts for C–C bond forming reactions, and through the carbonyl activation provide effective opportunities for upgrading classical MCRs. In particular, close attention must be paid to condensation reaction mechanism that includes the activation of carbonyl-containing electrophiles. The large number of investigations associated with chemical transformations mediated by organocatalysts[20] or by the Lewis acids in anhydrous organic media,[21] aqueous media[22] and in the absence of any media[23] has given a fundamental understanding of the internal dynamics of the adduct formation between the acid and the

carbonyl moieties and has shed light upon the role of these adducts in accelerating catalytic transformations.

II.A.B. Present work: Background and Objective

A well known example is the significant increase in the reaction rates for the Radziwenski synthesis which is attained by the excitation of a carbonyl group by a Lewis base center[24] or a Lewis acid center[23] or through the formation of the adducts. This chapter thus specifies recent advancements in solvent-free synthesis of a very vital biologically active part of a heterocyclic compound, the Imidazoles. In addition to the cleanness and simplicity of the procedure, the absence of any medium has been found to lead to various uncommon reactivities. The syntheses of imidazoles and their derivatives have also allowed us to draw evidences for the mechanistic study of excitation of carbonyls in solvent-free syntheses.

We have always tried to stick to a solvent-free non-catalytic approach by using simple heating. It focuses on the use of grinding to carry out reactions between solid reactants followed by heating of the mixture to form a melt. Though sometimes it was found that some reactions do not essentially go to completion on simple mechano-chemical activation, or even if it happens, it usually takes a longer time. Despite of this fact, mechanochemistry has been highly used for the synthesis of a large number of compounds. It has been found that providing a little additional heat to the mechanochemically shaken mixture gives promising results. The products were formed in a much lesser time, comparable to the microwave assisted reactions. And according to the arguments given in the literature, they could also be regarded as being more efficient (less time consuming), and thus being green. It could be stated as efficient because a fast reaction performed at a high temperature (Arrhenius equation) is likely to require very less energy when compared to a reaction that requires significantly longer reaction times at a lower temperature. However, as it is known that excess heat always has a tendency of charring the reaction mixture and also since there are certain possibilities of runaway reactions it becomes imperative that the shaken mixtures were heated to an optimum temperature to get the very best results. One of the best ways of highly optimizing the reaction conditions was done by carrying out the thermal analysis of the powdered mixture of the reactants. Thus, initially the optimization of the reaction conditions of the representative reactions were done using Thermal analysis techniques like the DSC. Subsequently the reaction optimization for the Imidazole synthesis was carried out by using HPLC where thermal reactions in solvent-free conditions were observed and

optimized by running HPLC of the reaction mixtures at various temperatures. The HPLC analysis of the reaction mixture at various time intervals also led to the determination of reaction kinetics.

II.A.C. Present work: Result and Discussion

II.A.C.1. Substituted Imidazoles

Imidazoles are heterocyclic compounds that are part of a vast number of highly significant biomolecules like the essential amino acid histidine and other related compounds, biotin and imidazole alkaloids.[25] Synthetic imidazoles are present in various fungicides and herbicides[26] and also in antiprotozoal, antihypertensive medications and antifungal.[27] Imidazole drugs have a broad application in several areas of clinical medicine.[28] The imidazole moiety is also present in various histaminergic ligands for histamine H1, H2 and H3 receptors as well as in various FTase inhibitors.[29] The vital therapeutic properties of imidazole drugs have been exploited by the medicinal chemists to synthesize and test a huge number of novel molecules. Several 5-lipoxygenase, 'P38' MAP and B-Raf Kinase inhibitors carrying the imidazole moiety have been synthesized.[30] Some substituted triarylimidazoles are efficient antagonists of the glucagon receptor[31] and inhibitors of Tie-2 and IL-1 biosynthesis.[32] The potency and wide applicability of the imidazole pharmacophore is attributed to its hydrogen bond donor–acceptor capability as well to its high affinity for metals, which are present in most of the protein active sites (e.g., Fe, Zn, and Mg). Thus, the synthesis reactions and biological properties of substituted imidazoles constitute an important part of the modern heterocyclic chemistry. Recent advancements in green chemistry and the organometallic chemistry have widely extended the boundaries of imidazoles to the synthesis and applications of a huge class of imidazoles as ionic liquids[33] and imidazole related N-heterocyclic carbenes.[34] In industry, imidazoles have been used widely as a corrosion inhibitor on several transition metals, such as copper.[35]

II.A.C.2. Synthesis of substituted Imidazoles

In the continuation of our studies for the development of synthetic procedures, and to study the mechanistic aspects of the solvent-free reactions, the synthetic route to Imidazoles and its derivatives were also investigated. Synthetic route to Imidazole, both tri- and tetra-substituted and their other derivatives like Imidazole N-oxides and 1-Hydroxy Imidazole N-oxides were also investigated for a few reasons; first of all they were easy to investigate

without a need to synthesize complex starting materials (easily available starting materials like benzil, glyoxal, dimethyl glyoxime etc were used); secondly it was highly challenging to come up with a new protocol (as simple as the thermo-chemical activation) which could compete with the recent technologies, in terms of their yield, reaction time, scalability and the greenness of reaction; and thirdly, the Imidazoles and compounds containing the imidazole ring have many pharmacological characteristics and play significant roles in biochemical processes, the reaction protocol could further be extended for syntheses of metal complexes. Metal complexes of many heterocyclic compounds have been found to show higher biological activities and catalytic activities then their simple ligand predecessors.

The artificial approach to the Imidazoles has been constantly redesigned over the past few years, some have resulted in better yields while others have looked for the greener catalysts to improve the yields and lower the reaction time. Modern organic synthesis mainly relies on the rapid development of efficient approaches to the chemically and biologically vital products from easily available inexpensive starting materials.[36] Historically, the first synthesis of imidazole core, starting from 1, 2-dicarbonyl compounds, aldehydes and ammonia, was first reported by Debus in 1858. Radziszewski and Japp later on fully developed the procedure in the year 1882.[37] Although, classical methods were obtained from this early success, the reaction suffered from low yields, mixtures of products and longer reaction times. Since then, the imidazole nucleus has over the years initiated the development of new and improved methodologies.

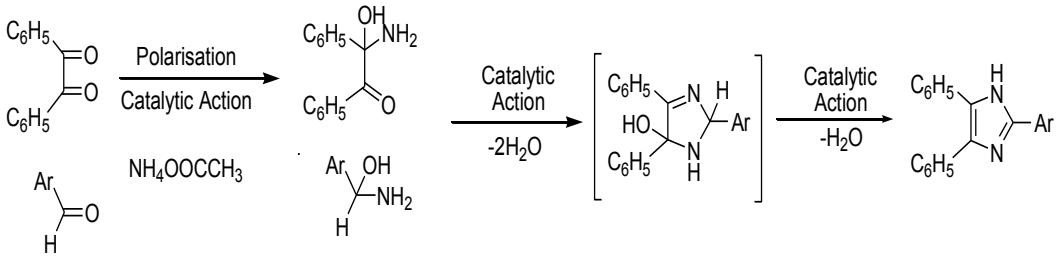
The literature has a large number of methods that can be given for the synthesis of 2, 4, 5-trisubstituted and 1, 2, 4, 5-tetrasubstituted imidazoles. While 2, 4, 5-trisubstituted imidazoles are synthesized by the three component cyclocondensation of 1, 2-diketone, α-hydroxyketone or α -ketomonoxime with aldehyde and ammonium acetate, the synthesis of 1, 2, 4, 5-tetrasubstituted imidazoles are mainly carried out by the four-component condensation of a 1, 2-diketone, α -hydroxyketone or α -ketomonoxime with an aldehyde, primary amine and ammonium acetate. Syntheses of Tri-and tetra-substituted imidazoles have been done using zeolites, HY/silica gel,[38] iodine,[39] L-proline,[40] ceric ammonium nitrate,[41] sulphanilic acid,[42] NaHSO3,[43] silica sulphuric acid,[44] and some common Lewis acids such as $LaCl_3$, $Yb(OTf)_3$, $NbCl_3$, $FeCl_3$, $AlCl_3$[45] or by traditionally refluxing in acetic acid.[46] To add to this, there are a few microwave (MW) assisted syntheses of imidazoles from 1, 2- diketones and aldehydes in the absence of any solvent[47] or in the presence of variety of catalysts like silica-

gel, Al_2O_3,[48] silica-gel/HY, $ZrCl_4$,[49] acetic acid,[50] $NiCl_2.6H_2O$,[51] ionic liquid[52] and DMF. Kidwai *et al* reported that during the MAOS of tri- and tetra substituted derivatives they became sticky solid which indicated that, it was not a cleaner approach[53] Ultrasound-promoted synthesis of imidazoles catalyzed by $Zr(acac)_4$,[54] and the perpetual flow of micro reactor system [55] are some recent techniques that have been added to the book of Imidazole synthetic methodologies.

The methods given above for the Imidazole synthesis have their own merits and demerits. While some of the methods suffer by the limitations of poor yield, longer reaction time, laborious work-up and effluent pollution, other methods use drastic reaction conditions, hazardous and very often expensive acid catalysts. Moreover, sometimes the products that are formed needs a very tedious purification. It is found that the synthesis of these heterocycles has been 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 highly expensive reagents, harsh reaction conditions, and sometimes tedious workup using toxic reagents or solvents. Therefore, the creation of a new non-catalytic method with an efficient and environmentally friendly protocol could overcome these drawbacks.

II.A.D. Optimization of reaction conditions for Imidazole synthesis with HPLC studies

The optimization of the reaction for Imidazole syntheses was the initial step to be carried out in our study. For this, a representative 2-(4-methoxyphenyl)-4,5-diphenylimidazole **[2]** was initially synthesized by a three-component reaction using the benzil, anisaldehyde, and ammonium acetate through a solvent-free catalyst-free procedure according to **Scheme II.A.1**.



Scheme II.A.1: A plausible solvent-free mechanism for the synthesis of Tri-substituted Imidazoles

Thus, in order to optimize the reaction reaction time and the temperature the reaction was carried out under solvent-free procedure for 20 minutes at various temperatures and the peak areas found from HPLC were plotted against temperature (^{o}C). As shown in the figure 22, at the beginning ammonia addition starts at relatively lower temperature, but the product (imidazole) formation begins at a much later stage and it was quite sensitive to temperature variation. The optimum temperature was found to be 125-135^{o}C.

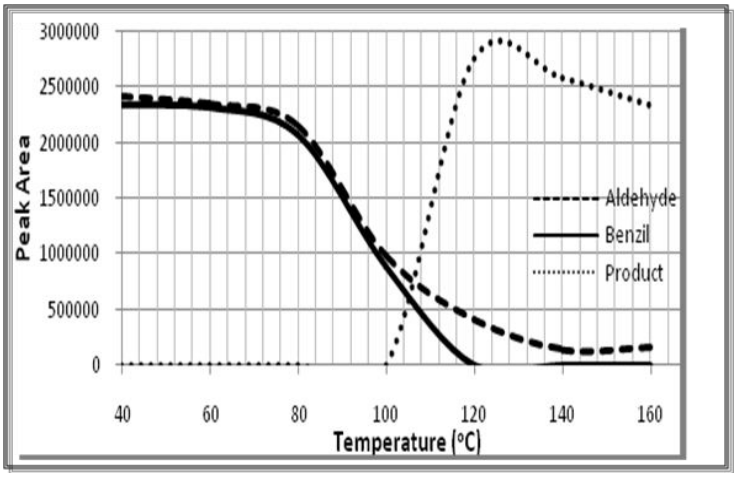


Figure II.A.1: HPLC Peak Area vs Temp. after 20 mins of reaction (Compound **[2]** in **Scheme II.A.1**).

