

**Green Synthetic Methodologies Using Innocuous
Reagents &
Removal of Nitrobenzene Using Cloud Point Extraction**

*A Dissertation Submitted to the
Indian Institute of Technology Guwahati
As Partial Fulfillment for the Degree of
Doctor of Philosophy*



Submitted by

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Guwahati-781 039

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Abstract

The contents of this thesis have been divided into two chapters based on the results of experimental works performed during the complete course of the research period. The first chapter of the thesis again has been divided into two parts, Part I and Part II. Part I presents overall introduction of the thesis. Part II describes various green synthetic methodologies using innocuous reagents. Part II has been further divided into four subsections. Section I describe the boric acid catalyzed bromination of a variety of organic substrates. Section II describes the syntheses of β -amino carbonyl and nitrile compounds using phosphate impregnated titania heterogeneous catalyst. Section III and Section IV illustrate syntheses of alkyl and aryl isothiocyanates and cyanamides via iodine mediated decomposition of alkyl and aryl dithiocarbamic salts. Chapters II describe the surfactant mediated cloud point extraction of nitro benzene from water. Each subsection of chapter I constitutes four sections, describing introduction, results and discussion, experimental work and spectral data respectively. Chapter II constitutes introduction, experimental work and results and discussion respectively

CHAPTER I

Part I

Introduction to Green Synthetic Methodologies & Cloud Point Extraction

This part of chapter I presents overall introduction of the thesis. Part I presents a brief account of the importance of Green chemistry, green synthetic methodologies and prior arts of reactions in water, ethanol, biphasic and solvent free media. Importance of development of environmentally benign catalyst or reagent mediated synthetic methodologies in the field organic syntheses are reviewed. It also emphasizes the need for development of safer, cost effective and environmentally benign processes for various industrially important reactions. This chapter highlights the literature background for the synthesis of brominated aromatic compounds, β -amino carbonyl or nitrile compounds and alkyl or arylisothiocyanates and cyanamdes. Also different iodine mediated reactions are described. Finally, the importance of cloud point extraction in removing nitrobenzene from water by a surfactant Tx100 is described in this chapter.

Part II

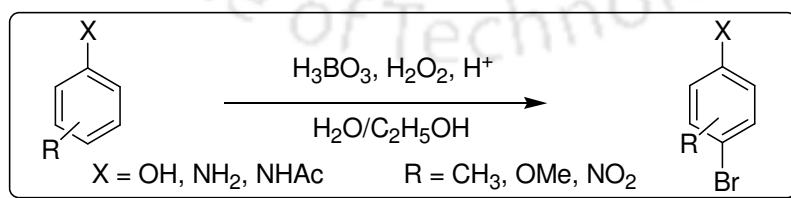
Section I: Boric Acid Catalyzed Bromination of Organic Substrates

This section of chapter I mainly focuses on the oxidative bromination of aromatic compounds involving boric acid as the catalyst, KBr as the source of bromide, and hydrogen peroxide as the oxidant.

Owing to their increasing commercial use brominated aromatic compounds are very important in synthetic organic chemistry. They are key intermediates in the preparation of many organometallic reagents and play vital roles in transition metal mediated coupling reactions such as Stille, Suzuki, Heck, and Sonogashira reactions. Many pesticides, insecticides, herbicides, pharmaceutically, and medicinally active molecules, and fire retardants carry bromo functionality.

The need for isomerically pure bromoaromatic compounds has led to develop selective brominating agents or bromination protocols. Most of the processes currently operating for the bromination of aryl compounds employ toxic corrosive and expensive molecular bromine. Oxybromination using HBr or bromide salt as bromine source and either H_2O_2 or O_2 as an oxidant was thought to be a possible solution to overcome these difficulties met with partial success, since HBr is highly toxic and corrosive and the systems reported for oxybromination so far require metal or other catalysts (vanadium, copper, zeolites) and volatile organic solvents.

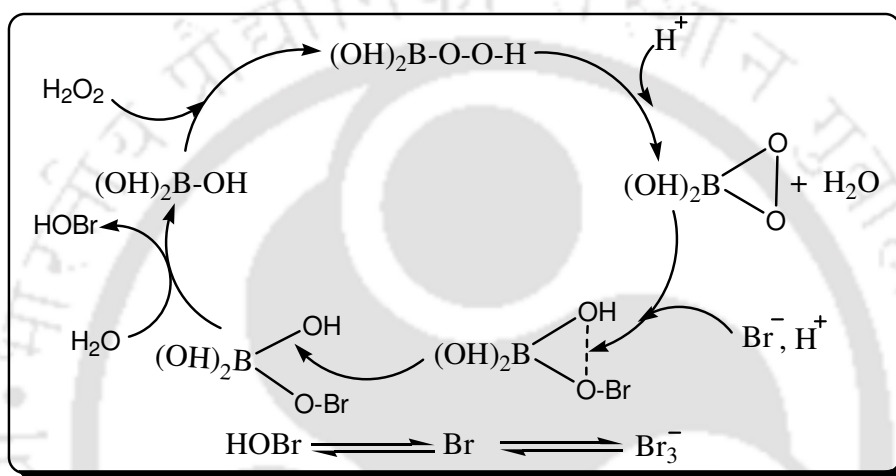
We have been looking for a softer approach to the oxybromination of aromatics, ketone and alkenes in a cleaner solvent without involving a metal catalyst. In continuation of this, we herein report an easy to operate, practical and environmentally benign protocol for the regioselective bromination of aromatic compounds involving boric acid as the catalyst, KBr as the source of bromide, and hydrogen peroxide as the oxidant. The solvent used is either water or ethanol both of which are environmentally friendly (*Scheme I*).



Scheme 1. Bromination of substrates using H_3BO_3 and H_2O_2

The catalyst boric acid is easily available, inexpensive, ecologically favourable, safe to handle, and is effective under milder conditions. It can be removed, after reaction, by an aqueous bicarbonate wash.

The present protocol is based on the (i) role of the catalyst as a Lewis acid in the activation of H_2O_2 forming peroxoborate species followed by (ii) the oxidation of bromide by peroxoborate intermediate in the presence of acid to Br_3^- as the active brominating agent and finally (iii) site-selective bromination of organic substrates to afford bromoorganic compounds (*Scheme 2*).



Scheme 2. Mechanism of Bromination of Organic Substrates Using H_3BO_3 and H_2O_2

This method was successfully applied to a wide range of phenols and anilines. Deactivated 2-fluoro aniline was smoothly brominated to the corresponding *p*-bromoaniline. Poly-cyclic phenol, β -naphthol selectively afforded 1-bromo β -naphthol in very high yield. The methodology also works well for bromination of ethylenic and carbonyl functions. 4-Methoxy-4'-methoxy-2'-hydroxychalcone was selectively brominated in the double bond in presence of an activated aromatic ring. bisphenol-A was brominated to tetrabromobisphenol-A (4,4'-isopropylidene-bis-(2,6-dibromophenol)). Finally, upon completion of the reaction, the catalyst recyclability was examined through a series of reactions and found that the reaction continued giving good yields with every cycle, however, with relatively long cycles due to leaching of the catalyst the activity goes down.

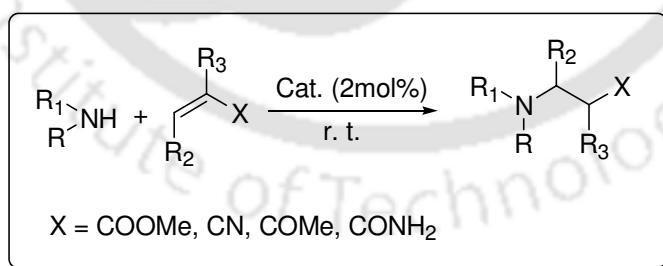
In conclusion, the present results demonstrate the production of bromoorganic compounds with very high selectivity under mild and metal free catalytic conditions. No use of Br₂ and volatile organic solvents in the synthesis, the involvement of cost effective, readily available and non-toxic catalyst, and water or ethanol as the reaction medium renders this protocol as green, attractive, and practically useful.

Section II: Phosphate Impregnated Titania: an Efficient Reusable Heterogeneous Catalyst for *aza*-Michael Reactions Under Solvent-free Condition

This section mainly focuses on the synthesis of β-amino carbonyl or nitrile compounds using phosphate impregnated titania.

The conjugate addition of a nitrogen nucleophile to an electron rich or electron deficient electrophile, known as the *aza*-Michael reaction to form a C-N bond, constitutes a key reaction in biosynthesis as well as in organic synthesis. β-Aminocarbonyl compound and their derivatives which are the adducts of the *aza*-Michael reaction, have been used as building blocks for many nitrogen-containing biologically important compounds such as β-aminoalcohols, 1,2-diamines, and β-lactams.

In continuation of our ongoing research, we reveal herein a new, mild and efficient protocol for *aza*-Michael reactions of amines with α,β-unsaturated carbonyl and nitrile compounds using acid phosphate impregnated titania [Ti₄H₁₁(PO₄)₉].nH₂O (n=1-4) as a heterogeneous catalyst at room temperature under a solvent-free condition (*Scheme 3*).



Scheme 3. *aza*-Michael Reactions Catalyzed by Phosphate Impregnated Titania

It was perceived that inherent acidity of the catalyst would facilitate the conjugate addition reactions. The catalyst containing 84.5% of TiO₂ and 15.5% of [Ti₄H₁₁(PO₄)₉].nH₂O (n = 1–4) is a phosphate-based solid acid catalyst which is easy to prepare, stable, easily separable from the reaction mixture and recyclable. Phosphate seems to enhance catalytic properties, to stabilize surface area and crystal phase, to improve the surface acidity and to make the impregnated material porous.

A variety of α,β -unsaturated compounds such as methyl acrylate, acrylonitrile, methyl vinyl ketone, acrylamide and methyl methacrylate underwent facile 1,4-addition with a wide range of aliphatic amines in the presence of phosphate impregnated titania (2 mol%) catalyst at room temperature to give the corresponding β -amino compounds in good to very good yields. Reactions of imidazole and pyrazole with methyl acrylate and acrylonitrile proceeded smoothly when the reaction temperature was elevated to 50 °C, and good yields of products were obtained. Aromatic amines are found to be unreactive under this condition.

Recovered catalyst was recharged by heating on a sand bath at 200–220 °C. Catalyst recyclability was examined by reusing it in the reaction of morpholine with methyl acrylate for three reaction cycles. For every cycle the catalyst was reactivated. It is found that the catalyst works efficiently upto third cycle without any remarkable loss of activity. After third cycle the activity of the catalyst decreases due to leaching of the catalyst.

In conclusion, we have developed an efficient method for the preparation of β -amino carbonyl and nitrile compounds with high yields by applying *aza*-Michael reactions under mild heterogeneous conditions. Easy experimental procedure, low catalyst loading, efficacy, redundancy of workup, use of ethanol in washing and recyclability of the catalyst along with solvent-free reaction condition render this protocol green, attractive and practically useful.

Section III: Molecular Iodine Mediated Preparation of Isothiocyanates from Dithiocarbamic Acid Salts

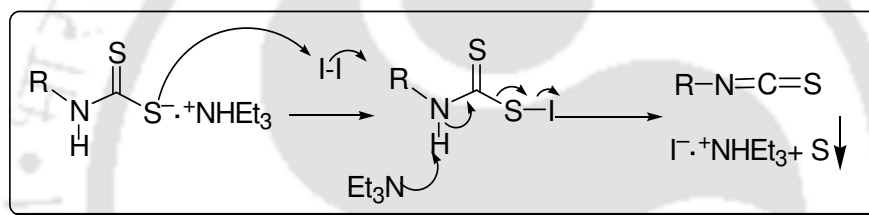
This section mainly focuses on the iodine mediated preparation of alkyl and arylisothiocyanates from dithiocarbamic acid salts.

Alkyl and arylisothiocyanates are versatile synthetic intermediates which are frequently encountered in many natural products and have been used as important precursors for heterocycles

such as thiohydantoin, thiopyrimidones, thioquinazolones, mercaptoimidazoles, thioamidazolones, pyridinethiones, pyrrolidine and benzothiazine. In continuation of our efforts and interest in developing methods for the synthesis of isothiocyanates, led us to consider iodine mediated decomposition approach using dithiocarbamic acid salts derived corresponding amines. For convenience, this work has been divided into two parts *viz.*, **Part A** and **Part B**.

Part A

This part contains the details of the development a general, economical and environmentally benign method for the preparation of isothiocyanate from the corresponding dithiocarbamic acid salt by using cheap and readily available reagent molecular iodine in the presence of triethylamine in acetonitrile solvent at room temperature (*Scheme 4*).



Scheme 4. Mechanism of Formation of Isothiocyanate from Dithiocarbamate

Molecular iodine is thiophilic in nature; we reasoned that it might be effective for the decomposition of dithiocarbamate to their corresponding isothiocyanate. The reagent iodine is low cost, non-toxic and readily available. Considering this, it was thought that iodine would be effective in desulfurizing dithiocarbamate to their corresponding isothiocyanate in the presence of a base.

In these reactions, the most crucial aspect is the preparation of dithiocarbamic acid salt, and once the dithiocarbamate salts are obtained, iodine proved to be an effective reagent for their decomposition to the desired isothiocyanates in excellent yields. Employing this Green synthetic protocol, several aromatic isothiocyanates were successfully prepared in high yields. Aromatic substrates containing a chlorine atom in their ortho, meta and para positions gave isothiocyanates in excellent yields (94-97%) when iodine was used as the desulfurizing agent. This strategy was successful even when electron withdrawing substituent such as $-NO_2$ group was attached to the

aromatic ring. Through this strategy we were able to obtain excellent yields of arylisothiocyanates from substrates, having various substituents in the aromatic ring.

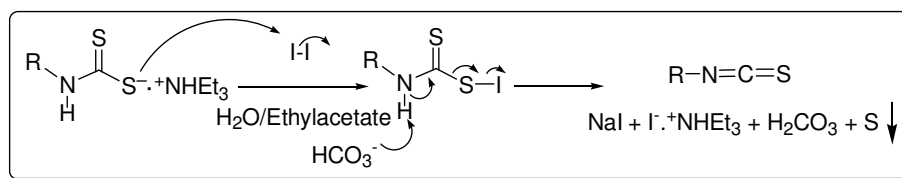
On the basis of the observation and mechanism proposed in (Scheme 4), we have sufficient reason to believe that amines having lower pK_a should yield the isothiocyanate better because of facile NH deprotonation. Triethylamine, is sufficiently basic (pK_a 10.78) in comparison to aromatic amines (pK_a in the range 2.46 to 5.63) and the acidity of the dithiocarbamate bound NH proton is expected to increase further upon salt formation. Other dithiocarbamate salt such as naphthyl compound gave its isothiocyanate in good yield. The decrease in the pK_a of NH proton upon formation of dithiocarbamate salt is further evident from the excellent formation of isothiocyanates from alkyl amines such as *n*-butyl (pK_a 10.77), cyclohexyl (pK_a 10.66) and benzylamine (pK_a 9.33), all of which have a similar basicity to that of triethylamine (pK_a 10.78). Sensitive amine such as furfuryl amine gave isothiocyanate in moderate yield.

In conclusion, we have developed a general, economical, and environmentally benign method for the preparation of isothiocyanates from the corresponding dithiocarbamic acid salts. In comparison to the existing methods of the decomposition of the dithiocarbamic acid salts, our procedure is perhaps the simplest yet most efficient method for the synthesis of isothiocyanates. The reagent is cheap and nontoxic. Although literature enumerates a number of procedures for the preparation of isothiocyanates, the simplicity, environmental acceptability, and cost effectiveness of our procedure makes it a practical alternative.

Part B

The above protocol, described in **Part A** has some drawbacks from a Green chemistry concept due to the use of toxic base (Et_3N) and expensive and toxic solvent acetonitrile. We were keen to further modify the iodine mediated preparation of isothiocyanate, keeping in view the environmental aspect, which would proceed efficiently without the use of any toxic chemicals and would not generate any toxic byproducts. Thus, a safe, water soluble inorganic base sodium bicarbonate and a cheap and biphasic water and ethyl acetate solvent system would serve the purpose. This part describes a modified, environmentally benign and cost effective method for the synthesis of

isothiocyanates *via* a iodine mediated decomposition of dithiocarbamate salt in the presence of sodium bicarbonate in water/ethyl acetate biphasic solvent system at room temperature (*Scheme 5*).



Scheme 5. Mechanism of Formation Isothiocyanates from Dithiocarbamates

The dithiocarbamic acid salt is readily converted into the corresponding isothiocyanate simply by treating it with iodine in presence of sodium bicarbonate in water/ethyl acetate biphasic medium in good to excellent yields in shorter time (15 minutes). The uses of water/ethyl acetate biphasic solvent system have several potential advantages. In addition to the benign character of both water and ethyl acetate, the coexistence of water with ethyl acetate helps in extracting the isothiocyanate to the organic layer leaving behind the impurities in the aqueous layer which in turn facilitates an easy workup. Iodine is soluble in ethyl acetate and on stirring, dissolves and gets delivered at the water-ethyl acetate interphase for desulfurization. Moreover, the water phase dissolves the base sodium bicarbonate and retains the dithiocarbamic acid salt in the aqueous layer. The use of sodium bicarbonate over organic bases offers a mild and effective Green approach towards the synthesis of isothiocyanates. Thus the method provides an ecologically and economically viable process for the preparation of isothiocyanates.

Various dithiocarbamic acid salts of arylamines with electron withdrawing groups in both ortho and para positions afforded excellent yields. 2-Iodo-4-methyl phenyl dithiocarbamate yields the corresponding isothiocyanate. Aromatic ring containing two fluoro groups in ortho and para positions gave isothiocyanate in excellent yield. Isothiocyanates were obtained in very high yields from their corresponding dithiocarbamate salts containing electron withdrawing substituents in meta and para position. This methodology worked well with substrates having electron donating groups. This method was effective as well with dithiocarbamate salts of *n*-butyl, dodecyl and cyclohexyl, benzyl, piperonyl and homoveratryl amines.

In conclusion, we have developed a cheap, environmentally acceptable and simple protocol for the preparation of a variety of alkyl and arylisothiocyanates from dithiocarbamic acid salts. The use of non-toxic and inexpensive reagents and solvent without the formation of any side products makes this methodology potentially useful. The products obtained in high yields are stable and observed to be pure without requirement of further purification.

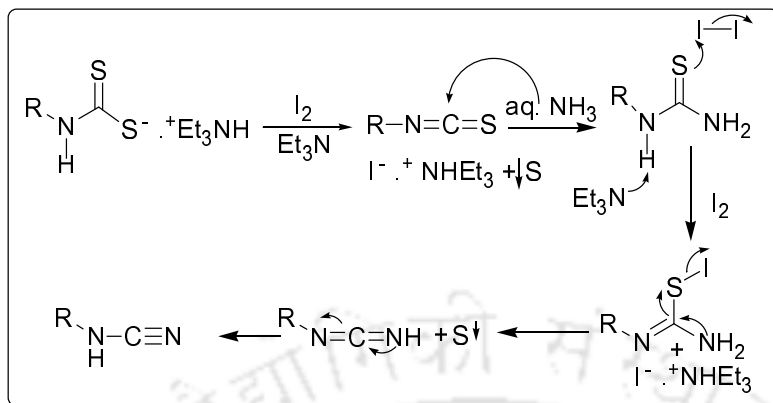
Section IV: A One-pot Preparation of Cyanamide from Dithiocarbamate Using Molecular Iodine

This section mainly focuses on the one-pot synthesis of cyanamides, involving the use of alkyl or aryl dithiocarbamate using iodine as double desulfurizing agent in an innocuous solvent ethyl acetate.

Alkyl and aryl cyanamides are an important class of compounds which are vital intermediates for the synthesis of various biologically active molecules and can be converted efficiently into other functionalities by simple chemical reactions. Cyanamides are key precursors to *N*-alkyl or *N*-aryl imides and also serve as useful protecting group in the synthesis of heterocycles containing secondary and tertiary amines. They are important precursors in the synthesis of herbicides and pharmaceutically active heterocycles such as tumor inhibitors, and a vasodilator medication called minoxidil, known for its ability to reduce hair loss and promote hair regrowth.

In continuation of our ongoing research, we reveal herein a methodology for the synthesis of cyanamides, involving the use of alkyl or aryl dithiocarbamate using iodine as double desulfurizing agent.

Our present methodology is based on: (i) formation of isothiocyanate from alkyl / aryl dithiocarbamate salt by desulfurization with iodine in the presence of triethylamine as the base in ethyl acetate solvent, (ii) treating the *in situ* generated isothiocyanate with aqueous NH_3 to afford alkyl / aryl thioamides and (iii) further oxidative desulfurization of thioamides to cyanamide with iodine in the presence of triethylamine (*Scheme 6*).



Scheme 6. Plausible Mechanism for the Formation of Cyanamide

The mechanism proposed in the scheme has been authenticated by isolation and characterization of all the intermediates. Isolation of the precipitated elemental sulfur further supports the mechanism proposed.

A variety of substituted aromatic dithiocarbamate salts undergo facile transformation to give their corresponding cyanamides by this methodology. This methodology is equally effective irrespective of the nature and positions (*o*-, *m*-, *p*-) of the substituents attached to the phenyl ring. The versatility of the method has been demonstrated by the tolerance of a number of functional groups such as -NO₂, -OMe, -COCH₃ and -OH. Dithiocarbamates of naphthylamine, aliphatic amines cyclohexyl, butyl and benzylic amine give their corresponding cyanamides in good yields. This method has also been successful in the preparation of cyanamide of homoveratryl amine starting from its dithiocarbamate salt.

In conclusion, we have developed a general, economical and environmentally benign method for the preparation of cyanamides from their corresponding dithiocarbamic acid salts. The simplicity, environmental acceptability, and cost effectiveness of this one pot strategy makes it a practical alternative. Though at first glance the product yields of the reactions seem to be moderate or may be just good, but when the fact that these are actually three step reactions done in a single-pot is brought to mind, the yields could in fact be considered as very good if not excellent.

CHAPTER II

Cloud Point Extraction of Nitrobenzene

Cloud point extraction is adopted to remove nitrobenzene from aqueous solutions. The effects of different operating conditions such as, temperature, pH, concentrations of non-ionic surfactant, nitrobenzene and salts on the extraction of both nitrobenzene and surfactant have been studied. Change in different thermodynamic parameters during extraction has been investigated in detail. A method is presented to calculate the feed surfactant concentration required for the removal of nitrobenzene up to a level of 1.0 mg/L. The efficiency of a solvent extraction process for surfactant recovery is also reported.

Performance of Cloud Point Extraction for the Removal of Nitrobenzene

The extent of extraction is defined as, $\text{Extraction} = (1 - C_d / C_0) \times 100 \%$. The influences of different operating conditions on the extent of extraction of nitrobenzene are described in the thesis. The extraction efficiency with temperature and salt is described herein.

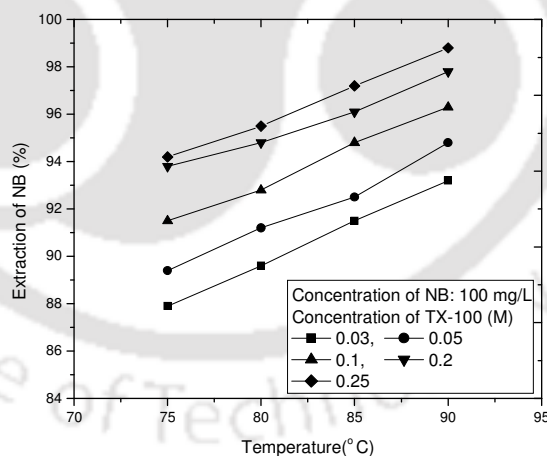
Effects of Temperature on Extraction

Fig. 1. Effect of Temperature on the Extraction of NB. Initial Concentration of NB: 100 mg/L, pH: 6.0

The effects of temperature on the efficiency of nitro benzene extraction are shown in Fig. 1 for an initial nitro benzene concentration of 100 mg/L at 0.03, 0.05, 0.10, 0.20 and 0.25(M) of TX-100. It

is clear from the figure that the extraction of nitro benzene increases with temperature and TX-100 concentration. It may be observed that the extraction of nitro benzene for 100 mg/L of feed nitro benzene and 0.25 (M) of TX-100 increases from about 94 to 99%, when the temperature increases from 75 to 90 °C.

Effects of Salt Concentration on Extraction

Figure 2 shows the variation of extraction efficiency with salt (NaCl and CaCl₂) concentration. It may be observed from the figure that the extraction of nitro benzene increases from about 95.4 to 99.7% when concentration of CaCl₂ increases from 0.1 to 0.6(M) at a fixed initial nitro benzene concentration (100 mg/L in this case) and TX-100 concentration (0.1(M)).

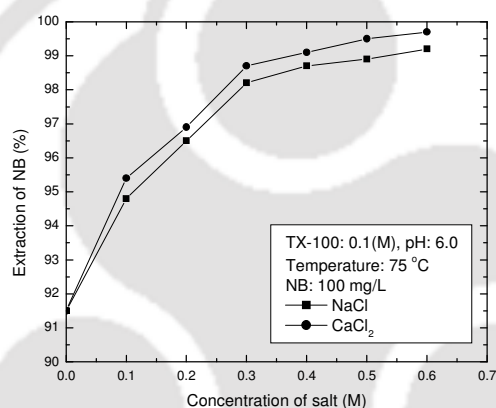


Fig. 2. Variation of NB Extraction with Salt Concentration. Concentration of TX-100: 0.1 (M), Temperature: 75 °C, pH: 6.0

Determination of Thermodynamic Parameters

The thermodynamic parameters ΔG^0 , ΔS^0 and ΔH^0 for this extraction process are determined and analysed in the thesis. The variation of Gibbs free energy (ΔG^0) change during CPE of NB is reported here.

Variation of Gibbs Free Energy (ΔG^0) change

Variations of ΔG^0 with temperature at four different surfactant concentration and at constant NB concentration (3.94×10^{-4} mole/L) are shown in Fig. 3. It may be noted from the figure that the

value of ΔG^0 increases linearly with temperature and decreases with TX-100 concentration. The negative values of ΔG^0 indicate that the NB solubilization process is spontaneous and thermodynamically favourable.

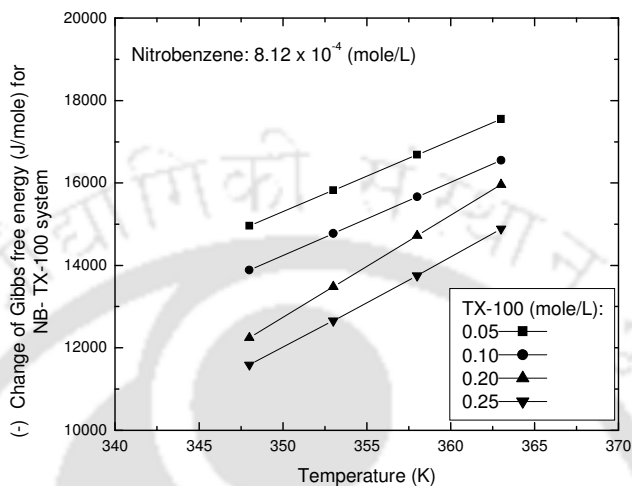


Fig. 3. Variation of Gibbs Free Energy Change (ΔG^0) with Temperature at Constant Nitrobenzene Concentration and at Four different TX-100 concentration

Determination of Design Parameters for the Cloud Point Extraction of NB Using TX-100

A model has been developed to calculate the TX-100 requirement for the removal of NB. It may be observed from figure 4 that the required surfactant concentration increases with feed NB concentration and is less at higher temperatures. Higher operating temperature requires higher energy input to the system. Therefore, there exists a trade off between the feed surfactant dose and the operating temperature with respect to the feed NB concentration to affect a desired level of NB removal.

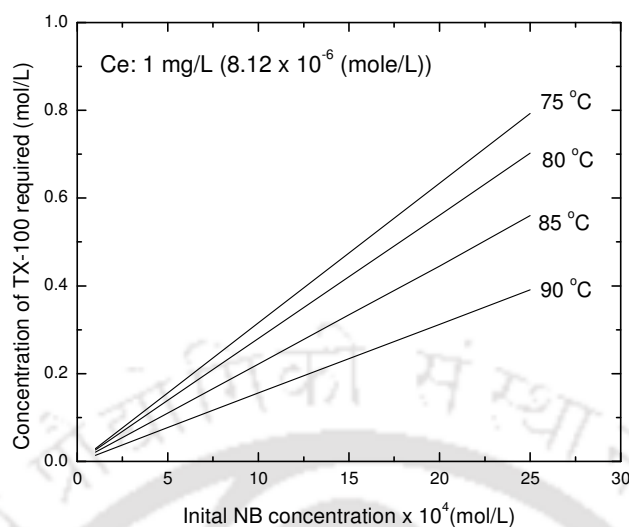


Fig. 4: Variation of the Requirement of TX-100 Concentration for Different Initial NB Concentration at Three Different Temperatures to Bring Down its Dilute Phase Concentration to 1 mg/L (8.12×10^{-6} mole/L)

Surfactant Recovery by Solvent Extraction (SE)

The performance of solvent extraction for the recovery of surfactant from the dilute phase has been described in the thesis in detail. The same procedure may be used for the recovery of surfactant from the coacervate phase using the optimum ratio of surfactant to solvent.

In conclusion, cloud point extraction is successfully used to remove nitrobenzene from synthetic wastewater using TX-100 as non-ionic surfactant. The effects of temperature, concentrations of surfactants and NB on the change in Gibbs free energy (ΔG^0), enthalpy (ΔH^0) and entropy (ΔS^0) of NB extraction have been studied in detail. Solubilization isotherm is developed from the CPE data. Temperature dependency of the constants of the isotherms is also evaluated. From the experimental results, a correlation has been developed to quantify the variation of fractional coacervate phase volume at different operating conditions. An approach to design a cloud point extractor has been proposed to estimate TX-100 requirement for a known temperature, initial and desired nitro benzene concentration. Finally, solvent extraction technique has been adopted using heptane and hexane as organic solvents to make the CPE process more economical.

IA. Introduction

Chemistry and chemical products are the basics of the economy of virtually every industrialized nation. The manufacture, processing, use and disposal of certain chemical substances have resulted in significant and measurable damage to human health and the environment. Over the past generation, more than a trillion dollars has been spent on environmental protection. Chemists now have the knowledge to design chemicals and chemical manufacturing processes that pose little or no risk to human health and the environment. Research in 'Green Chemistry' is making dramatic achievements in the design of chemical, chemical synthesis and chemical processes that are environmentally benign and economically feasible.¹ 'Green Chemistry' or 'Sustainable Technology' necessitates a paradigm shift from traditional concepts of process efficiency, that focus largely on chemical yield, to one that assigns economic value to eliminating waste at source and avoiding the use of toxic and/or hazardous substances.²

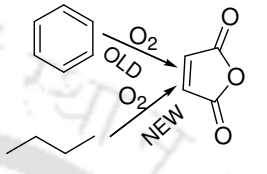
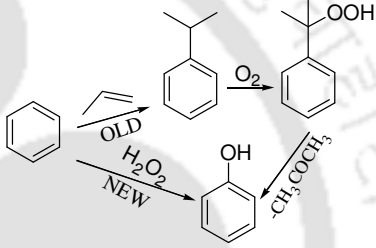
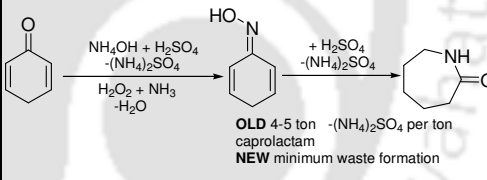
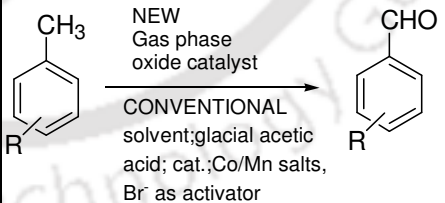
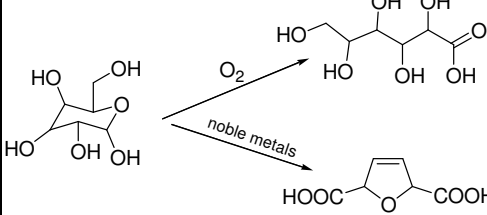
IA.1. Catalytic Organic Transformations

Green Chemistry benefits including lower energy requirements, higher selectivity, lower waste generation processing cost and decreased use of processing and separation agents and allows for the use of less toxic materials. Non catalytic stoichiometric organic transformations using conventional reagents are still being used in the production of a wide variety of pharmaceuticals, fragrances and agrochemicals etc. Stoichiometric reagents are being developed using Green Chemistry principles.^{1a} Despite the important role still played by stoichiometric reagents, the general trend is the development of catalytic processes to replace traditional stoichiometric reagents. An obvious reason for this has been the global concern for making chemical processes catalytic rather than stoichiometric, thereby rendering the protocols more cost-effective, efficient and selective associated with reduced environmental burden.

Developing green chemistry methodologies is a challenge that may be viewed through the framework of the "Twelve Principles of Green Chemistry".³ Catalysis which is considered as one of the fundamental pillars of Green Chemistry, is one of the most important tools for achieving the dual goals of environmental protection and economic benefit. Catalysis is a necessary and critical tool for achieving social and economic objectives. Table IA.1.1. summarizes the principles of "Green

chemistry” and compares them with the objectives of industrial catalysis; some examples are also given.⁴

Table IA.1.1.: Comparison of principle of Green chemistry and objectives of industrial catalysis

Principle of Green Chemistry	Objective of industrial catalysis	Examples
Atom economy	Avoid side reactions	
Simple and safe process	Reduce process complexity and formation of intermediates by making in a single step over a solid catalyst complex multistep reactions	
No waste	Reduce or avoid waste formation	 <p>OLD 4-5 ton $(\text{NH}_4)_2\text{SO}_4$ per ton caprolactam NEW minimum waste formation</p>
Avoid toxic chemicals or solvents	Avoid solvents using heterogeneous catalysis	 <p>NEW Gas phase oxide catalyst CONVENTIONAL solvent: glacial acetic acid; cat.: Co/Mn salts, Br as activator</p>
Use of renewable sources	Use of natural resources for production of chemicals	

Heterogeneous catalysis, in particular, addresses the goals of Green chemistry by providing the ease of separation of product and catalyst, thereby eliminating the need for separation through distillation or extraction.⁵ The invention of a newer clean and appropriate catalyst for a chosen transformation is extremely important and for this, a clear understanding of the chemistry of a prospective catalyst or a catalytic system as well as the transformation on which the catalyst is to be applied upon is an essential prerequisite. The domain of catalysis thus expands by crossing boundaries of several sub-disciplines including bio and abio chemistry and material science, for instance. The world market of catalysts is *ca* 12 billion US dollars, and the chemical transformations leading to specific products through catalysis is estimated to be 1.2-6.0 trillion US dollars.^{1a}

IA.2. Solid Acid Catalysts

Among the three types of catalysis *viz.* homogeneous, heterogeneous and biocatalysis, the heterogeneous has been widely practiced due to its advantages over the others. The principal advantages of heterogeneously catalytic reactions are (a) good dispersion of active sites, (b) constraints of the pores, (c) easier and safer to handle, (d) easier to remove from the reaction mixture and (e) reusability. However, there are disadvantages like addition of cost for the extra component, difficulty in ensuring good mixing etc. In contrast, the catalytic system is usually more efficient under homogeneous conditions. However, the catalyst reuse becomes generally more difficult.⁶

Catalysis using supported reagent and related materials is rapidly emerging as a new “enviro-technology”, which is designed to improve process efficiency, to replace environmentally unacceptable reagents and catalysts. They are either solid or liquid supported on solid having a variety of applications. This can be further classified based on organic or inorganic supports. In the former organic polymer like polystyrene is used, whereas inorganic supports are numerous which include silica, alumina, zeolites, celite, montmorillonite and clay. The most important factors in determining the best support for particular application are likely to include surface areas, pore size, and acidity-basicity.⁶

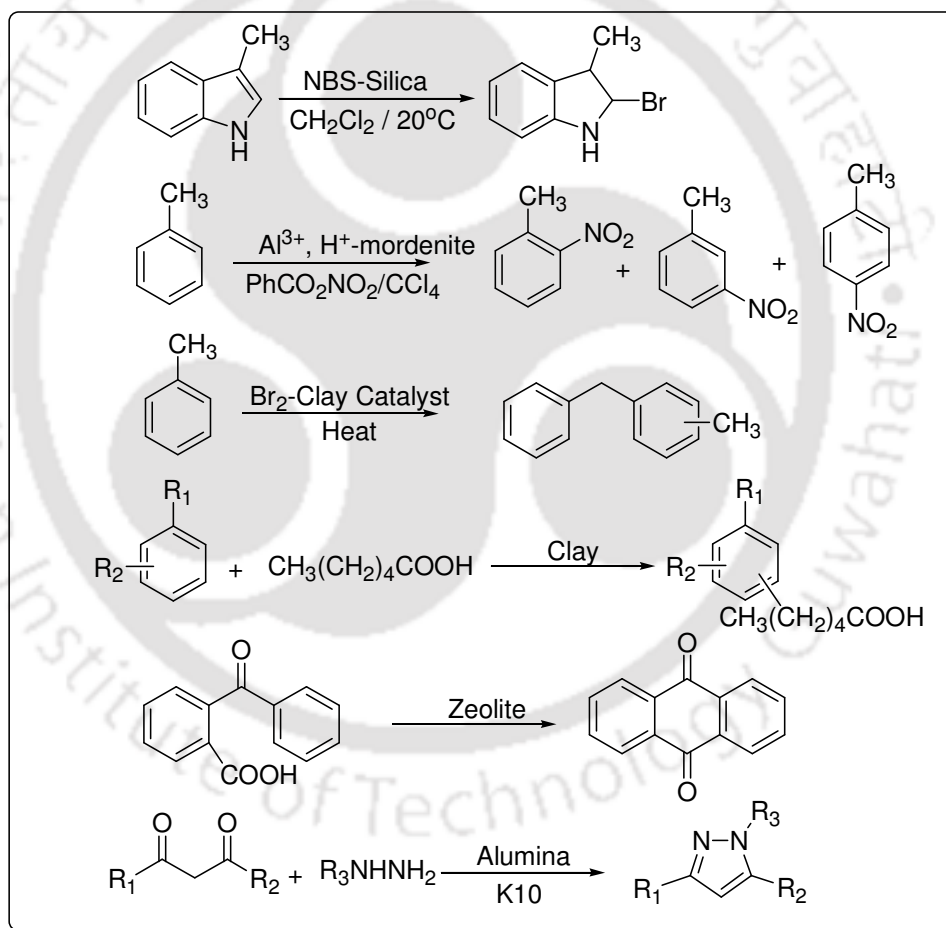
As far as large scale manufacturing of fine chemicals is concerned that require large quantities of mineral acid, solid acid catalysts have been enjoying spectacular success. It is a subject of the most detailed and extensive studies of all heterogeneous catalysts. They have been introduced to replace highly corrosive hydrogen fluoride in olefin alkylation, fuming sulphuric acid and molten sodium

hydroxide in the production of resorcinol. In addition, they have been used in important large-scale industrial processes as alkylation (zeolites, $\text{SiO}_2\text{-H}_3\text{PO}_4$), paraffin isomerization (chlorinated Pt- Al_2O_3), reforming (silicaalumina, noble metal support), and many others.^{6,7}

Several types of solid acids have been developed which include (a) solid Brönsted acids (b) solid Lewis acids, (c) solid superacids, (d) zeolites and (e) clays. Solid Brönsted acids are simple oxides possessing surface hydroxyls (silica, alumina etc.), mixed oxides (aluminosilicates), solid containing activated H_2O molecules (hydrated sulphates), and solids with protonic acids adsorbed on supports ($\text{SiO}_2\text{-H}_3\text{PO}_4$). The acidity of Lewis solid acids rise due to unsaturation in coordination of surface cations and the strength depends on the surrounding, which gives rise to a range of catalysts by change in the environment of their active sites. Niobium pentoxide, for example, when supported on silica and alumina shows both Lewis and Brönsted acid sites, whereas on magnesia, titania shows Lewis acidity. Solid superacids are the modified Lewis acids on supports. Treatment of alumina with P_2O_5 , and AlCl_3 results into solid superacids, of which catalytic activity is consistent with very high acidity. Zeolites are widely used as selective catalysts, especially in petrochemical industries.⁸ Further zeolites have been modified to enable a change in catalytic properties by increasing Brönsted acidity, changing Brönsted to Lewis acids centers,⁹ and changing Si-Al ratio¹⁰ Like zeolites, clays are also widely used in petrochemical industries. Ironically, clays have made much more impact than zeolites as acid catalysts in organic synthesis and are ready for a major breakthrough in the fine-chemical manufacturing industries.⁶

Some representative examples of solid catalyzed organic reactions have been shown in Scheme IA.2.1. Alumina and titania have been widely studied due to their use as catalysts or catalyst supports in various organic reactions especially in petrochemistry, since they add a dual functionality to the catalyst.¹¹ The surface properties of these catalysts are mainly responsible for the functionality; many strategies have been proposed to modify the surface properties. Additionally they have some unique properties such as acidity, basicity, redox activity, thermal shock resistance capacity, ionic conductivity, chemical inertness, and promoting metal support interaction.¹² Recently, much attention has been paid to prepare super-acid titania and alumina for many industrially important acid demanding reactions^{12,13} So-called “solid phosphoric acid” containing phosphoric acid together with oxide phase, is a typical acidic heterogeneous catalyst widely used in industry for many years for propylene oligomerization, alkylation and double-bond isomerisation etc. The use of phosphates as

promoting additives for alumina has been reported in some instances and their effects have been suggested to be two-fold. Phosphates have been claimed to play the role to support stabilizer,¹⁴ and to suitably modify the acid-base properties of the active carriers¹⁵ In the study of phosphate impregnated titania, alumina and zirconia it has been found that incorporation of phosphate ion in TiO_2 and Al_2O_3 enhances important catalytic properties, like stabilization of surface area, crystal phase, improvement in surface acidity and making the material porous.¹⁶ Direct phosphation resulted in the incorporation of phosphorus into the inorganic framework of aluminium oxides by the Al-O-P bonds and form a uniform macroporous structures.