In the view of the above understanding of the optimized conditions we then tried to obtain the mechanistic insights. The main objective was to look for the intermediate ammonia addition product using 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 **[2]** were recorded to locate the retention time of the substrates. It was found that pure benzil gave a peak with retention time of 5.872 minutes (**Figure II.A.2**) while the pure recrystallised product **[2]** which was previously prepared, gave a peak with retention time of 6.092 minutes (**Figure II.A.3**).

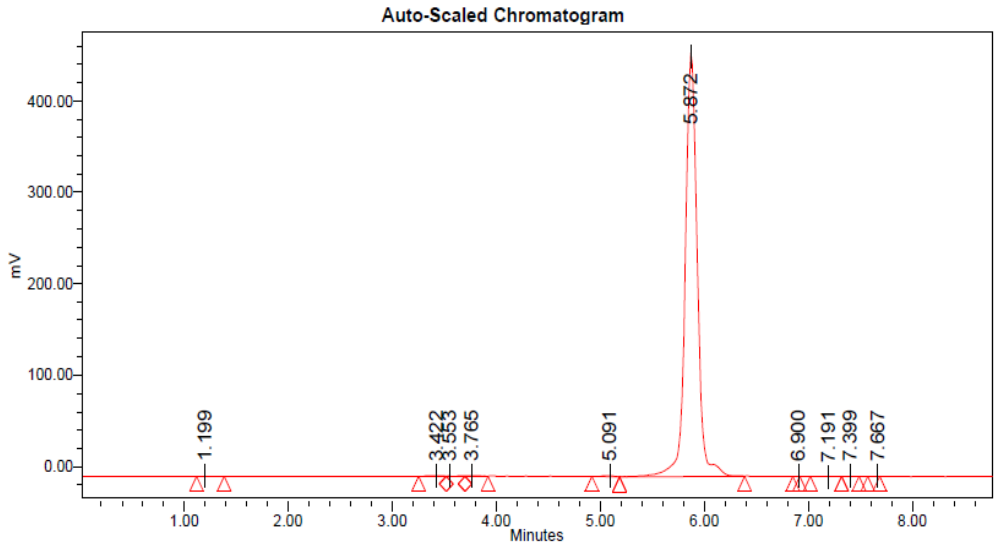


Figure II.A.2: HPLC chromatogram of pure benzil

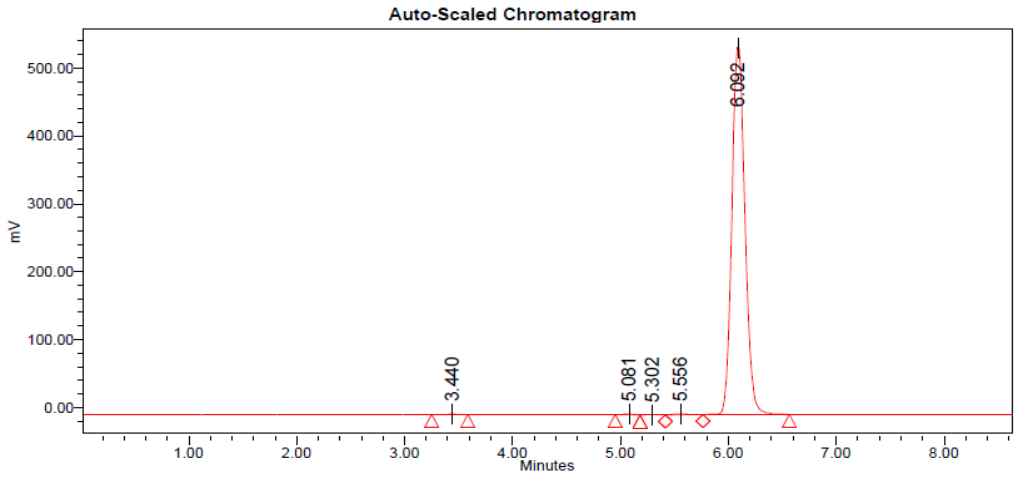


Figure II.A.3: HPLC chromatogram of the pure product 2-(4-methoxyphenyl)-4,5-diphenylimidazole **[2]**

Since the accepted mechanism for the synthesis Imidazole considers a benzyl-ammonia addition product as the intermediate, we tried to investigate a little further. 5 mili-moles of NH_4OAc was mixed with 1 mmole of benzil and then heated to 120^oC and was kept for 5 minutes. After 5 minutes, the reaction mixture was frozen in ice cold methanol and the HPLC chromatograms were obtained. The benzil and the NH_3 mixture show a major peak at 5.801 which is due to benzil (**Figure II.A.4**). A new peak was also observed at retention time of 8.075 indicating the benzil-ammonia addition product.

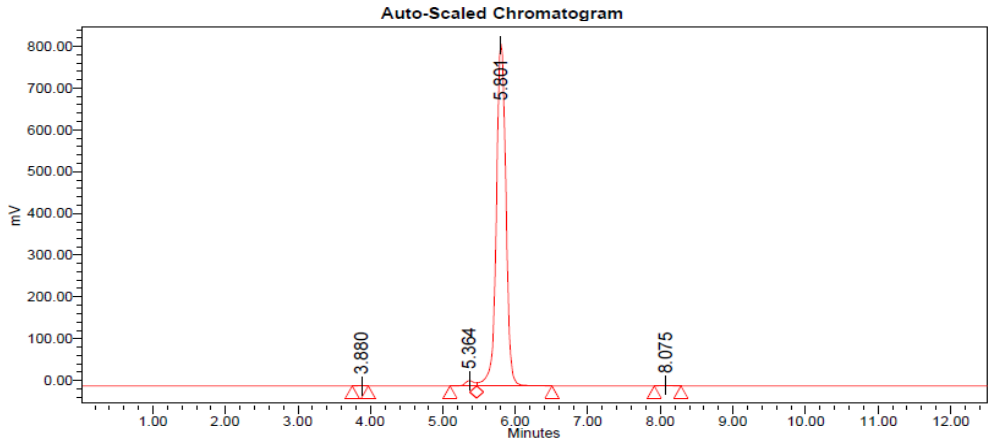


Figure II.A.4: HPLC chromatogram of benzil and ammonium acetate.

It is also highly significant to note that the peak at 8.075 is not observed in HPLC chromatogram of pure benzil (**Figure II.A.4**) but it is observable in chromatogram obtained from HPLC run of the reaction mixture leading to the formation of Imidazole, **[2]** (**Figure II.A.5**). It is also apparent from the chromatogram of the entire reaction mixture, the presence of the intermediate at 8.045 along with presence of Imidazole, **[2]** peak at 5.926, anisaldehyde peak at 5.543and the peak for benzil at 5.789.

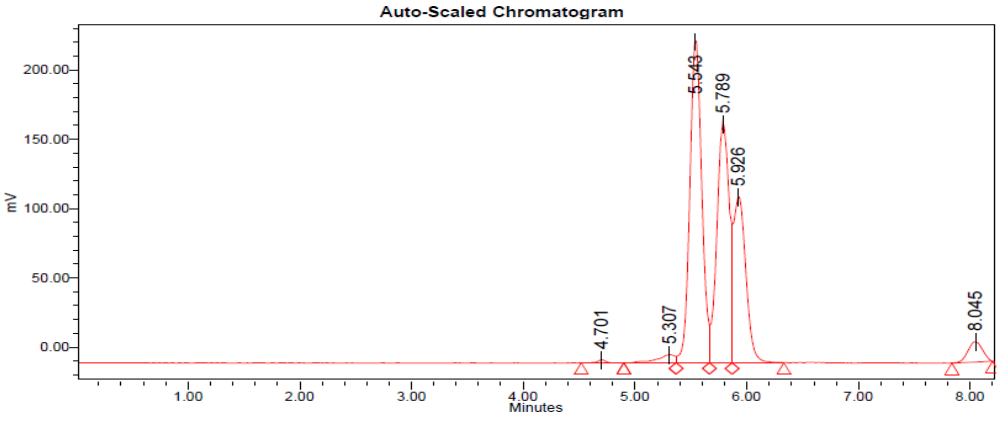


Figure II.A.5: HPLC chromatogram of reaction mixture of benzil, anisaldehyde and ammonium acetate after 15 minutes at 120^{o}C.

To authenticate our proposal, an HPLC chromatogram of the aldehyde and ammonia was carried out as been carried out with benzil and ammonia. The HPLC chromatogram of the aldehyde (anisaldehyde) when treated with ammonia under similar conditions showed no peak at a higher retention time than the aldehyde itself which shows only a single peak at retention time of 5.549 (**Figure II.A.6**).

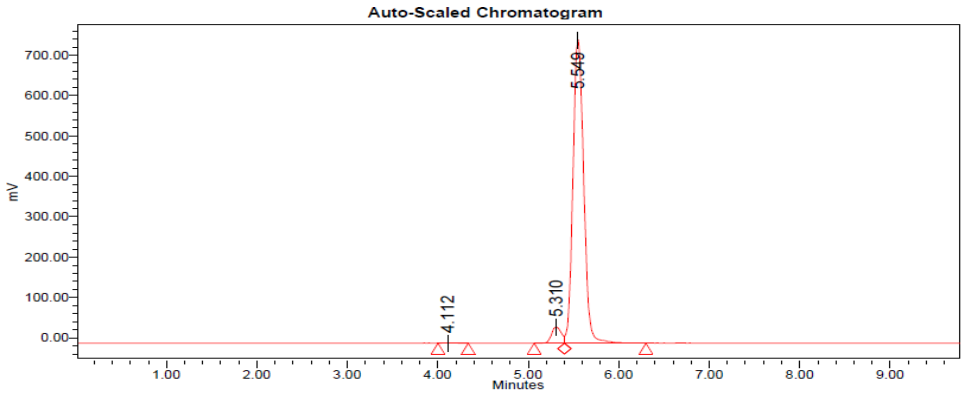


Figure II.A.6: HPLC chromatogram of Anisaldehyde and ammonium acetate.

Instead, a peak is observed at a retention time of 5.310 which was observed in chromatogram of the reaction mixture (**Figure II.A.6**).Of all the possibilities, this peak may be due to the aldehyde-ammonia addition product.