Scheme IA.2.1.: Solid Acid Catalyzed Organic Reactions

IA.3. Solvents in Organic Synthesis

Another important issue in 'Green Chemistry' is the use of organic solvents. In chemical manufacture, organic solvents are widely used in a variety of unit operations including extraction, recrystallization and the dissolution of solid for ease of handling. One of the key roles organic solvents play in the chemical industry, however, is that of reactant solvent allowing the homogenization of a chemical mixture, speeding up reactions through improved mixing, and in addition reducing energy consumption. Volatile organic compounds (VOC) were used as solvents because of their ease of removal or evaporation. The main environmental issue concerned with VOCs is their ability to form low-level ozone, smog through free radical air oxidation and adverse health effects.¹⁷ Solvent use is being subjected to close scrutiny and increasingly stringent environmental legislation. In the context of green chemistry there are several issues which influence the choice of solvents. It should be relatively nontoxic and nonhazardous, e.g. not inflammable or corrosive. The solvent should not be released to the environment. Removal of highly volatile residual solvent from reaction medium is usually achieved by evaporation or distillations were inevitable. Spillage and evaporation from reaction mixture during distillation leads to atmospheric pollution, a major global environmental issue. Many halogenated solvents pose serious health problems to workers when exposed. Polar aprotic solvents, such as dimethylformamide and dimethyl sulfoxide, that are the solvents of choice for many nucleophilic substitutions. They are high boiling and not easily removed by distillation. They are also water miscible which enables their separation by washing with water. Unfortunately, this inevitably leads to contaminated aqueous effluent.

These issues surrounding a wide range of volatile and nonvolatile, polar aprotic solvents have stimulated the fine chemical and pharmaceutical industries to seek more benign alternatives. There is a marked trend away from hydrocarbons and chlorinated hydrocarbons towards lower alcohols and esters. Inexpensive and environmentally benign solvent ethanol has the added advantage of being readily biodegradable. Solvent ethyl acetate, produced by combining two innocuous solvent *viz.* ethanol and acetic acid, is currently being touted as an environmentally attractive solvent for chemical reactions.^{2,18} Table IA.3.1. summarises properties of volatile organic solvents along with their hazard indicator.

Table IA.3.1.: Properties of volatile organic solvents¹⁷

Solvent	Boiling point (°C)	Flash point (°C)	TLV-TWA	Hazard indicator
Isopropanol	96	15	400	None
Ethylacetate	76	-2	400	None
2-Butanone	80	-3	200	Irritant
1-Butanol	117	12	100	Harmful
Toluene	110	4	100	Harmful
Tetrahydrofuran	65	-17	200	Irritant
Methanol	64	11	200	Toxic
Dichloromethane	40	none	100	Harmful, Suspected carcinogen
Hexane	68	-22	50	Harmful
Chloroform	61	none	10	Possible carcinogen

TLV-TWA: Threshold Limit Values-Time Weighted Average in Vapour

IA.4. Aqueous Mediated Reactions

Water minimises environmental impact, increases operational safety and can provide a low cost reaction medium for pursuing reaction chemistry. Furthermore it is the most abundant, cheap, non-toxic, safe and non-hazardous solvent hence can serve as an alternative solvent for organic reactions. But the lower solubility of organic apolar substrates (reactants), incompatibility of the intermediates in water and the competition between the desired reaction and hydrolysis restricts its use in organic synthesis. On the other hand, after Breslow's discovery of a positive effect on the reaction rates and selectivities of the Diels-Alder reaction, special attention has been focused on the origin of the aqueous acceleration. Breslow has demonstrated that the hydrophobic effect accelerates Diels-Alder reaction and gives high endo-exo selectivity.¹⁹ Despite the solubility problems of organic substrates in water after the seminal contribution of Breslow, new additions are continuously being made to the catalog of organic reactions that can be performed effectively with water as the solvent. In general, apolar organic compounds can be solubilized in water by addition of organic cosolvents, amphiphiles such as surfactant and by ionic derivatization with control of pH. The possibility of using water as the solvent for organic reactions with surprising and unanticipated results has been addressed in the literature.²⁰ Several books and reviews have been devoted towards the use of water in organic

reactions. A series of most of the fundamentally useful reactions such as aldol reactions, allylations, aminohydroxylations, cycloadditions, cyclopropanations, epoxidations, dihydroxylations, and hydrogenations, oxidation, organometallic reactions has been performed with similar or improved rates, yields and selectivity in aqueous media compared to the corresponding reactions in organic media.²¹ In addition, the experimental procedures using water as the reaction medium are simplified owing to easy isolation of products accompanied by recycling of water-soluble catalysts and reagents by phase separation.

IA.5. Bromination of Organic Compounds

In the domain of synthetic chemistry, bromination of organic compounds has received significant interest in recent years owing to the increasing commercial importance of bromo-organics in the preparation of a large number of natural products as well as in the manufacture of pharmaceuticals, intermediates for agrochemicals and numerous industrially viable products like pesticides, herbicides, and fire retardants. They are also key intermediates in the preparation of organometallic reagents²² and play vital roles in transition metal mediated coupling reactions such as Stille-Suzuki,²³ Heck,²⁴ and Sonogashira reactions²⁵

The first bromo organic compound, tyrian or royal purple was extracted from a Mediterranean sea mollusk and used as dyes.²⁶ Laurencin, α -synderol, β -synderol etc. are most important bioactive natural bromo containing cyclic terpenes (Figure 1A.5.1).²⁷ Several halogenated aromatic compounds have been used as intermediates for a natural products and bioactive materials.^{26,28}

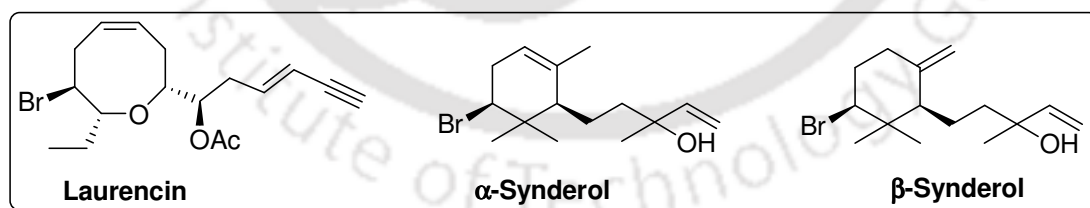


Figure 1A.5.1.

The potent feeding deterrent avrainvilleol found in the tropical green alga *Avrainvillea longicaulis* and *Avrainvillea rawsoni* has yielded the HMGCoA reductase inhibitor rawsonol are all bromonatural products (Figure 1A.5.2).²⁶

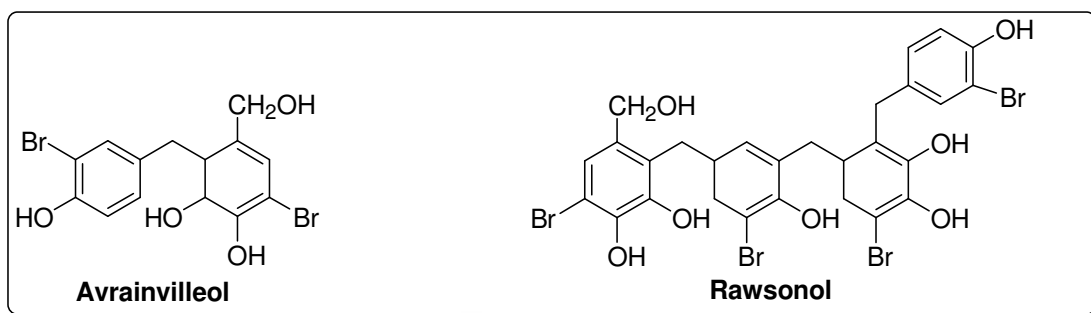


Figure IA.5.2.

Tetrabromobisphenol-A (TBBPA), hexabromocyclododecane (HBCD), poly brominated biphenyls (PBB) etc. are important fire retardants (Figure 1A.5.3.).²⁶

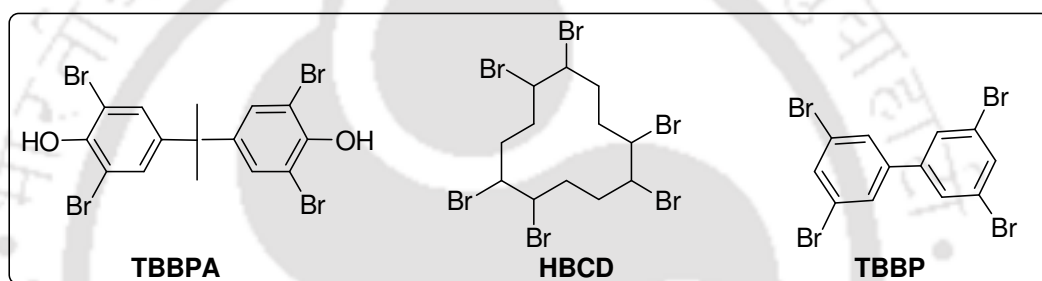


Figure IA.5.3.

Brominated chalcones 4-benzyloxy-3'-bromo-4',6'-dimethoxy-2'-hydroxychalcone (**I**) and 3'-bromo-4,4',6'-trimethoxy-2'-hydroxychalcone (**II**), (Figure 1A.5.4.) are important precursors to the flavonoids (eg. vitexin).²⁹

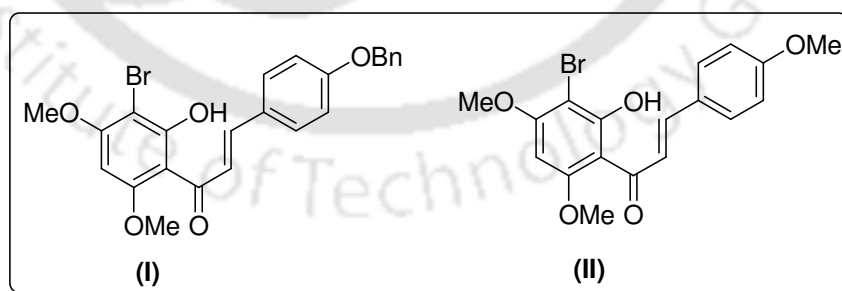


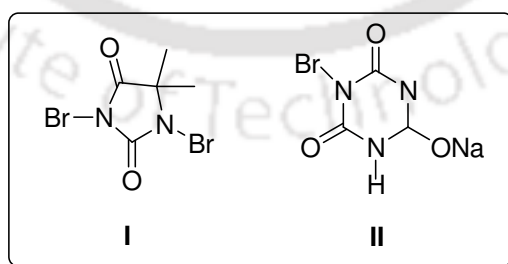
Figure IA.5.4.

IA.5.1. Methods for Bromination

In general molecular bromine is used for the bromination of organic substrates. Despite the wide spread use of molecular bromine as electrophilic reagent it is toxic, difficult to handle, low-boiling point and lachrymatory liquid causing severe burns on contact with skin.³⁰ Moreover, due to its oxidizing tendency, attempted bromination of complex organic substrate can cause undesired competing oxidation processes.³¹

N-Bromo succinamide (NBS) is a solid and easy to handle brominating agent.³² Alkylated aromatic compounds are either brominated in the side chain with NBS in the presence of benzoyl peroxide (Wohl- Ziegler reaction)³³ or in the aromatic ring in the absence of any radical initiators.³⁴ The nuclear bromination of aromatic compounds are favored in polar solvents like *N,N'*-dimethylformamide (DMF), CH_3CN etc.³⁵ Methoxybenzoic acid can be brominated to *p*-methoxybenzoic acid in an aqueous NaOH using NBS.³⁶ NBS is also used for the bromination of activated aromatics in the presence of acidic catalysts such as *p*-TsOH, SiO_2 , HZMS-5 zeolite, amberlyst, HCl, $\text{HBF}_4 \cdot \text{Et}_2\text{O}$ etc.³⁷ Room temperature ionic liquids are used as a green recyclable reaction media for the α -monohalogenation of 1,3-diketones, β -keto esters, and cyclic ketones with *N*-halosuccinimides in excellent yields in the absence of any catalyst.³⁸

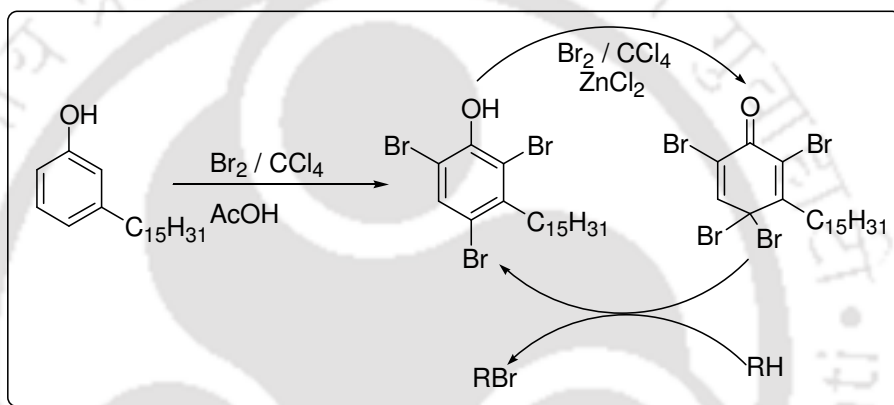
1,3-Dibromo-5,5-dimethylhydantoin (DBDMH) (**I**) (Scheme IA.5.1.1.) is another useful brominating reagent and is a suitable alternative to N-bromosuccinamide.³⁹ A variety of aromatic compounds with both activating and deactivating substituents were efficiently brominated with sodium monobromoisocyanurate (SMBI) (**II**) (Scheme IA.5.1.1.). This reagent is reported to be superior to NBS.⁴⁰



Scheme IA.5.1.1.

Bromochromates, such as pyridinium bromochromate (PBC),⁴¹ quinolinium bromochromate (QBC)⁴² and γ -picolinium bromochromate (γ -PBC)⁴³ are another class of bromineless brominating agent. Although bromochromates works well towards bromination but are inherently associated with strong oxidizing properties and the presence of the toxic metal chromium makes it further unsuitable for large scale reactions.

Very recently, 2,4,4,6-tetrabromo-3-n-pentadecyl-2,5-cyclohexadienone (TBPCO) has been synthesized and used as a new efficient, convenient and environmentally friendly brominating agent (Scheme IA.5.1.2.).⁴⁴



Scheme IA.5.1.2.

A facile bromination of various organic substrates has been demonstrated with a 2:1 bromide:bromate reagent prepared from the alkali intermediate of the conventional bromine recovery process. The reagent is acidified *in situ* to generate HOBr as the reactive species which effects the bromination. By obtaining the present reagent from the liquid bromine precursor, the twin advantages of avoiding liquid bromine and producing the reagent in a cost-effective manner are realized.⁴⁵

In addition, several other methodologies using, *N,N,N,N*-tetrabromobenzene-1,3-disulfonyl amide⁴⁶ and hexamethylenetetraamine-Br₂ complex⁴⁷ have been reported.

IA.5.2. Organic Tribromides

Organic ammonium tribromides are attractive solid brominating agents. These crystalline stable solids are convenient source of bromine owing to the ease in maintenance of their desired

stoichiometry and the ease in storage, transportation and handling. Several organic tribromides have been reported in the literature (Figure IA.5.2.1.), which includes tetramethylammonium tribromide (TMATB), tetrabutylammonium tribromide (TBATB), tetraethylammonium tribromide (TEATB), cetyltrimethylammonium tribromide (CTMATB), pyridine hydrobromide perbromide (PHPB), phenyltrimethylammonium tribromide (PTATB), benzyl trimethylammonium tribromide, 1,8-diazabicyclo [5.4.0]-undec-7-ene hydrobromide perbromide (DBUHBr₃), pentylpyridinium tribromide (PPTB), 1-benzyl-4-aza-1-azonia-bicyclo [2.2.2] octane tribromide and 1-butyl-3-methylimidazoliumtribromide ([bmim] Br₃).

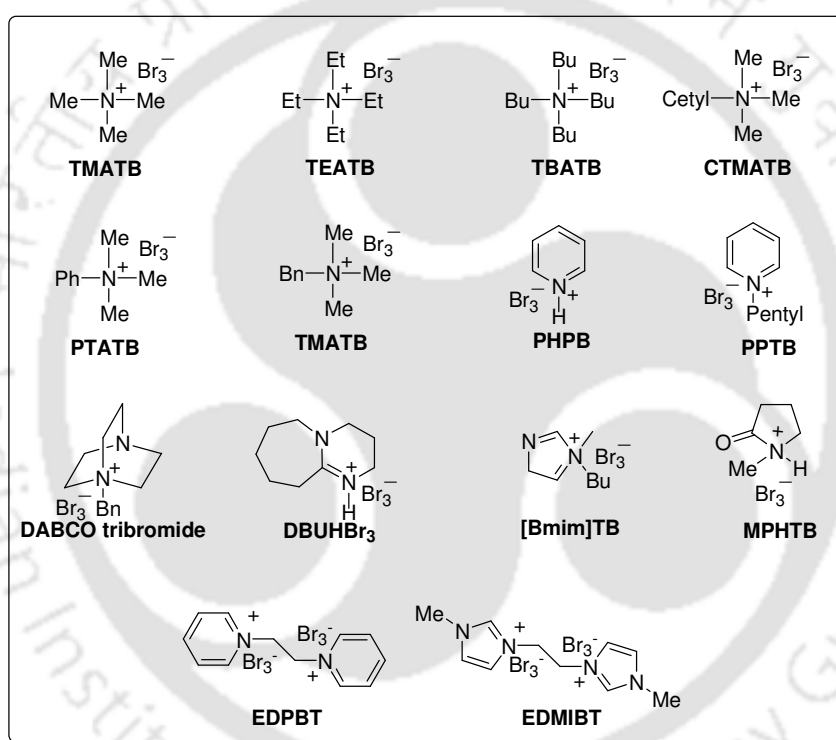
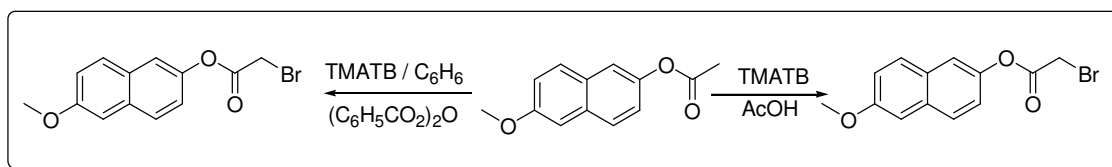


Figure IA.5.2.1.

IA.5.3. Bromination Using Tribromides

Chattway and Höfle were the first to report the preparation of tetramethylammonium tribromide (TMATB).⁴⁸ It was obtained by treating tetramethylammonium bromide with bromine in acetic acid. The product TMATB was found to contain 50.9% of active bromine. Its brominating property was studied by Avramoff and coworkers. TMATB furnished the sole nuclear bromination

product, 2-acetyl-5-bromo-6-methoxynaphthalene when reacted with 2-acetyl-6-methoxy-naphthalene in acetic acid but gave α -brominated product with change in reaction conditions (Scheme IA.5.3.1).⁴⁹

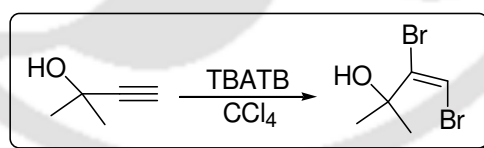


Scheme IA.5.3.1.

Tetra-*n*-butylammonium tribromide (TBATB) was proved to be an excellent brominating agent as reported by Buckles group.⁵⁰ Berthelot and coworkers have studied extensively on the bromination of different organic compounds with TBATB. Phenols and amines have been brominated with TBATB to give the corresponding *p*-bromo product in CHCl_3 . A mechanism involving electrophilic substitution by the tribromide has been suggested to account for the monobromination at the para position of phenols and amines in aprotic and non-basic solvents.⁵¹

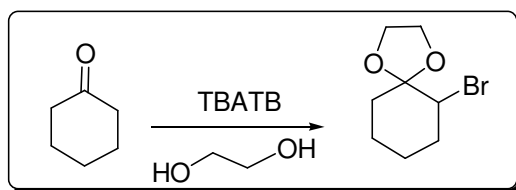
Our group has developed an environmentally benign route for the preparation of TBATB using peroxovanadium (V)-mediated biomimetic oxidation of bromide circumventing the use of Br_2 or HBr .⁵²

Stereoselective bromination of alkynes by TBATB has also been reported. Unlike the other reported methods using bromine, TBATB in CCl_4 gives the (*E*)-isomer exclusively (Scheme IA.5.3.2).⁵³



Scheme IA.5.3.2.

TBATB has been shown to be a convenient reagent for α -bromination of ketones, but when reacted in the presence of ethylene glycol simultaneously keto protection was observed (Scheme IA-5.3.3).⁵⁴



Scheme IA.5.3.3.

Khan *et al.* has reported a convenient and useful method for preparation of various acyclic and cyclic α -bromo enones from the corresponding enones using TBATB and CTMATB. The dibromoderivative of enone undergoes elimination in the presence of K₂CO₃ giving α -bromo enones (Scheme IA.5.3.4).⁵⁵



Scheme IA.5.3.4.

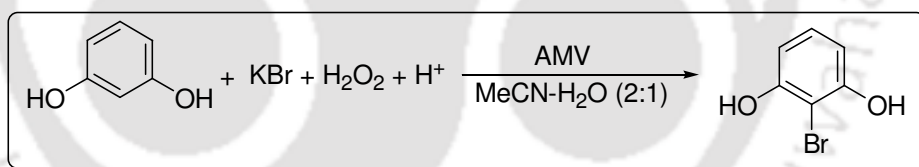
Organic ammonium tribromides such as benzyl trimethylammonium tribromide (BTMATB),⁵⁶ phenyl trimethylammonium tribromide (PTATB),^{56a,57} pyridine hydrobromide perbromide (C₅H₅N.HBr.Br₂ or PHPB),⁵⁸ 1-benzyl-4-aza-1-azonia-bicyclo [2.2.2] octane tribromide,⁵⁹ 1,8-diazabicyclo[5.4.0]undec-7-ene hydrotribromide (DBUHBBr₃),⁶⁰ 1-butyl-3-methylimidazolium tribromide [(bimim)Br₃],⁶¹ 3-methylimidazolium tribromide [(Hmim)Br₃],⁶² pentylpyridinium tribromide (PPTB)⁶³ and *N*-methylpyrrolidin-2-one hydrotribromide (MPHT)⁶⁴ have been used as the alternative for hazardous molecular bromine in various organic reactions.

Problems associated with these reagents are, some of the organic ammonium tribromides have phase transfer properties, hence a substantial amount gets extracted along with the organic products in an organic solvent during workup, thereby making the purification tedious and the method expensive for large-scale reaction. Recovery and recycling of expensive organic ammonium cations is also poor after the reaction. Pyridinium tribromide or pyridinium hydrobromide perbromide is not so stable compared to the other organic ammonium tribromides and is reported to have three different bromine compositions with different melting points.⁶⁵

However, we have reported a ditribromide reagent 1,2-dipyridiniumditribromide-ethane⁶⁶ as a efficient solid brominating agent. The crystalline ditribromide reagent is stable for months and acts as a safe source of bromine requiring just 0.5 equivalents for complete bromination. It has high active bromine content per molecule and shows a remarkable reactivity compared to other tribromide reagents.

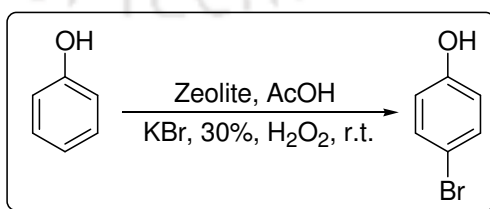
IA.5.4. Oxidative Bromination

In order to overcome the problems improved procedures involving the *in situ* preparation of 'bromonium species' by oxidation of bromide ion with suitable oxidants under various homogeneous and heterogeneous reaction conditions have been reported in the literature.⁶⁷ Main advantages of oxybromination compared to the classical direct bromination are atom economy, that is, a full utilization of bromine atoms with no formation of by-products and the use of low value and easy to handle halogenating agents rather than more expensive and hazardous ones, like molecular bromine. Pandey *et al.* have described an efficient oxybromination of selected aromatic compounds with ammonium metavanadate as the catalyst and KBr as the source of bromide and H₂O₂ as the oxidizing agent (Scheme IA.5.4.1).⁶⁸



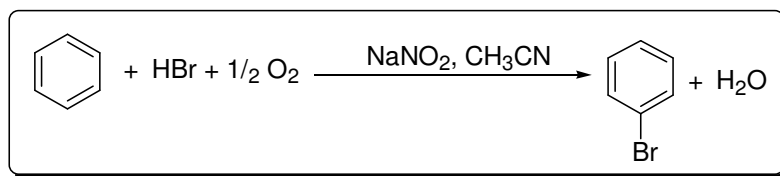
Scheme IA.5.4.1.

While Kulkarni *et al.* reported a liquid phase oxybromination of phenol in acetic acid as the solvent and CrZSM-5 as a catalyst (Scheme IA.5.4.2).⁶⁹



Scheme IA.5.4.2.

More recently Liang *et al.* performed the oxybromination of aromatics in CH₃CN-aqueous HBr mixture, mediated by NaNO₂ (Scheme IA.5.4.3.).⁷⁰

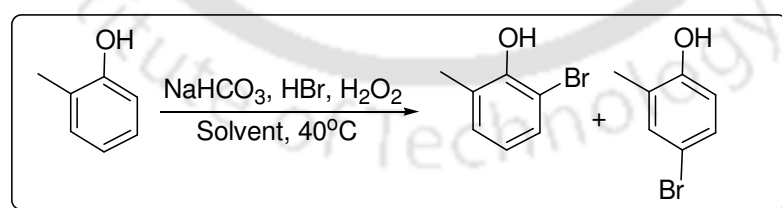


Scheme IA.5.4.3.

However, the systems reported for oxybromination so far require strongly acidic conditions, volatile organic solvents (VOCs) and metal or other catalysts such as vanadium, copper, zeolites.⁷¹ The bromide source is HBr or the bromide salt. The oxidizing equivalents are mostly provided by peroxides in the processes,⁷² although molecular oxygen could be activated in some instances.^{70,73} Although, these methods have many advantages, as well as some disadvantages like the use of metals, VOCs and HBr which is corrosive, limits its use in practical applications.

Hence, the need for development of bromination protocols based on oxidation of bromide salt by H₂O₂ with better atom economy in the presence of a nonmetallic catalyst. It is much safer and cheaper to transport and store large quantities of bromide salts than either Br₂ or HBr.

Recently an interesting work on a metal free oxybromination of phenols and anilines using NaBr-H₂O₂ in H₂O/scCO₂ at 40 °C has been reported (Scheme IA.5.4.4.).⁷⁴ Intrinsic acidity and generation of percarbonic acid in the reaction medium seem to be the driving force of the methodology. The reaction generally took longer duration and requirement of high pressure makes the procedure somewhat unappealing.



Scheme IA.5.4.4.

With respect to Green chemistry, there is a pressing need to find a method for bromination of aromatics with less environmental impact. In fact, several recent reports claim oxidative bromination to be the solution to replace all ecodeficient bromination reactions.^{52b,72a,72b,75}

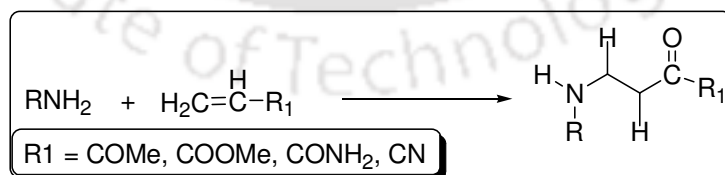
In order to circumvent practical difficulties, an alternative protocol is desirable which would neither use metal catalyst nor require HBr and VOCs thereby rendering it environmentally more benign. Also the protocol should be favorable to large scale preparations without any environmental impact. Our main concern was to develop an operationally simple, metal free catalytic methodology involving *in situ* generation of oxidized bromide species for the electrophilic bromination of aromatics in an environmentally cleaner way.

Development of an innovative catalytic system that uses cheap and easily available oxidants/catalysts for the mild and efficient oxybromination of a wide range of substrates, e.g., ketones and aromatics is still desired. Based on this, we reasoned that use of boric acid as the catalyst and KBr and hydrogen peroxide as the reactants would likely lead to a green and efficient catalytic system for the oxybromination of a wide range of target substrates.

In line with this it is proposed to study the catalytic activity of boric acid towards bromination of phenols and anilines in water with KBr as bromide source and H₂O₂ as oxidant as discussed in detail in **Section I of Chapter I**. It may not be out of place to mention that boron acids (i.e., boric and boronic acids) find their applications as catalyst in a number of transformations, for example, esterification of α -hydroxycarboxylic acids,⁷⁶ *aza*-Michael,⁷⁷ *thia*-Michael reactions,⁷⁸ and organic sulfide oxidation.⁷⁹

IA.6. Solid Acid Catalysed *aza*-Michael Reaction

The *aza*-Michael reaction involving the conjugate addition of a nitrogen nucleophiles to an α,β -unsaturated carbonyl or nitrile compounds constitutes an important reaction in organic synthesis for the construction of C–N bond and for the preparation of a β -amino carbonyl or nitrile compounds (Scheme IA.6.1.).⁸⁰

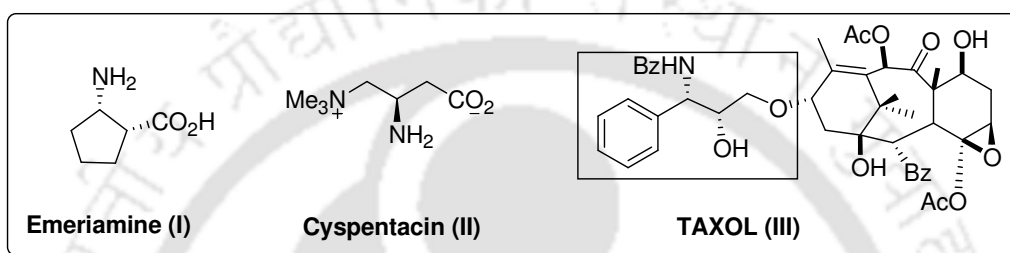


Scheme IA.6.1.

Various β -amino carbonyl compounds are present in bioactive natural products and are also useful for the synthesis of fine chemicals and pharmaceuticals.⁸¹ For example β -amino carbonyl

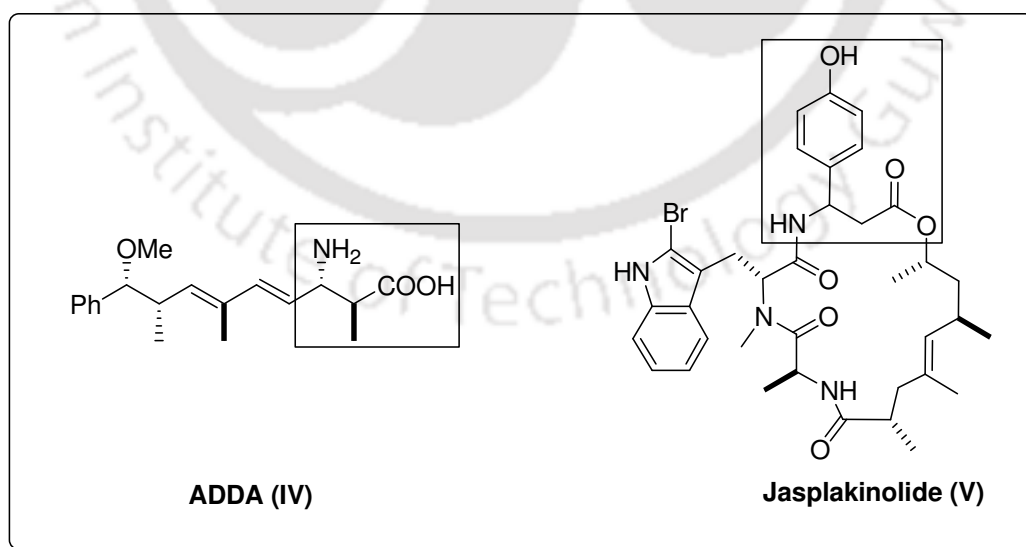
compounds and their derivatives serve as essential intermediates in the synthesis of β amino acids, β -aminoalcohols and β -lactam antibiotics.⁸²

The Michael adduct, β -amino acids in its free form shows interesting pharmacological properties. For instance, hypoglycemic and antiketogenic activities were observed in rats after oral intake of emeriamine (**I**) (Scheme IA.6.2).⁸³ Cispentacin (**II**) is an antifungal antibiotic (Scheme IA.6.2). Functionalized β -amino acids are key components of a variety of bioactive molecules such as taxol (**III**) (Scheme IA.6.2.) one of the most active antitumor agents.⁸⁴



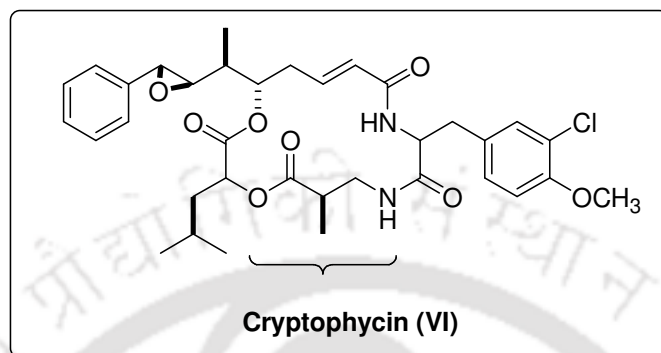
Scheme IA.6.2.

Unsaturated β -amino acid ADDA (**IV**) is present in the antibiotics cyanovinfirin RR, nodularin, as well as microcystin LR.⁸⁵ β -Tyrosine, a β -aryl- β -amino acid, is present in jasplakinolide (**V**) (Scheme IA.6.3.), which is a sponge metabolite with potent insecticidal, antifungal, and antihelminthic properties.⁸⁶

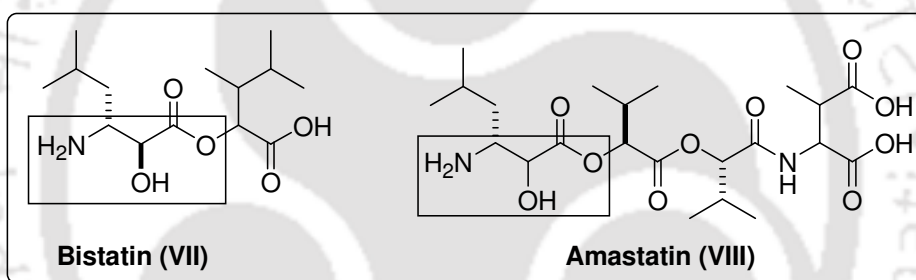


Scheme IA.6.3.

Other representative examples include cryptophycin⁸³ (VI) a potent tumor-selective depsipeptide, (Scheme IA.6.4.)⁸⁷ and aminopeptidase inhibitors bestatin (VII) and amastatin (VIII) (Scheme IA.6.5.).⁸⁸



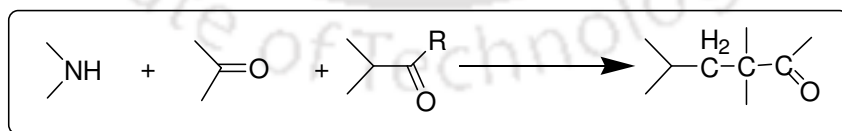
Scheme IA.6.4.



Scheme IA.6.5.

IA.6.1. Methods for the Synthesis of β -Amino Carbonyl Moiety (Michael Adduct)

The most common method for the preparation of β -amino ketones is the Mannich reaction (Scheme IA.6.1.1.).⁸⁹



Scheme IA.6.1.1.

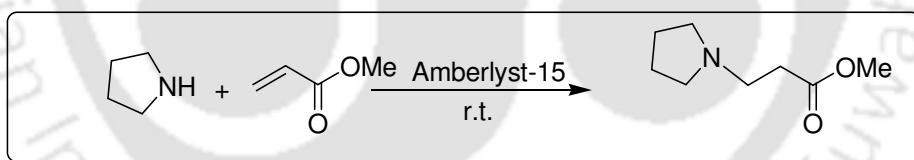
Classical Mannich type reactions are certainly very powerful but need quite severe reaction conditions and are rather sluggish. Conjugate addition reactions are, to the contrary, atom economic and

quite easy to carry out. However, these reactions require either basic conditions⁹⁰ or acidic catalysts,⁹¹ which would lead to by-products or undesired harmful residues. To avoid the problems associated with a strong acid or a base, various milder Lewis acids such as LiClO_4 ,⁹² $\text{Yb}(\text{OTf})_3$,⁹³ $\text{Bi}(\text{NO}_3)_2$,⁹⁴ $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$,⁹⁵ SmI_2 ⁹⁶ and $\text{Cu}(\text{OTf})_2$ ⁹⁷ were employed in the Michael protocol.

Other reagents or catalysts includes β -cyclodextrin,⁹⁸ bromodimethylsulfonium bromide,⁹⁹ and boric acid.¹⁰⁰ Recently, ionic liquids, either alone¹⁰¹ or in combination with quaternary ammonium salts,¹⁰² have been shown to catalyze efficiently conjugate addition to α,β -unsaturated compounds albeit with long reaction times.

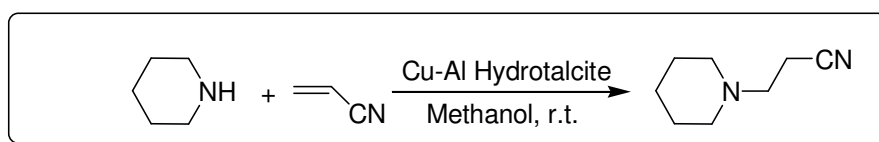
Heterogeneous solid acids have also been employed for this reaction. While considering organic reactions catalyzed by solid acids, the development of solid acid catalysed *aza*-Michael reactions has provided the incentive of finding a milder and more convenient approach towards the construction of β -amino ketone or esters. Towards this end, several research groups have recently reported *aza*-Michael reactions with solid acids or base catalysts to give β -amino carbonyl compounds. Some commonly used solid catalyst used are kaolinite clays, silica gel, Amberlyst-15, Cu-Al hydrotalcite, $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$ on montmorillonite K10,¹⁰³ imidazolium-based polymer supported CuI ¹⁰⁴ and gadolinium triflate¹⁰⁵

Amberlyst-15 was reported as an efficient reusable heterogeneous catalyst for *aza*-Michael reactions under solvent-free conditions (Scheme IA.6.1.2.).¹⁰⁶



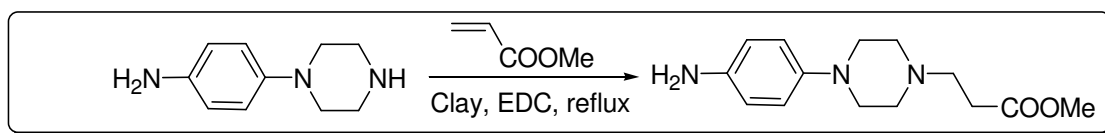
Scheme IA.6.1.2.

A recyclable protocol for *aza*-Michael addition of amines to α,β -unsaturated compounds using Cu-Al hydrotalcite is reported (Scheme IA.6.1.3.).¹⁰⁷



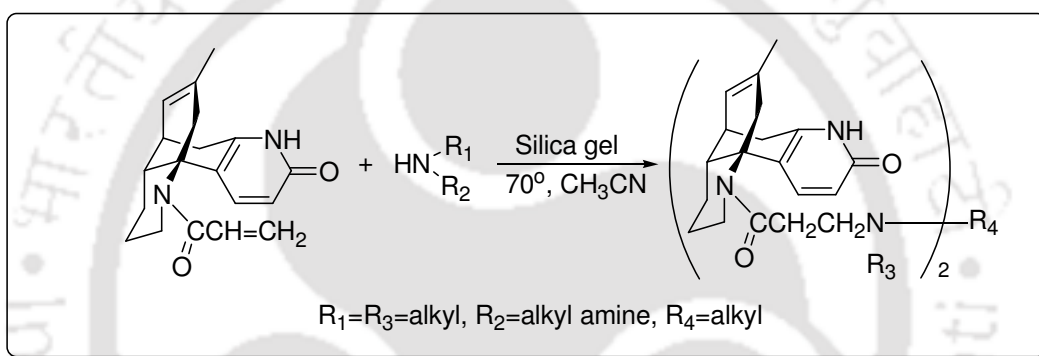
Scheme IA.6.1.3.

Clay was found to be an efficient catalyst for Michael type addition of aliphatic amines to α,β -ethylinic compounds (Scheme IA.6.1.4).¹⁰⁸



Scheme IA.6.1.4.

Recently silica gel in acetonitrile has been employed as efficient reaction systems for the *aza*-Michael addition of amines to electron-deficient olefins (Scheme IA.6.1.5).¹⁰⁹



Scheme IA.6.1.5.

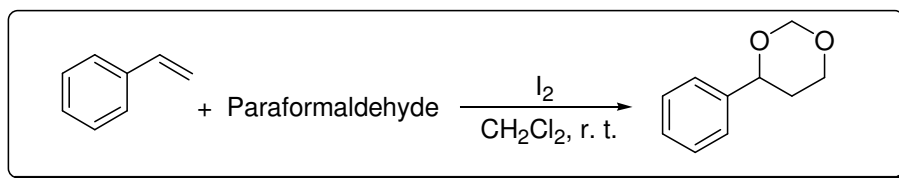
Although the recent advances made this route attractive, the development of simple, convenient, and environmentally benign recyclable approaches are highly desirable. Some more discussions on this will be made at the appropriate place where our results on *aza*-Michael reactions will be reported.

IA.7. Iodine Mediated Reactions

Recently, molecular iodine has received considerable attention in organic synthesis because of its low cost, non-toxicity and ready availability. The mild Lewis acidity associated with iodine has enhanced its use in organic synthesis to perform several organic transformations using stoichiometric levels to catalytic amounts.¹¹⁰

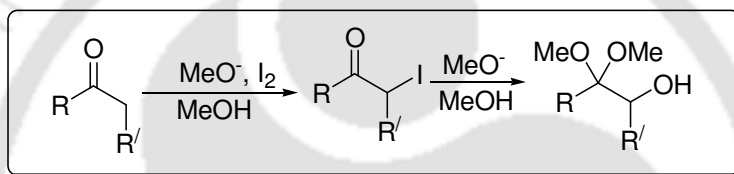
Owing to advantages associated with this eco-friendly reagent, molecular iodine has been explored as a powerful reagent¹¹¹ and catalyst¹¹² for various organic transformations.

Molecular iodine was used as a reagent for the synthesis of 1,3 dioxane by Prins reaction (Scheme IA.7.1).^{111a}



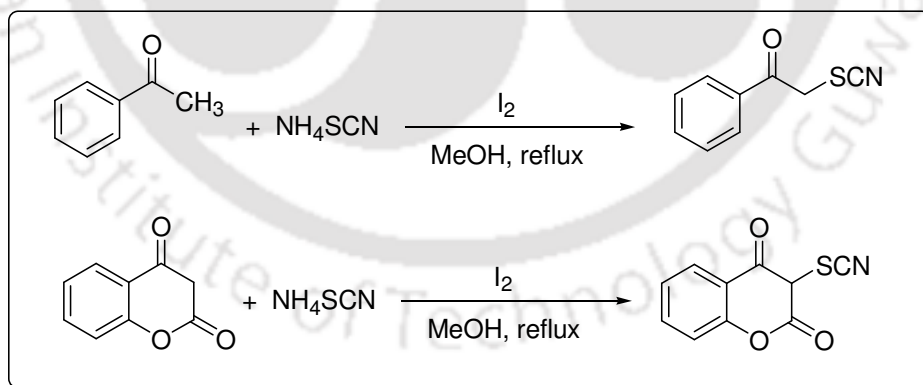
Scheme IA.7.1.

The α -hydroxylation of ketones and aldehydes to α -hydroxyketals mediated by iodine under basic conditions in MeOH is described (Scheme IA.7.2).^{111c}



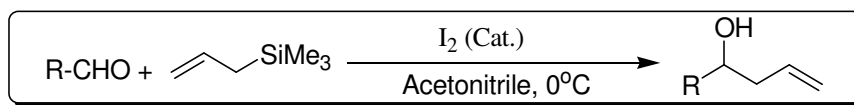
Scheme IA.7.2.

Iodine/MeOH was reported as a novel and versatile reagent system for the synthesis of α -kethiocyanates (Scheme IA.7.3).^{111d}

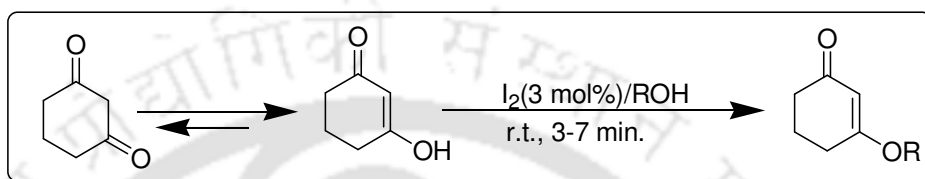


Scheme IA.7.3.

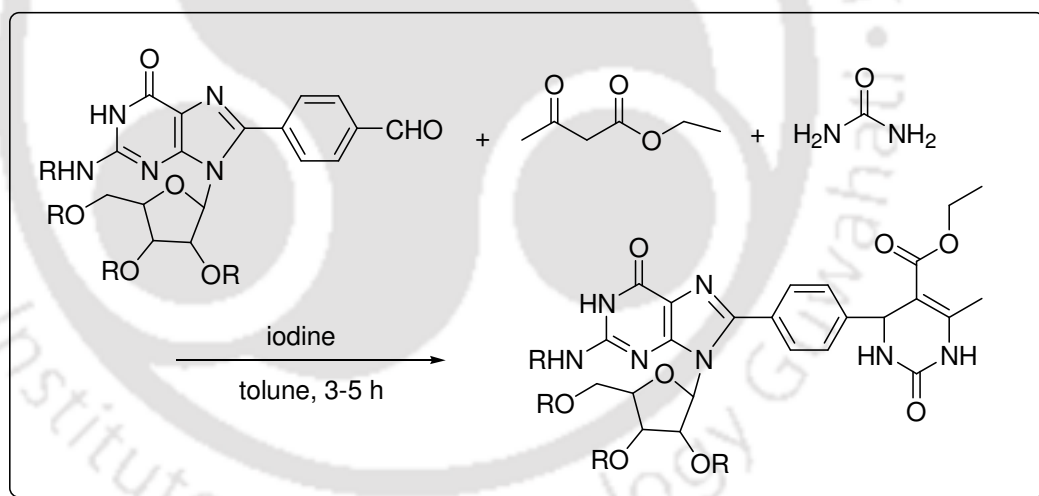
Iodine-catalysed allylation of aldehydes with allyltrimethylsilane is reported by Jadav *et al* (Scheme IA.7.4).¹¹³

**Scheme IA.7.4.**

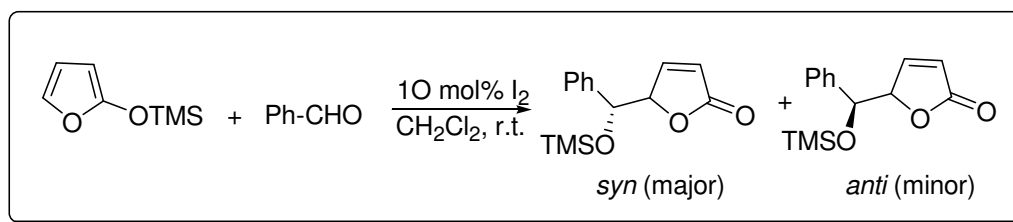
Iodine was found to be effective as a catalyst for the synthesis of β -keto enol ethers (Scheme IA.7.5).¹¹⁴

**Scheme IA.7.5.**

An efficient, high yield protocol for the one-pot synthesis of dihydropyrimidin-2(1H)-ones was achieved by iodine (Scheme IA.7.6).¹¹⁵

**Scheme IA.7.6.**

Iodine was reported as a mild and efficient catalyst for the diastereoselective synthesis of δ -silyloxy- γ -lactones (Scheme IA.7.7).¹¹⁶



Scheme IA.7.7.

IA.8. Isothiocyanates

Isothiocyanates constitute an important functional group in natural products and are present in pharmaceutically active compounds. They have been extensively used in organic synthesis,¹¹⁷ particularly in the synthesis of heterocycles as well as for the synthesis of various agrochemicals that have antifungal and anthelmintic properties.¹¹⁸ The isothiocyanate (ITC) moiety is found in many natural products and is also useful as a reactive functional group in chemical synthesis. Isothiocyanates occur in a wide variety of plants, many of which are consumed by humans on a regular basis.¹¹⁹ For example, mustard, garden cress, water cress, and broccoli (especially broccoli sprouts) are rich sources of allyl-ITC (AITC),¹²⁰ benzyl-ITC (BITC),¹²¹ phenethyl-ITC (PEITC),¹²² and sulforaphane (SF),¹²³ respectively. Isothiocyanates are synthesized by glucosinolates as part of cruciferous plants' defense mechanism.¹²⁴ The most important biological property discovered about ITCs is its anticarcinogenic property. For example figure IA.8.1. shows four potent anticarcinogens such as allyl-ITC (AITC), benzyl-ITC (BITC), phenethyl-ITC (PEITC), and sulforaphane (SF).¹²⁵

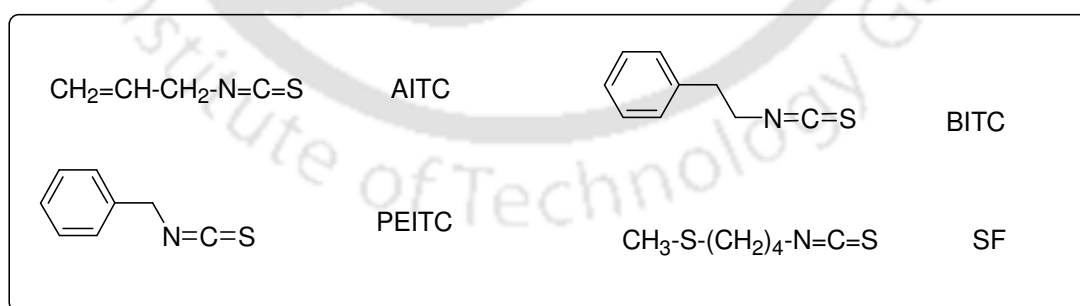


Figure IA.8.1.

The isothiocyanate functionality is also encountered in marine sesquiterpenes.¹²⁶ Additionally, synthetic isothiocyanates have been proved to have some biological activity, such as anti-

proliferatives¹²⁷ (Figure IA.8.2.) and enzyme inhibitors for the HIV virus.¹²⁸ Considering the antiproliferative activity found for ITCs, these compounds could be considered potentially responsible for the reduction of colorectal cancer associated to diets rich in cruciferous vegetables.

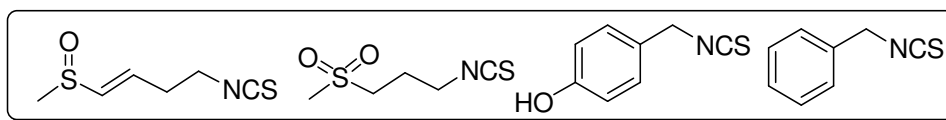


Figure IA.8.2.

Isothiocyanates are also one of the most important synthetic intermediates for the preparation of both sulfur and nitrogen containing organic compounds especially for heterocycles including thiohydantoin, thiopyrimidones, thioquinazolones, mercaptoimidazoles, thioamidazolones, and benzothiazines.^{117a,129} For example methyl 2-isothiocyanatobenzoate (**I**), (ethylthio)thiocarbonyl isothiocyanate (**II**), 2-isothiocyanatobenzyl bromide (**III**) and [N-aryl-N-(chloroacetyl)aminom]ethyl isothiocyanate (**IV**) (Figure IA.8.3.) are precursors of triazoloisoquinoline, 2-(ethylthio)-5,5-diphenyl-4-thioxo-5,6-dihydro-4H-1,3-thiazin, benzothiazine and thiadiazepines^{117a} respectively.

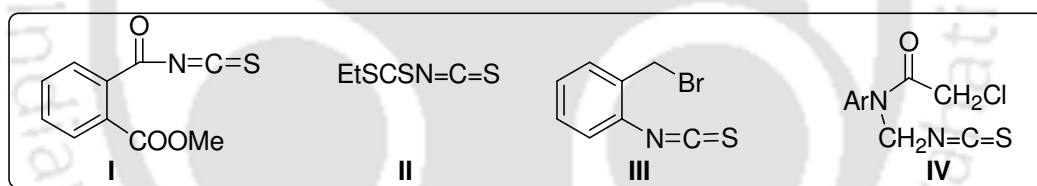


Figure IA.8.3.

Furthermore, isothiocyanates are widely applied as chemoselective electrophiles in bioconjugate chemistry because of their tolerance towards aqueous reaction conditions.¹³⁰ It has been proven to be a key reagent in Edman peptide sequencing and other biological assays of DNA and protein.¹³¹

IA.8.1. Methods for the Synthesis of Isothiocyanates

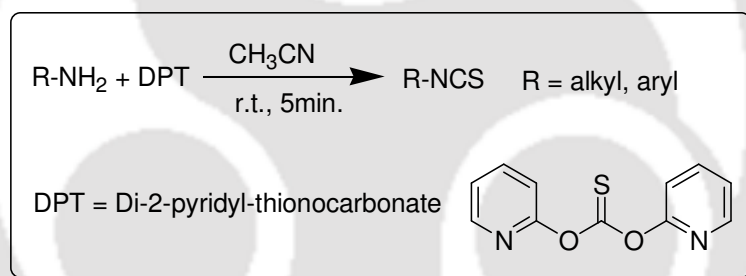
Due to their synthetic and biological importance numerous methods for the preparation of isothiocyanates from amines have been reported in the literature. The most well known method is being based on thiophosgene (Scheme IA.8.1.1.).¹³²

**Scheme IA.8.1.1.**

However, this method suffers from some limitations like high toxicity of thiophosgene and its incompatibility with many functional group. Various thiophosgene equivalents such as diethylthiocarbamoyl chloride, bis(diethylthiocarbamoyl) sulfide or disulfide, 1,1'-(thiocarbonyldioxy)di-benzotriazole, and 1,1'-thiocarbonyl-2,2'-dipyridone^{117a} and *bis*-(trichloromethyl) carbonate and trichloromethyl chloroformates¹³³ have been developed as the substitute of highly toxic thiophosgene. However, most are not readily available and often do not afford comparable reactivity.

Subsequent improvements of 'thiocarbonyl transfer' reagents are thiocarbonylditriazole,¹³⁴ thiocarbonyldiimidazole,¹³⁵ and dipyridyl-thionocarbonate (DPT).¹³⁶

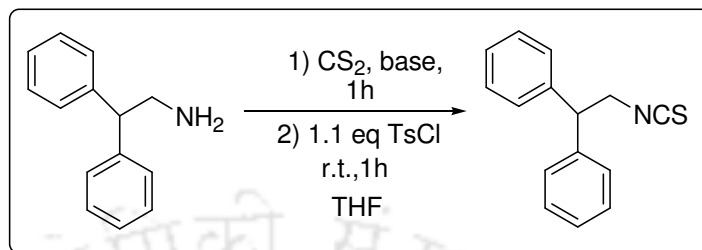
Thiophosgene derivative di-2-pyridyl thionocarbonate affords isothiocyanates on its reaction with an amine (Scheme IA.8.1.2.).¹³⁶

**Scheme IA.8.1.2.**

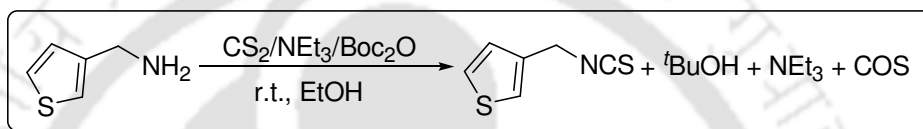
Albeit, these reagents are found to be effective in the specific formation of isothiocyanates and occasionally as desulfurylating agents for thioureas. They are somewhat limited in scope, and lead to extensive formation of the corresponding thiourea as a byproduct in the case of less reactive amines.

To avoid this side reaction, in recent years, an alternative method for the preparation of isothiocyanates from its corresponding dithiocarbamate salt has been carried out by various reagents.¹³⁷ The reagents includes uronium and phosphonium-based peptide coupling agents,¹³⁸ triphenylphosphine dibromide,¹³⁹ tosyl chloride (Scheme IA.8.1.3.),^{137b} hydrogen peroxide,¹⁴⁰ *bis*-(trichloromethyl) carbonate, trichloromethyl chloroformates. di-*tert*-butyl dicarbonate (Scheme IA.8.1.4.),^{137a} claycop (Scheme IA.8.1.5.),¹⁴¹ phosgene, phosphorus oxytrichloride, sodium

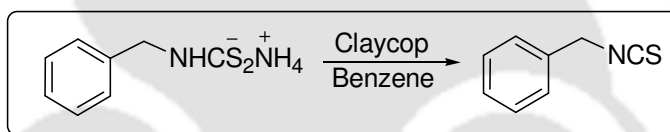
hypochlorite,¹⁴² cyanogen chloride,¹⁴³ sulfur dioxide,¹⁴⁴ or ethyl chloroformate with hydroxide¹⁴⁵ and 2-chloropyridinium salt¹⁴⁶ (Scheme IA.8.1.6.) etc.



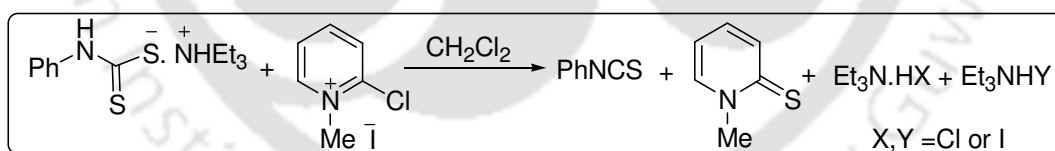
Scheme IA.8.1.3.



Scheme IA.8.1.4.



Scheme IA.8.1.5.



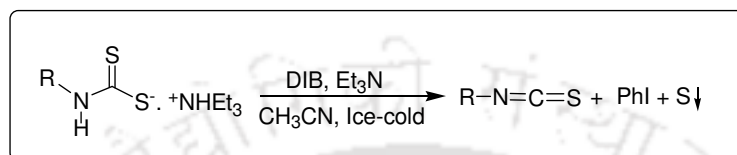
Scheme IA.8.1.6.

Most of the reagents and conditions known to affect decomposition of dithiocarbamic acid salts into isothiocyanates are often harsh and uses volatile organic solvents or result in intractable byproducts. Moreover, most of the methods suffer from low yields and the use of environmentally unattractive reagents.

With 'Green chemistry' becoming an important issue in the 21st century^{1a,3,147} developing methodologies for reagent mediated decomposition of dithiocarbamic acids to give isothiocyanates

without the use of any harmful organic solvents with environmentally benign reagents is highly desirable.

The group where the Ph.D. research was carried out has developed an excellent strategy for the preparation of isothiocyanates by diacetoxy iodobenzene (DIB) mediated decomposition of dithiocarbamate salts via oxidative desulfurization (Scheme IA.8.1.7.).¹⁴⁸



Scheme IA.8.1.7.

The expensive nature of the hypervalent iodine reagent became an obstacle for large scale requirements. So an alternative to hypervalent iodine for the decomposition of the dithiocarbamate salts was essential. Because molecular iodine is thiophilic in nature,¹⁴⁹ we reasoned that, it might also be equally effective as desulfurizing agent for the decomposition of dithiocarbamate to their corresponding isothiocyanate.

In view of the wide use of isothiocyanates, it become imperative to develop environmentally benign and economically attractive alternatives to these processes. More discussion on this aspect will find place later in **Section III of Chapter I**.

IA.9. Cyanamides

Akin to isothiocyanates, the unique structure and reactivity of cyanamides also have attracted many chemists to study these in organic chemistry¹⁵⁰ as well as in the fields of inorganic chemistry and material science.¹⁵¹ Cyanamides have been used not only as a building blocks for heterocyclic compounds but also as important intermediates for many biologically active compounds, such as minoxidil,¹⁵² and herbicides.¹⁵³ Cyanamides also find use as tumor inhibitors.¹⁵⁴ Cyanamides have been employed in multi-component Biginelli-type reactions as convenient building blocks to synthesize 4-aryl-2-cyanoimino-3,4-dihydro-1H-pyrimidine systems (**I**) containing the N-cyanoguanidiny moiety in their structure.¹⁵⁵ Cyanoguanidine moiety are organic cyanamide which are found in other biologically active molecules such as KATP channel activator, pinacidil (**II**)¹⁵⁶ and the potential antimycotic agent N-cyanoiminopyrimidine (**III**) (Figure IA.9.1.).¹⁵⁷

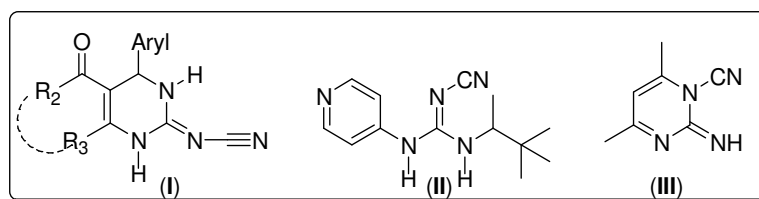
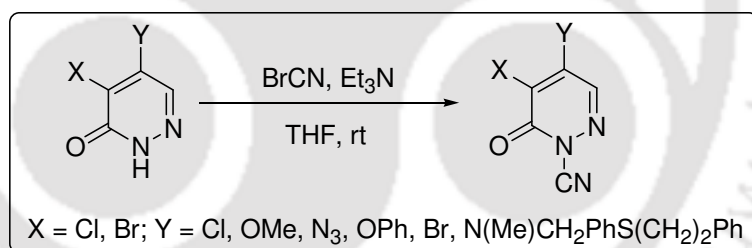


Figure IA.9.1.: Some organic cyanamides having pharmacological activity.

IA.9.1. Methods for the Synthesis of Cyanamides

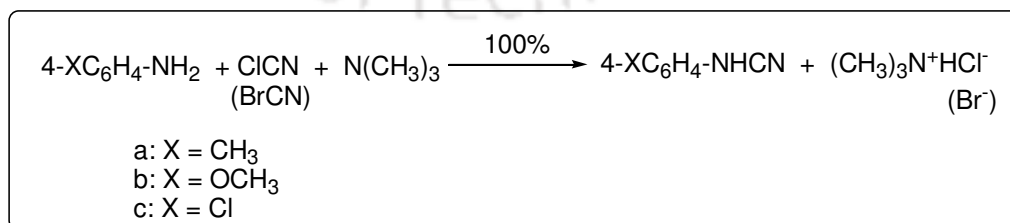
There are many approaches for the synthesis of this important class compound and the most generally used approach is cyanation of amines using cyanogen (CN^+) or cyanide ion (CN^-), using reagents such as cyanogen bromide,¹⁵⁸ tosyl cyanide,¹⁵⁹ thiocyanogen,¹⁶⁰ cyanogen azide,¹⁶¹ and metal cyanides.¹⁶² A second approach is construction of the cyanamide moiety from ureas and thioureas,¹⁶³ Tiemann rearrangement of amidoximes,¹⁶⁴ Pd-catalyzed coupling of isocyanides with allyl carbonates, and trimethylsilyl azide for synthesis of allyl cyanamides are other approaches.¹⁶⁵

2-Cyanopyridazin-3(2H)-one is reported as effective and chemoselective electrophilic cyanating agents (Scheme IA.9.1.1).¹⁶⁶



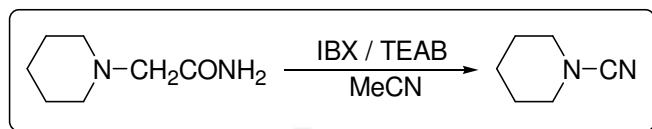
Scheme IA.9.1.1.

Also gas-solid reaction techniques was applied for the synthesis of cyanamides with ClCN and BrCN (Scheme IA.9.1.2).¹⁶⁷



Scheme IA.9.1.2.

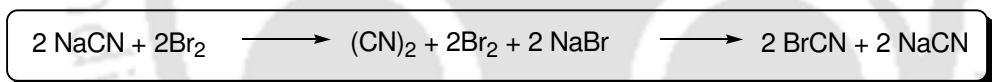
In an alternative method pentavalent iodine reagent 1-hydroxy-1,2-benziodoxyl- 3(1H)-one (IBX) in Combination with tetraethylammonium bromide (TEAB) in acetonitrile at room temperature was used to afford cyanamides (Scheme IA.9.1.3.).¹⁶⁸



Scheme IA.9.1.3.

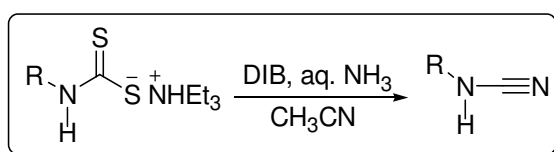
1-Cyanoimidazole is another useful mild and efficient electrophilic cyanating agent and is a suitable alternative to cyanogens halide.¹⁶⁹

The limitations of these methods are requirement of toxic reagents, use of strong alkaline conditions, corrosive reagents, and expensive reaction systems. Moreover, most of the reported methods use cyano cation (CN⁺) directly from highly toxic cyanogen bromide or indirectly from (CN⁺) synthons which, in turn, are prepared from toxic cyanogen halides. Moreover, cyanogen bromide is prepared from two toxic chemicals sodium cyanide and bromine (Scheme IA.9.1.4.).



Scheme IA.9.1.4.

The above processes do not adhere to the green chemistry and clean technology principles. Therefore, there is a need to develop environmentally acceptable alternatives. Due to ready availability, low toxicity, and easy handling, the use of hypervalent iodine reagents has shown some prospects in this regime (Scheme IA.9.1.5.).¹⁷⁰ In this strategy DIB was found to be effective as a double desulfurizing agent in the synthesis of cyanamides from its corresponding dithiocarbamate salts.



Scheme IA.9.1.5.

Taking cues from this work, we have reasoned that isothiocyanate can be obtained from the reaction of dithiocarbamic acid salt with iodine in the presence of triethylamine. The in situ generated isothiocyanate will react further with ammonia giving alkyl or aryl thiourea, which, on oxidative desulfurization with iodine and triethylamine, would form organic cyanamide. All these processes can be performed in one pot.

The **Section IV of Chapter I** describes an oxidative desulfurization approach for synthesis of cyanamides that has advantages of being mild, fast, and makes use of a nontoxic, eco-friendly and less expensive reagent system.

IA.10. Surfactant Mediated Cloud Point Extraction of Nitro Benzene From Water

Quite apart from what have been overviewed so far, application of different classes of surfactants is increasing nowadays in a number of technological areas. The main areas are biotechnology, electronic printing, high technology electronic ceramics, magnetic recording, microelectronics, non conventional energy production, novel pollution control and novel separation techniques. Among them, use of surfactant in separation processes is a major area of research in surfactant and separations science. Surfactant based separations have a number of potential advantages over traditional methods. They often are low energy intensive processes because large temperature or phase changes are not needed for separations. At times, surfactants offer improved selectivity over conventional solvent system. An additional advantage of micellar systems is that they are compatible with electrochemical detection while conventional organic solvents are not. Surfactants are often environmentally innocuous and of low toxicity, so that the leakage of a small amount of surfactant into an aqueous process stream from the separation may be tolerable, in contrast to toxic solvents from liquid-liquid extraction.

The main object of this section is to introduce some of the surprisingly large number of surfactant based separations which are known today. The techniques are divided into:

1. Processes with full-scale commercial utilization: (a) Froth flotation.^{171,172}
2. Processes with some commercial applications: (a) Adsorptive bubble separation^{173,174}
and (b) Surfactant based liquid-membranes.^{175,176}

3. Laboratory processes with high potential: (a) Micellar enhanced ultrafiltration¹⁷⁷, (b) Cloud point extraction¹⁷⁸, (c) Surfactant enhanced carbon regeneration¹⁷⁹, (d) Extraction into reverse micelles¹⁸⁰⁻¹⁸², (e) Micellar chromatography.^{183,184}

It is envisaged that surfactant based separations are likely to become a major area of technological development in environmental engineering in the next several decades. The process considered in this work is Cloud point extraction (CPE).

IA.10.1. Cloud Point Extraction (CPE)

In the last decade, increasing interest on the use of aqueous micellar solution has been found in the field of separation science.^{177,185} At certain temperature, aqueous solution of a nonionic surfactant becomes turbid. With further increase of temperature, the solution separates in two phases: a surfactant rich phase, which has small volume compared to the solution and is called coacervate phase and the bulk aqueous solution containing surfactant concentration slightly above the critical micelle concentration (CMC).¹⁸⁶ This temperature is known as the cloud point temperature (CPT) of the surfactant. The cloud point is strictly defined at a particular surfactant concentration (e.g., 1 wt%), but because the phase boundary between the two phases is fairly independent of concentration, the cloud point is generally quite close to the lower consolute solution temperature.¹⁸⁷ The solute present in aqueous solution of nonionic surfactant is distributed between the two phases at the cloud point temperature.¹⁸⁸ This phenomenon is known as cloud point extraction (CPE).

IA.10.2. Mechanism of Phase Separation

An aqueous solution of non ionic surfactant changes from single isotropic phase to two isotropic phases, when the temperature of the solution exceeds the CPT. This change of phase is reversible and on cooling, it reverts to a single isotropic phase. Actual mechanism of phase separation above CPT is not known. But, several authors proposed some mechanism using the phase separation phenomenon. The dielectric constant of water decreases with increase in temperature, which reduces the interaction between the hydrophilic portion of surfactant and water. Thus above the CPT, dehydration process occurs in the external layer of micelles of non-ionic surfactant.¹⁸⁹ On the other hand, the phase separation above CPT may also be due to the micellar attraction. This is because at lower temperature

(below CPT), inter micellar repulsive force is predominant which becomes attractive when temperature exceeds the CPT.¹⁸⁹

IA.10.3. Mechanism for the Solubilization of Solutes in Coacervate Phase

The insoluble, sparingly soluble or highly soluble solute in water dissolves extensively in/on the micelles of surfactant. The extent of solubilization and the location of solubilization in the micelles of non ionic surfactant are related to one another, but not clearly understood. Some authors have proposed that, for non ionic surfactant, the core is surrounded by a mantle of aqueous hydrophilic chains, and solubilization may occur in both the core and the mantle.¹⁹⁰ The relative amount of solubilization in these two regions of non ionic micelles depends on the polarity of solubilizate. Non ionic surfactants appear relatively more hydrophobic at higher temperatures, due to an equilibrium shift that favors dehydration of the ether oxygens. As the cloud point is approached, the solubilization of non polar solubilizates increases, probably due to an increase in the aggregation number of the micelles. For polar solubilizates, solubilization decreases owing to dehydration of the polyoxyethylene chains accompanied by coiling more tightly. These observations demonstrate that non polar compounds are solubilized in the core of micelles, while polar solubilizates are located on the mantle. Both of the temperature effects cited here are consistent with variations in the space available for the solubilized molecules in the micelles.¹⁹⁰

IA.10.4. Applications of Coacervate Phase Separation

The first applications of phase separation based on the cloud point phenomenon refer to the extraction of metal ions forming complexes sparingly soluble in water. The efficiency of the process depends on the hydrophobicity of the ligand and of the complex formed, on the apparent equilibrium constants in the micellar medium, and on the formation kinetics of the complex and on the transference between the phases. This type of extraction by the cloud point method was initially described by Watanabe and co-workers¹⁹¹ for the preconcentration of Zn(II) using 1-(2-pyridylazo)naphthol (PAN) as a ligand and PONPE as extractant. Later, this methodology was also applied to the determination of different metal ions in different types of samples. Another application of the CPE focuses on the isolation and purification of species of biological interest, mainly proteins. It is in this field of bioseparations that CPE currently finds one of its main use, as shown by the

considerable volume of literature related to the extraction and purification of membrane proteins and other biomaterials.^{192,193} The use of CPE for the extraction of organic compounds other than biomolecules is relatively recent.¹⁹⁴ CPE has been evaluated for the extraction of a series of chlorinated phenols from water.¹⁹⁵ Cloud point technique has been successfully employed for the preconcentration of polycyclic aromatic hydrocarbons,¹⁹⁶⁻¹⁹⁸ polychlorinated compound¹⁹⁵ and vitamins.^{194,199,200}

Chapter II describes the surfactant mediated cloud point extraction of nitro benzene from water.

IA.11. Objective of the Thesis

On the basis of brief review presented above, the following problems appear to require serious attention:

(i) Development of new homogeneous catalytic system for the bromination of organic substrates. No use of hazardous Br₂, volatile organic solvents in the synthesis. Involvement of cost effective, readily available, non-toxic catalyst, oxidant and a green solvent for the oxidative bromination of organic substrates is essential. Recyclability of the catalyst also requires attention.

(ii) Apart from the homogeneous catalysis, solid acid catalysis is also an important area of research. Use of solid acid catalysts for specific organic transformations is preferred. A solid acid not only replaces mineral acids in fine chemical manufacturing process but also catalyze the reaction heterogeneously. Therefore, this it is worthwhile to carry out *aza*-Michael reactions with Phosphate Impregnated Titania a heterogeneous catalyst.

(iii) Alkyl and arylisothiocyanates are versatile synthetic intermediates, thus there is a need for a commercially viable and environmentally acceptable protocol for the synthesis of isothiocyanates. The methods reported involve use of toxic reagents like phosgene etc. Therefore, development of a eco-friendly and cost effective method for the synthesis of isothiocyanates via reagent mediated decomposition of dithiocarbamate salt is essential.

(iv) Like isothiocyanates, cyanamides are an important class of compounds which are vital intermediates for the synthesis of various biologically active molecules. Procedures so far involve direct or indirect use of toxic and corrosive reagents like cyanogens bromide etc., strong alkaline conditions, high reaction temperatures. Accordingly, while looking at reaction strategies from a Green chemistry perspective, it would be worthwhile to investigate an alternative methodology for the synthesis of cyanamides, involving the use of alkyl or aryl dithiocarbamate using iodine as double desulfurizing agent.

(v) Apart from the green synthetic methodologies, surfactant based separation techniques with potential for wide industrial application is also an important area of research. One of the high potential surfactant based separation techniques is cloud point extraction. Cloud point technique has been successfully employed for the preconcentration of polycyclic aromatic hydrocarbons, polychlorinated compound and vitamins. The applicability of cloud point extraction technique for the removal of nitro benzene from their aqueous solution using a non ionic surfactant has to be investigated. Modest energy consumption, higher extraction efficiency, lower cost, experimental conveniences are some of the advantages of cloud point extraction. The cloud point extraction with non-ionic surfactants insures the low-cost, simple and accurate analytic procedure.

Research addressing the problems highlighted above is not only of topical importance but also expected to be rewarding. Accordingly, attempts have been made to address the problems defined above for the present Ph.D. research.

This thesis brings together some innocuous organic synthetic methodologies and a surfactant based separation technique for the removal of nitro benzene with a nonionic surfactant using cloud point extraction. The subject matter of the thesis has been divided into two chapters. **Chapter I** has been divided into two parts: Part I and Part II. While the present chapter (i.e. **Part I of Chapter I**) gives an overview of the state of current research in these areas, Part II of Chapter I has been further divided into four subsections, which describes four innocuous synthetic methodologies. The main themes of **Section I of Chapter I** is the development of an easy to operate, practical, and environmentally benign protocol for the regioselective bromination of aromatic compounds involving boric acid as the catalyst, KBr as the source of bromide, and hydrogen peroxide as the oxidant. The solvent used is either water or ethanol both of which are environmentally friendly. This work has been

published in *Green Chemistry Letters and Review*. The sources of chemicals and solvents that were used in the work, methods of preparation of a few starting materials, details of the methods of chemical analyses, and particulars of various instruments and equipment used for physico-chemical studies and characterization of the reported compounds have also been incorporated in this chapter. Each chapter (i.e. Section I-IV of Chapter I and Chapter II) has also been so design as to render it self contained. Thus a chapter begins with a brief introduction and sections on results and discussion, conclusions and experimental followed by references.

The **Section II of Chapter I** reports the heterogeneous catalyst, phosphate impregnated titania catalysed *aza*-Michael reactions under solvent-free condition. The results have been published in *Catalytic Letters*.

The **Section III of Chapter I** demonstrates a molecular iodine mediated preparation of isothiocyanates from dithiocarbamic acid salts. The results have been published in *European Journal of Organic Chemistry* and *Green Chemistry Letters and Review*.

The **Section IV of Chapter I** reports a one-pot preparation of cyanamide from dithiocarbamate salts using molecular iodine. This work has already been published in *Green Chemistry*.

CPE of nitro benzene is represented in **Chapter II**. Aqueous synthetic solution of NB in single component system is used for the initial study. The effects of different operating parameters, e.g., concentration of the feed mixture (both NB and surfactant), pH, temperature and the presence of mono and divalent salt on the extraction of both NB and surfactant have been studied in detail. Change in thermodynamic parameters like, enthalpy, entropy and Gibbs free energy for the CPE of nitrobenzene are reported. From the experimental data, a solubilization isotherm is developed to quantify the amount of NB solubilization. A method has been proposed to design a cloud point extractor for the separation of NB. To test the efficiency of surfactant recovery from the dilute phase, solvent extraction technique has been adopted and explained detail in the same chapter. The manuscripts are under preparation.

Section I.

IAI.1. Boric Acid Catalyzed Bromination of a Variety of Organic Substrates: An Eco-friendly and Practical Protocol

Owing to their increasing commercial use brominated aromatic compounds are very important in synthetic organic chemistry. They are key intermediates in the preparation of many organometallic reagents¹⁻⁴ and play vital roles in transition metal mediated coupling reactions such as Stille,⁵ Suzuki,⁶ Heck,^{7,8} and Sonogashira reactions.^{9,10} Many pesticides, insecticides, herbicides, pharmaceutically, and medicinally active molecules, and fire retardants carry bromo functionality.¹¹

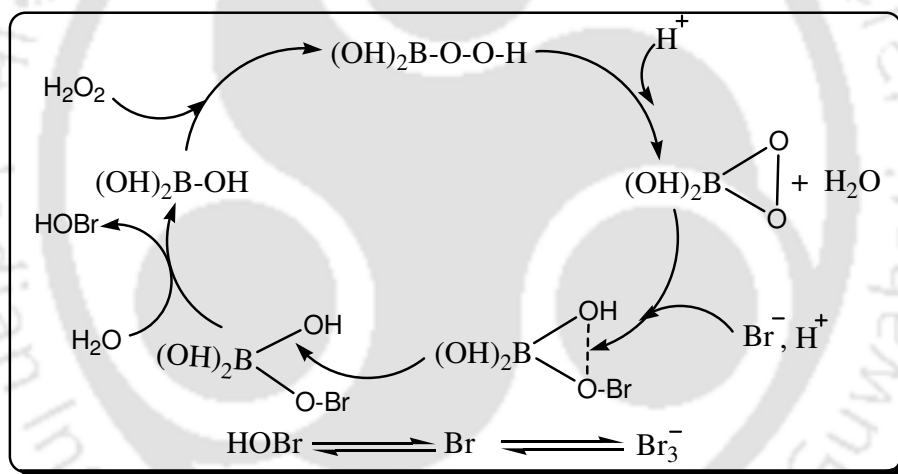
The need for isomerically pure bromoaromatic compounds has led to develop selective brominating agents or bromination protocols.¹² Most of the processes currently practiced for the bromination of aryl compounds employ toxic, corrosive, and rather expensive molecular bromine, resulting in the formation of large amount of HBr waste, thereby reducing the atom efficiency by 50%.¹¹ In large scale operations this causes environmental problem in addition to being expensive. Bromination using HBr with either H₂O₂^{11,13-15} or O₂¹⁶⁻¹⁸ as an oxidant was thought to be a possible solution. This, however, met with partial success. In addition, HBr is highly toxic and corrosive, and is as harmful as molecular bromine. These problems enhanced the appeal of bromination protocols based on oxidation of bromide salt by H₂O₂ with better bromide atom economy.^{13-16,19,20} The systems reported so far require metal or other catalysts and volatile organic solvents.^{16,19,21-24} Recently, Adimurthy et al. reported an 'eco-friendly and versatile' brominating reagent based on Br⁻/BrO₃⁻ (2:1) and HCl (2 Molar).²⁵

Our endeavor for an eco-benevolent method for bromination of organic substrates has culminated in the development of an easy to operate, practical, and environmentally benign protocol for the regioselective bromination of aromatic compounds involving boric acid as the catalyst, KBr as the source of bromide, and hydrogen peroxide as the oxidant. The solvent used is either water or ethanol both of which are environmentally friendly.

IAI.2. Results and Discussion

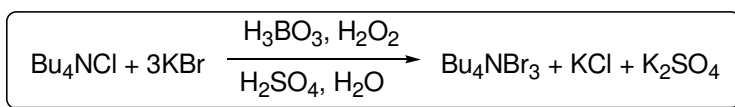
IAI.2.1. Background

Boric acid is easily available, inexpensive, ecologically favorable, safe to handle, and is effective under milder conditions. It can be removed, after reaction, by the aqueous bicarbonate wash. Notably, boron acids (i.e. boric and boronic acids) act as catalyst in a number of transformations, for example, esterification of α -hydroxycarboxylic acids,²⁶ *aza*-Michael,²⁷ *thia*-Michael²⁸ reactions and organic sulfide oxidations.²⁹ The present protocol is based on the (i) role of the catalyst as a Lewis acid in the activation of H_2O_2 forming peroxoborate species followed by (ii) the oxidation of bromide by peroxoborate intermediate in the presence of acid to Br_3^- as the active brominating agent and finally (iii) site-selective bromination of organic substrates to afford bromoorganic compounds (Scheme IAI.2.1.1).



Scheme IAI.2.1.1: Mechanism of bromination of organic substrates using H_3BO_3 and H_2O_2 .

Our earlier work on peroxoborate²⁹ and oxidative bromination of aromatics³⁰ suggested that the peroxoborate intermediate generated *in situ* would enable bromide oxidation in presence of an acid. The fact, that Br_3^- is formed in this process has been ascertained from an independent experiment wherein Br^- was oxidized by the present methodology in the absence of any organic substrate but in presence of tetrabutylammonium chloride and three equivalents of KBr leading to nearly quantitative isolation of tetrabutylammonium tribromide (TBATB) (98% yield) (Scheme IAI.2.1.2). The identity of TBATB has been ascertained by comparing with the authentic product.³¹⁻³³



Scheme IAI.2.1.2: Preparation of TBATB using KBr, H₃BO₃ and H₂O₂

IAI.2.2. Screening of Reaction Conditions

Initially, we choose phenol as a model substrate and reacted with potassium bromide in water in the presence of 30% H₂O₂ and 0.5 equivalent of 5 M H₂SO₄ at room temperature. A relatively poor yield (50%) of *p*-bromophenol was achieved in 3 h (entry 1, Table IAI.2.2.1).

Table IAI.2.2.1. H₃BO₃-Catalysed bromination of phenol with KBr and H₂O₂ in water under different reaction conditions

Entry	H ₃ BO ₃ (mol %)	Temp. (°C)	Time (min)	Conversion (%) ^a	Yield (%) ^a		
					Para	Ortho	Di (<i>o,p</i>)
1	Nil	25	180	70	50	17	3
2	5	25	20	99	75	20	5
3	5	5	480	75	52	20	3
4	5	65	10	99	71	15	13
5	10	25	10	99	70	17	12
6	7.5	25	15	99	74	20	5
7	2.5	25	40	86	67	17	2

^a Conversion and selectivity were determined by GC.