To start with, the kinetics of imidazoles 1b and 1c were thoroughly studied through HPLC monitoring of benzil and aldehyde (reactants) consumption along with the product (imidazoles) formation. When the ordinary logarithm values (-ve for reactants and +ve for products) of the peak area was plotted against time, a good linear relationship was observed in each case. The first order rate constant and half life ($t^{1/2}$) was determined from the slope of this curve using the first order rate equation given below:

$$dC/dt = (+/-)\ kC$$

$$C \ \alpha \ I$$

$$C = I*X$$

$$\pm \ln I = (+/-)\ kt + \text{integration constant}$$

Figure II.A.7: shows the observed dependence of reactants' concentrations (logarithm) and product formation with the variation of time (at reaction temperature 125^{o}C, temperature optimized for maximum conversion). It was found that the product peak in HPLC was not much prominent within the first 10 minutes.

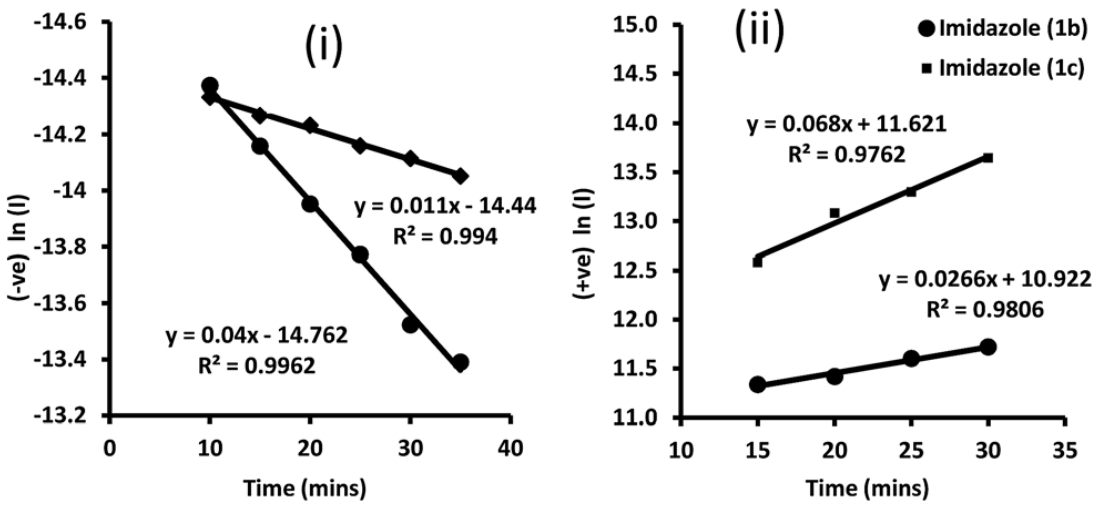


Figure II.A.8: (_ve)/(+ve) ln(I) vs. time (mins) of [i] benzil during formation of imidazoles (1b) and (1c); [ii] rate curve of the product imidazoles (1b) and (1c) formation; I = peak area.

The catalytic effect of some metal salts (5 mol%) at the same reaction temperature (125°C) was also compared. The corresponding rate constant and half life values are shown in **Table II.A.1**.

Table II.A.1: Rate constants and half lifes of reactant consumption and products 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

The organized results indicated that the catalysts acted at various stages of the reaction steps of the MCR reaction. A representative case of ytterbium triftate, a threefold increase in the rate of benzil consumption and five time increase in imidazole formation as against the catalyst free reaction was observed. Considering that in a reaction, catalysts are used in very small proportions. Thus only a small mole fraction of the reactant would have the chance to get associated with the catalyst and hence the possibility of the substrate taking part in the adduct formation would be further reduced. Hence with only trace amounts of a catalyst (5 mol% in the above case) added to a reaction, the rate should have been hardly affected as only a few molecules would have engaged in activated complex in comparison to the large number of un-associated molecules in the reaction media. We have also studied the reactions at various elevated temperatures and found that at the temperature range 150–160°C, almost quantitative products were formed in a very short period of time of 4 minutes; and that too without using any kind of catalyst. This is a landmark record in the imidazole synthesis (ESI†).

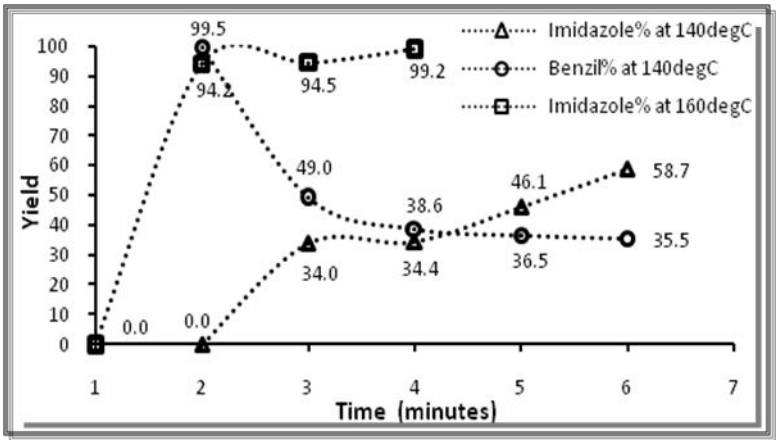


Figure II.A.9: Comparison of percentage yield of Imidazole, **[2]** at 140°C, 160°C and benzil consumption at 140°C versus time (mins).

Since, it was well known that the aldehydes have been frequently reacted with ammonium acetate to prepare 1, 2-diaminoethanes,[56] it was an initial assumption that the multi component reaction of the aldehydes with ammonium acetate and benzil under thermo chemical activation may not give quantitative results. Under these conditions, it has also been revealed that in the reaction hydrobenzamide is also formed in the initial stage which in turn gets transformed into amarine (*cis*-triphenylimidazoline). The compound further reacted with another molecule of aldehyde and through a series of intermediates formed the benzylidene benzoyl derivative. Contrary to what was expected, several other reported methods like

microwave, ultrasonication and catalytic methods, have been found to yield the Imidazoles efficiently. A possible reasoning may be that the presence of benzil actually hinders the formation of the said intermediates.

II.A.E. Optimization of reaction conditions for the synthesis of Imidazole derivatives with Thermal Analysis

Differential Scanning Calorimetry (DSC), one of the various methods for thermal analysis was used for the optimization of the reaction conditions for the synthesis of an Imidazole N-oxide. The study was carried out using diacetyl monoxime, p-hydroxy benzaldehyde and p-amino benzoic acid as the starting materials for their one-pot multicomponent synthesis of the corresponding Imidazole N-oxide as the model reaction. A DSC analysis of a powdered mixture containing equimolar amounts of each reactant for the synthesis of 1-substituted Imidazole N-oxides has shown that the reaction is highly exothermic. A detailed look at the DSC plot shows an exotherm at 112^{o}C which thereby indicates the onset of the reaction and the product formation probably begins at this temperature (**Figure II.A.10**).

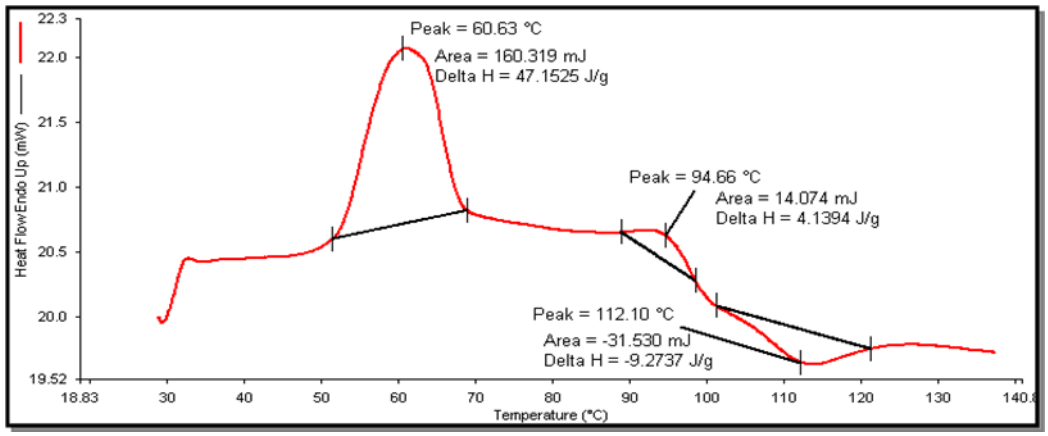


Figure II.A.10: DSC plot of a mixture of diacetyl monoxime, p-hydroxy benzaldehyde and p-amino benzoic acid

For 1-hydroxy 2, 4, 5-trisubstituted imidazole-3-oxides synthesis the DSC and TGA results gave more interesting results for the study. For the refinement of the present study, the DSC plots of the three systems were compared. The DSC trace of the ground mixture of diacetyl monoxime and m-nitrobenzaldehyde monoxime (**Figure II.A.11**) has shown two high peaks at 60^{o}C (sharp) and 222^{o}C. These two peaks correspond to m.p of diacetyl monoxime and the product m.p. respectively. There are also two broader humps at around

97°C and 125°C which corresponds to the sublimation of diacetyl monoxime and the m.p. of m-nitrobenzaldehyde monoxime (Litt. M.p.122-123°C) respectively.

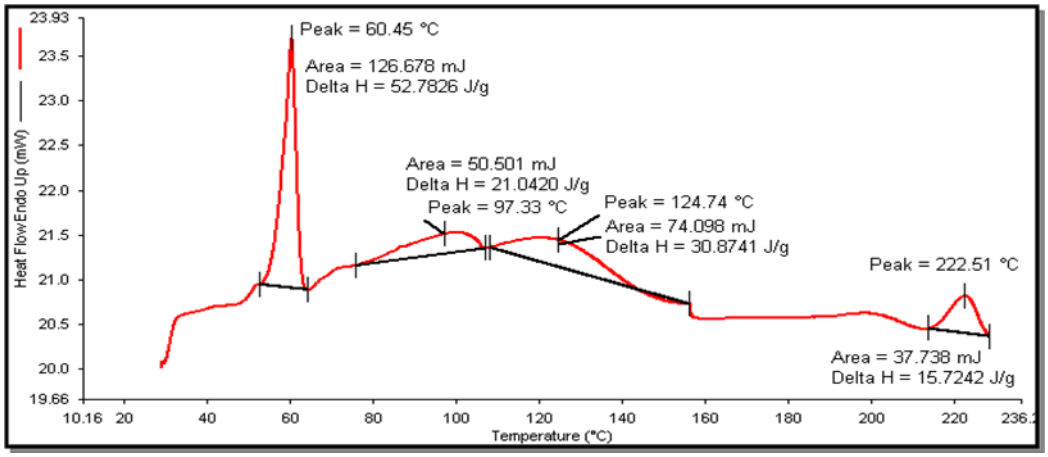


Figure II.A.11: DSC trace of a mixture of diacetyl monoxime and m-nitrobenzaldehyde monoxime

A Simultaneous Thermal Analysis (STA) was also been carried out to have some insight of the reaction scheme. It suffered from a serious technical disadvantage of being carried out only in an open sample holder. Since one of the reactants, diacetyl monoxime underwent through sublimation; a correct picture about the loss of water molecule cannot be obtained. Inspite of this, the TGA trace obtained from the STA of the reaction mixture of diacetyl monoxime and m-nitrobenzaldehyde oxime indicates the increase in temperature at around 90°C. Moreover, the m.p. peak of the product at 222-225°C cannot be observed in the DSC trace (**Figure II.A.12**).

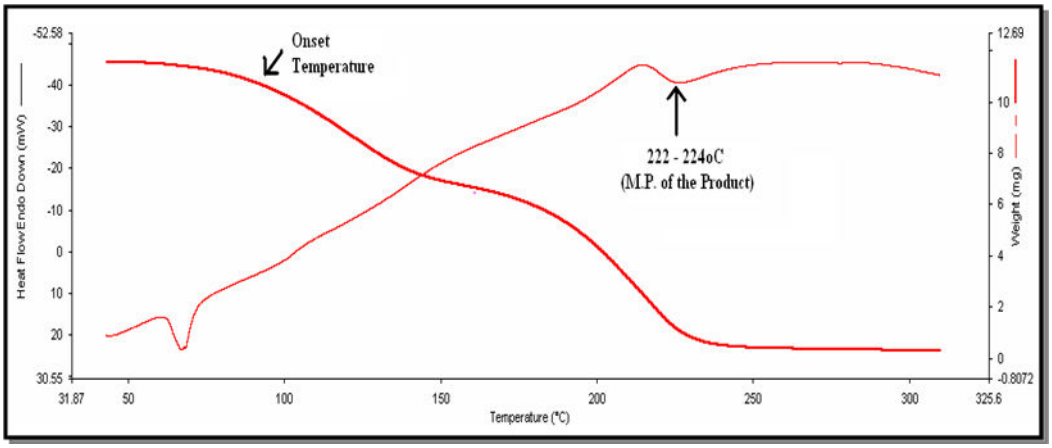


Figure II.A.12: STA of the mixture of diacetyl monoxime and m-nitrobenzaldehyde oxime

A second DSC analysis of the mixture of m-nitrobenzaldehyde and dimethyl glyoxime was also done (**Figure II.A.13**). The DSC plot shows around three peaks at 58°C, 60°C and 202°C corresponding to m.p. of 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) respectively.

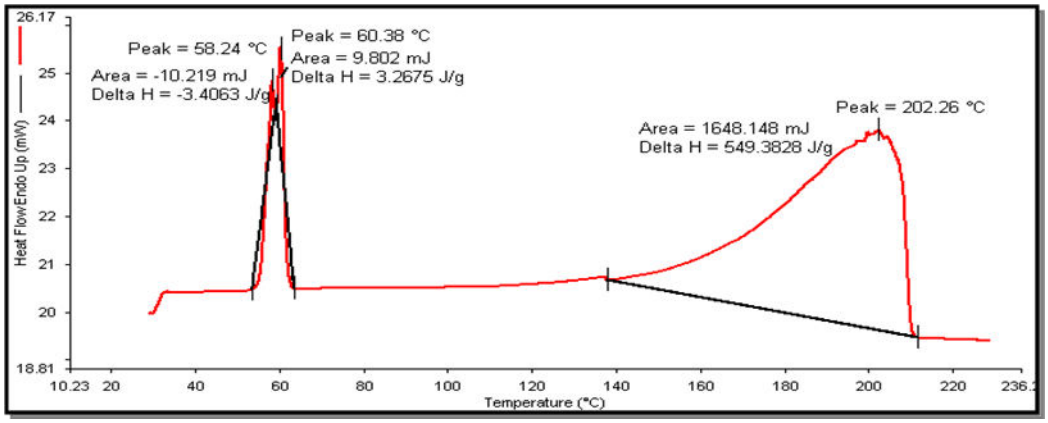


Figure II.A.13: DSC trace of a mixture of dimethyl glyoxime and m-nitrobenzaldehyde

Interestingly, the appearance of the at around peak at 60°C for the m.p of diacetyl monoxime in the second DSC curve, even in its absence as a starting material, suggests that there could be some mechanism involved wherein the dioxime at first gets transformed to the monoxime by the exchange of the oxime group between aldehyde and dioxime, a mechanism which was earlier proposed by John B. Wright[57] but not yet been verified. It is highly possible that the reaction then proceeds via a monoxime to yield the corresponding products. A DSC trace for the pure dimethyl glyoxime for comparison was also obtained (**Figure II.A.14**). No peak was actually seen at the m.p. of diacetyl monoxime or at 60°C as was actually observed earlier, when it was thoroughly mixed with the m-nitrobenzaldehyde. It can be concluded that the peak observed at 60°C arises only in the presence of aldehyde and is due to the diacetyl monoxime which always tends to melt at that high temperature in the mixture.

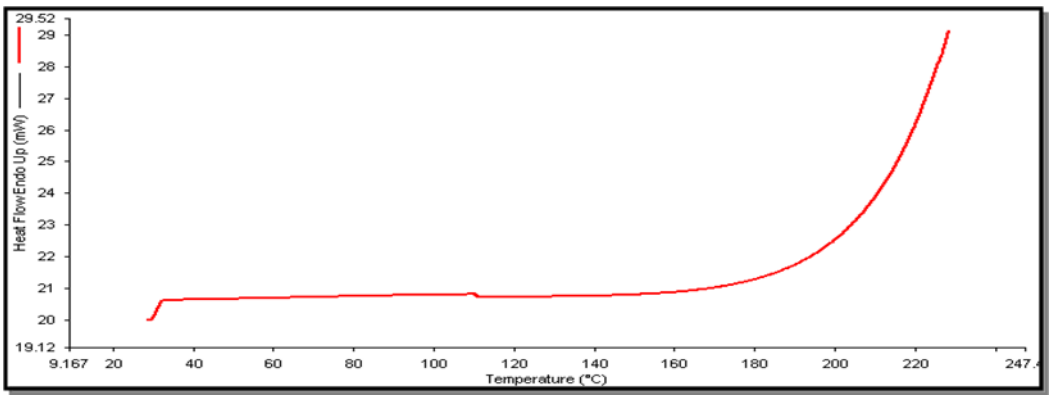


Figure II.A.14: DSC trace for pure dimethyl glyoxime

In the DSC trace of the pure diacetyl monoxime two peaks were observed. The peak at around 76^{o}C is for the m.p. of diacetyl monoxime while the second peak at around 153^{o}C actually confirms the appearance of the endotherm for sublimation of diacetyl monoxime (**Figure II.A.15**).

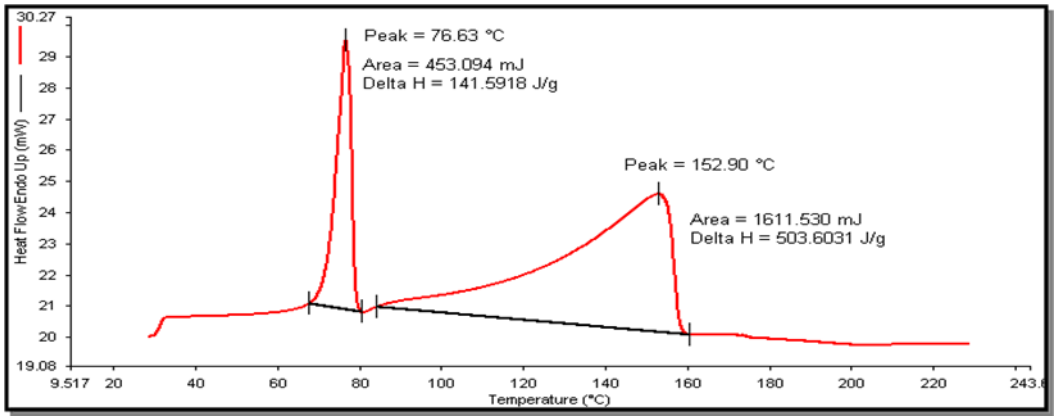


Figure II.A.15: DSC trace of pure diacetyl monoxime

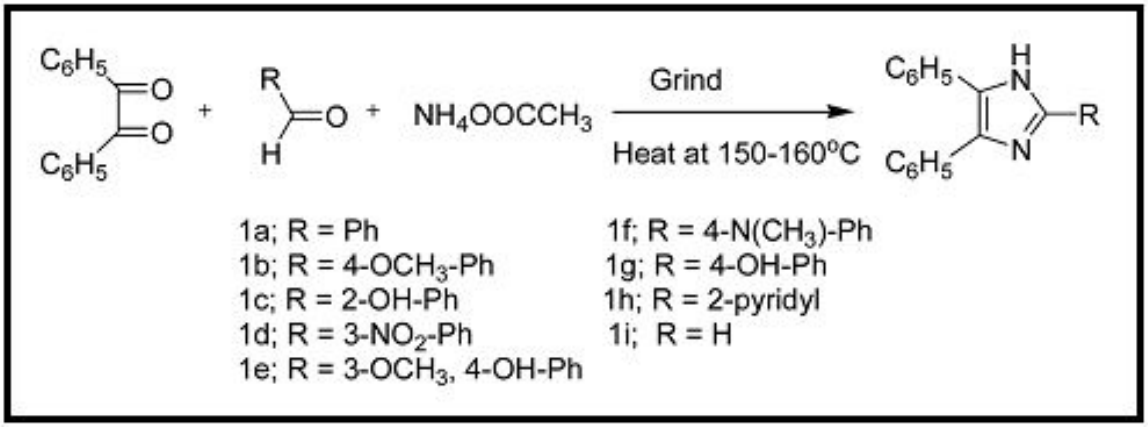
The peak at around 153^{o}C in the above shown DSC curve corresponds to the sublimation of the pure diacetyl monoxime, which in the above case is at a much higher temperature compared to the actual peak at 125^{o}C and is attributed for the same as in the case of the reaction mixture shown in **Figure II.A.15**. The depression by 28^{o}C in the sublimation peak which is observed in the reaction mixture could be due to the presence of some other compounds in the reaction mixture, which is quite similar to the observed depression of melting point of the diacetyl monoxime from 76^{o}C in the pure form to about 60^{o}C in the

reaction mixture. Overall, it may be concluded that the reaction actually proceeds via some monoxime in all the three cases. Whatever maybe the functionality of the substrate, the synthon in all the three reactions was found to be α-(hydroxyimino) ketones.

II.A.F. Solvent-free multi-component synthesis of Tri- and tetra-substituted Imidazoles

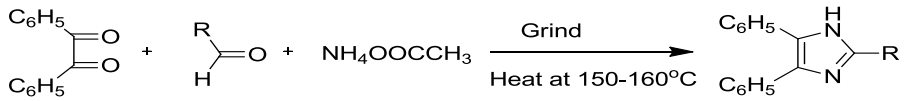
According to exixting literature Debus-Radziszewski imidazole synthesis in the solution state would take about 24 hrs to get a yield of good quantity.[58] Heather to,while the two most reported efficient syntheses are under the conditions of microwave irradiation where reactants are being irradiated at 180^{o}C in for 5 minutes in acetic acid[50] (Wolkenberg et al) and for 3-5 minutes at 120^{o}C [47] (Zhou et al) in the absence of catalyst. Both cases having yields which are almost quantitative. The reaction in first case was catalyzed by acetic acid while focused heating of microwave in the solvent-free condition helped in second case. It is seen that solvent-free condition is being responsible for mostly the self-catalytic effect. basic chemistry in all cases remains the same; changes in polarizability and electrophilicity of carbonyl group has an influence on rate of reaction. Quantitative yields of under four minutes are obtained even in solvent free thermal conditions without the presence of catalyst. Reactions based on thermal heating might be more practical to use out in the scaled up syntheses.