Addition of boric acid (5 mol%) under identical conditions, increased the yield to 75% (entry 2, Table IAI.2.2.1) within 20 mins. This success encouraged us to conduct the reaction at different temperatures (Table IAI.2.2.1). Although the conversion increased at higher temperature (65 °C), the selectivity was a little lower (71% *p*-bromophenol). Conversely, the reaction was not complete at 5 °C even after 8 h (yield 52%, entry 3, Table IAI.2.2.1). Thus, room temperature was found to be conducive with minimal energy requirement. Similarly, the experiments on catalyst optimization (Table IAI.2.2.1) suggested that the presence of 5 mol% of the catalyst afforded the best result at ambient temperature. Bromination of a variety of aromatic compounds was carried out under the standardized experimental conditions in either water (for liquid substrates) or C₂H₅OH (for solid substrates). The details including the isolated yields are shown in Table IAI.2.2.2.

Table IAI.2.2.2. Bromination of organic substrates using KBr and H₃BO₃-H₂O₂ system

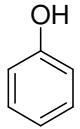
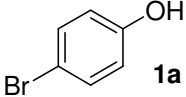
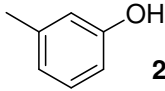
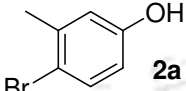
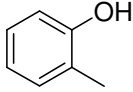
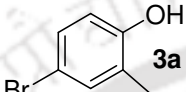
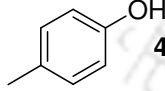
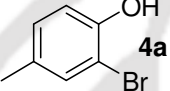
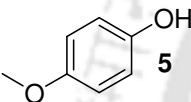
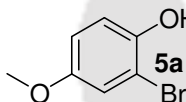
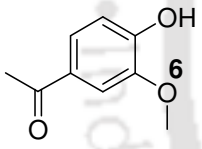
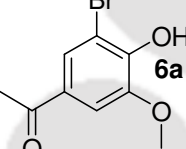
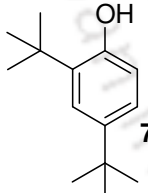
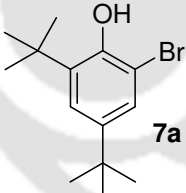
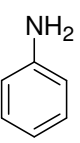
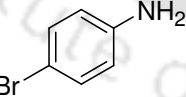
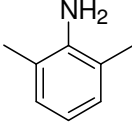
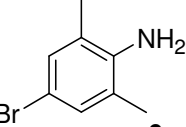
Substrate ^a	Product	Substrate : KBr	Solvent	Time/h	Yield ^b (%)	Ortho:Para:Di (o,p)
 1	 1a	1:1.2	H ₂ O	0.3	75 ^c , 78 ^d	20:75:5 ^e
 2	 2a	1:1.2	H ₂ O	0.58	85	9:85:6 ^e
 3	 3a	1:1.2	H ₂ O	0.58	80	8:80:16 ^e
 4	 4a	1:1.2	H ₂ O	0.58	75	75:-:15 ^f
 5	 5a	1:1.2	C ₂ H ₅ OH	0.75	76	-
 6	 6a	1:1.2	C ₂ H ₅ OH	20	60	60:-:10 ^f
 7	 7a	1:1.2	C ₂ H ₅ OH	2	77	-
 8	 8a	1:1.2	H ₂ O	0.58	80	-
 9	 9a	1:1.2	H ₂ O	0.46	95	-

Table contd.

Table IAI.2.2.2. Bromination of organic substrates using KBr and H₃BO₃-H₂O₂ system

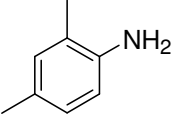
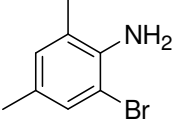
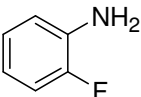
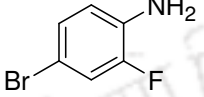
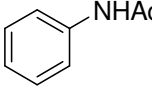
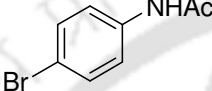
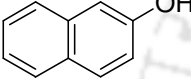
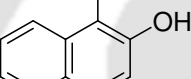
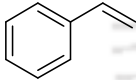
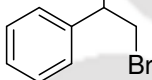
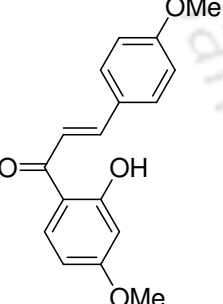
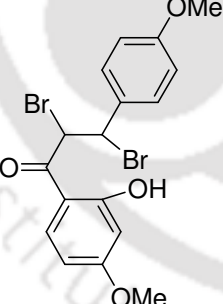
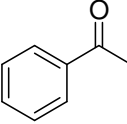
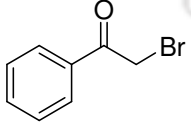
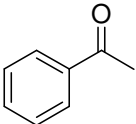
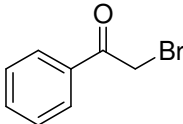
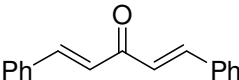
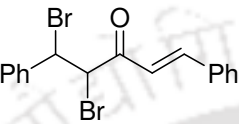
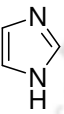
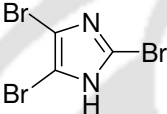
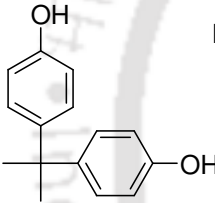
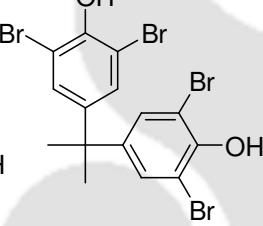
Substrate ^a	Product	Substrate : KBr	Solvent	Time/h	Yield ^b (%)	Ortho:Para:Di (o,p)
		1:1.2	H ₂ O	0.33	99	-
10	10a					
		1:1.2	H ₂ O	2	85	5:80:10 ^e
11	11a					
		1:1.2	C ₂ H ₅ OH	2	86	-
12	12a					
		1:1.2	C ₂ H ₅ OH	0.83	87	-
13	13a					
		1:2.2	H ₂ O	0.58	85	-
14	14a					
		1:2.2	C ₂ H ₅ OH	2	70	-
15	15a					
		1:1.2	H ₂ O	24	76	-
16	16a					

Table contd.

Table IA1.2.2.2. Bromination of organic substrates using KBr and H₃BO₃-H₂O₂ system

Substrate ^a	Product	Substrate : KBr	Solvent	Time/h	Yield ^b (%)	Ortho:Para:Di (o,p)
		1:1.2	H ₂ O	24	76	-
16	16a					
		1:2.2	C ₂ H ₅ OH	1.5	90	-
17	17a					
		1:4	C ₂ H ₅ OH	0.83	70	-
18	18a					
		1:6	C ₂ H ₅ OH	0.66	40	-
19	19a					

^aReactions were monitored by TLC. ^bIsolated yields of the major product. ^cYields were determined by GC. ^dYield on 5 g scale. ^e o,p selectivity is with respect to OH and NH₂ group. ^f o,o` selectivity is with respect to OH group

Phenols **1-3** and anilines **8** and **9** were found to be the most reactive to give the corresponding *p*-bromophenols **1a-3a** and *p*-bromoanilines **8a** and **9a**, respectively. Regioselective bromination of aromatics is an important protocol in organic synthesis because of their use as synthetic intermediates for a variety of transformations.²² Thus, acetanilide **12** gave exclusively the para-derivative in very high yield. Similar results were obtained with the substrates **4-5**, **7**, **10**, and **11** bearing different functional groups. Also substrate **6** having oxidizable group (-CHO) was successfully brominated to its corresponding bromo analogue. Deactivated aniline **11** was smoothly brominated to the corresponding *p*-bromoaniline **11a** in 2 hr. Poly-cyclic phenol, β-naphthol **13** selectively afforded 1-bromo β-naphthol in very high yield. This is rather tedious by some other methodologies using *N*-

methylpyrrolidin-2-one hydrotribromide (MPHT) as a brominating agent in the presence of aqueous 30% hydrogen peroxide in methanol.³⁴

The methodology also works well for bromination of ethylenic and carbonyl functions. For example, vinyl benzene **14** was efficiently brominated to the corresponding dibromo derivative. Quite interesting is the reaction of 4-methoxy-4'-methoxy-2'-hydroxychalcone **15**, where double bond in the chalcone is selectively brominated in the presence of an activated aromatic ring. Product **15a** is an important precursor for flavonoids (cf. vitexin).³⁰ α -Bromination of acetophenone **16**, is achieved over aromatic bromination because of the deactivating nature of the aromatic ring, thus, exclusively giving the corresponding α -bromo acetophenone **16a** in high yield. This compound **16a** is an important precursor for heterocycle synthesis^{35,36} and Suzuki coupling reactions.³⁷ Also important is the chemoselective bromination of one of the double bond in a substrate containing two symmetrical double bonds, as demonstrated for dibenzylidene acetone **17** giving product **17a**. Imidazole **18**, which is sensitive to usual bromination,³¹ was brominated to 2,4,5-tribromoimidazole **18a** in high yield. This product (**18a**) is believed to be capable of catalytically reactivating phosphorylated acetylcholinesterase.³⁸ In yet another interesting reaction bisphenol-A **19** was brominated to tetrabromobisphenol-A (4,4'-isopropylidene-bis-(2,6-dibromophenol)) **19a** under the conditions used herein. This is otherwise difficult to achieve because of formation of side products, requirement of high temperature and long-reaction time. Tetrabromobisphenol-A is possibly the largest selling flame retardant used extensively to provide flame retardency for styrenic thermoplastics and for some thermo set resins.³⁹ Our attempt to achieve bromination of benzene was unsuccessful. Finally, upon completion of the reaction, the catalyst recyclability was examined through a series of reactions involving phenol and the recyclable mother liquor containing boric acid, H₂SO₄ and additional amount of bromide (Table IAI.2.2.3.).

Table IAI.2.2.3.: Recycling of the catalyst for the reaction of phenol in water

Cycle	Conversion (%)	Time (h)
1	99	0.75
2	92	3.5
3	91	5

The reaction continued giving good yields, however, with relatively long reaction times due to leaching of the catalyst.

In conclusion, the present results demonstrate the production of bromoorganic compounds with very high selectivity under mild and metal free catalytic conditions. No use of Br₂ and volatile organic solvents in the synthesis, the involvement of cost effective, readily available and non-toxic catalyst, and water or C₂H₅OH as the reaction medium renders this protocol green, attractive, and practically useful.

IAI.3. Experimental

IAI.3.1. General Remarks

All the reagents were of reagent grade (AR grade) and were used as purchased without further purification. The solvents were of commercial grade and purified according to established procedures. Following are the sources of the chemicals and solvents: S.D. fine-chem ltd, Qualigens Fine Chemicals, Rankem (India), E. Merck (India) Limited, Sisco Research Laboratories Pvt. Ltd, Central Drug House (P) Ltd, Bengal Chemicals and Pharmaceuticals Ltd, Loba Chemie Industries, and Spectrochem (India), Sigma- Aldrich (India), Lancaster (India).

Organic extracts were dried with anhydrous sodium sulfate. Solvents were removed in a rotary evaporator under reduced pressure. Silica gel (60-120 mesh size) was used for column chromatography. Reactions were monitored by TLC on silica gel GF₂₅₄ (0.25 mm).

IAI.3.2. Characterization of Organic Substrates

Melting points were recorded with a Büchi B-540 melting point apparatus. Elemental analysis was performed with a Perkin-Elmer 2400 Series II CHNS/O Analyzer. Fourier transform-infra red (FT-IR) spectra were recorded on Nicolet Impact-410 instrument either as neat liquid or in KBr pellets. pH values of the reaction solutions were recorded with a Systronics Type 335 digital pH meter and also by using Merck pH indicator paper. UV-visible spectra were recorded, by dissolving a calculated amount of the sample in an appropriate solvent, on a Perkin-Elmer UV-visible λ-45 Spectrophotometer. GC-MS was recorded on a Perkin-Elmer Precisely Clarus 500 instrument using a capillary column (30×0.25×0.25 mm) in EI mode. GC was recorded on Thermo Trace GC Ultra 2000 instrument using, TIPO BP1 capillary column (30m x 0.25mm). NMR spectra were recorded in

CDCl_3 or $[\text{D}_6]$ DMSO with tetramethylsilane as the internal standard for ^1H (400 MHz) or CDCl_3 or $[\text{D}_6]$ DMSO solvent as the internal standard for ^{13}C (100 MHz) on a Varian 400MHz.

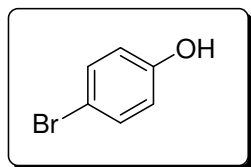
IAI.3.3. General Procedure

IAI.3.3.1. General experimental procedure for bromination of phenol

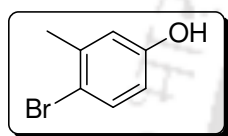
To an aqueous solution of boric acid (3.1 mg, 0.05 mmol) in 30% H_2O_2 (338 μL , 3 mmol), phenol (94 mg, 1 mmol) was added. To this KBr (142.8 mg, 1.2 mmol), 5M H_2SO_4 (100 μL , 0.5 mmol) were added and the whole was stirred at room temperature. The progress of the reaction was monitored by thin layer chromatography. After completion of the reaction, the mixture was washed with 5 % Na_2SO_3 solution (10 mL) to destroy any excess of H_2O_2 if present and then extracted with ethylacetate (2 x 10 mL). The organic extract was dried over anhydrous Na_2SO_4 . Evaporation of the solvent left the crude product, which was further purified by column chromatography on silica gel with hexane as the eluent to afford the pure product. The aqueous layer containing boric acid and sulfuric acid was reused for the next run with an additional amount of bromide.

IAI.3.3.2. General experimental procedure for bromination of anilines

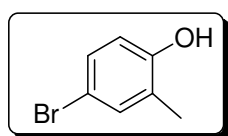
To a solution of boric acid (3.1 mg, 0.05 mmol) in 30% H_2O_2 (338 μL , 3 mmol), substrate (1 mmol) was added. To this KBr (142.8 mg, 1.2 mmol), 5M H_2SO_4 (100 μL , 0.5 mmol) were added and the whole was stirred at room temperature. For liquid substrates water (2.5 mL) and for solid substrates $\text{C}_2\text{H}_5\text{OH}$ (2.5 mL) were used as solvents. The progress of the reaction was monitored by thin layer chromatography. After completion of the reaction, the mixture was successively washed with 5% NaHCO_3 (2 x 5 mL), water, brine (2 x 5 mL) and 5 % Na_2SO_3 solution (2 x 5 mL) and then extracted with ethylacetate (2 x 10 mL). After extraction the organic extract was dried over anhydrous Na_2SO_4 . Evaporation of solvent left the crude product, which was purified by column chromatography on silica gel with ethylacetate and hexane (ratio varied with product) as the eluent to afford the pure product. However, solid products were recrystallized in ethylacetate. The aqueous layer containing boric acid and sulfuric acid was reused for the next run with an additional amount of bromide.

IAI.4. Spectral Data**4-Bromo-phenol (1a):**

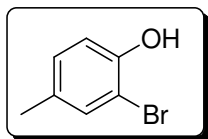
Oily liquid. ^1H NMR (400 MHz, CDCl_3): δ 5.03 (brs, 1H), 6.72 (d, $J = 8.8$ Hz, 2H), 7.32 (d, $J = 7.6$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 112.9, 117.4, 132.6, 154.8. IR (neat): 3401, 1588, 1489, 1474, 1243, 1070, 1007, 823, 606, 500 cm^{-1} . Mass (EI): 172 / 174 (M^+).

4-Bromo-3-methyl-phenol (2a):

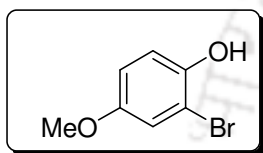
White solid. Mp: 58-60 $^\circ\text{C}$. ^1H NMR (400 MHz, CDCl_3): δ 2.3 (s, 3H), 5.16 (s, 1H), 6.53 (dd, $J_1 = 7.2$ Hz, $J_2 = 8.8$ Hz 1H), 6.71 (d, $J = 3.2$ Hz, 1H), 7.33 (d, $J = 8.8$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 23.4, 114.6, 115.8, 118.0, 133.2, 139.2, 154.8. IR (neat): 3394, 2981, 2923, 1603, 1578, 1474, 1290, 1240, 1163, 1029, 857, 805, 601 cm^{-1} . MS (EI): 186 / 188 (M^+).

4-Bromo-2-methyl-phenol (3a):

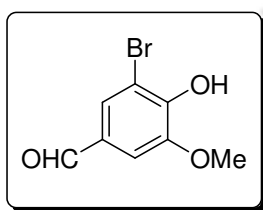
White solid. Mp: 64-66 $^\circ\text{C}$. ^1H NMR (400 MHz, CDCl_3): δ 2.21 (s, 3H), 4.96 (brs, 1H), 6.63 (d, $J = 8.0$ Hz, 1H), 7.16 (dd, $J_1 = 5.6$ Hz, $J_2 = 2.4$ Hz, 1H), 7.22 (d, $J = 2.4$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 15.8, 112.7, 116.6, 126.4, 129.8, 133.6, 152.9. IR (KBr): 3407, 2933, 1492, 1407, 1263, 1178, 1118, 814, 630 cm^{-1} .

2-Bromo-4-methyl-phenol (4a):

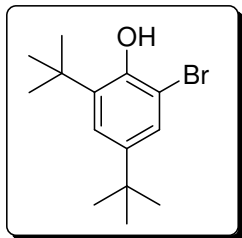
Oily liquid. ^1H NMR (400 MHz, CDCl_3): δ 2.26 (s, 3H), 5.34 (s, 1H), 6.9 (d, $J = 8$ Hz, 1H), 7.01 (d, $J = 8.4$ Hz, 1H), 7.26 (d, $J = 6.8$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 20.1, 109.5, 115.8, 118.0, 129.9, 132.2, 132.5, 150.1. IR (neat): 3394, 2981, 2923, 1603, 1578, 1474, 1290, 1240, 1163, 1029, 857, 805, 601 cm^{-1} .

2-Bromo-4-methoxy phenol (5a):

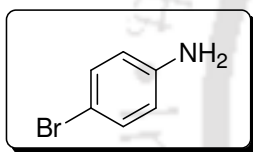
^1H NMR (400 MHz, CDCl_3): δ 3.74 (s, 3H), 5.32 (brs, 1H), 6.77 (m, 1H), 6.92 (m, 1H), 7.00 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 56.3, 110.1, 115.5, 116.6, 117.1, 146.6, 153.9. IR (KBr): 3431, 2950, 2842, 1588, 1495, 1208, 1039, 768 cm^{-1} .

3-Bromo-4-hydroxy-5-methoxy-benzaldehyde (6a):

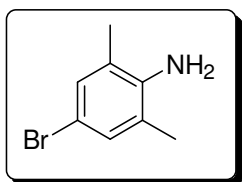
Yellow solid. Mp: 165-166 $^\circ\text{C}$. ^1H NMR (400 MHz, CDCl_3): δ 3.98 (s, 3H), 6.55 (s, 1H), 7.35 (d, $J = 1.4$ Hz 1H), 7.63 (s, $J = 1.4$ Hz 1H), 9.80 (s, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 56.9, 108.3, 108.4, 130.2, 130.3, 147.8, 149.0, 189.6. IR (KBr): 3314, 2976, 2945, 2848, 1685, 1588, 1511, 1429, 1358, 1291, 1158, 1055, 682 cm^{-1} .

2-Bromo-4,6-di-tert-butyl-phenol (7a):

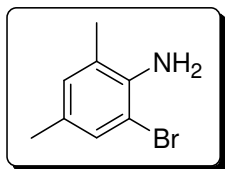
Yellow solid. Mp: 58.2-60.3 °C. ^1H NMR (400 MHz, CDCl_3): δ 1.28 (s, 9H), 1.40 (s, 9H), 5.64 (s, 1H), 7.24 (s, 1H) 7.31 (s, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 26.8, 29.5, 29.6, 31.7, 34.6, 35.7, 111.1, 126.4, 136.9, 143.9, 148.2. IR (KBr): 3519, 2955, 2863, 1577, 1485, 1362, 1275, 1178, 870, 840, 742, 712 cm^{-1} .

4-Bromo-aniline (8a):

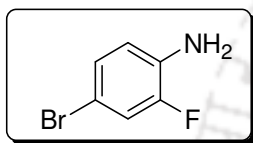
Greenish solid. Mp: 58-62 °C. ^1H NMR (400 MHz, CDCl_3): δ 3.65 (brs, 2H), 6.56 (d, $J = 8$ Hz, 2H), 7.24 (d, $J = 6.4$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 110.3, 116.8, 132.1, 145.5. IR (KBr): 3375, 3032, 2925, 1629, 1491, 1281, 1178, 1071, 810, 605, 502 cm^{-1} .

4-Bromo-2,6-dimethyl-aniline (9a):

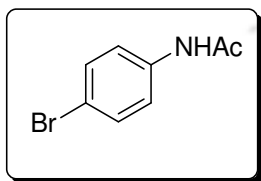
Reddish solid. Mp: 47-50 °C. ^1H NMR (400 MHz, CDCl_3): δ 2.21 (s, 6H), 7.05 (s, 2H), 8.10 (s, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 17.6, 18.46, 109.6, 123.8, 130.7, 131.0, 131.4, 131.5, 141.9. IR (KBr): 3394, 1624, 1473, 1265, 1230, 859, 737 cm^{-1} .

2-Bromo-4,6-dimethyl-aniline (10a):

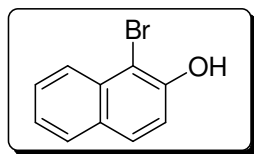
Brownish oil. ^1H NMR (400 MHz, CDCl_3): δ 2.17 (s, 6H), 5.28 (s, 2H), 6.79 (s, 1H), 7.10 (s, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 18.4, 20.2, 53.6, 109.6, 123.7, 128.6, 130.4, 130.5, 139.8. IR (KBr): 3387, 2926, 1624, 1483, 1289, 850, 738 cm^{-1} .

4-Bromo-2-fluoro-aniline (11a):

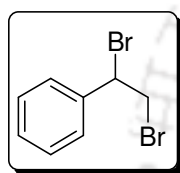
Yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 3.72 (brs, 2H), 6.65 (m, 1H), 7.05 (m, 1H), 7.13 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 109.0, 117.9, 118.0, 118.7, 118.9, 127.5, 127.6, 134.0, 150.0, 152.6. IR (KBr): 3391, 3088, 2925, 1711, 1486, 1419, 1209, 1071, 892, 697, 564 cm^{-1} .

4-Bromo-acetanilide (12a):

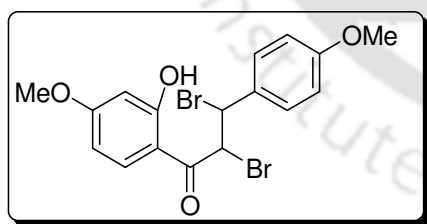
White solid. Mp: 167-168 $^\circ\text{C}$. ^1H NMR (400 MHz, DMSO-d_6): δ 2.02 (s, 3H), 7.27 (d, $J = 8.4$ Hz, 2H), 7.44 (d, $J = 8.8$ Hz, 2H), 9.56 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 23.5, 114.8, 120.6, 130.7, 137.6, 168.3. IR (KBr): 3293, 3261, 3186, 3052, 1665, 1601, 1524, 1488, 1391, 1325, 1007, 830, 742 cm^{-1} .

1-Bromo-2-naphthol (13a):

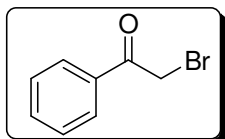
Black solid. Mp: 79-80 °C. ^1H NMR (400 MHz, CDCl_3): δ 5.92 (brs, 1H), 7.35 (m, 1H), 7.38 (m, 1H), 7.56 (m, 1H), 7.75 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 106.3, 117.3, 124.3, 125.5, 128.0, 128.4, 129.5, 132.4, 150.7. IR (KBr): 3300, 2920, 2850, 1500, 1450, 1350, 1300, 1230, 980, 930, 810, 750, 650 cm^{-1} .

1,2-(Dibromo-ethyl)-benzene (14a):

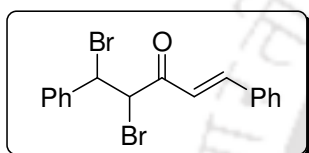
White solid. Mp: 71-73 °C. ^1H NMR (400 MHz, CDCl_3): δ 4.05 (m, 2H), 5.14 (dd, $J_1 = 5.6$ Hz, $J_2 = 5.2$ Hz 1H), 7.39 (m, 5H). ^{13}C NMR (100 MHz, CDCl_3): δ 35.23, 51.3, 127.9, 129.1, 129.4, 138.8. IR (KBr): 3064, 3033, 1496, 1455, 1431, 1231, 1198, 1155, 907, 769, 691, 590 cm^{-1} .

4-Methoxy-4'-methoxy-2'-hydroxy-dibromochalcone (15a)

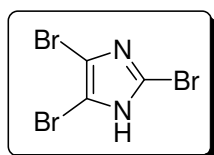
^1H NMR (400 MHz, CDCl_3): δ 3.16 (s, 3H), 3.91 (s, 3H), 4.75 (d, $J = 9.6$ Hz, 1H), 5.04 (d, $J = 10$ Hz, 1H), 5.27 (s, 1H), 6.91 (d, $J = 8.4$ Hz, 1H), 7.35 (dd, $J_1 = 4$, $J_2 = 8.4$ Hz, 1H), 7.49 (m, 2H), 7.64 (d, $J = 2$ Hz, 1H), 8.0 (d, $J = 7.6$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 47.4, 56.4, 57.9, 82.5, 111.56, 129.0, 131.6, 132.7, 134.0, 135.2, 156.3, 193.1. IR (KBr): 3065, 2931, 1688, 1598, 1496, 1459, 1284, 1258, 1096, 1053, 1020, 806, 779, 687, 652, 615 cm^{-1} .

2-Bromo-1-phenyl-ethanone (16a):

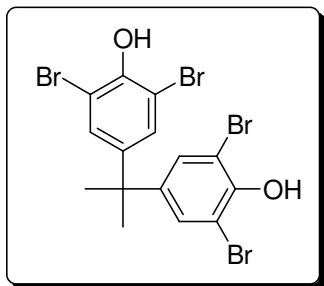
Yellow solid. Mp: 47-49 °C. ^1H NMR (400 MHz, CDCl_3): δ 4.46 (s, 2H), 7.48 (m, 2H), 7.6 (m, 1H), 7.9 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 31.2, 128.44, 128.71, 133.27, 134.12, 191.42. IR (KBr): 3058, 2935, 1690, 1593, 1450, 1281, 1194, 1020, 764, 687, 615 cm^{-1} .

4,5-Dibromo-1,5-diphenyl-pent-1-en-3-one (17a):

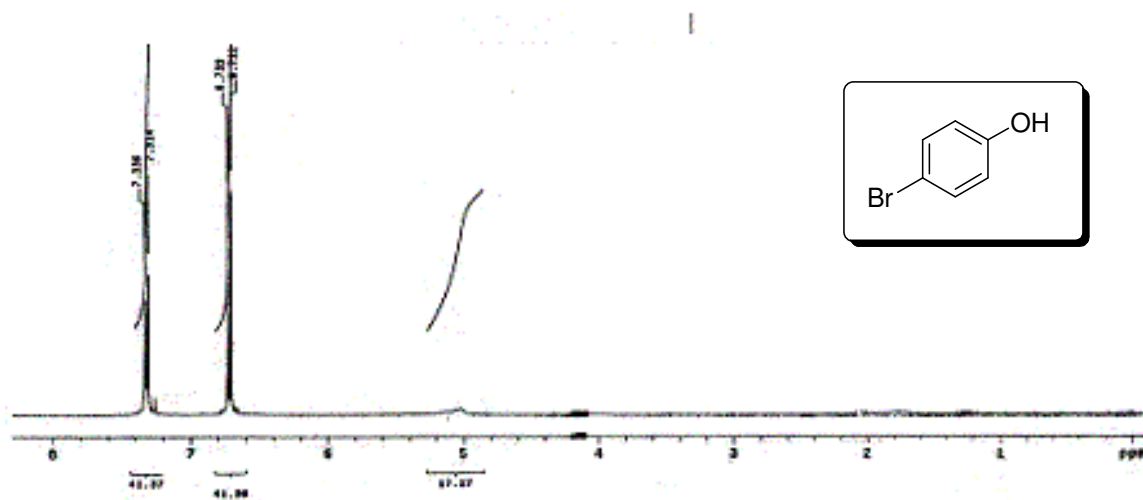
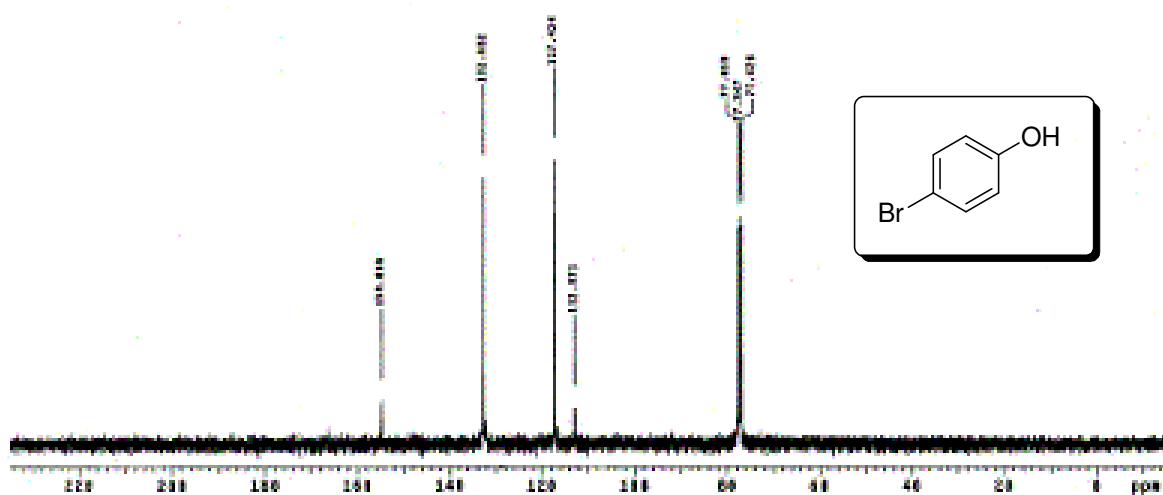
^1H NMR (400 MHz, CDCl_3): δ 5.22 (d, $J = 11.6$ Hz, 1H), 5.49 (d, $J = 11.6$ Hz, 1H), 6.97 (d, $J = 15.6$ Hz, 1H), 7.44 (m, 8H), 7.63 (m, 2H), 7.87 (d, $J = 15.6$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 49.9, 51.9, 114.8, 122.3, 128.4, 129.0, 129.1, 129.2, 129.4, 129.6, 131.4, 134.2, 138.3, 146.3, 189.9. IR (KBr): 3057, 3028, 2995, 1690, 1661, 1610, 1575, 1455, 1334, 1202, 1071, 979, 763, 691, 564 cm^{-1} . MS (CI): 393 / 395 / 397 (M^+).

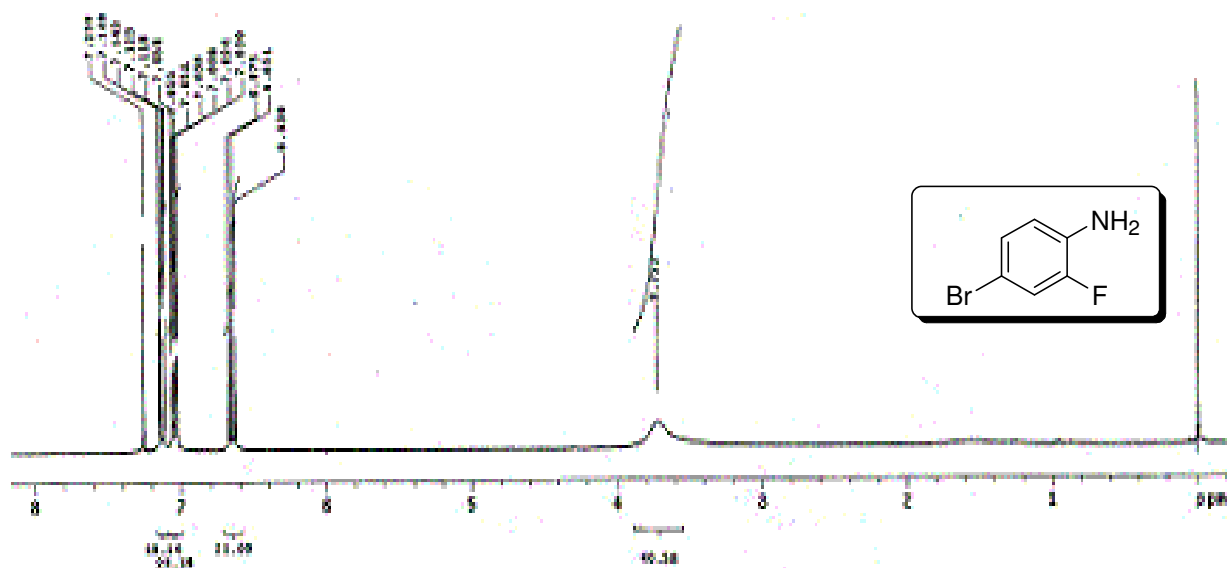
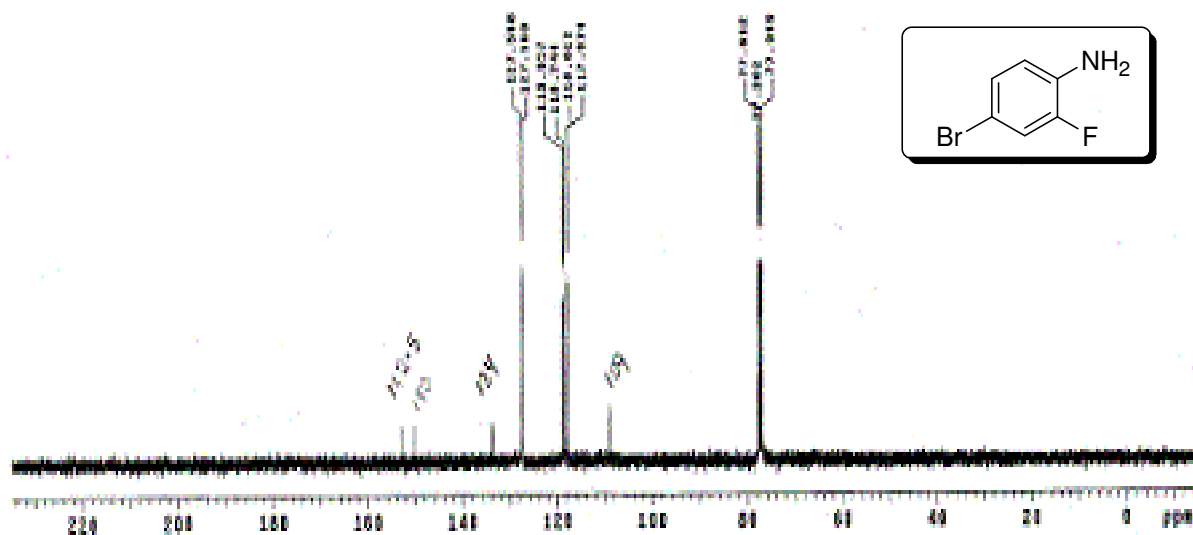
2,4,5-Tribromoimidazole (18a):

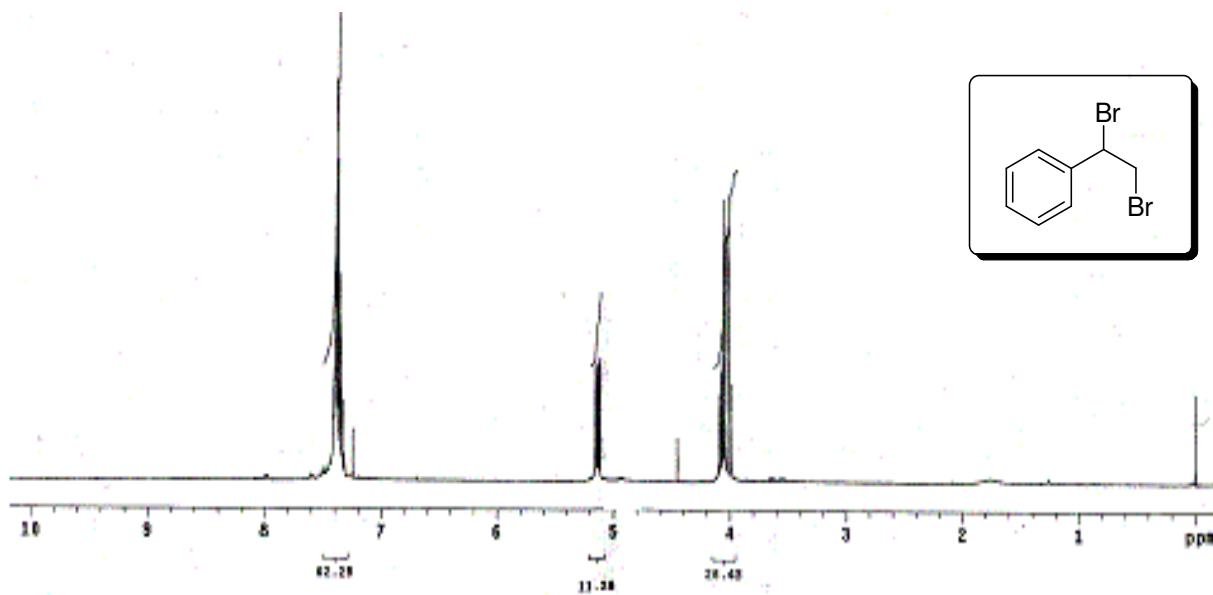
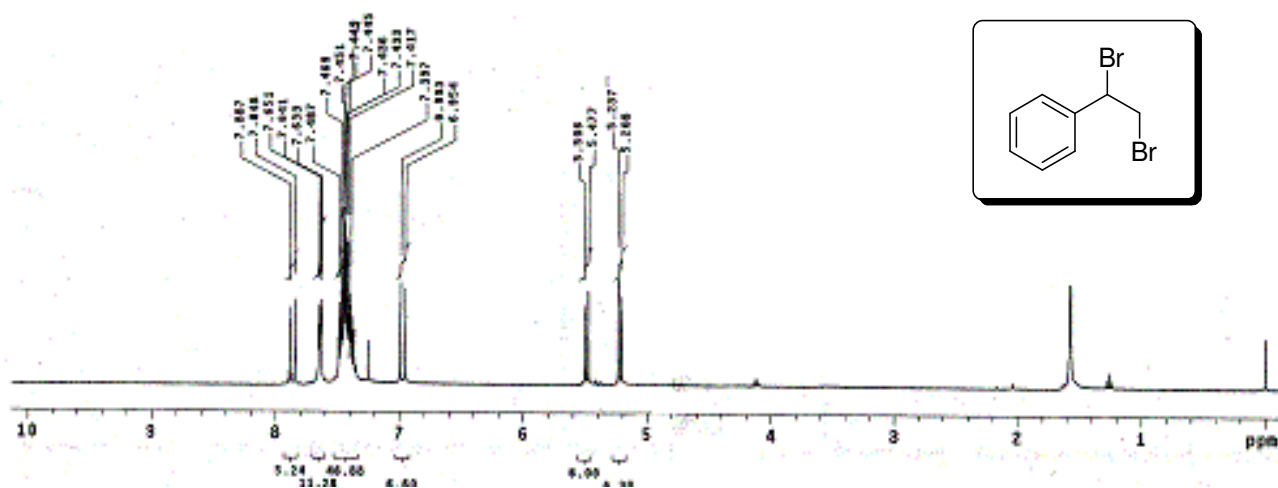
White solid. Mp: 219-220 °C. ^1H NMR (400 MHz, CDCl_3): δ 1.6 (brs, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 123.5, 139.2. IR (KBr): 3069, 3005, 2924, 2813, 2712, 2618, 1537, 1528, 1394, 1301, 1183, 1004, 980, 837, 661, 515 cm^{-1} . Mass (EI): 304/306 (M^+).

4,4'-Isopropylidene-bis-2,6-dibromophenol (19a):

White solid. Mp: 178-180°C. ^1H NMR (400 MHz, CDCl_3): δ 1.57 (s, 6H), 5.8 (s, 2H), 7.25 (s, 4H). ^{13}C NMR (100 MHz, CDCl_3): δ 30.86, 42.09, 109.9, 130.5, 144.85, 147.85. IR (KBr): 3476, 2981, 2926, 1557, 1473, 1391, 1326, 1271, 1247, 1175, 1133, 867, 735, 707 cm^{-1} .

IAI.5. Spectra of some selected compounds**4-Bromo-phenol (1a): ^1H NMR(400 MHz, CDCl_3):****4-Bromo-phenol (1a): ^{13}C NMR(100 MHz, CDCl_3):**

4-Bromo-2-fluoro-aniline (11a): ^1H NMR (400 MHz, CDCl_3):**4-Bromo-2-fluoro-aniline (11a): ^{13}C NMR (100 MHz, CDCl_3):**

1,2-(Dibromo-ethyl)-benzene (14a): ^1H NMR (400 MHz, CDCl_3):**1,2-(Dibromo-ethyl)-benzene (14a): ^{13}C NMR (100 MHz, CDCl_3):**

IAI.6. References

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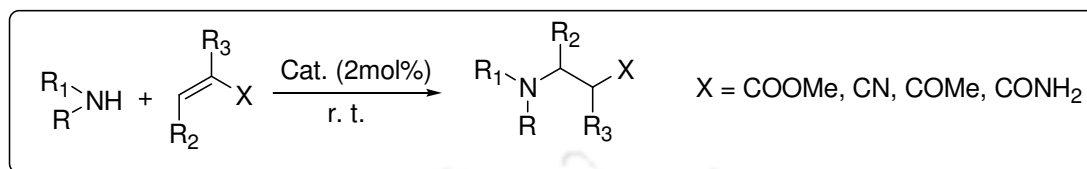
Section II.

IAII.1. Phosphate Impregnated Titania: An Efficient Reusable Heterogeneous Catalyst for *aza*-Michael Reactions Under Solvent-free Condition

β -Amino ketone and their derivatives have been used as building blocks for many nitrogen-containing biologically important compounds¹⁻⁴ such as β -aminoalcohols, 1,2-diamines, and β -lactams.⁵⁻⁷ Therefore, a number of efficient methods for the preparation of this unit have been developed. The most common method for the preparation of β -amino ketones is the Mannich reaction.⁸ Classical Mannich type reactions are certainly very powerful but need quite severe reaction conditions and are rather sluggish. Conjugate addition reactions are, to the contrary, atom economic and quite easy to carry out. However, these reactions require either basic conditions^{9,10} or acidic catalysts,¹¹ which can be detrimental to the desired synthesis. Moreover, most Lewis acid catalysts are likely to be poisoned by alkyl and arylamine reagents.¹² In order to overcome some of these limitations, a number of alternative procedures have been reported over the past few years using a variety of catalysts such as $\text{PdCl}_2(\text{MeCN})_2$,¹³ InCl_3 ,¹⁴ $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$,¹⁵ $\text{Yb}(\text{OTf})_3$,^{16,17} SmI_2 ,¹⁸ $\text{Cu}(\text{OTf})_2$,^{19,20} $\text{Bi}(\text{NO}_3)_2$,²¹ LiClO_4 ,²² TMSCl ,²³ Boric acid,²⁴ Borax,²⁵ and acidic solids.²⁶ Heterogeneous solid salts,^{22,27} fluoride,²⁷ ionic liquid,²⁸ β -cyclodextrin,²⁹ and sodium dodecylsulfate (SDS)³⁰ have also been used for this transformation. In addition solvent-free and catalyst-free procedures at elevated and room temperature have been demonstrated.^{31,32} However, despite satisfactory results, many of these methods used heavy metal salts and hazardous organic solvents, which are not desirable from Green chemistry point of view. Owing to the growing environmental concern, development of green processes using heterogeneous catalysts under solvent free condition has aroused great interest in recent years. Solid acid catalysts are more advantageous over homogeneous acid catalysts as they can be easily recovered from reaction mixture by simple filtration and can be reused several times, making the process more economically and environmentally viable.

In continuation of our ongoing research, we reveal herein a new, mild and efficient protocol for *aza*-Michael reactions of amines with α,β -unsaturated carbonyl and nitrile compounds using acid phosphate impregnated titania as a heterogeneous catalyst at room temperature under solvent-free condition (Scheme IAI.1.1.).

It was perceived that inherent acidity of the catalyst would facilitate the conjugate addition reactions. Development of this catalyst and its use in aromatic nitration and chemoselective sulfoxidation has been described in two very recent papers^{33,34} published from our labs.



Scheme IAI.1.1. Aza-Michael reactions catalyzed by phosphate impregnated titania

IAII.2. Results and Discussion

The catalyst containing 84.5% of TiO₂ and 15.5% of [Ti₄H₁₁(PO₄)₉].nH₂O (n = 1–4) is a phosphate-based solid acid catalyst which is easy to prepare, stable, easily separable from the reaction mixture and recyclable. Phosphate seems to enhance catalytic properties, to stabilize surface area and crystal phase, to improve the surface acidity and to make the impregnated material porous. Synthesis and characterization of the catalyst were done as reported³³ earlier by us. In order to ascertain the efficacy of the catalyst under solvent-free condition, the conjugate addition reaction of morpholine to methyl acrylate were separately conducted in six different solvents and under solvent-free condition. The results are summarized in Table IAI.2.1.

A blank reaction of morpholine and methyl acrylate in absence the of catalyst was carried out under solvent-free condition which gave 90% conversion of the desired Michael adduct after 2 h at room temperature.^{23a} The same reaction in the presence of 2 mol% of catalyst at room temperature (Table IAI.2.1., entry 3), gave 95% conversion in 15 min. It is also evident that the reaction takes place in each case with the best performance being in the absence of any solvent. An amount of 2 mol% of the catalyst was found to afford the best result. Accordingly, all the reactions discussed hereafter were conducted with 2 mol% of catalyst under solvent-free condition. However when the reaction was carried out with 2 mol % TiO₂ only 30% yield of the Michael adduct was obtained.

Table IAI.2.1. Michael addition of morpholine to methyl acrylate under different reaction conditions

Entry	Catalyst (mol %)	Solvent	Time/h	Conversion (%)
1	-	-	2	90 ^{23a}
2	3	-	2	70
3	2	-	0.25	95
4	1	-	2	75
5	2	CH ₃ OH	2	48
6	2	C ₂ H ₅ OH	2	45
8	2	THF	2	40
9	2	n-C ₄ H ₉ OH	2	55
10	2	H ₂ O	2	65

A variety of α,β -unsaturated compounds such as methyl acrylate, acrylonitrile, methyl vinyl ketone, acrylamide and methyl methacrylate underwent facile 1,4-addition with a wide range of aliphatic amines in the presence of phosphate impregnated titania (2 mol%) catalyst at room temperature to give the corresponding β -amino compounds in good to very good yields. The results are summarized in Table IAI.2.2. The corresponding reactions being conducted under similar experimental conditions, but without using the chosen catalyst, were far sluggish with significantly low conversions. A comparison of the results has been set out in Table IAI.2.2.

In general, acyclic secondary amines were introduced at the β -position of the Michael acceptor in excellent conversions irrespective of steric bulkiness (**23**, **24**, **28** and **34** Table IAI.2.2.). Secondary amines gave higher conversions than primary amines. It is pertinent to mention that benzylamines gave only mono adducts (**22b**, **29c** and **32b** Table IAI.2.2.) whereas the reaction with aliphatic primary amines suffered from over-alkylation producing more of bis-adducts (**25** and **26** Table IAI.2.2.). However, when increased amount of α , β -unsaturated carbonyl and nitrile compound (2 equivalent) was employed, the di-substituted product formed exclusively. Cyclic amines such as morpholine (**20** Table IAI.2.2.), and piperidine (**21** Table IAI.2.2.) also underwent the conjugate addition successfully.

Table IAI.2.2. Phosphate impregnated titania catalyzed conjugate addition of amine to α , β -unsaturated compounds under solvent-free condition at room temperature

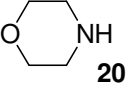
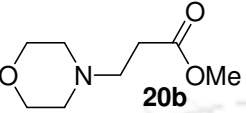
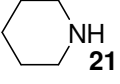
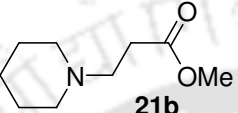
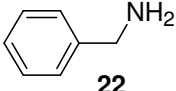
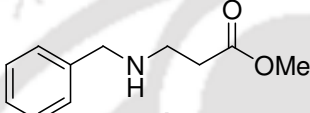
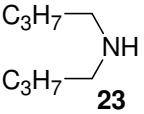
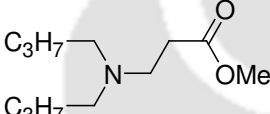
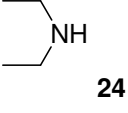
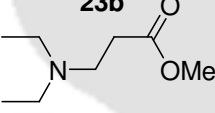
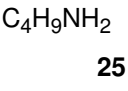
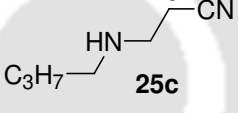
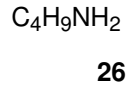
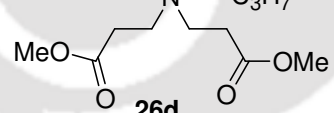
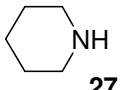
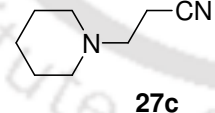
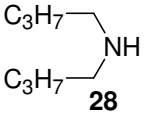
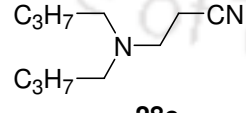
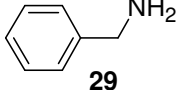
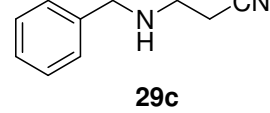
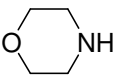
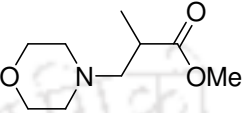
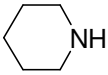
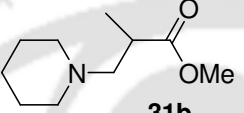
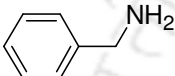
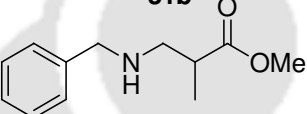
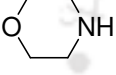
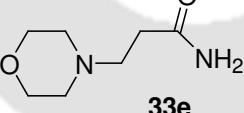
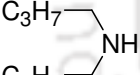
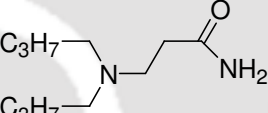
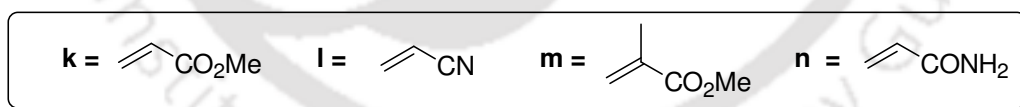
Amine	α , β -Enone	Product	Time (h) / Conversion (%) ^a (without catalyst)	Time (h) / Conversion (%) ^a (with catalyst)
	k		(2)/90	0.25/95, 96 ^b
	k		3/60	0.41/94
	k		3/51	1.5/85
	k		3/44	2/87
	k		3/50	2/88
	l		3/30	1/35+40 ^c (85 ^c)
	k		3/35	1/25+45 ^c (90 ^c)
	l		3/52	0.5/85
	l		3/55	2/90
	l		3/57	1/88

Table contd.

Table IAI.2.2. Phosphate impregnated titania catalyzed conjugate addition of amine to α , β -unsaturated compounds under solvent-free condition at room temperature

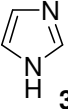
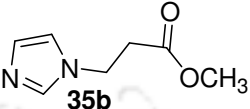
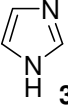
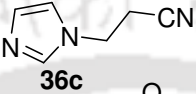
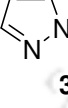
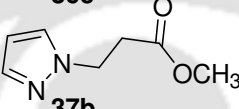
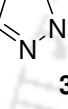
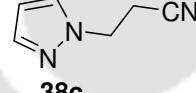
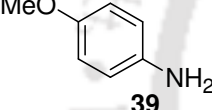
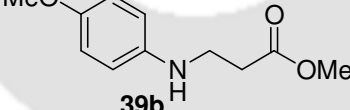
Amine	α , β -Enone	Product	Time (h) / Conversion (%) ^a (without catalyst)	Time (h) / Conversion (%) ^a (with catalyst)
 30	m	 30b	3/40	1.5/85
 31	m	 31b	3/42	2/86
 32	m	 32b	3/50	3/85
 33	n	 33e	6/35	6/80
 34	n	 34e	6/30	6/80

^a Conversion; ^b Conversion on 5g scale; ^c Bis product (with 2 equiv of α , β -unsaturated compound)

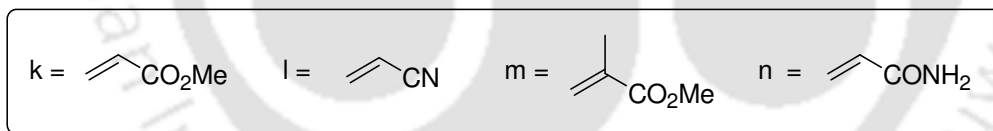


Whereas, reactions of imidazole (**35**, **36** Table IAI.2.3.), and pyrazole (**37**, **38** Table IAI.2.3.) with methyl acrylate and acrylonitrile proceeded smoothly when the reaction temperature was elevated to 60 °C, and good conversions of products were obtained.

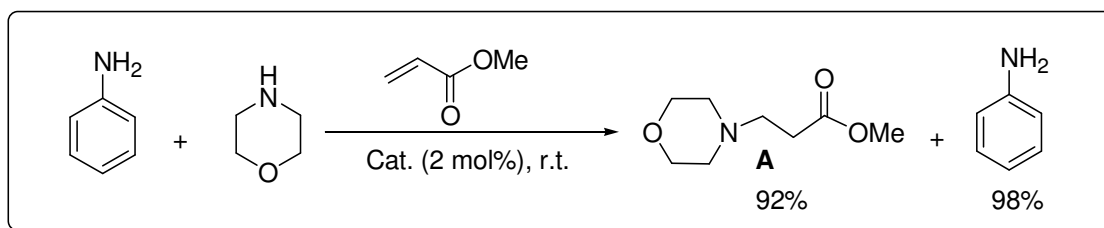
Table IAI.2.3. Phosphate impregnated titania catalyzed conjugate addition of amine to α , β -unsaturated compounds under solvent-free condition at room temperature

Amine	α , β -Enone	Product	Time (h) / Conversion (%) ^a (without catalyst)	Time (h) / Conversion (%) ^a (with catalyst)
	k		6/15	6/85 ^d
	l		5/20	5/83 ^d
	k		10/10	10/63 ^d
	l		9/15	9/60 ^d
	k		24/--	24/--

^a Conversion; ^b Conversion on 5g scale; ^c Bis product (with 2 equiv of α , β -unsaturated compound); ^d This reaction was performed at 50 °C.



The method also worked well with α -substituted Michael acceptors (**30-32**, Table IAI.2.2.). However, an aromatic amine, *p*-methoxy aniline was found to be inactive under similar experimental condition (**39** Table IAI.2.3.). Low reactivity of aromatic amines enables us to state that this protocol is more appropriate for aliphatic amines. In order to lend support to our assertions, a separate reaction was conducted between methyl acrylate and an equimolar mixture of aniline and morpholine (Scheme IAI.2.1.). After 20 min, morpholine adduct (product A) was obtained almost exclusively with 92% conversion.



Scheme IAI.2.1. Reaction between methyl acrylate, aniline and morpholine

Finally, upon completion of the reaction, catalyst recyclability was examined by recovering the catalyst from the reaction mixture through simple filtration and washing with ethanol. The catalyst was then recharged by heating on a sand bath at 200-220 °C. This was reused in the reaction of morpholine with methyl acrylate for three reaction cycles (Table IAI.2.4.). For every cycle the catalyst was reactivated.

Table IAI.2.4. Recycling of the catalyst for the reaction of morpholine and methyl acrylate under solvent-free condition

Cycle	Conversion (%)	Time/h
1	95	0.25
2	88	0.58
3	85	1.16
4	70	1.66
5	68	2.5

It is evident from the results (Table IAI.2.4.) that the catalyst works efficiently up to third cycle without any remarkable loss of activity. After third cycle the activity of the catalyst decreases due to leaching of the catalyst (Table IAI.2.4.).

Table IAI.2.5. Comparison of phosphate impregnated titania with other catalyst for the reaction of morpholine with methyl acrylate

Entry	Catalyst	Time/h	Conversion	Reference
1	Amberlyst-15	0.5	79	25
2	[DBU]-derived ionic liquid	1.5	90	26
3	[Ni((R,S)-Pigiphos)(L)] ²⁺ L= THF or CH ₃ CN	24	70	27
4	Clay	3	91	18
5	Phosphate impregnated titania	0.25	95	present work

The efficacy and versatility of the catalyst was further proved by comparing the reaction of morpholine with methyl acrylate with other reported catalysts (Table IAI.2.5.).

In conclusion, we have developed an efficient method for the preparation of β -amino carbonyl and nitrile compounds with high conversions by applying *aza*-Michael reactions under mild heterogeneous conditions. Easy experimental procedure, efficacy, redundancy of workup, use of ethanol in washing and recyclability of the catalyst along with solvent-free reaction condition render this protocol green, attractive and practically useful. The reactions do not work well, in terms of reaction time and conversion, in the absence of the catalyst.

IAII.3. Experimental

IAII.3.1. General Remarks

As described in Section IAI.3.1. Page no. 57.

IAII.3.2. Characterization of Organic Substrates

As described in Section IAI.3.2. Page no. 57.

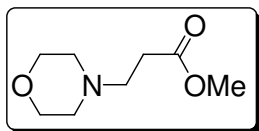
IAII.3.3. General Procedures

IAII.3.3.1. Preparation of the catalyst

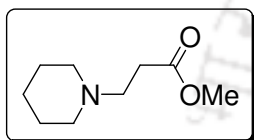
Catalyst was prepared by first mixing titania with phosphoric acid (88%), in the molar ratio of TiO_2 : H_3PO_4 as 1:1, in a silica boat followed by heating at 200-220 °C on a hot sand bath. The mixture was stirred at the stipulated temperature until the swampy mass, which formed in the process, solidified. The temperature of the sand bath was then reduced to ca. 100 °C. The silica boat was then placed in a vacuum desiccator and cooled to ambient temperature. The catalyst thus prepared was finally stored in an air-tight sample vial.

IAII.3.3.2. General experimental procedure for aza-Michael reaction of methyl acrylate and morpholine

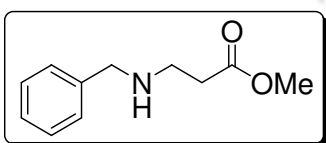
To a mixture of methyl acrylate (172 mg, 2 mmol) and morpholine (158 mg, 2 mmol) was added the catalyst titania $[\text{Ti}_4\text{H}_{11}(\text{PO}_4)_9] \cdot n\text{H}_2\text{O}$ ($n=1-4$) (67 mg, 0.04 mmol) and the whole was stirred at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, ethyl alcohol (10 mL) was added to the reaction mixture and the catalyst was separated by filtration. The catalyst was washed three times with ethyl alcohol. The filtrate contains the crude product. Evaporation of the solvent left the residue, which was purified by column chromatography on silica gel with ethylacetate and hexane as eluent to afford the pure β -amino adduct (314 mg, 95%). The recovered catalyst was then recharged by heating on silica bath at 200-220 °C and reused for the next run. The recycled catalyst was consecutively used for three times for the above reaction to furnish the product with a little variation of its conversion (Table IAII.2.4.).

IAII.4. Spectral Data**Methyl 3-morpholin-4-yl-propionate (20b):**

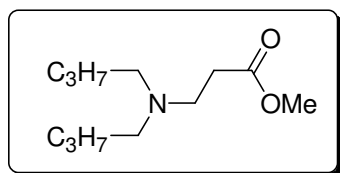
^1H NMR (400MHz, CDCl_3): δ 2.46 (t, $J = 4.4$ Hz, 4H), 2.51 (t, $J = 7.6$ Hz, 2H), 2.68 (t, $J = 7.6$ Hz, 2H), 3.68-3.70 (m, 7H). ^{13}C NMR (100MHz, CDCl_3): δ 32.2, 52.9, 53.7, 54.2, 67.1, 172. IR (KBr): 2954, 2854, 2812, 1739, 1438, 1373, 1298, 1118, 1012, 871 cm^{-1} . MS (EI): m/z 173 (M^+).

Methyl 3-piperidin-1-yl-propionate (21b):

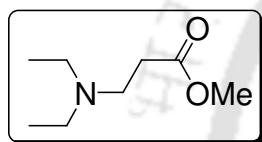
Colourless oil. ^1H NMR (400MHz, CDCl_3): δ 1.38-1.47 (m, 2H), 1.52-1.62 (m, 4H), 2.34-2.42 (m, 4H), 2.44-2.50 (m, 2H), 2.58-2.66 (m, 2H), 3.67 (s, 3H). ^{13}C NMR (100MHz, CDCl_3): δ 25.6, 26.2, 33.5, 50.1, 50.8, 52.3, 172.1. IR (KBr): 2937, 2854, 2808, 2954, 2854, 2812, 1739(s), 1438, 1373, 1045, 861, 751 cm^{-1} . MS (EI): m/z 171 (M^+).

Methyl 3-benzylamino-propionate (22b):

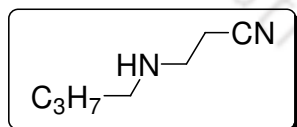
^1H NMR (400MHz, CDCl_3): 1.87 (s, 1NH), 2.52 (t, $J = 6.8$ Hz, 2H), 2.88 (t, $J = 6$ Hz, 2H), 3.66 (s, 3H), 3.79 (s, 2H), 7.20-7.30 (m, 5H). ^{13}C NMR (100MHz, CDCl_3): δ 35.5, 44.2, 50.2, 55.5, 127.2, 129.4, 138, 173. IR (KBr): 3467, 3032, 2955, 2832, 1742, 1614, 1501, 1445, 1173, 1127 cm^{-1} .

Methyl 3-(*N,N*-dibutylamino)-propionate (23b):

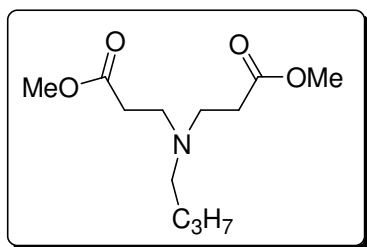
^1H NMR (400MHz, CDCl_3): 0.90 (t, $J = 6.8$ Hz, 6H), 1.26-1.44 (m, 8H), 2.39 (t, $J = 7.2$ Hz, 4H), 2.60 (t, $J = 7.2$ Hz, 2H), 2.77 (t, $J = 7.6$ Hz, 2H), 3.66 (s, 3H). ^{13}C NMR (100MHz, CDCl_3): δ 14.5, 21.0, 29.7, 32.6, 47.1, 49.7, 50.1, 51.8, 54.0, 173.4. IR (KBr): 2956, 2872, 2805, 1743, 1481, 1481, 1436, 1202, 1100, 743 cm^{-1} . MS (EI): m/z 215 (M^+).

Methyl 3-diethylamino-propionate (24b):

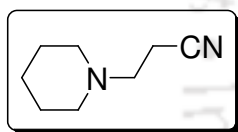
White semisolid. ^1H NMR (400MHz, CDCl_3): δ 1.03 (t, $J = 6.8$ Hz, 6H), 2.46 (t, $J = 7.2$ Hz, 2H), 2.52 (q, $J = 8$ Hz, 4H), 2.80 (t, $J = 7.2$ Hz, 2H), 3.68 (s, 3H). ^{13}C NMR (100MHz, CDCl_3): δ 12.2, 32.4, 47.1, 48.3, 51.9, 173.3. IR (KBr): 2954, 2873, 2812, 1739(s), 1434, 1197, 1091, 743 cm^{-1} . MS (EI): m/z 159 (M^+).

3-Butylamino-propionitrile (25c):

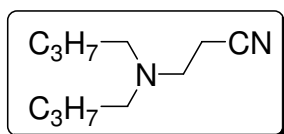
^1H NMR (400MHz, CDCl_3): 0.92 (t, $J = 7.2$ Hz, 3H), 1.35 (m, 2H), 1.48 (qt, $J = 7.2$ Hz, 2H), 1.60 (brs, 1NH), 2.53 (t, $J = 6.4$ Hz, 2H), 2.63 (t, $J = 7.2$ Hz, 2H), 2.93 (t, $J = 6.4$ Hz, 2H). ^{13}C NMR (100MHz, CDCl_3): δ 14.1, 20.3, 20.8, 34.4, 44.7, 49.1, 118.7. IR (KBr): 3324, 2966, 2930, 2868, 2254, 1470, 1429, 1319, 1132, 753 cm^{-1} .

Methyl 3-[butyl-(2-methoxycarbonyl-ethyl)-amino]-propionate (26d):

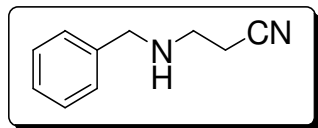
^1H NMR (400MHz, CDCl_3): 0.90 (t, $J = 7.6$ Hz, 3H), 1.28 (m, 2H), 1.40 (qt, $J = 7.6$ Hz, 2H), 2.40 (t, $J = 7.6$ Hz, 2H), 2.44 (t, $J = 7.2$ Hz, 4H), 2.76 (t, $J = 6.8$ Hz, 4H), 3.66 (s, 6H). ^{13}C NMR (100MHz, CDCl_3): δ 13.7, 20.8, 32.2, 33.4, 50.1, 51.7, 54.3, 173.2. IR (KBr): 2960, 2872, 1752(s), 1481, 1461, 1446, 1199, 1055, 743 cm^{-1} .

3-Piperidin-1-yl-propionitrile (27c):

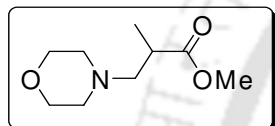
^1H NMR (200MHz, CDCl_3): δ 1.42-1.44 (m, 2H), 1.55-1.59 (m, 4H), 2.41-2.51 (m, 6H), 2.64-2.68 (m, 2H). ^{13}C NMR (100MHz, CDCl_3): δ 15.61, 24.07, 25.79, 53.97, 54.13, 119.12. IR (KBr): 2937, 2854, 2808, 2259, 1455, 1353, 1259, 1158, 1117, 1045, 861, 751, 416 cm^{-1} . MS (EI): m/z 138 (M^+).

3-Dibutylamino-propionitrile (28c):

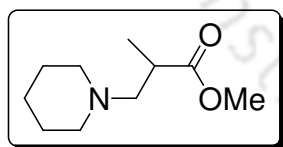
^1H NMR (200MHz, CDCl_3): δ 0.92 (t, $J = 4.8$ Hz, 6H), 1.25-1.45 (m, 8H), 2.35-2.44 (m, 6H), 2.76 (t, $J = 7.6$ Hz, 2H). ^{13}C NMR (100MHz, CDCl_3): δ 14, 18, 21.8, 32.2, 50.5, 54.1, 117.7. IR (KBr): 2958, 2925, 2871, 2812, 2259, 1466, 1377, 1219, 1086, 771 cm^{-1} . MS (EI): m/z 182 (M^+).

3-Benzylamino-propionitrile (29c):

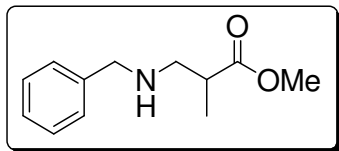
^1H NMR (200MHz, CDCl_3): δ 1.50 (s, 1NH), 2.47 (t, $J = 4.4$ Hz, 2H), 2.90 (t, $J = 4.6$ Hz, 2H), 3.81 (s, 2H), 7.24-7.28 (m, 5H). ^{13}C NMR (100MHz, CDCl_3): δ 20.2, 44.5, 54.6, 118.2, 127.8, 129.1, 129.3, 137.2. IR (KBr): 3334, 3037, 2945, 2843, 2254, 1500, 1460, 1230, 1132, 779, 707 cm^{-1} . MS (EI): m/z 160 (M^+).

Methyl 2-methyl-3-morpholin-4-yl-propionate (30b):

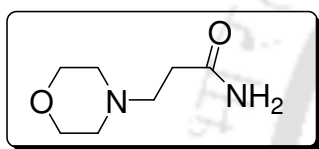
^1H NMR (200MHz, CDCl_3): δ 1.14 (d, $J = 4.6$ Hz, 3H), 2.6-2.38 (m, 5H), 2.44-2.48 (m, 2H), 3.63 (t, $J = 3.2$ Hz, 4H), 3.67 (s, 3H). ^{13}C NMR (100MHz, CDCl_3): δ 12.9, 38.4, 50.7, 55.9, 57.8, 72.5, 175.4. IR (KBr): 2954, 2853, 2809, 1739, 1388, 1275, 1200, 1118, 1013, 865, 750 cm^{-1} . MS (EI): m/z 187 (M^+).

Methyl 2-methyl-3-piperidin-1-yl-propionate (31b):

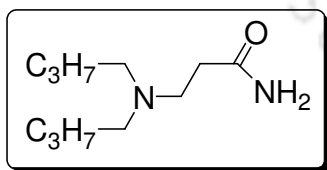
^1H NMR (200MHz, CDCl_3): δ 1.14 (d, $J = 4.6$ Hz, 3H), 1.39-1.55 (m, 6H), 2.22-2.35 (m, 5H), 2.50-2.60 (m, 2H), 3.66 (s, 3H). ^{13}C NMR (100MHz, CDCl_3): δ 13, 26, 27.2, 38.5, 51.7, 53.6, 56.7, 175.3. IR (KBr): 2853, 2761, 2377, 1741, 1455, 1271, 1219, 1171, 871, 771 cm^{-1} . MS (EI): m/z 185 (M^+).

Methyl 3-benzylamino-2-methyl-propionate (32b):

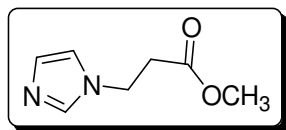
^1H NMR (200MHz, CDCl_3): δ 1.16 (d, $J = 4.6$ Hz, 3H), 1.71 (bs, 1NH), 2.63 (m, 2H), 2.83 (m, 1H), 3.67 (s, 3H), 3.76 (s, 2H), 7.18 - 7.27 (m, 5H). ^{13}C NMR (100MHz, CDCl_3): δ 12.6, 40.6, 50.7, 51.2, 56.2, 127.2, 128.1, 128.3, 137.2, 175.5. IR (KBr): 3350, 3032, 2930, 1742, 1578, 1455, 1281, 1194, 764, 712 cm^{-1} . MS (EI): m/z 207 (M^+).

3-Morpholin-4-yl-propionamide (33e):

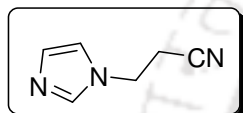
^1H NMR (200MHz, CDCl_3): δ 2.36 (t, $J = 6.6$ Hz, 2H), 2.48 (t, $J = 4.8$ Hz, 4H), 2.62 (t, $J = 5.4$ Hz, 2H), 3.68 (t, $J = 4.6$ Hz, 4H), 5.89 (bs, 1NH), 7.73 (bs, 1NH). ^{13}C NMR (100MHz, CDCl_3): δ 37.1, 49.3, 56.2, 71.8, 177.9. IR (KBr): 3401, 3212, 2960, 2807, 1675, 1424, 1286, 1122, 1009, 876, 636 cm^{-1} . MS (EI): m/z 158 (M^+).

3-(*N,N*-Dibutylamino)-propionamide (34e):

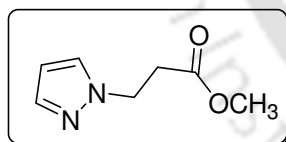
^1H NMR (200MHz, CDCl_3): δ 0.93 (t, $J = 7.4$ Hz, 6H), 1.22-1.52 (m, 8H), 2.37 (t, $J = 4.4$ Hz, 2H), 2.44 (t, $J = 6.8$ Hz, 4H), 2.66 (t, $J = 6$ Hz, 2H), 5.60 (brs, 1NH). ^{13}C NMR (100MHz, CDCl_3): δ 14.3, 21.2, 33.1, 36.5, 49.6, 53.7, 177.8. IR (KBr): 3339, 3193, 2957, 2932, 2871, 2282, 1672, 1465, 1377, 1102 cm^{-1} . MS (EI): m/z 200 (M^+), 157 (90), 86 (90%).

Methyl 3-imidazolylpropionate (35b):

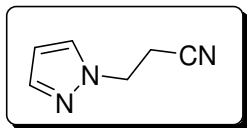
^1H NMR (400MHz, CDCl_3): δ 2.77 (t, $J = 4.4$ Hz, 2H), 3.68 (s, 3H), 4.25 (t, $J = 7.6$ Hz, 2H), 6.92 (s, 1H), 7.02 (s, 1H), 7.50 (s, 1H). ^{13}C NMR (100MHz, CDCl_3): δ 35.48, 42.08, 51.88, 118.80, 129.08, 137.06, 170.88. IR (KBr): 2950, 2851, 1728(s), 1508, 1440, 1369, 1229, 1171, 1080, 828, 749, 663 cm^{-1} .

3-Imidazole-1-yl-propionitrile (36c):

^1H NMR (400MHz, CDCl_3): δ 2.81 (t, $J = 4.4$ Hz, 2H), 4.26 (t, $J = 7.6$ Hz, 2H), 7.01 (s, 1H), 7.09 (d, $J = 4.4$ Hz, 1H), 7.55 (s, 1H). ^{13}C NMR (100MHz, CDCl_3): δ 19.8, 41.7, 118.3, 121.3, 129.2, 136.5. IR (KBr): 2961, 2846, 2252, 1637, 1508, 1451, 1286, 1231, 1080, 916, 825, 751, 661 cm^{-1} .

3-Pyrazol-1-yl-propionic acid methyl ester (37b):

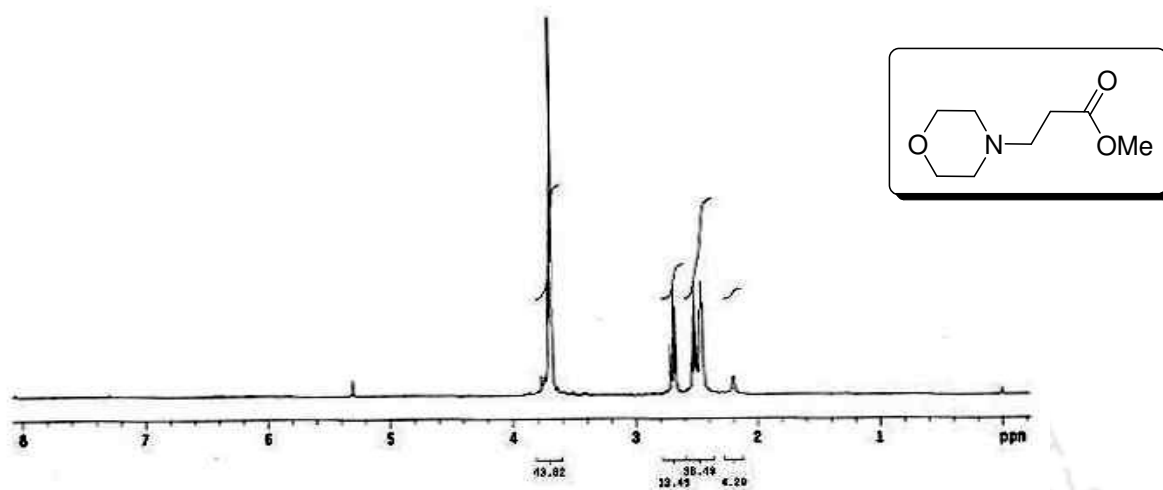
^1H NMR (400MHz, CDCl_3): δ 2.90 (t, $J = 4.4$ Hz, 2H), 3.67 (s, 3H), 4.43 (t, $J = 7.6$ Hz, 2H), 6.21 (s, 1H), 7.40 (d, $J = 4.4$ Hz, 1H), 7.60 (s, 1H). ^{13}C NMR (100MHz, CDCl_3): δ 34.8, 47.3, 105.0, 133.7, 139.8, 170.0. IR (KBr): 3060, 2983, 1728, 1508, 1133, 1031, 760, 611 cm^{-1} .

3-Pyrazol-1-yl-propionitrile (38c) :

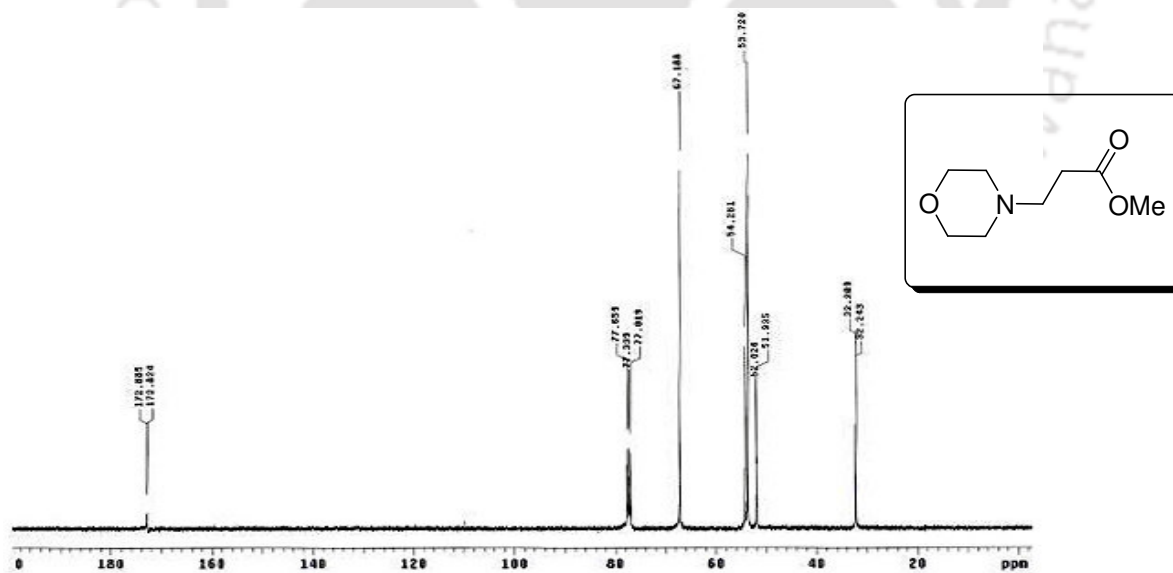
^1H NMR (400MHz, CDCl_3): δ 2.92 (t, $J = 4.4$ Hz, 2H), 4.39 (t, $J = 7.6$ Hz, 2H), 6.34 (s, 1H), 7.61 (s 1H), 8.08 (s, 1H). ^{13}C NMR (100MHz, CDCl_3): δ 16.5, 51.6, 108.1, 118.7, 132.3, 139.2. IR (KBr): 3020, 2973, 2242, 1508, 1093, 1055, 751, 661 cm^{-1} .