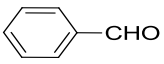
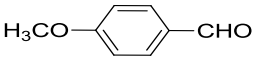
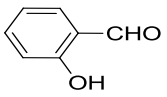
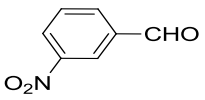
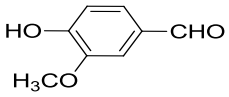
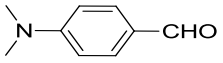
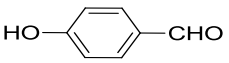
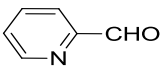
We examined variety of aldehydes (both aliphatic and aromatic) with different substituents for establishing catalyst-free solvent-free protocol for the following reaction (**Scheme II.A.2**). A variety of *ortho*-, *meta*-, and *para*-substituted aromatic aldehydes undergo this one-pot multi-component synthesis with the 1, 2-diketones and ammonium acetate to give, 4, 5-trisubstituted imidazoles in good quantitative yields (**Table II.A.2**). For all cases, it was observed that reaction profile was very clean with no side-products. The imidazoles synthesized have all been characterized with the basis of elemental and spectral studies.



Scheme II.A.2: R-I synthesis of tri-substituted imidazoles **.**

Table II.A.2. Solvent free synthesis of 2,4,5-trisubstituted Imidazoles.



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

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. [7]

Along the usual methods of spectroscopy for structure determination, we used single crystal X-ray diffraction (Sc-XRD) data of 1 of the representative compounds: 4,5-diphenyl-1Himidazole, **9**, to confirm its structure. Single crystals of compound suitable for Sc-XRD were formed by slow evaporation from the methanol/hexane mixture. This compound crystallizes in a monoclinic crystal system with space group $P2_1/c$ (Hall group - P_{2ybc}); a= 11.0471(4) A°, b = 9.2483(3) A°, c = 11.5780(4) A°, α = 90°, β = 93.921(3)°, γ = 90°, Z = 4, μ = 0.577 mm^{-1}, F_{000} = 468.0 and Kα = 1.54184 °A. The ORTEP diagram has been presented in **Figure II.A.16**. Its heterocyclic ring has been seen as planar. An interesting thing in the following diagram is attachment of a proton in every nitrogen atom reflecting an overall excess of a proton. The N_7–C_{11} and N_9–C_{10} bond lengths are identical (1.380 A° and 1.3799 A° respectively), Also N_7–C_8 and N_9–C_8 bond lengths are close as well (1.3157 A° and 1.3462 A° respectively); also the N7 and N9 centered bond angles are quite close (107.83° and 105.91°). Intermolecular transfer rate of extra proton in imidazole has been reported in order of 0.3 $\times 10^{-12}$ second[31] but no such data is there for intramolecular N to N transfer of proton due to shift of N–C double bond in the imidazole; thus it's difficult to tell the process would be faster than the X-ray diffraction time (10^{-18} second). However, bond lengths are between C–N single bond (1.47 A°) and double bond (1.25 A°). As both nitrogen atoms are similar, and on basis of probability the Hydrogen atoms might have been added to both atoms during the computation. This extra proton is not being originated from imidazolinium salt as in such case the counter ion would have been in the unit cell; and also non equivalence of nitrogen atoms would be observed.

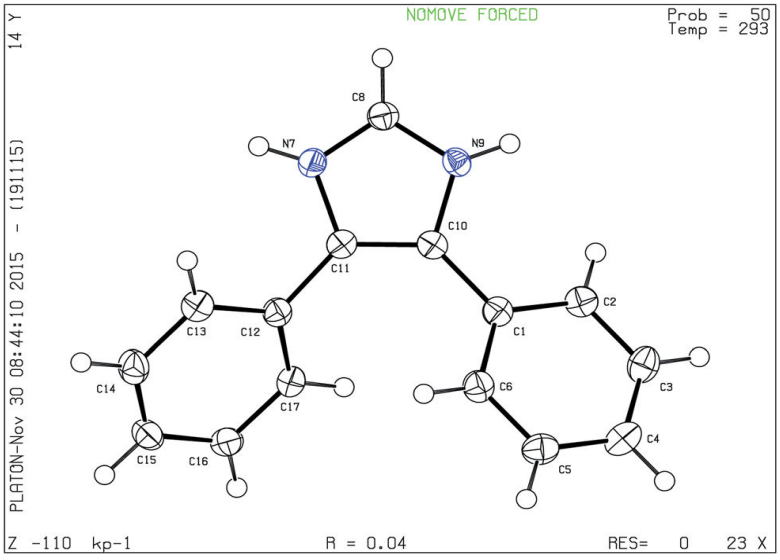
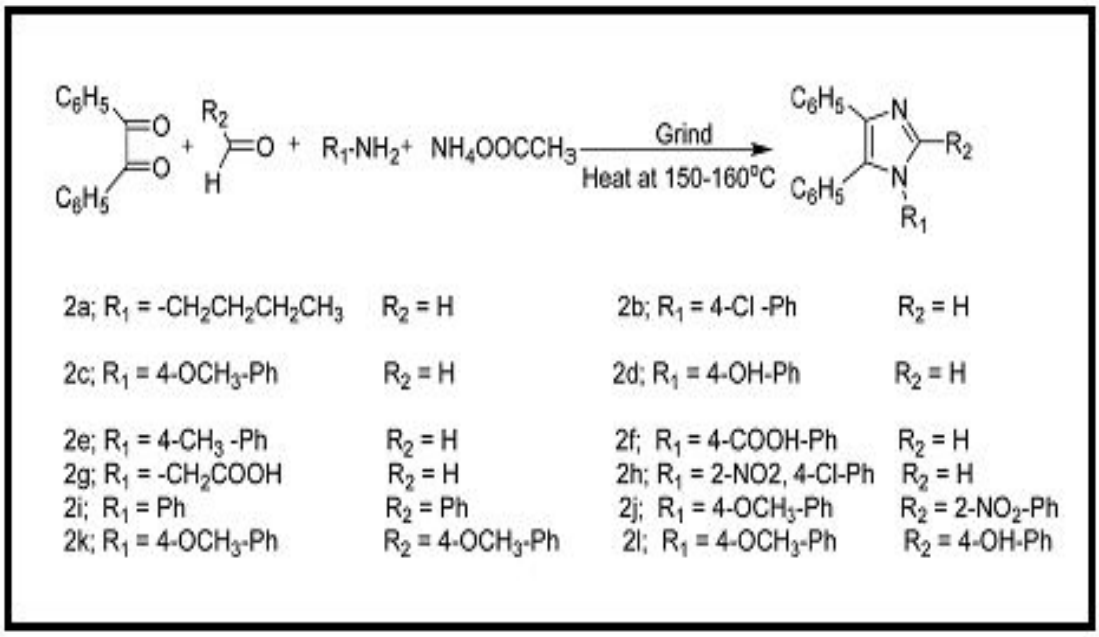


Figure II.A.16: ORTEP diagram of **9** derived from single crystal data

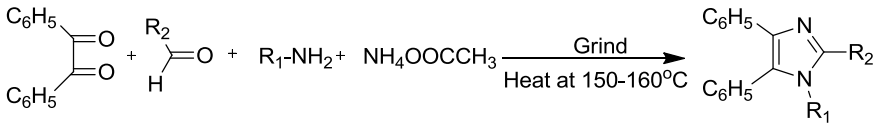
The reaction woukld be extended under same conditions to synthesize of 1, 2, 4, 5-tetrasubstituted imidazoles via a one-pot, four-component condensation of benzil (1mmol), a primary amine (1mmol), an aldehyde (1mmol), and ammonium acetate (5mmol) as is shown in **Scheme II.A.3**.

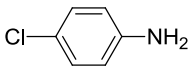
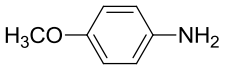
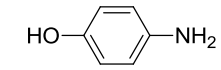
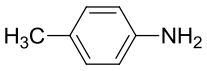
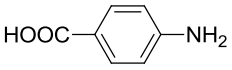
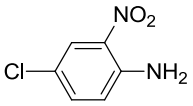
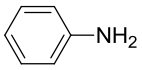
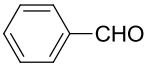
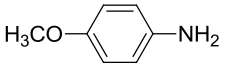
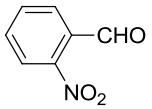
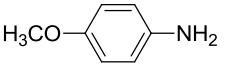
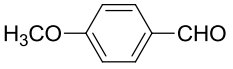
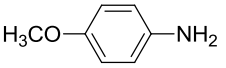
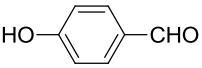


Scheme II.A.3: R-I synthesis of tetra-substituted imidazoles.

The tetra-substituted Imidazoles can be synthesized in the quantitative yields in very short time and also with minimal product purification procedures (**Table II.A.3**). It's also found that aromatic and aliphatic amines also along with aromatic and aliphatic aldehydes can be subjected to the following protocol successfully.

Table II.A.3: 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	$CH_3CH_2CH_2CH_2NH_2$		**[10]**	78-80	4 min
2			**[11]**	209-211	4 min
3			**[12]**	180-182	4 min
4			**[13]**	218-220	4 min
5			**[14]**	170-172	4 min
6			**[15]**	>270	4 min
7	NH_2CH_2COOH		**[16]**	173-175	4 min
8			**[17]**	206-208	4 min
9			**[18]**	78-80	4 min
10			**[19]**	209-211	4 min
11			**[20]**	180-182	4 min
12			**[21]**	218-220	4 min

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

II.A.G. Imidazole N-Oxides and 1-hydroxy Imidazole 3-oxide

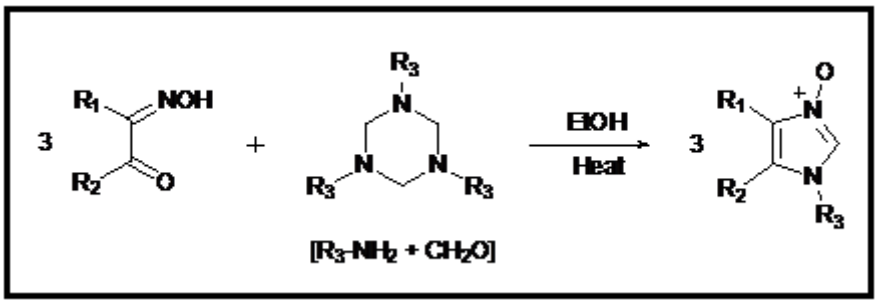
Substituted heterocycles having an imidazole backbone are frequently found to have some interesting biological activities. Imidazole N-oxides having oxide functionality at N-3 position and the 1-Hydroxy Imidazole-3-oxides with hydroxy function at N-1 and oxide functionality at N-3 positions are also no exceptions. These heterocycles with bioactivity with

an imidazole ring system, being a part of the large number of very significant biomolecules, have a lot of pharmacological properties along with playing significant some roles in the biochemical processes. Further, it's observed that there's a well-known *N*-oxide group effect leading to a significant change in the reactivity of heteroaromatic *N*-oxides, compared to their unoxidized analogues, thus activating them to nucleophilic, electrophilic and radical agents.[59] Presence of an N-oxide group, or an N- hydroxy group in the ring of imidazole is thought to alter the properties of diazole compound.