IAII.5. Spectra of some selected compounds

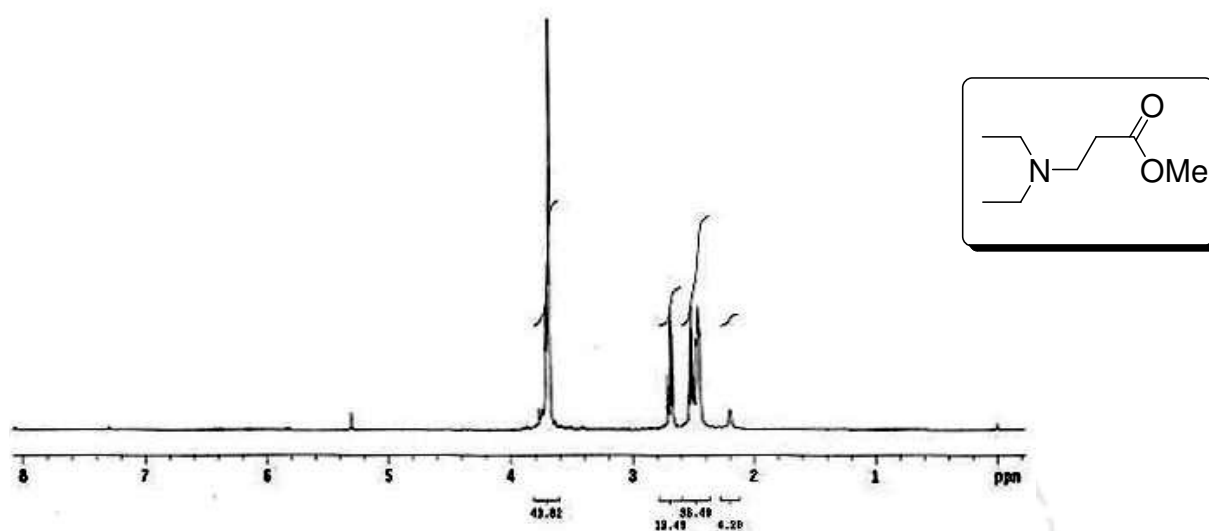
Methyl 3-morpholin-4-yl-propionate (20b): ^1H NMR(400 MHz, CDCl_3):



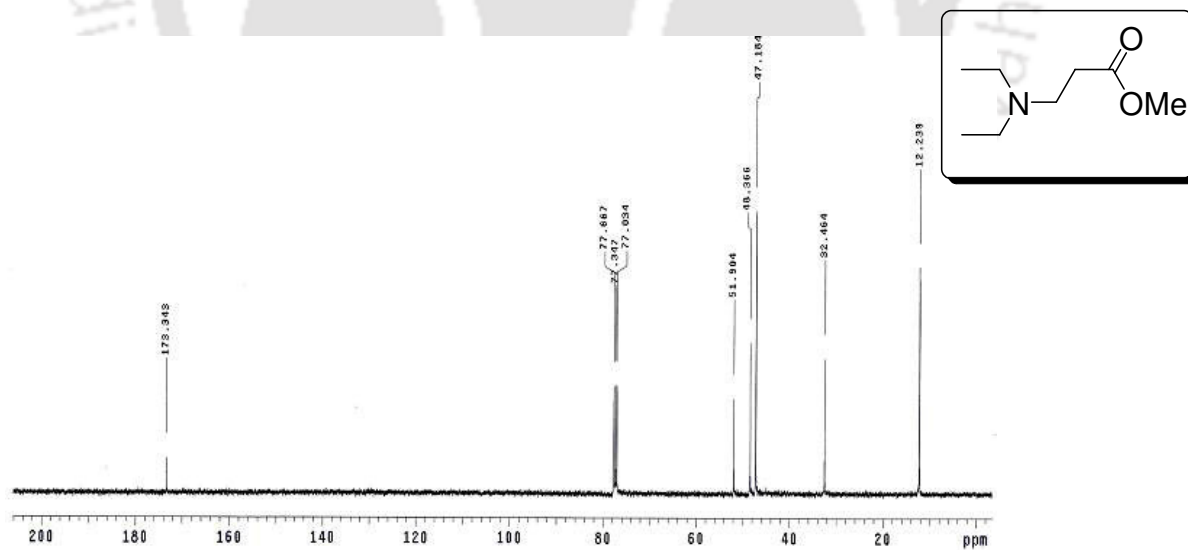
Methyl 3-morpholin-4-yl-propionate (20b): ^{13}C NMR(100 MHz, CDCl_3):

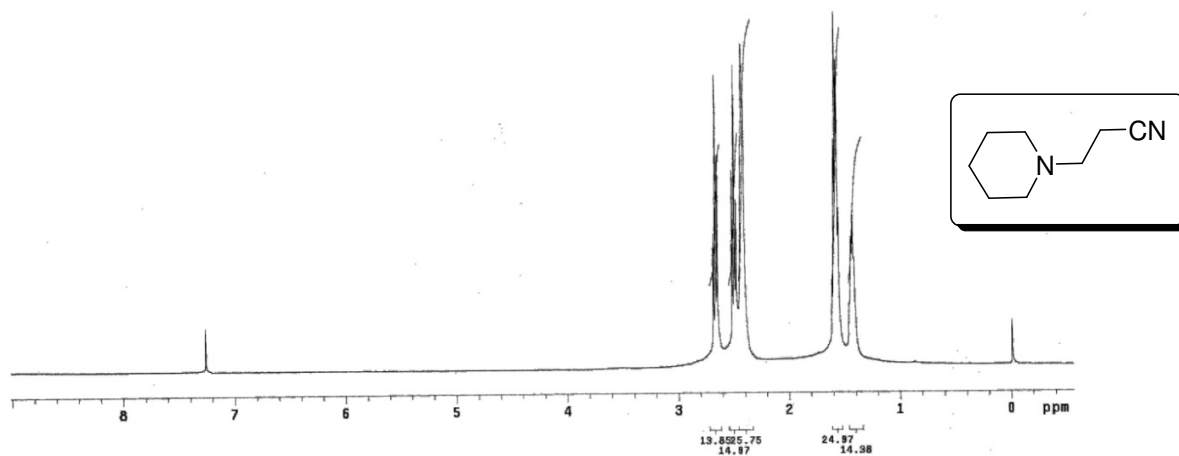
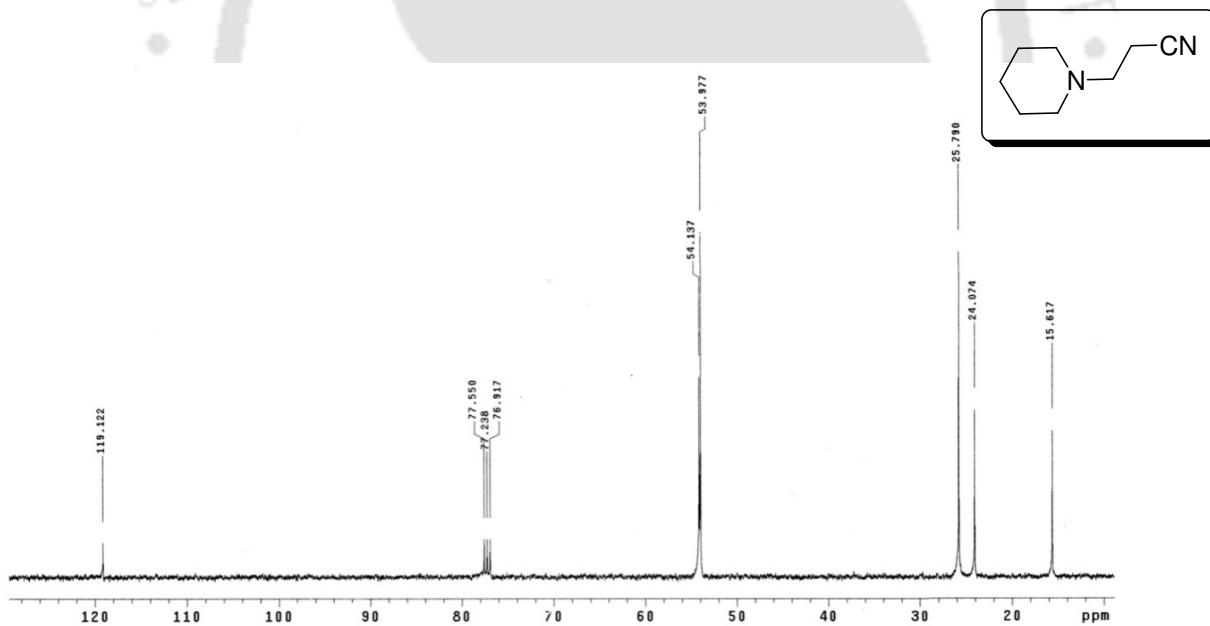


Methyl 3-Diethylamino-propionate (24b): ^1H NMR(400 MHz, CDCl_3):

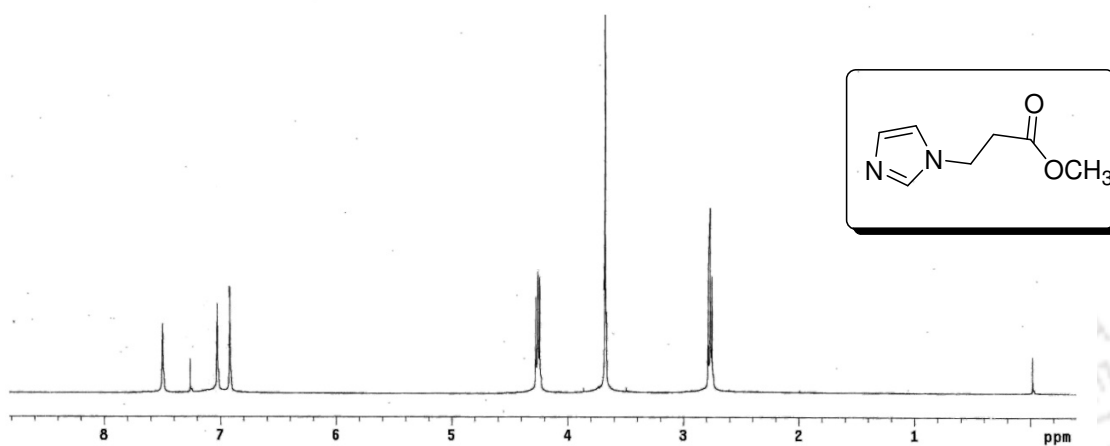


Methyl 3-Diethylamino-propionate (24b): ^{13}C NMR(100 MHz, CDCl_3):

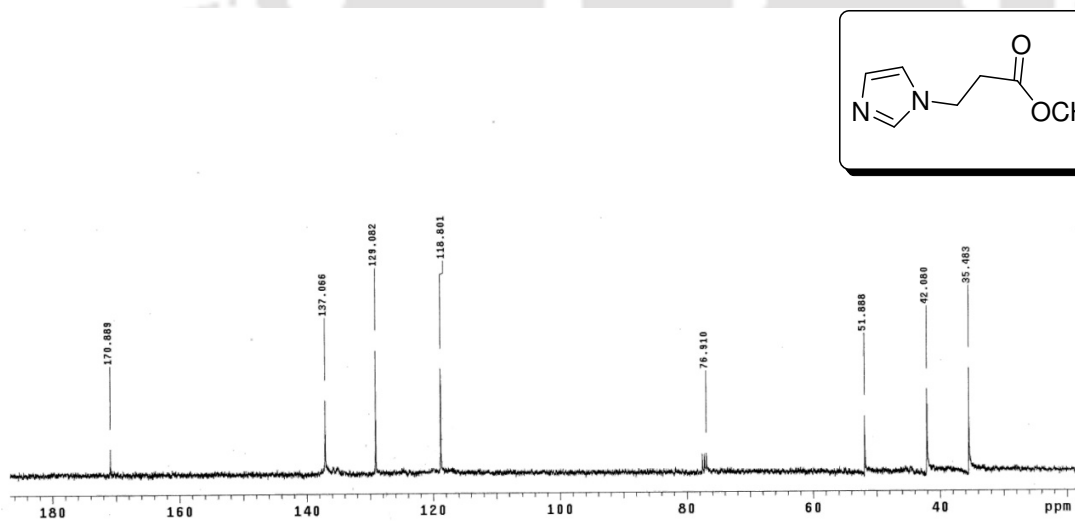


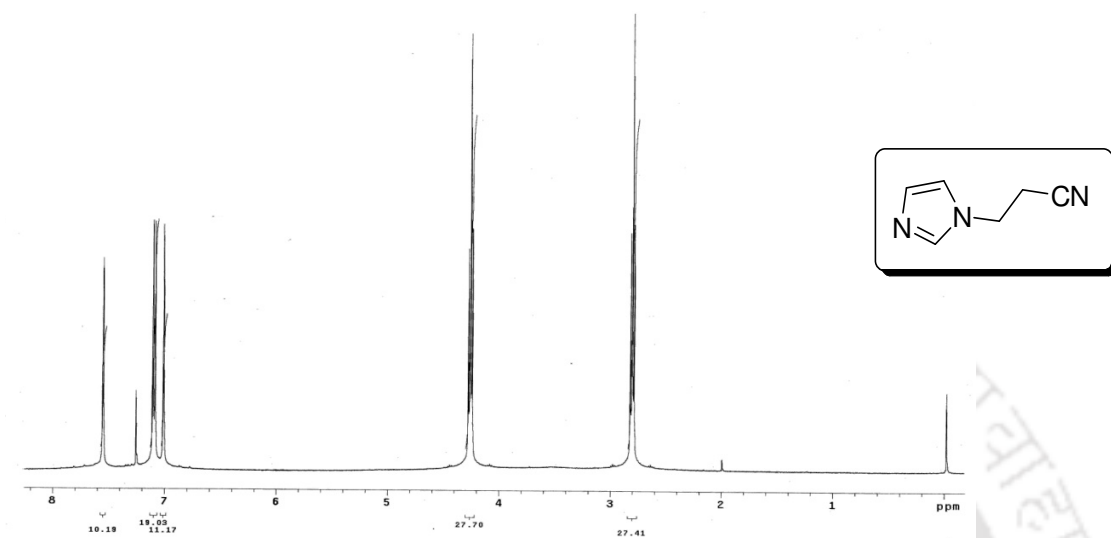
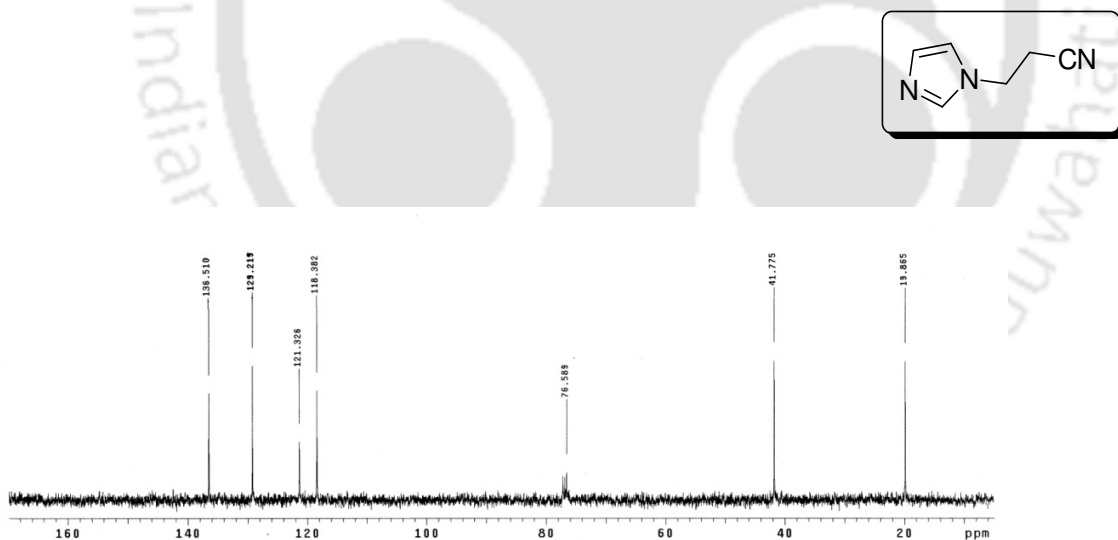
3-Piperidin-1-yl-propionitrile (27c): ^1H NMR(400 MHz, CDCl_3):**3-Piperidin-1-yl-propionitrile (27c): ^{13}C NMR(100 MHz, CDCl_3):**

Methyl 3-imidazolylpropionate (35b): ^1H NMR(400 MHz, CDCl_3):



Methyl 3-imidazolylpropionate (35b): ^{13}C NMR(100 MHz, CDCl_3):



3-Imidazole-1-yl-propionitrile (36c): ^1H NMR(400 MHz, CDCl_3):**3-Imidazole-1-yl-propionitrile (36c): ^{13}C NMR(100 MHz, CDCl_3):**

IAII.6. References

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Section III.

IAIII.1. Molecular Iodine Mediated Preparation of Isothiocyanates from Dithiocarbamic Acid Salts

Alkyl and arylisothiocyanates are versatile synthetic intermediates which are frequently encountered in many natural products and have been used as important precursors for heterocycles such as thiohydantoins, thiopyrimidones, thioquinazolones, mercaptoimidazoles, thioamidazolones, pyridinethiones, pyrrolidine and benzothiazine.¹ In addition, several isothiocyanates are also used in the synthesis of various agrochemicals that have antifungal and anthelmintic activities.² They are important reagents for amide ligation³ and are widely applied as chemoselective electrophiles in biconjugate chemistry because of their tolerance towards aqueous reaction condition.⁴ Synthetic isothiocyanates have been proved to have some biological activity, such as anti-proliferatives,⁵ anticancer properties,^{6,7} enzyme inhibitors for the HIV virus⁸ and reagent in Edman peptide sequencing⁹ and other biological assays of DNA and proteins.^{10, 11}

The most generally used method for the preparation of isothiocyanates consists of the reaction of thiophosgene with amines.¹² Due to the excessive toxicity of thiophosgene, its incompatibility with many functional groups, and the difficulties encountered in handling, it has been replaced by several other 'thiocarbonyl transfer' reagents such as thiocarbonylditriazole,¹³ thiocarbonyldiimidazole,¹⁴ bis(trichloromethyl) carbonate (BTC), trichloromethyl chloroformates (TFC), di-2-pyridyl thionocarbonate (DPT)¹⁵ and bis(trichloromethyl) pentathiodiperoxycarbonate.¹⁶ However, most of these reagents are not readily available and formation of thiourea byproduct limits the scope of these methodologies.

Isothiocyanates can also be synthesized by the desulfurization of dithiocarbamic acid salts with various reagents such as uronium and phosphonium-based peptide coupling reagents,¹⁷⁻¹⁹ di-*tert*-butyl dicarbonate,²⁰ ethyl chlorocarbonate,²¹ hydrogen peroxide²² and tosyl chloride.²³ These reagents have proved to be efficient, but some of them are environmentally unattractive, and their utilization involves harsh reaction conditions, formation of byproducts and longer reaction times which in turn limits their applications. Thus, there is still need for a commercially viable and environmentally acceptable protocol for the synthesis of isothiocyanates. In order to overcome many of these

limitations, if not all, endeavour has been made by us to develop methodologies, which is indeed the main theme of **Section III of Chapter I**. For convenience, the subject matter of this section is divided into two subsections viz., **Subsection IAIII.2.1** and **Subsection IAIII.2.2**.

Subsection IAIII.2.1 contains the details of the development a general, economical and environmentally benign method for the preparation of isothiocyanate from the corresponding dithiocarbamic acid salt by using cheap and readily available reagent molecular iodine. Recently we developed an excellent strategy for the preparation of isothiocyanates by diacetoxy iodobenzene (DIB) mediated decomposition of dithiocarbamate salts.²⁴ In spite of the superiority of the method, the expensive nature of the hypervalent iodine reagent became an obstacle for large scale requirements. So an alternative to hypervalent iodine for the decomposition of the dithiocarbamate salts was essential. Accordingly it became incumbent upon us to modify this synthetic protocol. Because molecular iodine is thiophilic in nature,²⁵ we reasoned that it might also be equally effective for the decomposition of dithiocarbamate to their corresponding isothiocyanate. The reagent iodine is low cost, non-toxic and readily available. Considering this, it was thought that iodine would be effective in desulfurizing dithiocarbamate to their corresponding isothiocyanate in presence of a base.

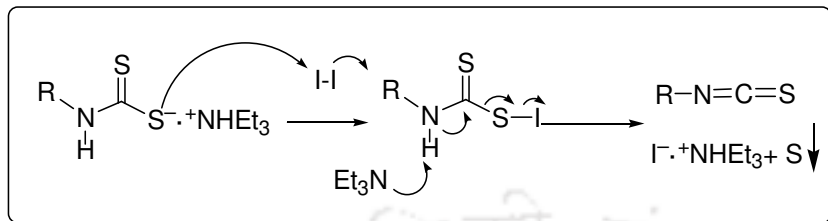
Subsection IAIII.2.2 describes a modified, environmentally benign and cost effective method for the synthesis of isothiocyanates via iodine mediated decomposition of dithiocarbamate salt in the presence of sodium bicarbonate in water/ethyl acetate biphasic solvent system at room temperature.

IAIII.2. Results and Discussion

IAIII.2.1. Molecular iodine mediated preparation of isothiocyanates from dithiocarbamic acid salts in presence of base triethylamine in acetonitrile

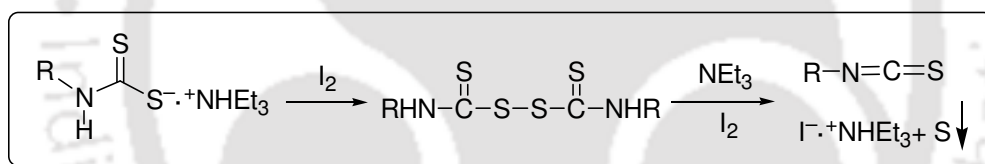
When triethylammonium salt of dithiocarbamate **40** (1 equiv.) was treated with iodine (1 equiv.) in the presence of triethylamine (1.5 equiv.) in acetonitrile, isothiocyanate **40f** (Scheme IAIII.2.1.1.) was obtained in nearly quantitative yield in <10 minutes after the complete addition of iodine. The reaction temperature was generally maintained below 5 °C but the reaction can also be carried out at room temperature. Addition of iodine to the suspension of dithiocarbamate salt must be

carried out slowly over a period of 10-15 minutes. The proposed mechanism is shown in (Scheme IAI.2.1.1.) which is supported by the isolation of the precipitated elemental sulfur.



Scheme IAI.2.1.1. Mechanism of formation of Isothiocyanate from Dithiocarbamate

Alternatively, a mechanism proposed by some others, involving the formation of thiuram disulfide also cannot be ruled out.²² When the dithiocarbamate salt was treated with iodine in the absence of any base, thiuram disulfide was isolated in good yield. The isothiocyanate was obtained in excellent yield when triethylamine and iodine were added to the isolated thiuram disulfide (Scheme IAI.2.1.2.).



Scheme IAI.2.1.2. Alternative mechanism for the formation of isothiocyanate from thiuram disulfide

In these reactions, the most crucial aspect is the preparation of dithiocarbamic acid salt,^{22,23,26} and once the dithiocarbamate salts are obtained, iodine proved to be an effective reagent for their decomposition to the desired isothiocyanates in excellent yields. Thus the use of molecular iodine overcomes many of the problems associated with the preparation of isothiocyanate. Employing this green synthetic protocol, several aromatic isothiocyanates were successfully prepared in high yields (Table IAI.2.1.1.). Aromatic substrates having a Cl substituent in their ortho, meta and para positions (i.e., **41-43**), gave isothiocyanates in excellent yields (94-97%) when iodine was used as the

Table IAI.2.1.1. Preparation of isothiocyanate from dithiocarbamate salt and iodine^a

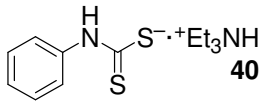
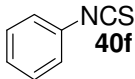
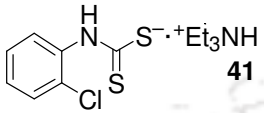
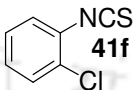
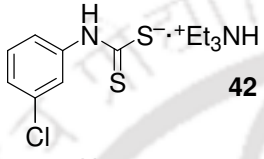
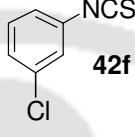
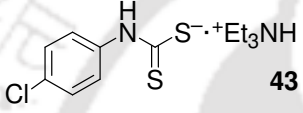
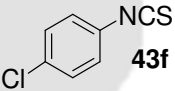
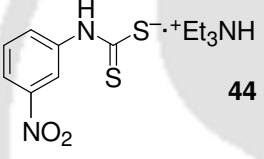
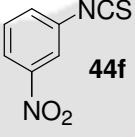
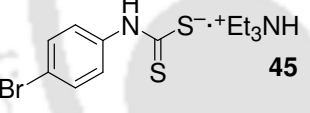
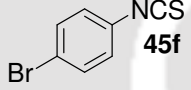
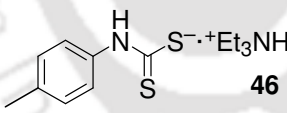
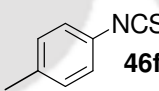
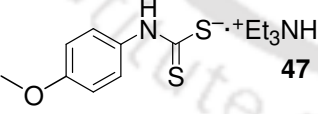
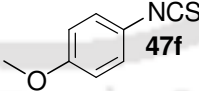
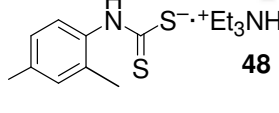
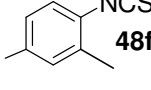
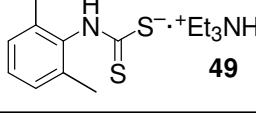
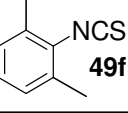
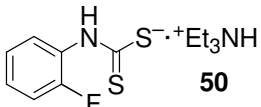
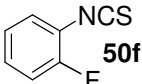
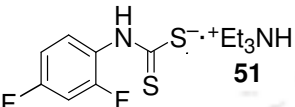
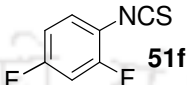
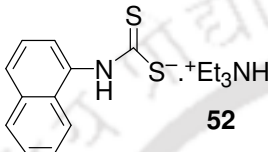
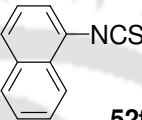
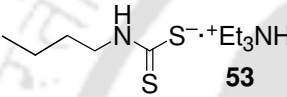
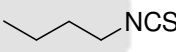
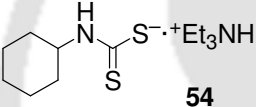
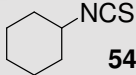
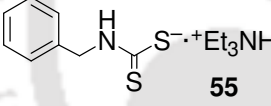
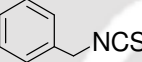
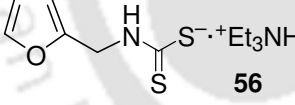
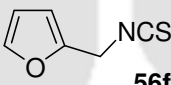
Substrate	Product ^b	Yield (%) ^c
 40	 40f	98
 41	 41f	97
 42	 42f	98
 43	 43f	94
 44	 44f	94
 45	 45f	96
 46	 46f	98
 47	 47f	90
 48	 48f	90
 49	 49f	95

Table contd.

Table IAI.2.1.1. Preparation of isothiocyanate from dithiocarbamate salt and iodine^a

Substrate	Product ^b	Yield (%) ^c
 50	 50f	83
 51	 51f	94
 52	 52f	91
 53	 53f	65
 54	 54f	84
 55	 55f	97
 56	 56f	70

^a Reactions were monitored by TLC. ^b Confirmed by IR, ¹HNMR and ¹³CNMR. ^c Isolated yield

desulfurizing agent. This strategy was successful even when electron withdrawing substituent such as NO₂ group (i.e., **44**) was attached to the aromatic ring. Through this strategy we were able to obtain excellent yields of arylisothiocyanates (**45f-51f**) from substrates (**45-51**), having various substituents in the aromatic ring (Table IAI.2.1.1.).

Recently, our group have demonstrated the *pK_a* dependent regioselective *N*-acylation of unsymmetrical 1,3-disubstituted thiourea.¹⁷ Now, on the basis of the observation and mechanism proposed in (Scheme IAI.2.1.1.), we have sufficient reason to believe that amines having lower *pK_a* should yield the isothiocyanate better because of facile NH deprotonation. Triethylamine, is

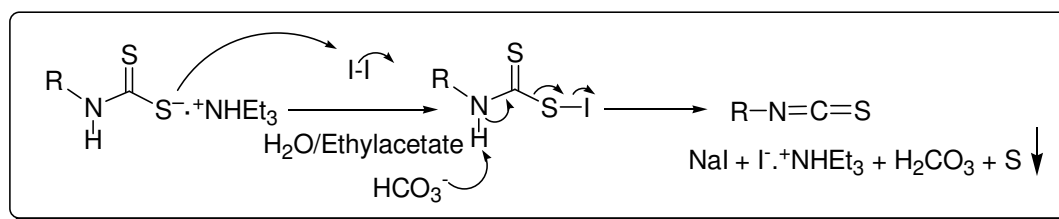
sufficiently basic (pK_a 10.78) in comparison to aromatic amines (pK_a in the range 2.46 to 5.63) and the acidity of the dithiocarbamate bound NH proton is expected to increase further upon salt formation. Other dithiocarbamate salt such as naphthyl compound (**52**) gave its isothiocyanate (**52f**) in good yield. The decrease in the pK_a of NH proton upon formation of dithiocarbamate salt is further evident from the excellent formation of isothiocyanates (**53f-55f**) from alkyl amines such as *n*-butyl (pK_a 10.77), cyclohexyl (pK_a 10.66) and benzylamine (pK_a 9.33), all of which have a similar basicity to that of triethylamine (10.78). Sensitive amine such as furfuryl amine (**56**) gave isothiocyanate (**56f**) in moderate yield.

IAIII.2.2. Improved procedure for the preparation of isothiocyanates via iodine-mediated desulfurization of dithiocarbamic acid salts

We have recently reported a strategy for the preparation of isothiocyanates via diacetoxy iodobenzene (DIB) mediated decomposition of dithiocarbamate salts.²⁴ The use of expensive hyper-valent iodine reagent, toxic triethylamine and acetonitrile makes this methodology impractical for large scale preparations. In another report we have modified this methodology by replacing DIB with non-toxic and inexpensive molecular iodine.^{25,26} This protocol, however, has some drawbacks from a Green chemistry concept due to the use of toxic base (Et_3N) and expensive and toxic solvent acetonitrile. We were keen to further modify the iodine mediated preparation of isothiocyanate, keeping in view the environmental aspect, which would proceed efficiently without the use of any toxic chemicals and would not generate any toxic byproducts. Thus, a safe, water soluble inorganic base sodium bicarbonate was used instead of triethylamine and the use of expensive and toxic acetonitrile was replaced by a cheap and biphasic water and ethylacetate solvent system.

Synthesis of isothiocyanates via iodine mediated decomposition of dithiocarbamate salt in the presence of sodium bicarbonate in water/ethyl acetate biphasic solvent system at room temperature (Scheme IAIII.2.2.1.) is described in this section.

The dithiocarbamic acid salt is readily converted into the corresponding isothiocyanate **40f**, (Table IAIII.2.2.1.) simply by treating it with iodine in the presence of sodium bicarbonate in water/ethylacetate biphasic medium in good to excellent yields in shorter time (15 minutes). The uses of water/ethylacetate biphasic solvent system have several potential advantages. In addition to benign



Scheme IAI.2.2.1. Mechanism of formation isothiocyanates from dithiocarbamates

character of both water and ethyl acetate, the coexistence of water with ethylacetate helps in extracting the isothiocyanate to the organic layer leaving behind the impurities in the aqueous layer which in turn facilitates an easy workup. Iodine is soluble in ethyl acetate and on stirring, dissolves and gets delivered at the water-ethylacetate interphase for desulfurization. Moreover, the water phase dissolves the base sodium bicarbonate and retains the dithiocarbamic acid salt in aqueous layer. The use of sodium bicarbonate over organic bases offers a mild and effective Green approach towards the synthesis of isothiocyanates. Thus the method provides an ecologically and economically viable process for the preparation of isothiocyanates.

The preparation of isothiocyanates was performed on freshly prepared dithiocarbamate salts synthesized from a variety of structurally different alkyl and aryl amines. The results are summarized in Table IAI.2.2.1. and Table IAI.2.2.2.

Various dithiocarbamic acid salts of arylamines with electron withdrawing groups in both ortho and para positions (**41**, **43** and **50** Table IAI.2.2.1.) afforded excellent yields. 2-Iodo-4-methyl phenyl dithiocarbamate yields the corresponding isothiocyanate (**57** Table IAI.2.2.1.). Aromatic ring containing two fluoro groups in ortho and para positions (**51** Table IAI.2.2.1.) gave isothio-cyanate (**51f**) in excellent yield. Isothiocyanates were obtained in very high yields from their corresponding dithiocarbamate salts containing highly electron withdrawing substituents in meta and para positions (**44**, **58**, **59**, **60** Table IAI.2.2.1.). This methodology worked well with substrates having electron donating groups (**147**, **61**, **46**, **48** Table IAI.2.2.). The fused ring compound α -naphthyl amine gave the expected 1-isothiocyanato-naphthalene (**52f**) (**52** Table IAI.2.2.1.) in very high yield.

Table IAIII.2.2.1. Preparation of isothiocyanates from dithiocarbamates and iodine.^a

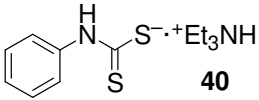
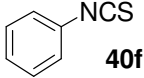
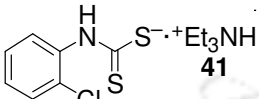
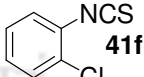
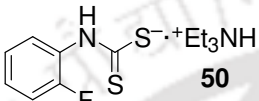
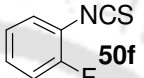
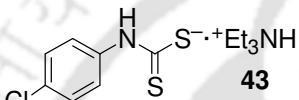
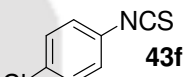
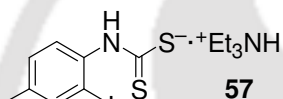
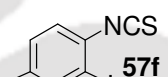
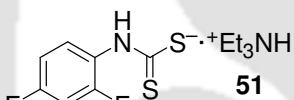
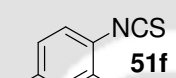
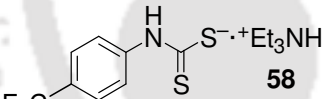
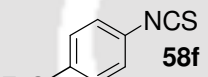
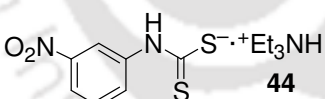
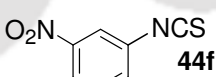
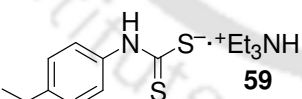
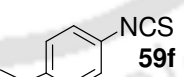
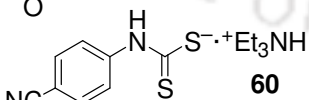
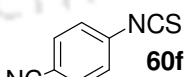
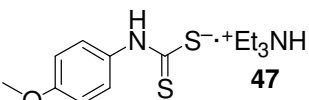
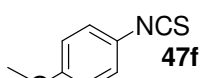
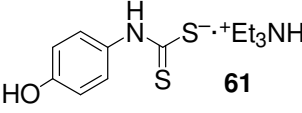
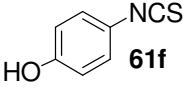
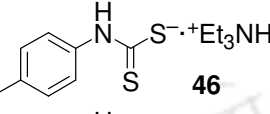
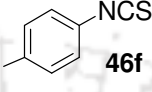
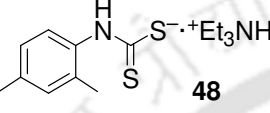
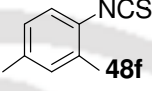
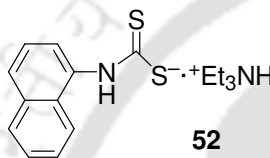
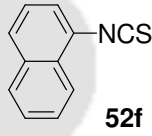
Substrate	Product ^b	Yield (%) ^c
 40	 40f	80
 41	 41f	92
 50	 50f	81
 43	 43f	92
 57	 57f	92
 51	 51f	90
 58	 58f	77
 44	 44f	90
 59	 59f	85
 60	 60f	80
 47	 47f	92

Table contd.

Table IAIII.2.2.1. Preparation of isothiocyanates from dithiocarbamates and iodine.^a

Substrate	Product ^b	Yield (%) ^c
 61	 61f	88
 46	 46f	86
 48	 48f	90
 52	 52f	88

^a Reactions were monitored by TLC. ^b Confirmed by IR, ¹H NMR and ¹³C NMR. ^c Isolated yield.

Following similar methodology, we have successfully obtained aliphatic isothiocyanates of *n*-butyl, dodecyl and cyclohexyl dithiocarbamates (**53**, **62** and **54** Table IAIII.2.2.2.). This method was effective as well with dithiocarbamate salts of benzyl, piperonyl and homoveratrylamines (**55**, **63** and **64** Table IAIII.2.2.2.).

Table IAIII.2.2.2. Preparation of isothiocyanates from dithiocarbamates and iodine.^a

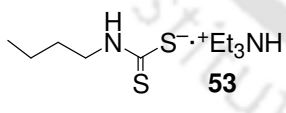
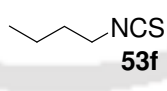
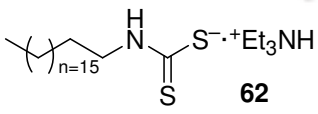
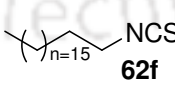
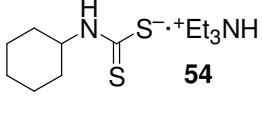
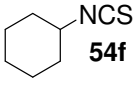
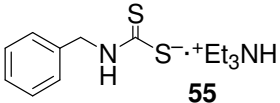
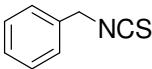
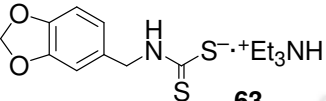
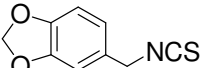
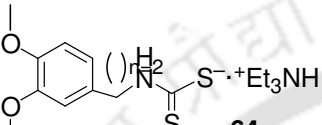
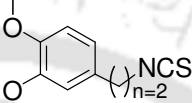
Substrate	Product ^b	Yield (%) ^c
 53	 53f	60
 62	 62f	70
 54	 54f	80

Table contd.

Table I AIII.2.2.2. Preparation of isothiocyanates from dithiocarbamates and iodine.^a

Substrate	Product ^b	Yield (%) ^c
 55	 55f	85
 63	 63f	80
 64	 64f	70

^a Reactions were monitored by TLC. ^b Confirmed by IR, ¹H NMR and ¹³C NMR. ^c Isolated yield.

The reactions were clean and thiourea and other byproducts are not obtained during the preparation of isothiocyanates. The reactions are rapid and facile and accomplished at room temperature. The product obtained in high yields is observed to be substantially pure without requiring any further purification.

In conclusion we have developed two new protocols for the synthesis of isothiocyanates from dithiocarbamates. While one of the protocols is based on the decomposition of dithiocarbamate to isothiocyanate in presence of iodine and triethylamine in acetonitrile and the other is based on the iodine mediated decomposition of dithiocarbamate to corresponding isothiocyanate in presence of sodium bicarbonate in water/ethylacetate biphasic system. In the second approach the base sodium bicarbonate used is to the best of our knowledge perhaps the soft base to be used for the purpose. The use of benign water/ethylacetate biphasic solvent system makes the protocol environmentally attractive. The other attributes in these methodologies are the use of non-toxic and inexpensive reagents and solvents without the formation of any side products. The products obtained in high yields are stable and observed to be pure without requirement of further purification. The methods are general, economical and environmentally benign. In comparison to the existing methods of decomposition of dithiocarbamic acid salt, our procedures are perhaps the simplest, yet most efficient method for the synthesis of isothiocyanates. Although literature enumerates a number of procedures

for the preparation of isothiocyanate, the simplicity, environmental acceptability, and cost effectiveness of our procedures makes it a practical alternative.

IAIII.3. Experimental

IAIII.3.1. General Remarks

As described in Section IAI.3.1. Page no. 57.

IAIII.3.2. Characterization of Organic Substrates

As described in Section IAI.3.2. Page no. 57.

IAIII.3.3. General Procedures

IAIII.3.3.1. General experimental procedure for the preparation of phenyl dithiocarbamate salt of amine.

To a stirred ice cooled solution of carbon disulfide (152 mg, 2 mmol) and triethylamine (303 mg, 3 mmol) in a round bottom flask, aniline (93 mg, 1 mmol) was added drop wise. A light yellow color compound has started appearing. Stirring was continued for 0.5-1.5 h. The precipitate was filtered off and wash with ether (2 x 5 mL) and product dried in vacuo to furnish phenyl dithiocarbamic acid salt **40** (243 mg, 90%).

IAIII.3.3.2. General experimental procedure for molecular iodine mediated preparation of isothiocyanates from dithiocarbamic acid salts.

To a stirred and ice cooled suspension of dithiocarbamate salt **40** (540 mg, 2 mmol) in acetonitrile (5 mL), was added triethylamine (417 μ L, 3 mmol). To this was added iodine (508 mg, 2 mmol) portion wise over a period of 30 minutes. A light yellow color precipitate of sulfur started separating out during this period. The precipitated sulfur was filtered; the organic layer was concentrated and admixed with hexane (15 mL). The hexane layer was washed with 1N HCl (2 x 5 mL), and water (1 x 5 mL). The organic layer was dried with anhydrous Na₂SO₄, concentrated under reduced pressure and

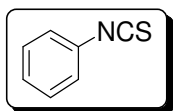
purified over a short column of silica gel (100% hexane) to afford the isothiocyanate **40f** (259 mg, 96%). The results are summarized in **Table IAIII.2.1.1**.

IAIII.3.3.3. General experimental procedure for molecular iodine mediated preparation of isothiocyanates from dithiocarbamic acid salts using sodium bicarbonate in water/ethylacetate biphasic solvent system.

To a stirred and ice cooled biphasic solvent system water/ethyl acetate (1 : 1, 10 mL) was added dithiocarbamate salt **40** (540 mg, 2 mmol) followed by sodium bicarbonate (336 mg, 4 mmol). To this was then added iodine (508 mg, 2 mmol) pinch wise over a period of 15-20 minutes. During this period a light yellow color precipitate of sulfur was observed and settles at water ethyl acetate interface. The ethyl acetate layer was washed with sodium thiosulfate (5%) (1 x 5 mL) followed by water (1 x 5 mL). The precipitated sulfur was filtered and the filtrate was dried over anhydrous Na_2SO_4 . The organic layer was concentrated under reduced pressure and purified over a short column of silica gel (100% pentane) to give the isothiocyanate **40f** (216 mg, 80 %). The results are summarized in **Table IAIII.2.2.1** and **IAIII.2.2.2**.

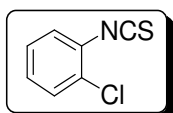
I AIII.4. Spectral Data

1-Isothiocyanato-benzene (40f):



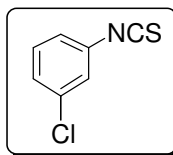
Liquid. ^1H NMR (400 MHz, CDCl_3): δ 7.21-7.37 (m, 5H). ^{13}C NMR (100 MHz, CDCl_3): δ 125.8, 127.4, 129.6, 131.3, 135.3. IR (KBr): 3064, 2164, 2063, 1591, 1489, 1474, 1451, 1070, 927, 905, 749, 684 cm^{-1} .

1-Chloro-2-isothiocyanato-benzene (41f):

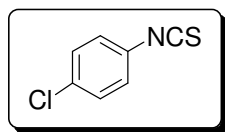


Yellow liquid. ^1H NMR (400 MHz, CDCl_3): δ 7.20 (m 3H), 7.39 (d, 1H, $J = 8.0$ Hz). ^{13}C NMR (100 MHz, CDCl_3): δ 125.9, 126.4, 126.6, 127.6, 128.0, 130.1, 131.7. IR (KBr): 3066, 2562, 2126, 2053, 1582, 1472, 1442, 1068, 937, 750, 723, 660 cm^{-1} .

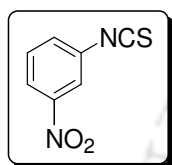
1-Chloro-3-isothiocyanato-benzene (42f):



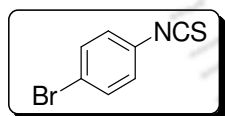
Oily liquid. ^1H NMR (400 MHz, CDCl_3): δ 7.09-7.12 (m, 1H), 7.21-7.28 (m, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 123.8, 125.7, 127.4, 130.3, 132.4, 134.9, 137.5. IR (KBr): 3060, 2560, 2230, 2197, 2071, 1931, 1585, 1572, 1470, 1423, 1070, 1089, 960, 864, 776, 751, 672, 532 cm^{-1} .

1-Chloro-4-isothiocyanato-benzene (43f):

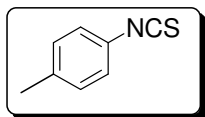
Yellow solid. Mp: 43-45 °C. ^1H NMR (400 MHz, CDCl_3): δ 7.16 (d, 2H, $J = 8.0$ Hz), 7.32 (d, 2H, $J = 8.0$ Hz). ^{13}C NMR (100 MHz, CDCl_3): δ 127.0, 129.8, 130.0, 133.0, 136.8. IR (KBr): 3082, 2928, 2175, 2126, 2086, 1482, 1089, 928, 824, 495 cm^{-1} .

1-Isothiocyanato-3-nitro-benzene (44f):

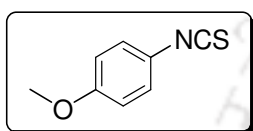
^1H NMR (400 MHz, CDCl_3): δ 7.54 (s, 2H), 8.06 (s, 1H), 8.11-8.14 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 120.7, 121.9, 130.6, 131.6, 133.3, 139.6, 148.8. IR (KBr): 3091, 3074, 2227, 2161, 2106, 1526, 1470, 1348, 1302, 892, 809, 736, 665 cm^{-1} .

1-Bromo-4-isothiocyanato-benzene (45f):

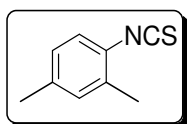
Yellow solid. Mp: 58 °C. ^1H NMR (400 MHz, CDCl_3): δ 7.09 (d, 2H, $J = 8.8$ Hz), 7.47 (d, 2H, $J = 8.8$ Hz). ^{13}C NMR (100 MHz, CDCl_3): δ 120.8, 127.2, 130.5, 132.8, 136.9. IR (KBr): 3074.1, 2925.8, 2171.6, 2071.3, 1578.5, 1478.0, 1474.1, 1399.3, 1067.1, 1011.8, 923.1, 818.4, 490.1, 438.0 cm^{-1} .