Imidazole N-oxides and the 1-hydroxy imidazole-3-oxides currently are of interest as they can be building blocks for chosen transformations of the diverse imidazole derivatives, including the enantiomerically pure compounds.[60]Also, they have been found to possess various biological activities.[61]Heterocyclic aromatic N-oxides, or dioxides in specific are antitumor agents exhibiting DNA-damaging properties.[62] Further, presence of supplementary hydroxyl substituent in the imidazole framework in 1-hydroxy imidazole N-oxides has been used frequently for preparing 1-hydroxy imidazoles by selective reduction,[63] as 1-hydroxyimidazoles [64] are useful intermediates to prepare pharmaceuticals and agricultural chemicals. Nowadays they are some of the most widely produced compounds in organic synthesis to serve as precursors for a class of various alternative media, [65] where *N*-bulky substituted imidazole 3-oxides act as attractive starting material to synthesize new and stable nucleophilic carbenes (NHC) through three step deoxygenation-quaternization-elimination process.[66] Apart from synthetic and pharmacological utilities, 1-hydroxyimidazole-3-*N*-oxides are found to be acting as effective inhibitors of aluminum corrosion.[67]

II.A.H. Synthesis of Imidazole N-Oxides and 1-hydroxy Imidazole 3-oxide

Normally, imidazole *N*-oxides can't be prepared through direct oxidation of parent compound. Still, preparation of 1-methylimidazole *N*-oxide by the treatment of 1-methyl-1*H*-imidazole in THF along with H_2O_2 at room temperature is described recently.[68] 2-unsubstituted imidazole *N*-oxides are conveniently synthesized by the condensation of the *α*-(hydroxyimino) ketones with *in situ* generated formimides,[69] of *α*-amino oximes with orthoformates,[70] and of diimines with formaldoxime.[71] However, the method of choice for their preparation is via the condensation of α-(hydroxyimino) ketones with aldehyde and a corresponding primary amine. The reaction can be carried out either by refluxing in alcohol or in presence of acetic acid (**Scheme II.A.4**). The amines are converted into formaldimines (monomeric forms) or hexahydro-1, 3, 5-triazine using either paraformaldehyde or formalin.



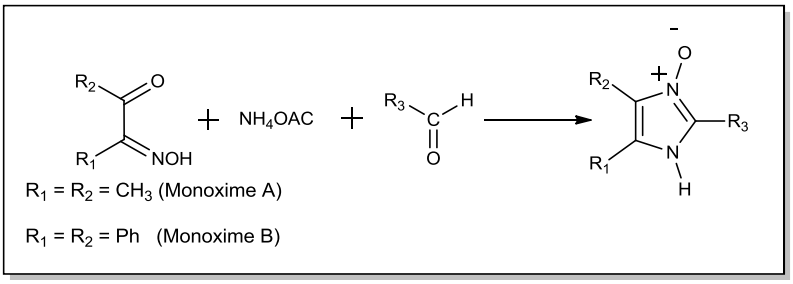
Scheme II.A.4: Conventional synthesis of Imidazole N-oxides

Just like above, 1-hydroxyimidazole-N-oxides could be prepared through condensation of either α-(hydroxyimino) ketones and aldehyde monoximes or through condensation of dioximes with aldehydes. Still, here also the method of choice for the preparation has been three-component cyclization of 1, 2-diketone, an aldehyde, and hydroxylamine.[63] Drawback of the begining two procedures was that they are very time consuming while given third procedure includes an elaborate process extending over 24 hours.

Keeping the view of the general uses of N-oxides and 1-hydroxy imidazole-3-oxides in the synthetic biology and organic chemistry, an one-pot, solvent-free path for synthesis of derivatives of imidazole would provide simple yet environmentally friendly alternative to the previous reported methods. In published papers that deal with preparation of Imidazole N-oxides and 1-hydroxy imidazole-3-oxides, the solvent free processes have not yet been explored and their mechanistic investigations have still not been dealt. While elaboration of simple yet efficient procedures of their synthesis is a real challenge, it becomes more interesting and also significant when scope of this study extends positively with even more newer findings. A simple and versatile process to synthesize Imidazole N-oxides and 1-hydroxyimidazole-3-oxides in a good yield has already been demonstrated in this section of work. This study investigates the processes of synthesis and characterization of these compounds (some of which were unpublished earlier) through a solvent-free method. There's been no report published on solvent-free method of synthesis of such heterocyclic compounds till date.

II.A.I. Solvent-free multicomponent synthesis of Imidazole N-oxides and 1-hydroxyimidazole-3-oxides

It is to be kept in mind that the traditional methods for the preparation of the Imidazole N-oxide using refluxing conditions for as long as 3-6 hours. It implied that the above method brings about a considerable reduction in the reaction time. A variety of Imidazole N-oxides were further synthesized under the highly optimized reaction conditions using a diverse range of aliphatic/aromatic aldehydes and ammonium acetate instead of amine component according to **Scheme II.A.5**.

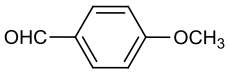
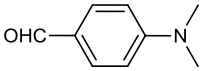
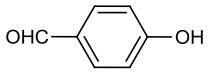
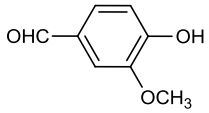
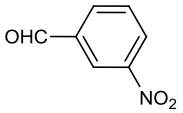
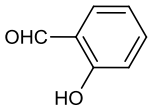
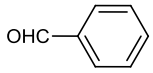
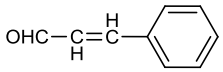
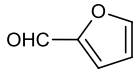
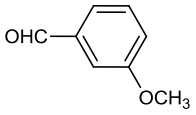
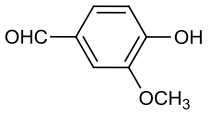
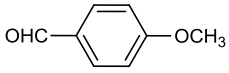
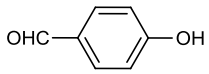
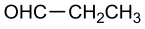


Scheme II.A.5: One-pot solvent free method for synthesis of Imidazole N-oxides

In a reaction 1 mili mole of each of the monoxime and the aldehyde was finely grinded with 5 mili mole of ammonium acetate and the thorough mixture was heated to 115-120^{o}C for about 10 minutes. It was then cooled until a black sticky precipitate resulted. To the black precipitate was then added a very small volume of diethyl ether until a brown precipitate got separated. The precipitate was evenly washed with ethyl acetate to produce the pure products. The black precipitates got dissolved in ethanol and then water was added gradually a hazy solution was formed. The milkiness disappeared on heating. Creamy colored precipitates were obtained after cooling.

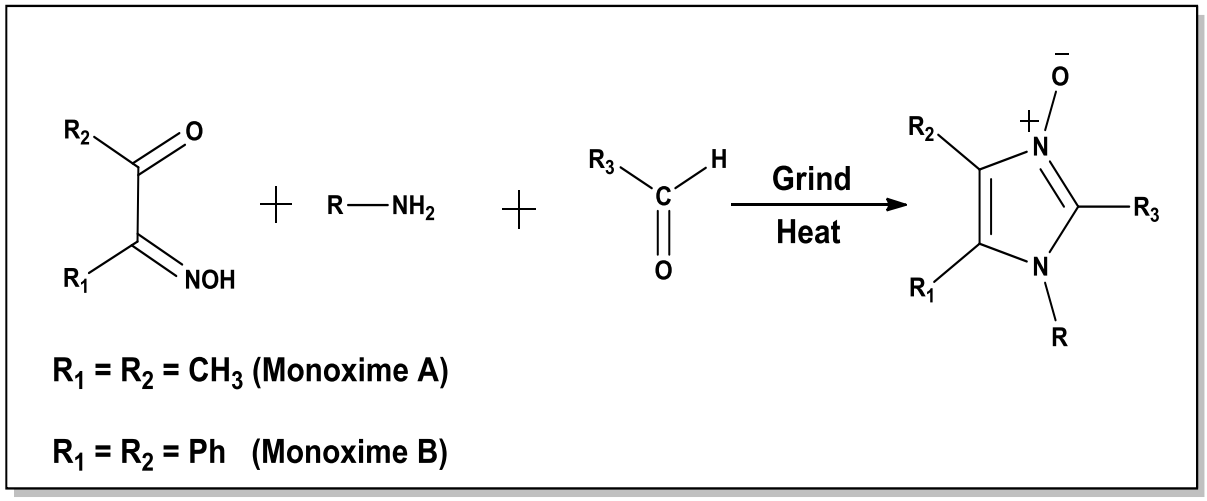
A wide variety of Imidazole N-oxides can actually be prepared by employing a diverse range of aliphatic and aromatic aldehydes. Various monoximes can also be taken, the methods worked well with all kinds of substitution on monoxime. The reaction was found to proceed smoothly to give quantitative yields of the products and the results are briefly summarized in **Table II.A.4**.

Table II.A.4: Synthesis of Imidazole N-oxides under catalyst-free and solvent-free conditions

Entry	Monoxime	Aldehyde	Product	Melting Point (^{o}C)
1	A		**[22]**	138-140
2	A		**[23]**	233-235
3	A		**[24]**	>260-270
4	A		**[25]**	258-259
5	A		**[26]**	172-174
6	A		**[27]**	233-235
7	A		**[28]**	125-127
8	A		**[29]**	116-118
9	A		**[30]**	95-97
10	A		**[31]**	118-120
11	B		**[32]**	197-199
12	B		**[33]**	95-96
13	B		**[34]**	230-232
14	B		**[35]**	72-74
15	B		**[36]**	88-90

Initial one-pot reaction of α-(hydroxyimino) ketones using a wide range of aromatic/ aliphatic aldehydes and aliphatic/aromatic amines were also carried out. The products, N-

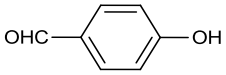
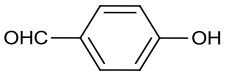
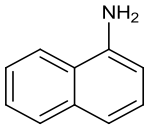
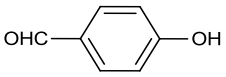
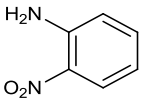
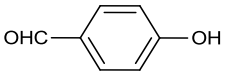
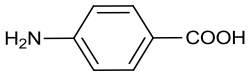
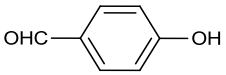
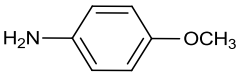
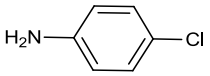
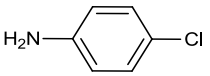
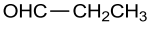
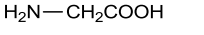
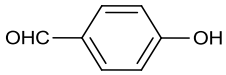
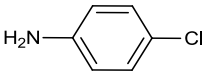
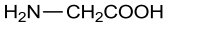
substituted imidazole N-oxides were actually formed in quantitative yields at an optimized temperature of 115-120^{o}C within 10 minutes. The yield of the product was actually not affected by the structure of amine. An overview of the synthetic details has been summarized in **Scheme II.A.6**.