1-Isothiocyanato-4-methyl-benzene (46f):

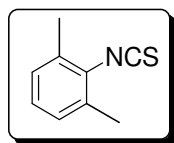
Oily liquid. ^1H NMR (400 MHz, CDCl_3): δ 2.33 (s, 3H), 7.06-7.13 (m, 4H). ^{13}C NMR (100 MHz, CDCl_3): δ 21.2, 125.4, 128.2, 130.1, 134.4, 137.4. IR (KBr): 2920, 2094, 1503, 929, 812, 790, 497 cm^{-1} .

1-Isothiocyanato-4-methoxy-benzene (47f):

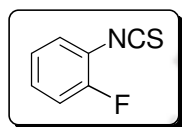
Oily liquid. ^1H NMR (400 MHz, CDCl_3): δ 3.80 (s, 3H), 6.85 (d, 2H, $J = 8.8$ Hz), 7.16 (d, 2H, $J = 8.8$ Hz). ^{13}C NMR (100 MHz, CDCl_3): δ 55.4, 114.6, 123.2, 126.8, 133.7, 158.4. IR (KBr): 3000, 956, 2835, 2170, 2098, 1580, 1599, 1503, 1459, 1440, 1292, 1251, 1179, 1166, 1028, 927, 824, 614, 513 cm^{-1} .

1-Isothiocyanato-2,4-dimethyl-benzene (48f):

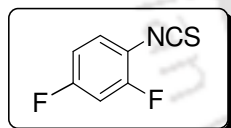
Colourless liquid. ^1H NMR (400 MHz, CDCl_3): δ 2.30 (s, 3H), 2.33 (s, 3H), 6.96 (d, 1H, $J = 9.2$ Hz), 7.01 (s, 1H), 7.07 (d, 1H, $J = 8.0$ Hz). ^{13}C NMR (100 MHz, CDCl_3): δ 18.2, 21.1, 125.6, 127.4, 131.2, 134.6, 137.4. IR (KBr): 2920, 2131, 2085, 1490, 1455, 1379, 1229, 1036, 947, 901, 875, 812 cm^{-1} .

1-Isothiocyanato-2,6-dimethyl-benzene (49f):

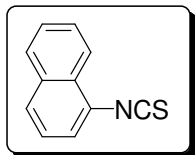
Liquid. ^1H NMR (400 MHz, CDCl_3): δ 2.37 (s, 6H), 7.05 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 18.5, 126.8, 127.9, 129.4, 134.8, 135.6. IR (KBr): 2920, 2148, 2086, 1592, 1469, 1442, 1379, 1165, 1032, 924, 770, 747, 719, 550 cm^{-1} .

1-Fluoro-2-isothiocyanato-benzene (50f):

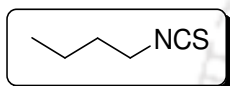
Oily liquid. ^1H NMR (400 MHz, CDCl_3): δ 7.08-7.26 (m, 4H). ^{13}C NMR (100 MHz, CDCl_3): δ 116.4, 116.6, 120.3, 120.4, 124.8, 124.9, 126.5, 128.5, 128.6, 140.9, 157.3, 159.9. IR (KBr): 3407, 3069, 2927, 2104, 2036, 1587, 1496, 1458, 1265, 1212, 1104, 941, 808, 752 cm^{-1} .

1-Isothiocyanato-2,4-difluoro-benzene (51f):

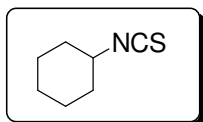
Oily liquid. ^1H NMR (400 MHz, CDCl_3): δ 6.83-6.88 (m, 1H), 6.89-6.94 (m, 1H), 7.15-7.18 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 104.8, 105.1, 105.2, 105.3, 111.8, 111.9, 112.0, 112.1, 116.8, 116.9, 126.9, 127.0, 141.6, 157.3, 157.5, 159.6, 159.7, 159.9, 160.0, 162.1, 162.2. IR (KBr): 3082, 2705, 2535, 2104, 2034, 1607, 1504, 1459, 1438, 1305, 1261, 1216, 1145, 1099, 970, 852, 811, 605, 572 cm^{-1} .

Isothiocyanato-naphthalene (52f):

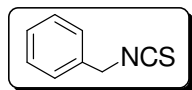
White solid. Mp: 56-57 °C. ^1H NMR (400 MHz, CDCl_3): δ 7.36-7.38 (m, 2H), 7.51-7.59 (m, 2H), 7.74 (t, 1H, $J = 4.0$ Hz), 7.84 (d, 1H, $J = 8.0$ Hz), 8.07 (d, 1H, $J = 8.0$ Hz). ^{13}C NMR (100 MHz, CDCl_3): δ 122.6, 123.4, 125.4, 127.1, 127.3, 127.7, 128.4, 129.2, 133.0. IR(KBr): 3054, 2473, 2100, 1589, 1506, 1388, 913, 857, 789, 760, 656, 553, 536 cm^{-1} .

1-Isothiocyanato-n-butane (53f):

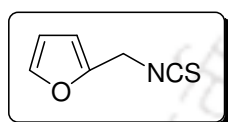
Colourless liquid. ^1H NMR (400 MHz, CDCl_3): δ 0.92 (t, 3H, $J = 7.4$ Hz), 1.47-1.37 (m, 2H), 1.69-1.61 (m, 2H), 3.42 (t, 2H, $J = 6.6$ Hz). ^{13}C NMR (100 MHz, CDCl_3): δ 13.2, 19.7, 31.9, 44.7, 129.4., IR (KBr): 2925, 2087, 1597, 1401, 1218, 1166, 753 cm^{-1} .

Isothiocyanato-cyclohexane (54f):

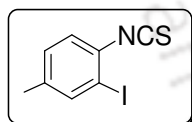
Colourless liquid. ^1H NMR (400 MHz, CDCl_3): δ 1.28-1.96 (m, 10H), 3.67 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 23.0, 24.9, 33.0, 55.2, 129.6. IR (KBr): 2937, 2858, 2175, 2102, 2060, 1450, 1361, 1320, 986, 891, 720, 702 cm^{-1} .

1-Isothiocyanatomethyl-benzene (55f):

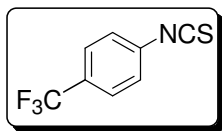
Yellow liquid. ^1H NMR (400 MHz, CDCl_3): δ 4.72 (s, 2H), 7.31-7.41 (m, 5H). ^{13}C NMR (100 MHz, CDCl_3): δ 48.5, 126.7, 128.2, 128.8, 131.8, 134.1. IR (KBr): 3033, 2925, 2175, 2094, 1454, 1347, 1028, 700, 574 cm^{-1} .

Furfuryl isothiocyanate (56f):

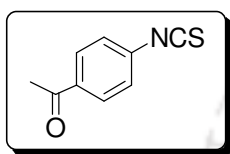
Brown liquid. ^1H NMR (400 MHz, CDCl_3): δ 4.64 (d, 2H, $J = 0.8$ Hz), 6.33-6.37 (m, 2H), 7.41-7.42 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 42.0, 108.8, 110.7, 134.9, 143.3, 147.3. IR (KBr): 2917, 2153, 2076, 1503, 1432, 1333, 1144, 1009, 910.8, 743, 685 cm^{-1} .

2-Iodo-1-isothiocyanato-4-methylbenzene (57f):

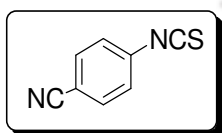
White solid. Mp: 62-65 $^\circ\text{C}$. ^1H NMR (400 MHz, CDCl_3): δ 2.30 (s, 3H), 7.13 (m, 2H), 7.62 (s, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 20.9, 94.2, 126.7, 130.1, 132.3, 136.1, 139.1, 139.9. IR (KBr): 2916, 2134, 1633, 1474, 1042, 929, 811 cm^{-1} .

1-Isothiocyanato-4-trifluoromethyl-benzene (58f):

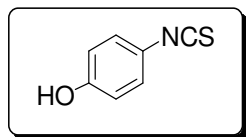
Colourless solid. Mp: 43 °C. ^1H NMR (400 MHz, CDCl_3): δ 7.32 (d, $J = 8.4$ Hz, 2H), 7.61 (d, $J = 8.4$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 122.4, 125.1, 126.1, 126.9, 127.0, 129.0, 129.4, 135.15, 138.4. IR (KBr): 3427, 2081, 1613, 1413, 1325, 1137, 1106, 1066, 839 cm^{-1} .

1-(4-Isothiocyanato-phenyl)-ethanone (59f):

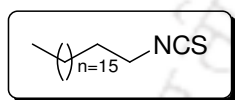
Colourless liquid. ^1H NMR (400 MHz, CDCl_3): δ 2.60 (s, 3H), 7.29 (d, $J = 8.8$ Hz, 2H), 7.95 (d, $J = 8.8$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 26.8, 126.0, 129.9, 135.5, 135.8, 138.0, 196.6. IR (KBr): 3070, 2925, 2190, 2124, 1682, 1589, 1409, 1354, 1254, 1107, 961, 927, 843 cm^{-1} .

4-Isothiocyanato-benzonitrile (60f):

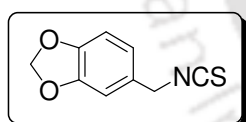
Colourless crystal. Mp: 119-120 °C. ^1H NMR (400 MHz, CDCl_3): δ 7.31(d, $J = 8.8$ Hz. 2H), 7.66 (d, $J = 8.8$ Hz. 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 110.6, 117.9, 126.5, 133.6, 135.9, 139.4. IR (KBr): 3435, 2197, 2124, 1598, 1492, 1277, 933, 836 cm^{-1} .

1-Isothiocyanato-4-hydroxy-benzene (61f):

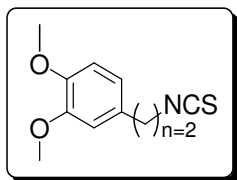
Oily liquid. ^1H NMR (400 MHz, CDCl_3): δ 6.05 (brs, 1H), 6.79 (d, $J = 8.8$ Hz, 2H), 7.09 (d, $J = 8.8$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 116.5, 123.8, 127.4, 133.7, 154.6. IR (KBr): 3373, 2923, 2117, 1607, 1504, 1352, 1269, 1094, 831 cm^{-1} .

1-Isothiocyanato-octadecane (62f):

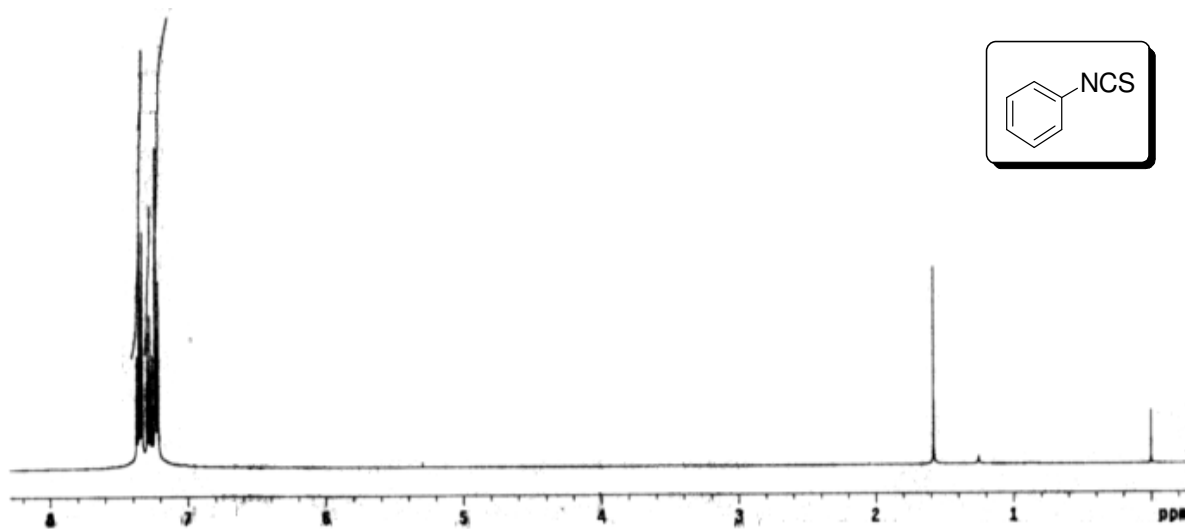
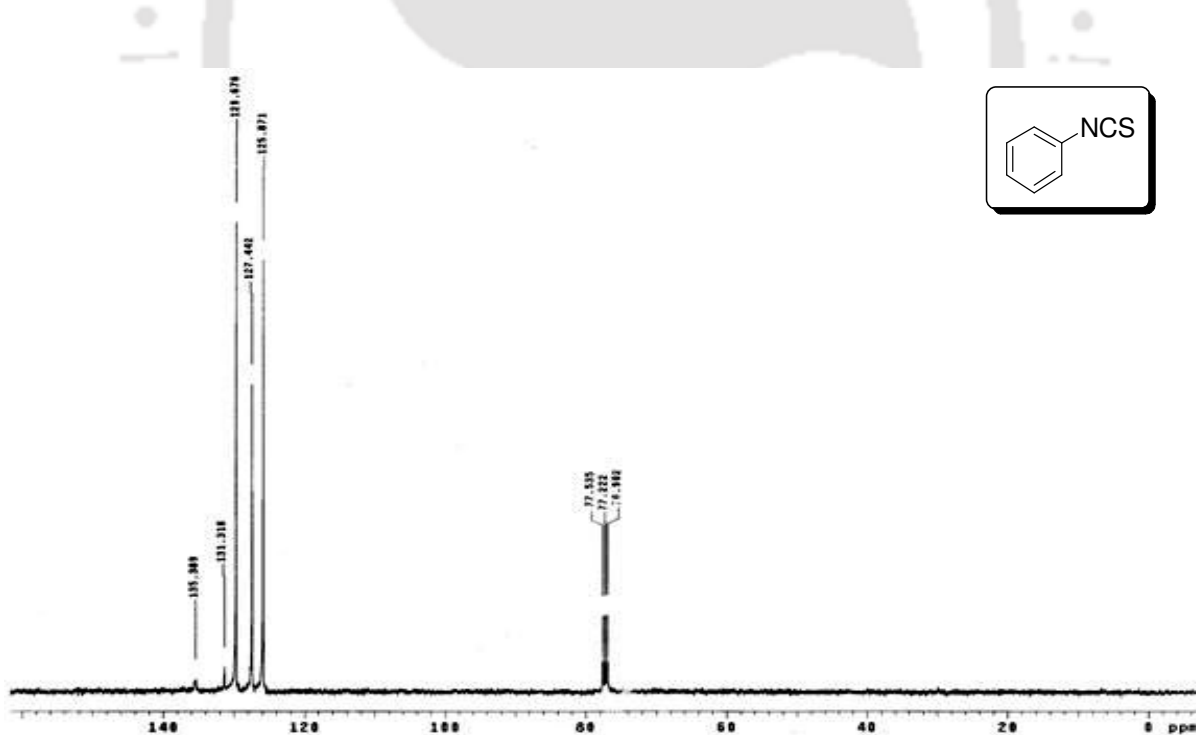
Oily liquid. ^1H NMR (400 MHz, CDCl_3): δ 0.879 (t, $J = 6.8$ Hz, 3H), 1.25 (s, 28H), 1.71-1.72 (m, 4H), 3.50 (t, $J = 6.4$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 14.3, 22.8, 26.7, 29.0, 29.5, 29.7, 29.8, 30.1, 32.1, 45.2. IR (KBr): 2923, 2853, 2185, 2096, 1463, 1455, 1346, 721 cm^{-1} .

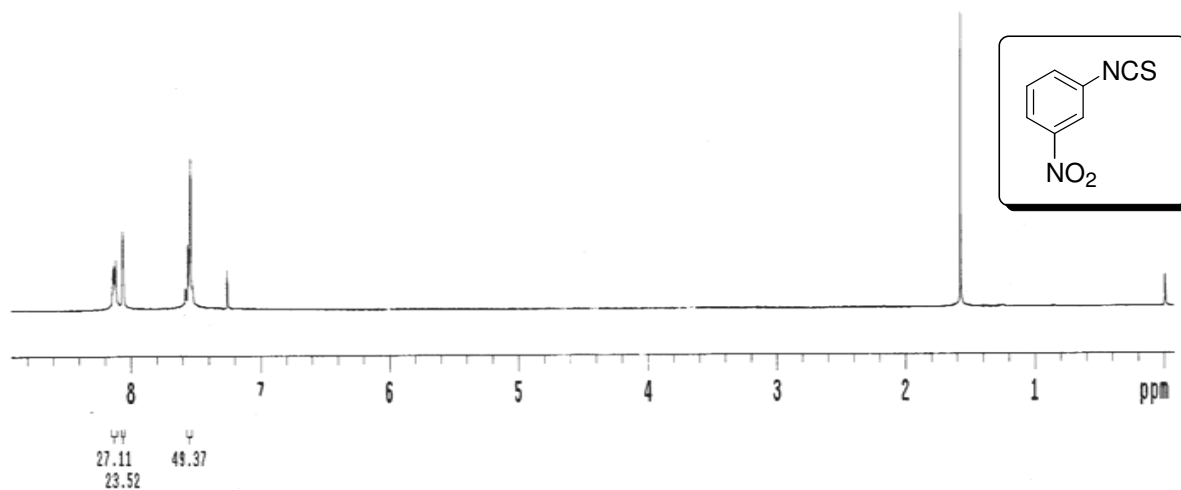
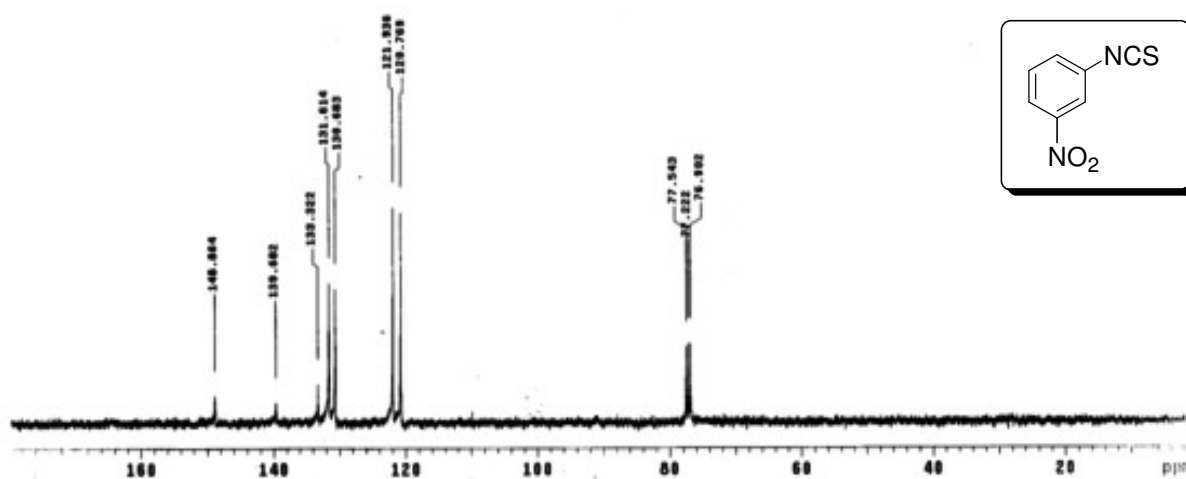
5-(Isothiocyanatomethyl)benzo[d][1,3]dioxole (63f):

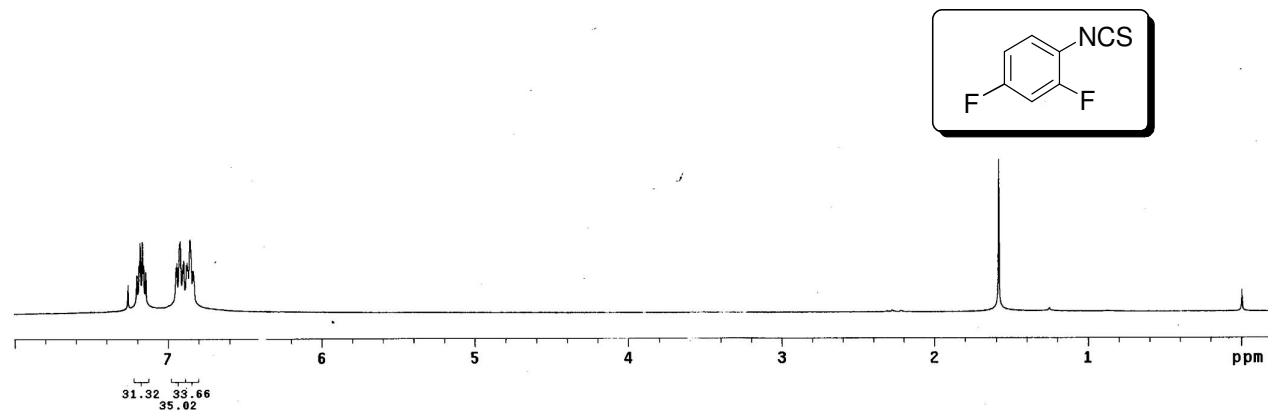
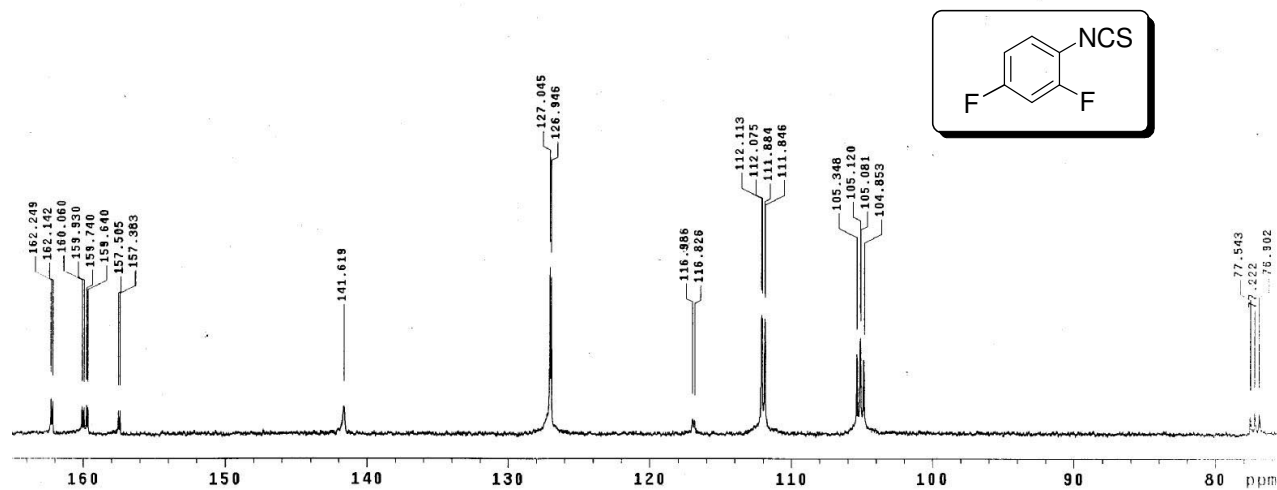
Reddish oil. ^1H NMR (400 MHz, CDCl_3): δ 4.59 (s, 2H), 5.98 (s, 2H), 6.74-6.80 (m, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 48.7, 101.5, 107.7, 108.6, 120.7, 128.0, 132.1, 147.8, 148.2. IR (KBr): 2895, 2087, 1503, 1445, 1369, 1322, 1251, 1101, 1028, 924 cm^{-1} .

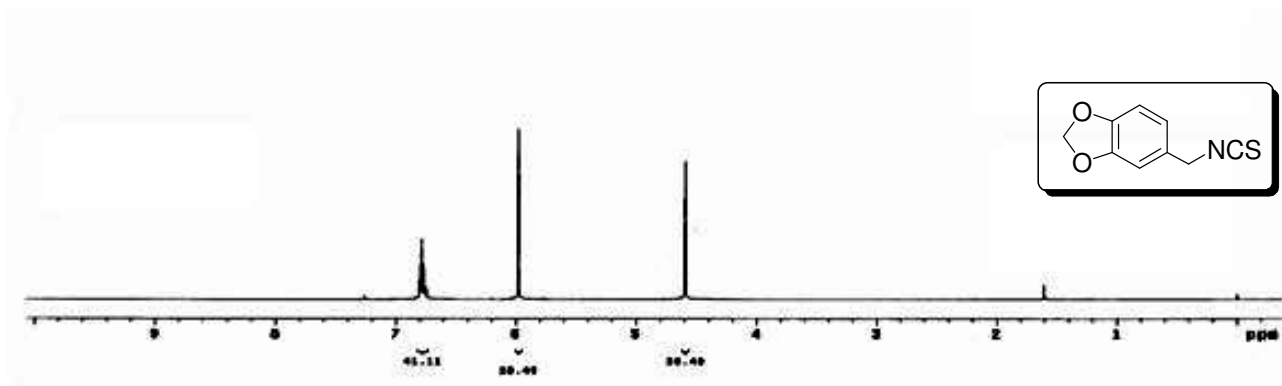
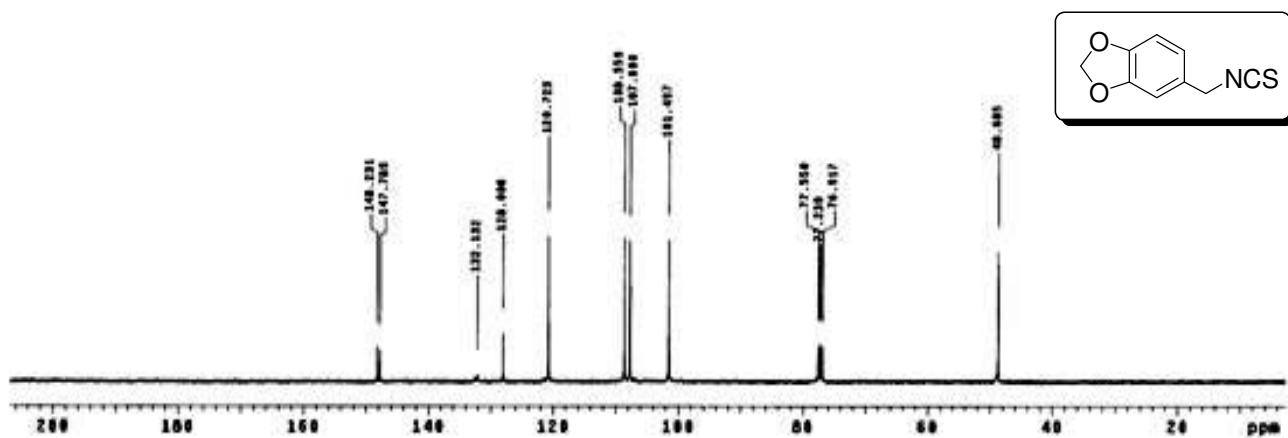
4-(2-Isothiocyanato-ethyl)-1,2-dimethoxy benzene (64f):

Oily liquid. ^1H NMR (400 MHz, CDCl_3): δ 2.90 (t, $J = 6.6$ Hz, 2H), 3.68 (t, $J = 6.6$ Hz, 2H), 3.85 (s, 3H), 3.88 (s, 3H), 6.79 (m, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 36.0, 46.6, 55.8, 55.8, 111.3, 111.9, 120.8, 129.5, 130.3, 148.0, 148.9. IR (KBr): 3000, 2935, 2835, 2181, 2100, 1592, 1515, 1455, 1347, 1263, 1142, 1028, 909 cm^{-1} .

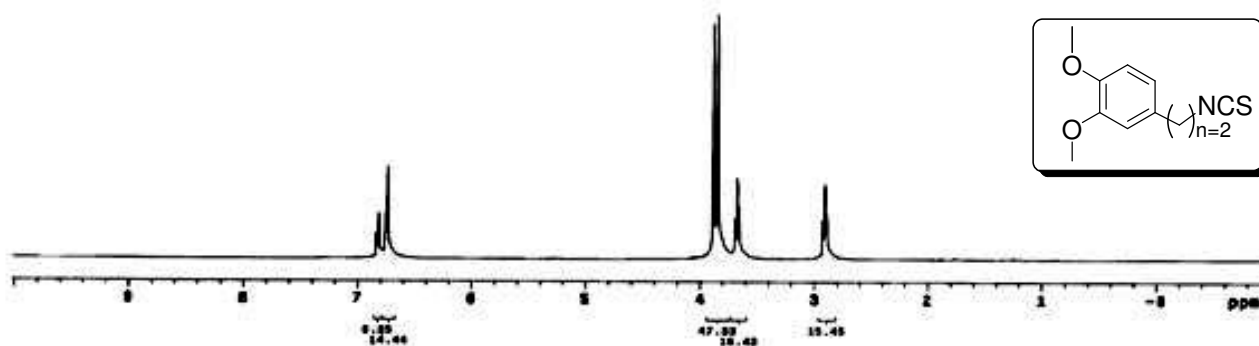
IAIII.5. Spectra of some selected compounds**1-Isothiocyanato-benzene (40f): ^1H NMR (400 MHz, CDCl_3):****1-Isothiocyanato-benzene (40f): ^{13}C NMR (100 MHz, CDCl_3):**

1-Isothiocyanato-3-nitro-benzene (44f): ^1H NMR (400 MHz, CDCl_3):**1-Isothiocyanato-3-nitro-benzene (44f): ^{13}C NMR (100 MHz, CDCl_3):**

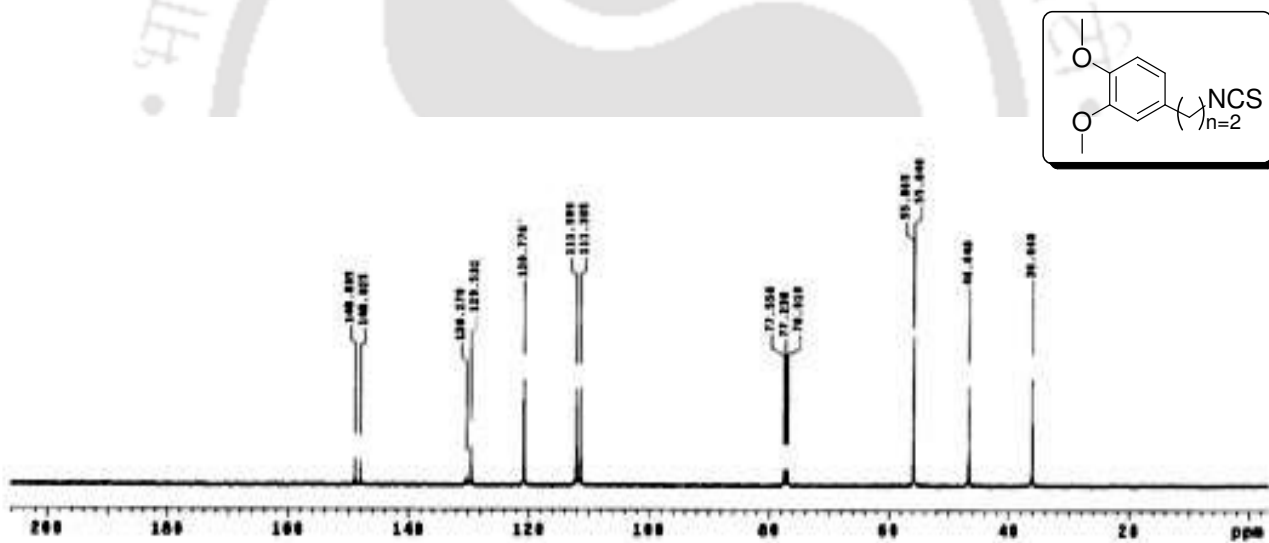
1-Isothiocyanato-2,4-difluoro-benzene (51f): ^1H NMR (400 MHz, CDCl_3):**1-Isothiocyanato-2,4-difluoro-benzene (51f): ^{13}C NMR (100 MHz, CDCl_3):**

5-(Isothiocyanatomethyl)benzo[d][1,3]dioxole (63f): ^1H NMR. (400MHz, CDCl_3):**5-(Isothiocyanatomethyl)benzo[d][1,3]dioxole (63f): ^{13}C NMR (100 MHz, CDCl_3):**

4-(2-isothiocyanato-ethyl)-1,2-dimethoxy benzene (64f): ^1H NMR. (400MHz, CDCl_3):



4-(2-isothiocyanato-ethyl)-1,2-dimethoxy benzene (64f): ^{13}C NMR (100 MHz, CDCl_3):



IAIII.6. References

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IAIV.1. A One-pot Preparation of Cyanamide from Dithiocarbamate Using Molecular Iodine

Alkyl and aryl cyanamides are an important class of compounds which are vital intermediates for the synthesis of various biologically active molecules and can be converted efficiently into other functionalities by simple chemical reactions. Due to their unique structure and reactivity, cyanamides have attracted considerable attention in organic synthesis¹ as well as in the fields of inorganic and material sciences.² Cyanamides are key precursors to *N*-alkyl or *N*-aryl imides³ and also serve as an useful protecting group in the synthesis of heterocycles containing secondary and tertiary amines.⁴ They are important precursors in the synthesis of herbicides⁵ and pharmaceutically active heterocycles such as tumor inhibitors,⁶ and a vasodilator medication called minoxidil,⁵ known for its ability to reduce hair loss and promote hair regrowth.

The wide sprade applications of cyanamides have resulted in the development of several methods for their synthesis over the years. Commonest among these is the reaction of cyanogen chloride / bromide with amines or with imide salts.⁷ However this method involves the use of potassium / sodium cyanide and bromine for the preparation of cyanogen halide (which is again highly toxic), making the protocol environmentally unacceptable.

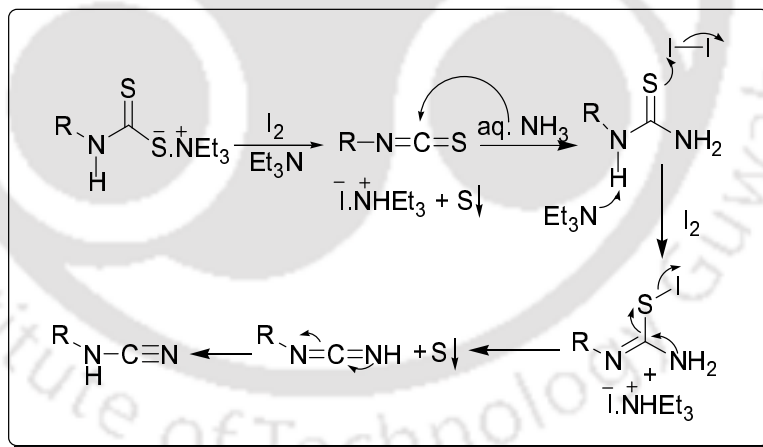
Literature reports various other methods for the preparation of cyanamide using different synthetic strategies such as cyanation of amines using CN^+ equivalents as synthons,⁸⁻¹⁴ Tiemann rearrangement of amidoximes,¹⁵ coupling reactions involving Pd isocyanides, allyl carbonates and trimethylsilyl azide,¹⁶ and sodium bis(trimethylsilyl)amide as deoxygenating or desulfurizing agents.¹⁷ Yet another method for the preparation of cyanamides involves the reaction of hypervalent iodine (V) species with *N,N'*-disubstituted glycyamide.¹⁸ However, all the procedures reported so far seem to have severe environmental concern as they involve direct or indirect use of toxic and corrosive reagents, strong alkaline conditions, expensive reagents and catalysts, high reaction temperatures and tedious purification procedures.

We have been interested to an extent in the synthesis of isothiocyanates and cyanamides and in this context we recently developed a method involving hypervalent iodine reagent, diacetoxyiodobenzene (DIB) as an efficient thiophilic / desulfurizing agent for the preparation of

these compounds from dithiocarbamate salts.¹⁹ However, this method although efficient, is not economically viable when applied to large scale reactions. In yet another related work we demonstrated that the hypervalency of iodine is not really essential, particularly for the transformation of dithiocarbamate to isothiocyanate and molecular iodine was found to be equally effective.²⁰ In continuation of these studies, and also while looking at reaction strategies from a Green chemistry perspective, we thought it would be worthwhile to investigate an alternative methodology for the synthesis of cyanamides, involving the use of alkyl or aryl dithiocarbamate using iodine as double desulfurizing agent.

IAIV.2. Results and Discussion

Our present methodology is based on: (i) formation of isothiocyanate from alkyl / aryl dithiocarbamate salt by desulfurization with iodine in the presence of triethylamine as the base in ethylacetate solvent, (ii) treating the *in situ* generated isothiocyanate with aqueous NH_3 to afford alkyl / aryl thioamides and (iii) further oxidative desulfurization of thioamides to cyanamide with iodine in the presence of triethylamine (Scheme IAIV.2.1).



Scheme IAIV.2.1. Plausible mechanism for the formation of cyanamide.

Using aqueous NH_3 as the base instead of triethylamine did not work as expected, due to the competing reactions between ammonia and molecular iodine forming nitrogen triiodide (NI_3), which of course is well documented in the literature.²¹ The mechanism which is proposed in the

scheme has been authenticated by isolation and characterization of all the intermediates. Isolation of the precipitated elemental sulfur further supports the mechanism proposed.

Based on these findings, we thus report herein a practical, environmentally benign, high yielding and one-pot preparation of cyanamides from dithiocarbamate salts using cheap and non-toxic reagent molecular iodine in an innocuous solvent ethylacetate.

A variety of substituted aromatic dithiocarbamate salts²² undergo facile transformation to give their corresponding cyanamides by this methodology (Table IAIV.2.1). This methodology is equally effective irrespective of the nature and positions (*o*-, *m*-, *p*-) of the substituents attached to the phenyl ring. Strongly activating (**66**, **71** and **74**), weakly deactivating (**67-69** and **73**), moderately deactivating (**72**) and strongly deactivating (**70**) systems all give products with equal ease. The versatility of the method has been demonstrated by the tolerance of a number of functional groups such as -NO₂ (**70**), -OMe (**66**, **71**), -COCH₃ (**72**) and -OH (**74**). Hindered and trisubstituted dithiocarbamates (**75-78**) also efficiently give their corresponding cyanamides (**75g-78g**) in excellent yields.

Table IAIV.2.1. Preparation of cyanamides from dithiocarbamates and iodine^a

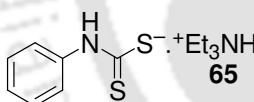
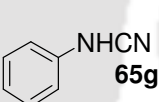
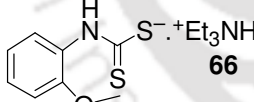
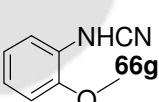
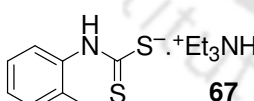
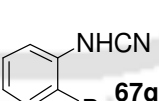
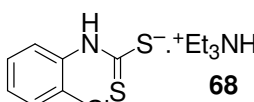
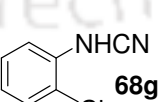
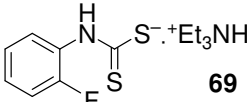
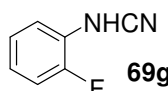
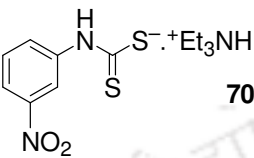
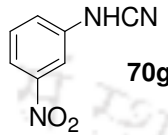
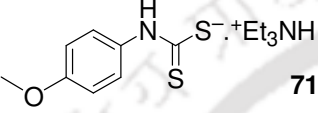
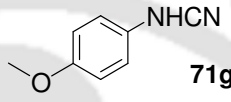
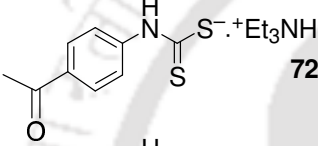
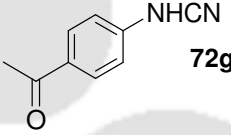
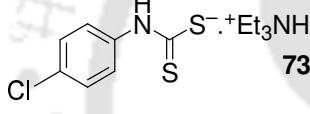
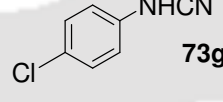
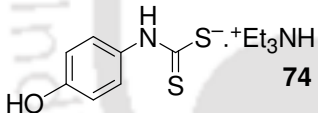
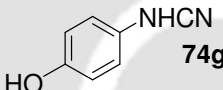
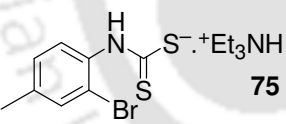
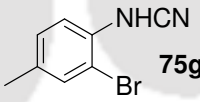
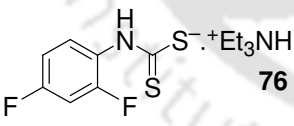
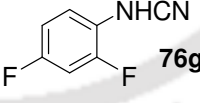
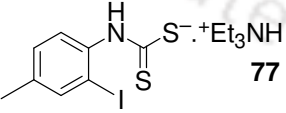
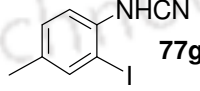
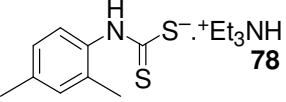
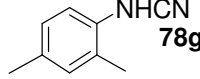
Substrate	Product ^b	Yield (%) ^c
 65	 65g	80
 66	 66g	72
 67	 67g	80
 68	 68g	70

Table contd.