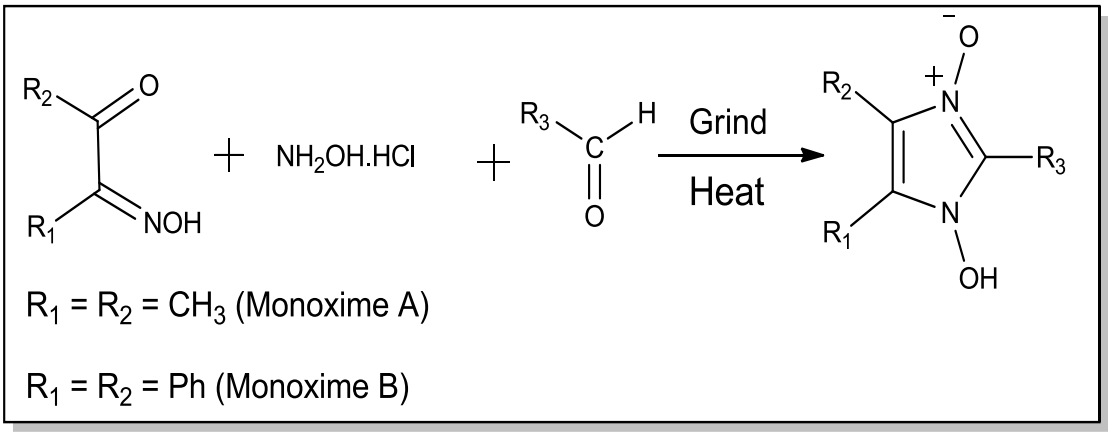
Scheme II.A.6: One-pot solvent free method for synthesis of N-substituted Imidazole N-oxides

In a typical reaction, 1 mili mole each of monoxime and the aldehyde was mixed with 1.5 mmole of the amine and was heated. The completion of the reaction was indicated through TLC. The product formed was thoroughly washed with a very little amount of ether and further by heated ethyl acetate. A little excess of the amine was actually used as a stoichiometric amount resulted in only 75% yield and the reactant spots were clearly visible in the TLC only after 10 minutes of the reaction. When 1.5 mili mole of amine was used, within 10 minutes, a single spot of the product was observed and the reactant spots actually disappeared. With this approach ten imidazole N-oxides were actually prepared in high quantitative yields and were characterized by IR, ^{1}H NMR, ^{13}C NMR and Mass spectra.

Table II.A.5: Synthesis of N-substituted Imidazole N-oxides under catalyst-free and solvent-free conditions

Entry	Monoxime	Aldehyde	Primary amine	Product	Melting Point
1	A		$CH_3CH_2CH_2CH_2NH_2$	**[37]**	128-130
2	A			**[38]**	232-235
3	A			**[39]**	272-273
4	A			**[40]**	210-213
5	A			**[41]**	205-207
6	A			**[42]**	238-240
7	B			**[43]**	170-172
8	B			**[44]**	>260
9	B			**[45]**	182-184
10	B			**[46]**	248-250

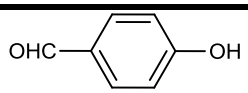
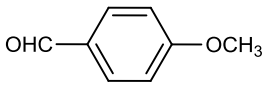
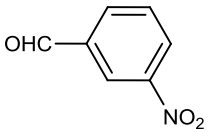
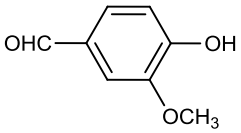
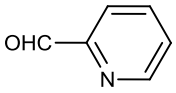
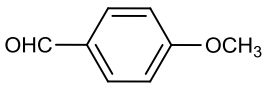
When the same approach was extended to the synthesis of 1-hydroxy Imidazole-3-oxides, it was actually found to be even more successful as it highly reduces the reaction time from 24 hours (traditional method) to 10 minutes. Usually in the optimized solvent-free preparation of 1-hydroxyimidazole-N-oxides, usual grinding of equi-molar amounts of monoxime and the aldehyde and an excess amount of hydroxylamine hydrochloride using a mortar pestle over a period of ca. 3 min was done. Subsequent heating for another 7 mins at about 110-120^{o}C (**Scheme II.A.7**) gave the products in near quantitative yield. The products mainly remained as eutectic melt on cooling and then immediately precipitate out on adding a liitle amount of ether. It was further washed with water and ethyl acetate.



Scheme II.A.7: One-pot solvent free method for synthesis of 1-hydroxyImidazole-3-oxides

A appreciable observation that deserves actual mentioning is that including only the mechanochemical process of grinding the representative reaction including benzil monoxime, anisaldehyde and an excess amount of hydroxylamine hydrochloride at room temperature took about 8 days to yield the products which precipitated from water and could be re-crystallized to get very pure crystals. The solvent-free method produced the product in just 10 minutes. Analysis of the product by ^{1}H and ^{13}C NMR has shown only the pure products. The 1-hydroxy 2,4,5-trisubstituted imidazole-3-oxides were prepared at an optimized temperature in excellent yields without requiring any extensive workup or purification and that too in a very short period of time (**Table II.A.6**). Apart from the lower reaction times (energy saving), the other advantage of using this solvent-free approach is that the product obtained is of high purity. Single crystals of the product could also be obtained for characterization purposes.

Table II.A.6: Synthesis of 1-hydroxyImidazole-3-oxides under catalyst-free and solvent-free conditions

Entry	Monoxime	Aldehyde	Product	Melting Point
1	A		**[47]**	165-168
2	A		**[48]**	196-198
3	A		**[49]**	209-211
4	A		**[50]**	201-203
5	A		**[51]**	hygroscopic
6	A		**[52]**	136-137
7	B		**[53]**	233-235

This is the initial report of the solvent-free condensed phase protocol for the oxide and hydroxyl oxide derivatives of the imidazoles. The advantages of the above mentioned method are many:

- The synthetic strategy is highly facile, leading to the higher yields and is susceptible to up-scaling.
- It is operationally simple, efficient and a very green route to synthesize biologically important imidazole N-oxides and 1-hydroxyimidazole-3-oxides.
- The high yields and low waste generation of this procedure gives it highly attractive green chemistry metrics, not to mention its remarkable versatility.
- The approach actually avoids the use of those organic solvents and the extensive work-up and thus makes it highly attractive and practical for the library synthesis of such compounds.

The useful synthesis of the N-substituted imidazole N-oxides and 1-hydroxyimidazole-3-oxides within the 10 minutes of reaction was actually also based on the same synthetic procedure as with the Imidazoles. The synthesis also proves that acetic acid, generated in the reaction, is not the only catalyzing factor for increasing the reaction rates under the solvent-free conditions. The synthesis of N-substituted Imidazole N-oxide requires the use of an amine compound instead of ammonium acetate while hydroxylamine hydrochloride is actually used during the preparation of the 1-hydroxyImidazole-3-oxide.

II.A.J. Evidences for Carbonyl activation in Solvent-free reactions

We have seen in the preceding sections that solvent-free procedures involving the carbonyl moiety in the substrate undergo mechano-chemical activation very easily. The reaction tends to proceed even faster than in solvents. Therefore, it becomes imperative on our part to investigate, in order to understand, at least partially, why these reactions proceed so efficiently under solvent-free conditions. To this purpose, a combination of methods viz., reactivity, spectroscopy and computational studies have been used.

II.A.J.1. Infrared studies

In order to contemplate the cause behind the efficacy in solvent-free procedure, the IR-spectra of pure benzil in thin film as well as that with catalyst was studied. A thin solid film of benzil was prepared and its IR spectra taken. Subsequently, a thin film of a mixture of benzil with the catalyst ytterbium triflate was also taken. The carbonyl region of the benzil thin film and that with 5 mmol% of ytterbium triflate has been presented in **Figure II.A.17**.

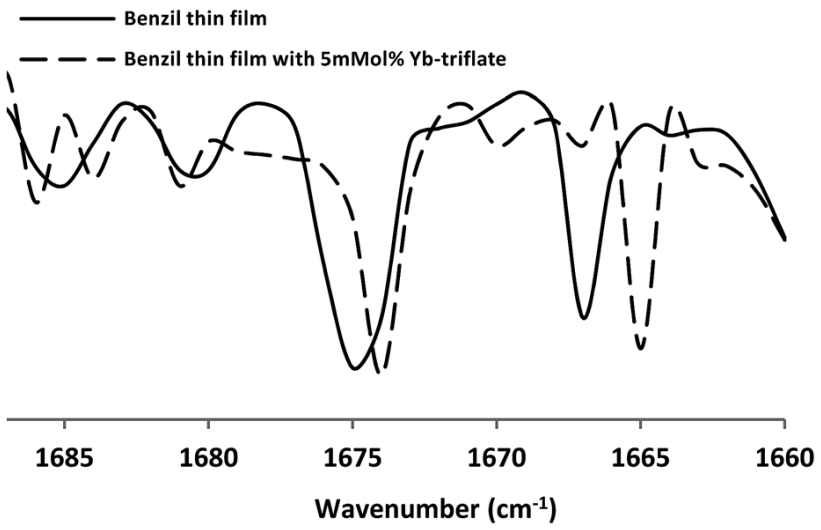


Figure II.A.17: IR spectra of benzil thin film, with and without a catalyst.

It can be seen that the free carbonyl band (with catalyst) at 1676 cm^{-1} has apparently increased in intensity with simultaneous shifting to lower frequency compared to the corresponding band for benzil. It was earlier reported[72] that the C=O stretching band of benzil appears at 1676 cm^{-1} in the crystalline state and at 1685 cm^{-1} in solution. The red-shift and the enhancement in intensity of the peak have obviously been brought about by the presence of the catalyst. Hence we could consider this phenomenon as a marker of catalytic effect. Alike shift of carbonyl stretching frequency in TiO_2 surface for benzophenone has already been reported.[73] The difference in stretching frequency (9 cm^{-1}; red-shift) indicates a greater degree of single bond character in the C=O bond (polarisation enhancement) in the solid state compared to that in the solution state for benzil. The shifting of carbonyl stretching manifested as a sharp peak provides an indication of bulk polarization of benzil in the solid state. Since a similar effect is also observed with catalysts in the solid state, it is highly indicative of polarizations occurring in bulk, rather than being partial.

To substantiate, the study was extended further to be carried out in solution. The extent of the shift caused by the presence of trace amounts of ytterbium triflate and zirconyl nitrate on benzil carbonyl stretching frequency in hexane solution was also studied. The IR spectra in the carbonyl range have been presented in **Figure II.A.18**. As is apparent from the figure, in the presence of a catalyst the free carbonyl peak of benzil at 1685 cm^{-1} and all other associated peaks are shifted to lower frequencies. In addition to this, the intensity of the free carbonyl peaks (particularly the peak at 1680 cm^{-1}) is seen to be diminished while the intensities of some other peaks are found to increase at lower frequencies in the presence of traces of catalyst.

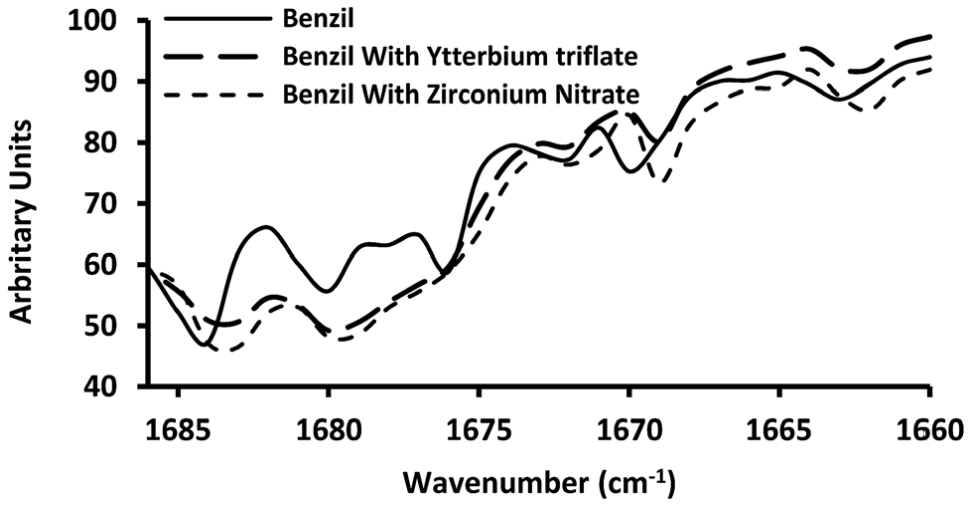


Figure II.A.18: Solution IR spectra in the carbonyl range of benzil in hexane.

Apparently the catalyst, zirconyl nitrate, is found to polarize benzil to a greater extent than ytterbium triflate. A quick perusal of Table 1 also points to the fact that the catalytic effect of zirconyl nitrate is a better for benzil consumption rate as well. It is observed that in both the solution as well as in the solid state there is a noticeable enhancement of the band at 1680 cm^{-1} in the presence of catalyst. The peak at 1680 cm^{-1} has been described as another C=O stretching band associated with a different symmetry of the molecule.[74] Enhancement of the band near 1680 cm^{-1} in presence of catalyst suggests that the catalysts not only polarize the carbonyl but also influence the conformation of benzil. The IR spectroscopic investigation thus strongly provides evidences for bulk polarization of the C=O moiety in the condensed phase. This in turn may lead to a marginal increase of the electrophilicity of the carbonyl carbon. The above observation suggests that catalysts bind to the carbonyl oxygen and the weak interaction activates the carbonyl group with the enhancement of polarization.

II.A.J.2. Computational studies

Since the IR spectroscopic results hinted at bulk polarization of the substrate molecules, it was thought that quantum mechanical calculations carried out on simple molecules bearing the same functionality i.e., the C=O group could provide more insight to the study. Therefore, CBS-QB3 model chemistry calculations of a HCHO monomer and trimer were performed. We carried out a geometry optimization for a linear arrangement of the trimer (**Figure II.A.19**).

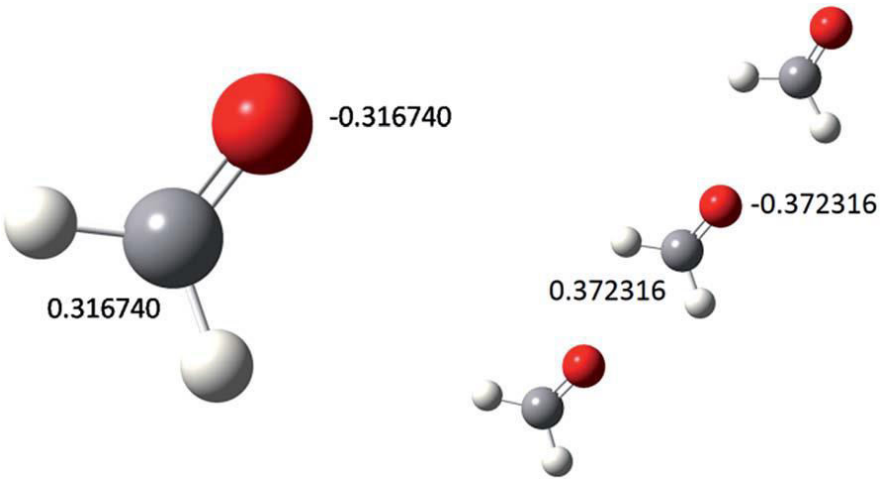


Figure II.A.19: Minimum energy models with partial charges.

It is expected that a number of minimum energy conformations with different geometries could be feasible when molecules remain in association. To serve our purpose, we searched for minimum energy that would result when the molecules are arranged linearly. The calculations terminated on convergence to such minima. A quick comparison of the partial charges on the carbon and oxygen atoms of the monomer and trimer showed that it was enhanced in the case of the trimer where the molecules were associated. It was found that the dipole moment of the associated monomer was also enhanced in the trimer as compared to the monomer (**Table II.A.7**).

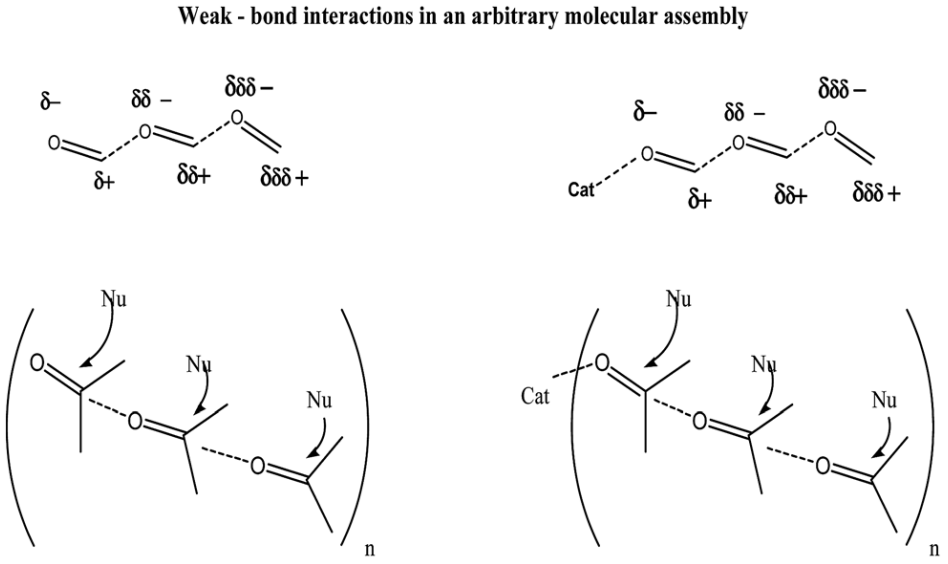
Table II.A.7: Mulliken atomic charges, dipole moment and C–O bond distances in monomers and trimer from the CBS-QB3 model

Parameter	Monomer	Trimer
Mulliken charge at C (au)[a]	0.316740	0.372316
Mulliken charge at O (au)[a]	-0.316740	-0.372316
Dipole moment (Debye)	2.8542	3.2133[b]
C–O bond distance (°A)	1.20001	1.20259
Symmetry	C_{2v}	C_1

Note: [a] atomic charges with hydrogens summed into heavy atoms; [b]average value.

As is evident from the results, there is a sizeable increase in the atomic charges in the associated monomers than those in the isolated free monomer. It implies that on association there is sizeable charge reorganization in such molecular assemblies. These may be interpreted as atomic expressions of sizeable cooperative effects. As a consequence, the charge reorganization brings about enhanced polarization in the carbonyl groups in such environment due to the increase of partial charges in each atom. The possibility of a dipole–dipole type of intermolecular interaction and the absence of H-bond (or a small possibility) in formaldehyde itself has also been previously reported.[75] It indirectly convinced us that the electrophilic behavior of the carbonyl group was enhanced under solvent-free condition. It is the result of the cooperative effect of very weak forces that bulk of carbonyl groups gets

activated. Therefore, the activation of the C=O group can be attributed to a unique spatial organization of the carbonyl moieties. We, thus propose that in reactions occurring under solvent-free conditions, an arbitrary molecular assembly comes into play, where polarization transfer through a non-covalent bond (weak bond interactions) as shown in **Scheme II.A.8**.



Scheme II.A.8: Polarization transfer through a non-covalent bond without and with a catalyst.

In this proposed supramolecular assembly a pseudo-conjugated pi-system makes the system more chemically soft (more polarizable). Thus, with respect to a free carbonyl, we observe better reactivity in solvent free reaction media. It can also be envisaged that in such an assembly, a set of reacting molecules participates in a cycle making the process faster. This self-activating effect will continue to work even if some oxyphilic substance were present in catalytic amounts. When the catalyst is bonded to the terminal carbonyl oxygen it further activates the trail of carbonyls and thereby brings about a further enhancement in the catalytic effect (**Scheme II.A.8**).

The study focuses on unearthing the challenge of using weak forces as a design tool for studying new properties and performance in molecules and materials. The present work has utilised the concept of constitutional dynamic chemistry (CDC) as propagated by Prof. Lehn. With the help of CDC we are hopeful of resolving the existing paradox in the process of catalysis (involving carbonyl activation). CDC hints at supramolecular entities being

assembled entities of discrete number of molecular sub-units held together reversibly through weak interactions (non-covalent interactions).[76] If we extend the concept to the carbonyl system, we could think of the carbonyl molecular sub-units to be held together through similar type of weak interactions, since they are inherently polar. This is true for all the catalytic effects on carbonyls in solution state as well as in solvent-free molten state. The un-catalyzed Radziwenski synthesis of imidazole and the syntheses of Imidazole oxides and hydroxy imidazole-N-oxides under solvent-free conditions as described in the previous sections could be taken as evidences. In all the above syntheses, it was found that the reaction took less time than when they were carried out in solvents. The reason being, that in polar solvents, since there are stronger solute-solvent interactions the weak but favorable conformation of the carbonyl cluster breaks. Thus solvents may be adversely affecting the self-catalytic effect which is pronounced under solvent-free conditions.

The higher reaction rates of such reactions may be possible due to ***self-activation*** of the carbonyl group in the appropriate condensed phase. A proper understanding of the genesis of the catalytic effect in such condensed-phase reactions thus becomes highly significant. In order to understand, why these reactions proceed so efficiently under solvent-free conditions, a combination of the methods viz., reactivity, spectroscopy and theories have been used.

II.A.K. Conclusion

The polarizability of organized carbonyl functionalities in condensed phase contributes for the observed self-catalysis. High yields of many different imidazoles were obtained from the simply mechanical grinding and heating of MCR starting materials, even in the absence of Lewis acid catalysts. The very weak dipole of carbonyls can induce polarization in bulk because the carbonyl bonds are very much polarisable and the net result is the enhancement of electrophilicity of carbonyls. 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. This phenomenon can be well utilized to generate a self-catalytic effect without using any catalytic substance.

II.B.L. References

References are given in BIBLIOGRAPHY under Chapter II, Section A (pp 268-272).