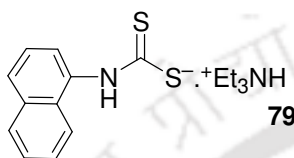
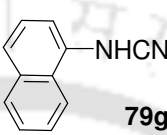
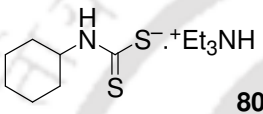
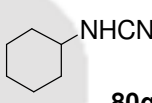
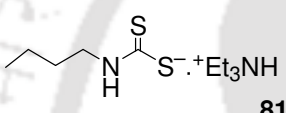
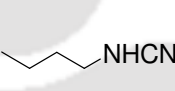
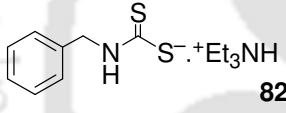
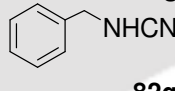
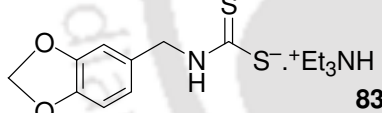
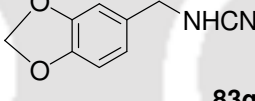
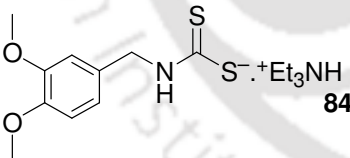
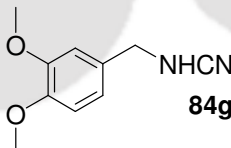
Table IAIV.2.1. Preparation of cyanamides from dithiocarbamates and iodine ^a

Substrate	Product ^b	Yield (%) ^c
 69	 69g	75
 70	 70g	79
 71	 71g	78
 72	 72g	77
 73	 73g	65
 74	 74g	75
 75	 75g	75
 76	 76g	81
 77	 77g	73
 78	 78g	80

^a Reactions were monitored by TLC. ^b Confirmed by IR, ¹H NMR and ¹³C NMR. ^c Isolated yield.

As shown in Table IAIV.2.2, dithiocarbamates of naphthylamine (**79**), aliphatic amines (**80** and **81**) and benzylic amines (**82** and **83**) give their corresponding cyanamides in good yields. This method has also been successful in the preparation of cyanamide (**84g**) of homoveratryl amine starting from its dithiocarbamate salt (**84**).

Table IAIV.2.2. Preparation of cyanamides from dithiocarbamates and iodine^a

Substrate	Product ^b	Yield (%) ^c
		80
79	79g	80
		72
80	80g	72
		60
81	81g	60
		82
82	82g	82
		72
83	83g	72
		60
84	84g	60

^a Reactions were monitored by TLC. ^b Confirmed by IR, ¹H NMR and ¹³C NMR. ^c Isolated yield.

In conclusion, we have developed a general, economical and environmentally benign method for the preparation of cyanamides from their corresponding dithiocarbamic acid salts. Although literature enumerates a number of procedures for the preparation of cyanamides, the simplicity, environmental acceptability, and cost effectiveness of this one pot strategy makes it a practical

alternative. Though at first glance the product yields of the reactions seem to be moderate or maybe just good, but when the fact that these are actually three step reactions done in a single-pot is brought to mind, the yields could infact be considered as very good if not excellent.

IAIV.3. Experimental

IAIV.3.1. General Remarks

As described in **Section IAI.3.1. Page no. 57.**

IAIV.3.2. Characterization of Organic Substrates

As described in **Section IAI.3.2. Page no. 57.**

IAIV.3.3. General Procedures

IAIV.3.3.1. General experimental procedure for the preparation of dithiocarbamate salt of amine

As described in **Section IAIII.3.3.1. Page no. 106.**

IAIV.3.3.2. General procedure for the synthesis of cyanamides

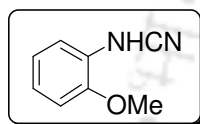
To a stirred and ice cooled suspension of dithiocarbamate **65** (540 mg, 2 mmol) in ethylacetate (5 mL), was added triethylamine (415 μ l, 3 mmol). To this was then added iodine (506 mg, 2 mmol) pinch wise over a period of 10-15 minutes to yield phenylisothiocyanate. During this period precipitation of elemental sulfur and triethylammonium iodide salt was observed. After complete addition of iodine, 25% aqueous NH_3 (2.5 mL) was added drop wise to the stirred reaction mixture to give 1-phenylthiourea. After stirring for 10 minutes at room temperature the excess of NH_3 was removed in a rotary evaporator where by the solvent ethylacetate was also simultaneously removed leaving behind the aqueous layer. To the crude reaction mixture was then further added ethylacetate (5 mL) and triethylamine (553 μ l, 4 mmol). To the resultant solution, iodine (506 mg, 2 mmol) was added in small pinches, during which further precipitation of elemental sulfur was observed. The conversion of the 1-phenylthiourea to

phenylcyanamide (**65g**) was observed within 5 minutes of the complete addition of iodine. Completion of the reaction was confirmed by TLC. The precipitated sulfur was filtered, washed with ethylacetate (2 x 5 mL). The organic layer was washed with water (2 x 5 mL) and dried over anhydrous Na₂SO₄, concentrated under reduced pressure and purified over a short column of silica gel and eluting it with hexane:ethylacetate (97:3) to give the pure product **65g** (184 mg, 78%, oily liquid). The results are summarized in **Table IAIV.2.1** and **IAIV.2.2**.

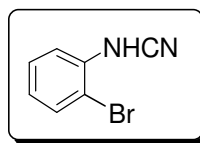


IAIV.4. Spectral Data**Phenyl cyanamide (65g):**

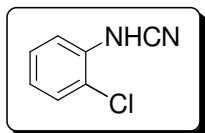
Gummy. ^1H NMR (400 MHz, CDCl_3): δ 7.02-7.07 (m, 3H), 7.28-7.33 (m, 2H), 7.64 (brs, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 112.2, 115.5, 123.6, 129.8, 137.4. IR (KBr): 3175, 2919, 2227, 1600, 1501, 1249, 891, 748 cm^{-1} . Elemental analysis for $\text{C}_7\text{H}_6\text{N}_2$ (118.13): calcd. C 71.17, H 5.12, N 23.71; found C 71.27, H 5.09, N 23.67.

2-Methoxy-phenyl cyanamide (66g):

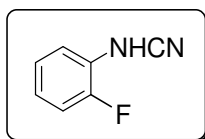
Oily liquid. ^1H NMR (400 MHz, CDCl_3): δ 3.87 (s, 3H), 6.88 (m, 1H), 6.95-7.05 (m, 2H), 7.18 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 55.9, 110.8, 111.0, 114.9, 121.5, 123.8, 126.8, 146.9. IR (KBr): 3219, 2939, 2839, 2224, 1603, 1509, 1454, 1259, 1026, 746 cm^{-1} . Elemental analysis for $\text{C}_8\text{H}_8\text{N}_2\text{O}$ (148.16): calcd. C 64.85, H 5.44, N 18.90; found C 64.51, H 5.40, N 18.851.

2-Bromo-phenyl cyanamide (67g):

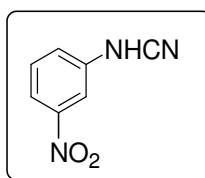
White solid. Mp: 94.5 $^\circ\text{C}$. ^1H NMR (400 MHz, CDCl_3): δ 6.36 (brs, 1H), 6.96-7.01 (m, 1H), 7.25-7.39 (m, 2H) 7.52-7.53 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 109.9, 110, 116.1, 124.9, 129.2, 133.0, 135.3. IR (KBr): 3150, 2237, 1602, 1504, 1425, 1286, 1026, 738 cm^{-1} .

2-Chloro-phenyl cyanamide (68g):

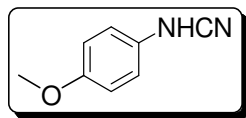
White solid. Mp: 101-103 °C. ^1H NMR (400 MHz, CDCl_3): δ 6.56 (brs, 1H), 7.05 (m, 1H), 7.31 (m, 2H), 7.35 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 110.0, 116.2, 120.4, 124.5, 128.6, 129.9, 134.3. IR (KBr): 3163, 2921, 2243, 1598, 1500, 1426, 1295, 1049, 746 cm^{-1} .

2-Fluoro-phenyl cyanamide (69g):

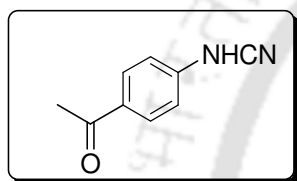
White solid. Mp: 95 °C. ^1H NMR (400 MHz, CDCl_3): δ 6.68 (brs, 1H), 6.90-7.45 (m, 4H). ^{13}C NMR (100 MHz, CDCl_3): δ 110.9, 115.7, 115.9, 116.8, 124.1, 124.1, 125.09, 125.12, 125.6, 125.8, 150.1, 152.5. IR (KBr): 3339, 3069, 2233, 1679, 1621, 1503, 1455, 1378, 1266, 1198, 1109, 1061, 756 cm^{-1} .

3-Nitro-phenyl cyanamide (70g):

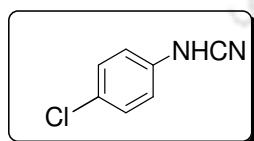
Yellow solid. Mp: 133-135 °C. ^1H NMR (400 MHz, $\text{CDCl}_3 + \text{DMSO}$): δ 7.38 (d, $J = 8.4$ Hz, 1H), 7.52 (t, $J = 8.4$ Hz, 1H), 7.85 (m, 2H). ^{13}C NMR (100 MHz, $\text{CDCl}_3 + \text{DMSO}$): δ 109.6, 110.7, 116.8, 120.8, 130.1, 139.9, 148.4. IR (KBr): 3147, 2919, 2241, 1621, 1531, 1354, 1260, 1071, 937, 871, 733 cm^{-1} .

4-Methoxy-phenyl cyanamide (71g):

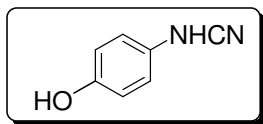
White solid. Mp: 86-89 °C. ¹H NMR (400 MHz, CDCl₃): δ 3.78 (s, 3H), 6.87 (d, *J* = 8.8 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 55.8, 112.8, 115.2, 117.0, 130.6, 156.1. IR (KBr): 3180, 2926, 2218, 1509, 1295, 1238, 1105, 1037, 826 cm⁻¹. Elemental analysis for C₈H₈N₂O (148.17): calcd. C 64.85, H 5.44, N 18.91; found C 64.91, H 5.40, N 18.93.

4-Acetyl-phenylcyanamide (72g):

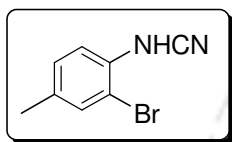
White solid. Mp: 153-157 °C. ¹H NMR (400 MHz, CDCl₃ + DMSO): δ 2.56 (s, 3H), 7.08 (d, *J* = 8.8 Hz, 2H), 7.91 (d, *J* = 8.8 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃ + DMSO): δ 25.9, 110.9, 114.5, 129.8, 131.2, 142.9, 196.2. IR (KBr): 3188, 2966, 2228, 1666, 1599, 1585, 1411, 1362, 1278, 1176, 962 cm⁻¹.

4-Chloro-phenyl cyanamide (73g):

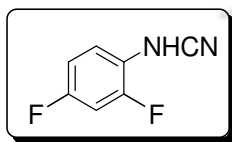
White solid. Mp: 95 °C. ¹H NMR (400 MHz, CDCl₃): δ 6.91 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 111.4, 116.9, 128.9, 129.9, 136.2. IR (KBr): 3166, 2954, 2234, 1600, 1494, 1399, 1251, 1091, 1011, 820 cm⁻¹.

4-Hydroxy-phenyl cyanamide (74g):

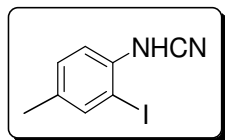
White solid. Mp: 259-261 °C. ^1H NMR (400 MHz, CDCl_3 + DMSO): δ 5.67 (brs, 1H), 6.77 (d, $J = 8.8$ Hz, 2H), 6.83 (d, $J = 8.8$ Hz, 2H), 8.98 (brs, 1H). ^{13}C NMR (100 MHz, CDCl_3 + DMSO): δ 112.8, 115.6, 115.8, 129.5, 152.2. IR (KBr): 3213, 2992, 2230, 1613, 1519, 1444, 1258, 1224, 815 cm^{-1} .

2-Bromo-4-methyl-phenyl cyanamide (75g):

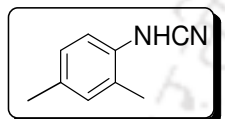
Brown solid. Mp: 91-93 °C. ^1H NMR (400 MHz, CDCl_3): δ 2.31 (s, 3H), 6.23 (s, 1H), 7.14-7.19 (m, 2H) 7.34 (s, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 20.5, 109.6, 110.4, 115.9, 129.8, 132.7, 133.2, 135.0. IR (KBr): 3211, 2923, 2226, 1608, 1509, 1424, 1287, 1038, 863, 804, 743 cm^{-1} .

2,4-Difluoro-phenyl cyanamide (76g):

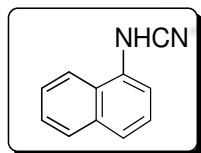
Gummy. ^1H NMR (400 MHz, CDCl_3): δ 6.06 (s, 1H), 6.88-6.96 (m, 2H), 7.20-7.23 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 104.0, 104.2, 104.3, 104.5, 111.2, 111.3, 111.5, 111.5, 111.7, 117.3, 117.4, 117.4, 111.5, 122.9, 123.0, 149.5, 149.7, 152.0, 152.1, 156.2, 156.3, 158.7, 158.8. IR (KBr): 3167, 2927, 2258, 1611, 1524, 1433, 1269, 1215, 1150, 1125, 1087, 962, 852, 804 cm^{-1} .

2-Iodo-4-methyl-phenyl cyanamide (77g):

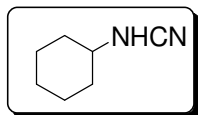
White solid. Mp: 144 °C. ^1H NMR (400 MHz, CDCl_3): δ 2.29 (s, 3H), 6.17 (brs, 1H), 7.17 (m, 2H), 7.56 (s, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 20.4, 84.2, 110.7, 115.4, 130.9, 135.4, 139.6. IR (KBr): 3229, 2919, 2217, 1603, 1502, 1420, 1383, 1283, 1032, 866, 805 cm^{-1} .

2,4-Dimethyl-phenyl cyanamide (78g):

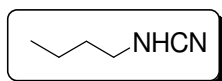
White solid. Mp: 115-119 °C. ^1H NMR (400 MHz, CDCl_3): δ 2.18 (s, 3H), 2.26 (s, 3H), 6.74 (brs, 1H, NH), 6.93 (s, 1H), 6.99 (d, $J = 8.0$ Hz, 1H), 7.05 (d, $J = 8.0$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 17.3, 20.7, 112.8, 115.7, 124.7, 127.9, 131.8, 133.2, 133.3. IR (KBr): 3186, 2915, 2233, 1599, 1512, 1433, 1271, 1031, 812 cm^{-1} .

1-Naphthyl cyanamide (79g):

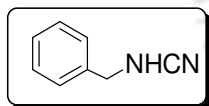
Mp: 139 °C. ^1H NMR (400 MHz, CDCl_3): δ 6.57 (s, 1H), 7.41 (m, 1H), 7.48 (m, 1H), 7.56 (m, 2H), 7.64 (d, $J = 8$ Hz, 1H), 7.75 (m, 1H), 7.90 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 110.9, 112.6, 120.5, 122.7, 123.1, 125.2, 125.5, 125.9, 127.8, 133.5, 133.7. IR (KBr): 3181, 3052, 2944, 2234, 1584, 1530, 1480, 1403, 1344, 1258, 782, 758 cm^{-1} .

Cyclohexyl-cyanamide (80g):

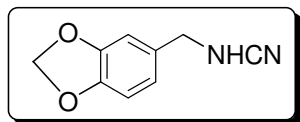
Gummy. ^1H NMR (400 MHz, CDCl_3): δ 1.31 (m, 5H), 1.61 (m, 1H), 1.78 (m, 2H), 1.95 (m, 2H), 3.09 (m, 1H), 3.91 (brs, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 24.3, 25.1, 32.6, 54.3, 115.9. IR (KBr): 3196, 2933, 2857, 2217, 1453, 1367, 1167, 892 cm^{-1} .

***n*-Butyl-cyanamide (81g):**

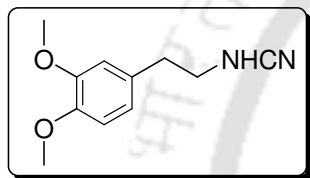
Gummy. ^1H NMR (400 MHz, CDCl_3): δ 0.94 (t, $J = 7.6$ Hz, 3H), 1.40 (m, 2H), 1.58 (m, 2H), 3.06 (m, 2H), 4.61 (brs, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 13.6, 19.5, 31.7, 45.7, 117.2. IR (KBr): 3207, 2961, 2875, 2221, 1614, 1463, 1373, 1171, 1015 cm^{-1} .

Benzyl cyanamide (82g):

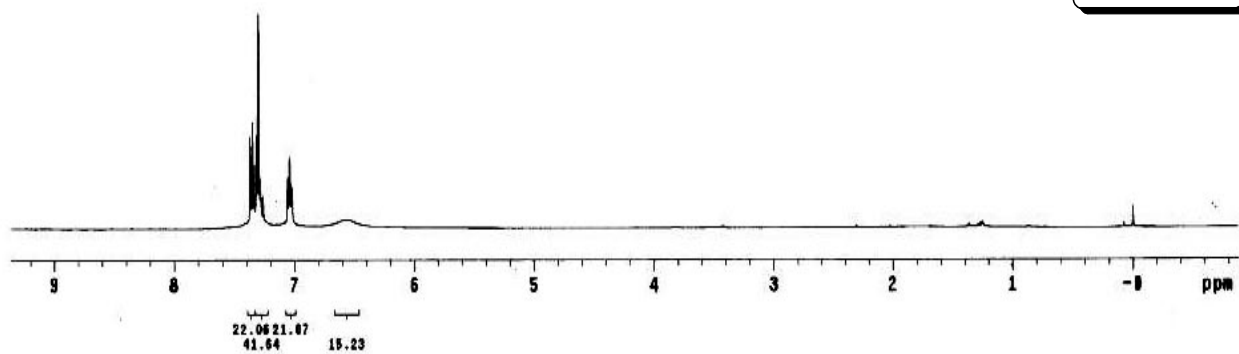
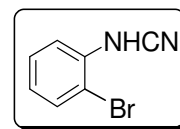
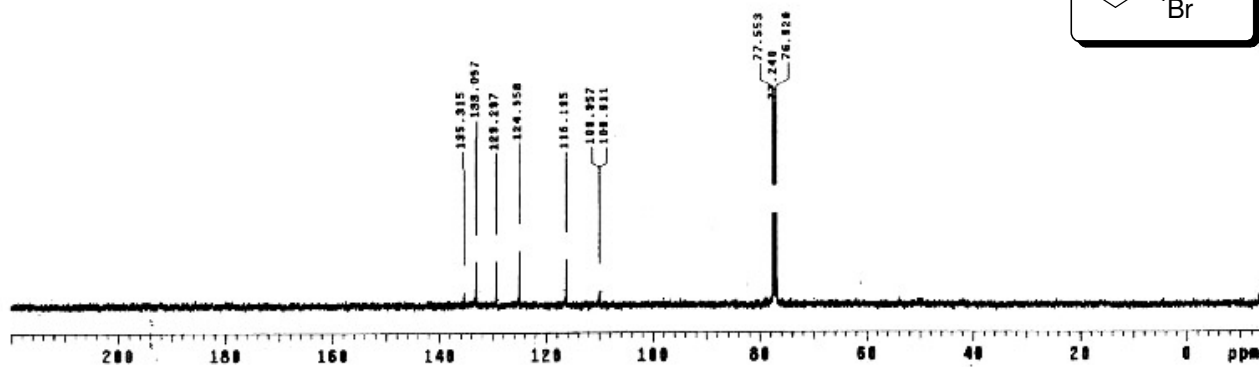
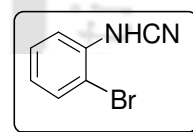
Gummy. ^1H NMR (400 MHz, CDCl_3): δ 4.11 (d, $J = 5.2$ Hz, 2H), 4.66 (brs, 1H), 7.27-7.37 (m, 5H). ^{13}C NMR (100 MHz, CDCl_3): δ 49.9, 116.7, 127.9, 128.4, 128.9, 136.4. IR (KBr): 3207, 2925, 2220, 1455, 1359, 1210, 1155, 1014, 895 cm^{-1} .

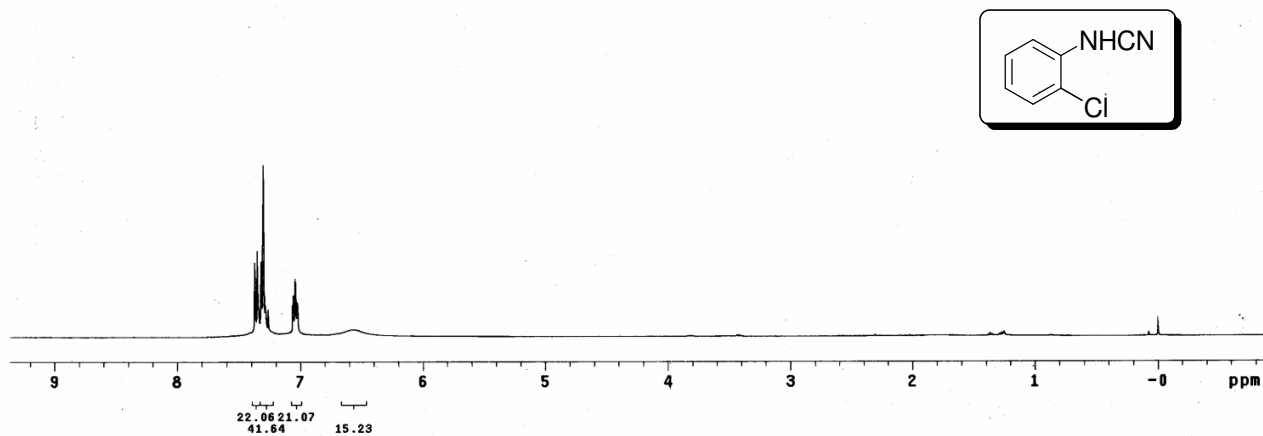
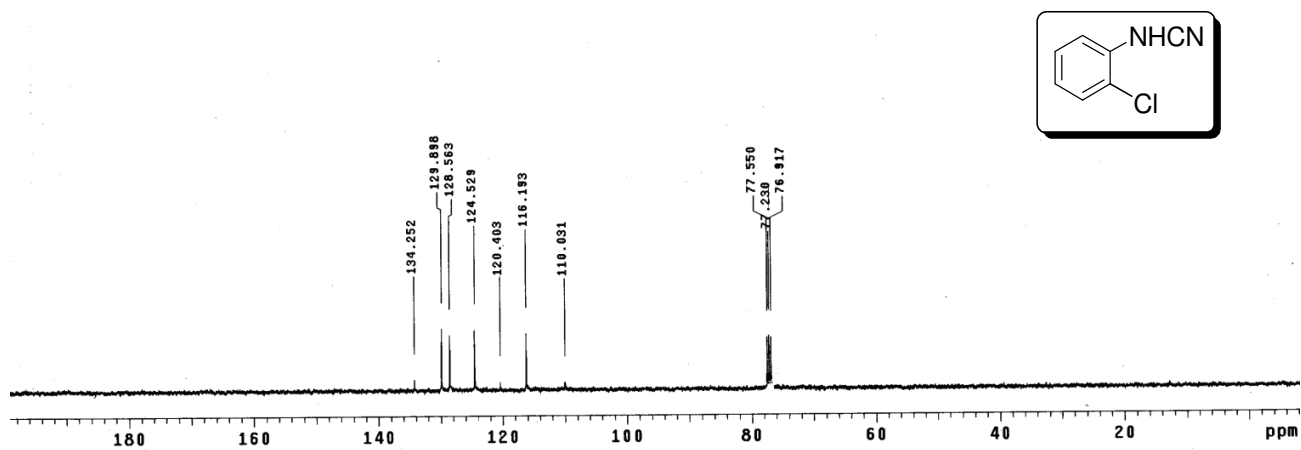
Benzo[1,3]dioxol-5-ylmethyl-cyanamide (83g):

White Solid. Mp: 82-84 °C. ¹H NMR (400 MHz, CDCl₃): δ 4.05 (d, *J* = 5.2 Hz, 2H), 4.57 (brs, 1H), 5.94 (s, 2H), 6.77 (m, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 49.9, 101.4, 108.5, 108.5, 116.5, 121.7, 130.1, 147.8, 148.2. IR (KBr): 3233, 2952, 2897, 2220, 1850, 1609, 1500, 1445, 1370, 1323, 1252, 1038, 925, 862, 809 cm⁻¹.

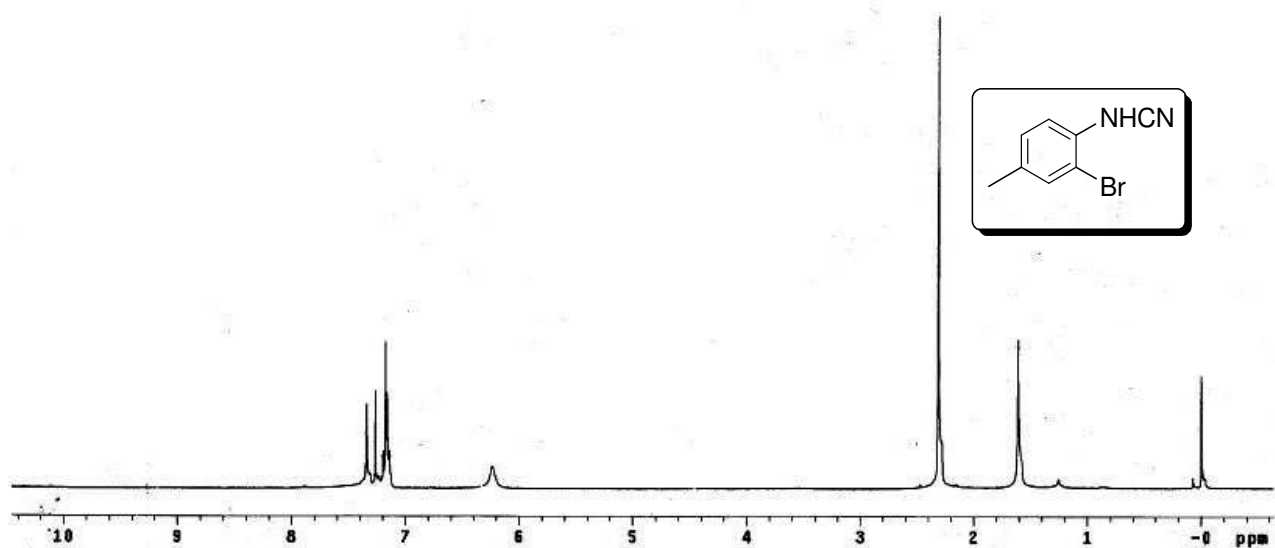
3,4-Dimethoxyphenylethylcyanamide (84g):

Gummy. ¹H NMR (400 MHz, CDCl₃): δ 2.84 (t, 2H, *J* = 7.2 Hz), 3.28 (q, 2H, *J* = 7.2 Hz), 3.83 (s, 3H), 3.84 (s, 3H), 4.37 (brs, 1H), 6.72-6.82 (m, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 35.5, 47.5, 55.9, 56, 111.4, 111.9, 116.5, 120.9, 130.0, 147.8, 148.9. IR (KBr): 3274, 2937, 2219, 1592, 1517, 1464, 1262, 1236, 1156, 1142, 1026, 913 cm⁻¹.

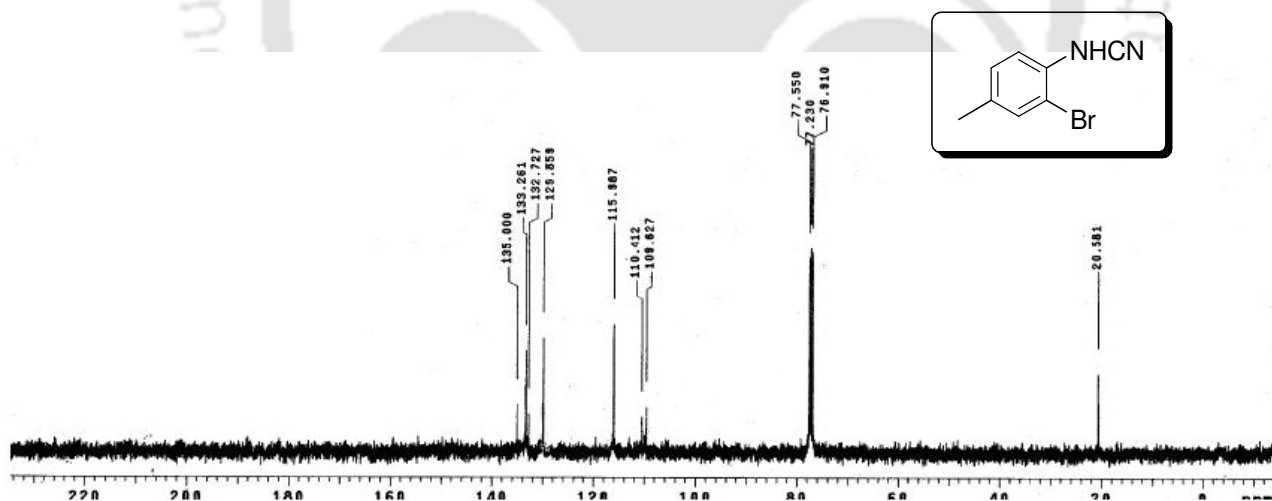
IAIV.5. Spectra of some selected compounds**2-Bromo phenyl cyanamide (67g): ^1H NMR (400 MHz, CDCl_3):****2-Bromo phenyl cyanamide (67g): ^{13}C NMR (100 MHz, CDCl_3):**

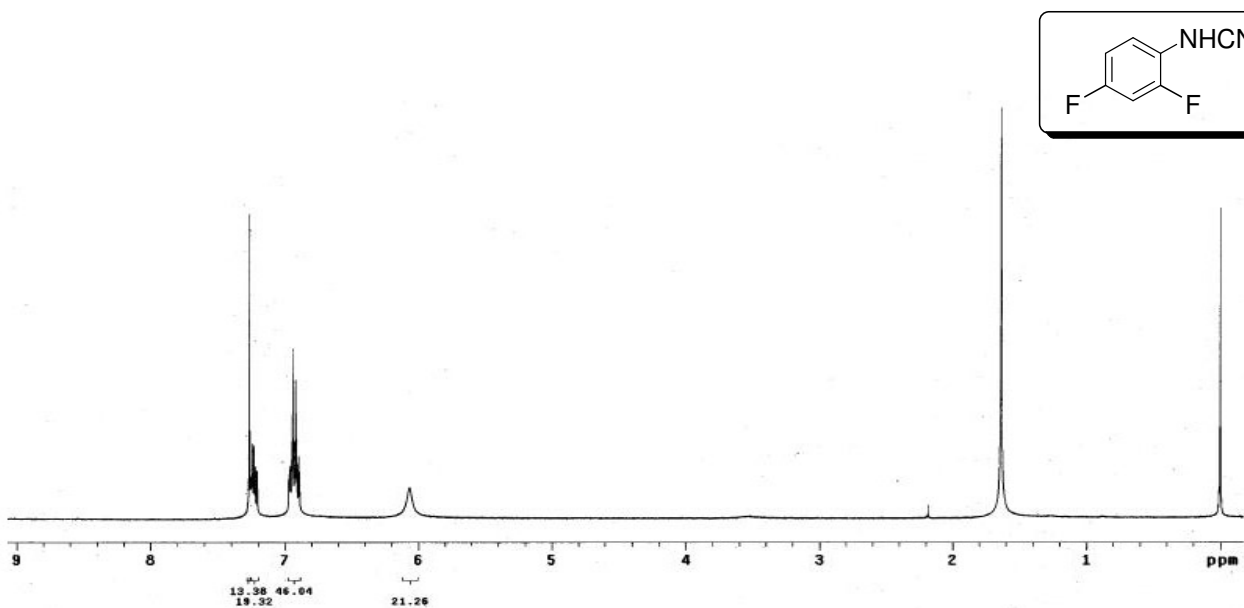
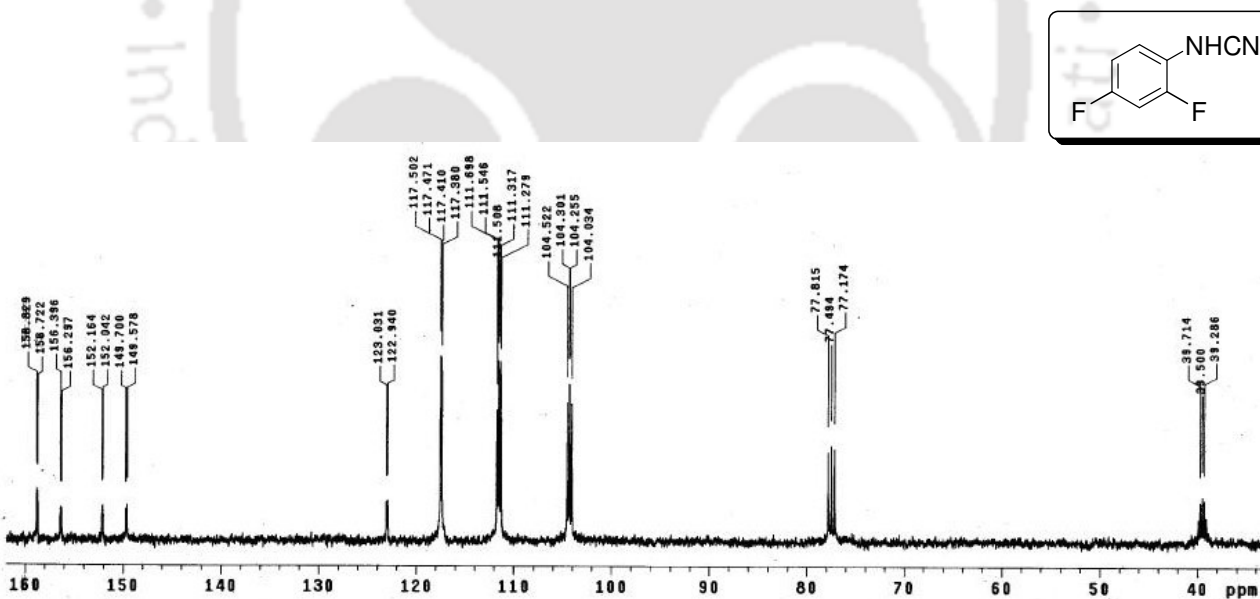
2-Chloro-phenyl cyanamide (68g): ^1H NMR (400 MHz, CDCl_3):**2-Chloro-phenyl cyanamide (68g): ^{13}C NMR (100 MHz, CDCl_3):**

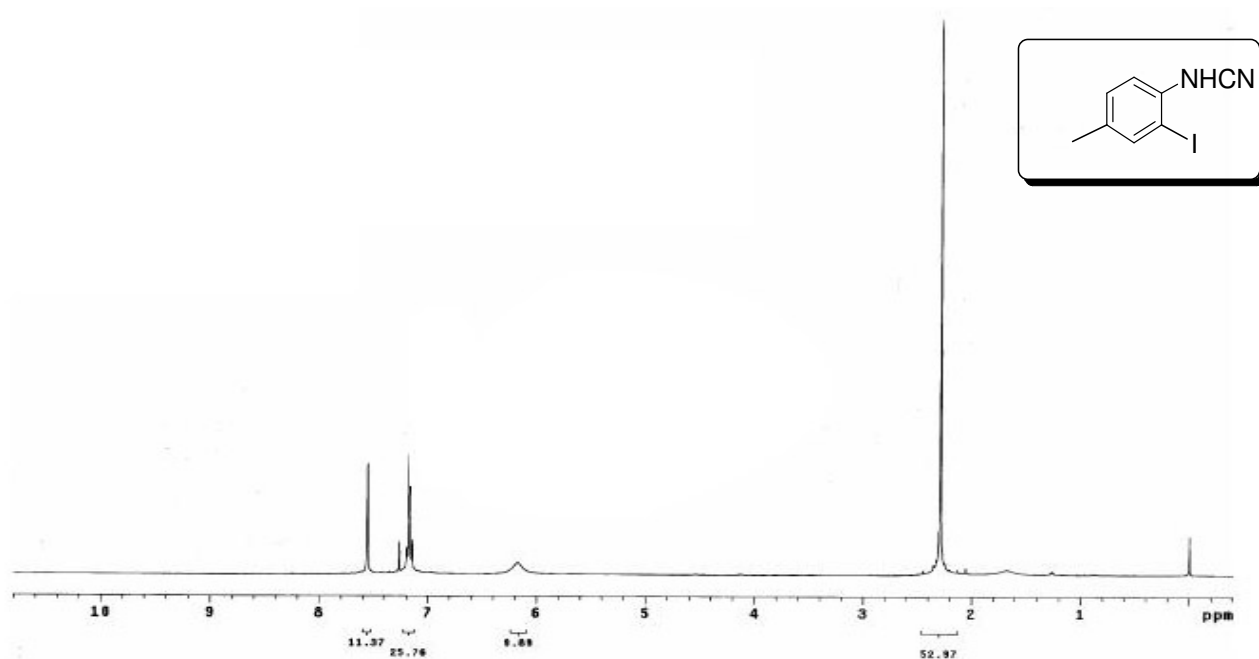
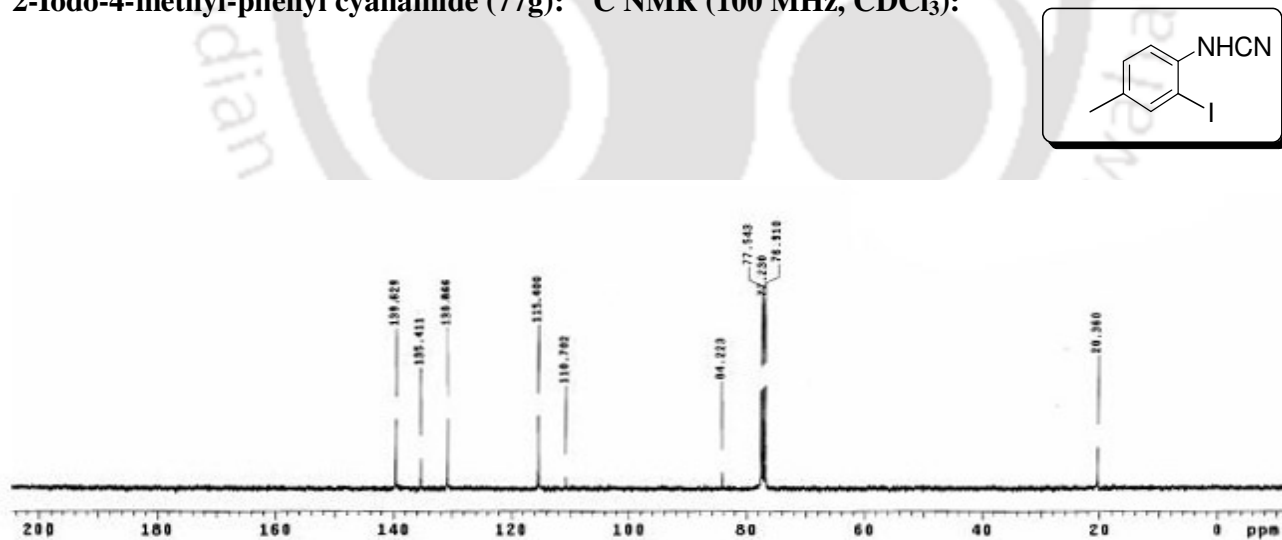
2-Bromo-4-methyl-phenyl cyanamide(75g): ^1H NMR (400MHz, CDCl_3):



2-Bromo-4-methyl-phenyl cyanamide(75g): ^{13}C NMR (100 MHz, CDCl_3):



2,4-Difluoro-phenyl cyanamide (76g): ^1H NMR (400 MHz, CDCl_3):**2,4-Difluoro-phenyl cyanamide (76g): ^{13}C NMR (100 MHz, CDCl_3):**

2-Iodo-4-methyl-phenyl cyanamide (77g): ^1H NMR (400 MHz, CDCl_3):**2-Iodo-4-methyl-phenyl cyanamide (77g): ^{13}C NMR (100 MHz, CDCl_3):**

IAIV.6. References

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Chapter II

IIA.1. Cloud Point Extraction of Nitro Benzene

This chapter describes the cloud point extraction (CPE) of nitro benzene (NB) from synthetic aqueous solution using TX-100 as nonionic surfactant. The effects of pH, temperature, concentrations of surfactant, NB and salt on extraction of both NB and surfactant have been studied. Variation of change in different thermodynamic parameters like, enthalpy, entropy and Gibbs free energy for the CPE of NB is reported. An approach to design a cloud point extractor is described. Experimental investigation has been performed to observe the potential of solvent extraction to recover surfactant from the dilute phase.

IIA.2. Experimental

IIA.2.1. Materials

Triton X-100 (Iso-octyl phenoxy polyethoxy ethanol, Molecular weight: 628, λ_{\max} : 226 nm, supplied by Loba chemie, Mumbai, India) has been used as non-ionic surfactant. The critical micellar concentrations (CMC) of TX-100 is 2.8×10^{-4} (M).¹ Cloud point temperature of TX-100 in aqueous solution is 65 °C.² Nitro benzene (Molecular weight: 123.11, λ_{\max} : 268 nm, purity: 98.5%), used in this study is supplied by Rankem, Delhi, India. Heptane, hexane, sodium chloride, calcium chloride, sodium hydroxide and hydrochloric acid are procured from S.D. Fine Chem. Ltd., Mumbai, India.

IIA.2.2. Methods

Solutions (50 ml) of surfactant and nitro benzene are prepared by dissolving accurately weighed amount of surfactant and nitro benzene in distilled water at different concentrations. Each experiment is conducted using a 50 ml measuring cylinder containing different concentration of surfactants, nitro benzene and salt solution in a constant temperature bath (supplied by Testing Instruments Manufacturing Company Ltd, Kolkata, India) for 20 minutes. After complete phase separation, the measuring cylinder is removed from the temperature bath and cooled for 2 minutes. The volumes of the coacervate phase and concentration of dilute phase have been measured.

Operating conditions

For CPE, the concentrations of nitro benzene in the feed are 100, 200, 300 and 400 mg/L. The concentrations of TX-100 in the feed are varied from 0.03 to 0.25 (M) separately. All the experiments have been conducted at four different temperatures (75 °C, 80 °C, 85 °C and 90 °C). To observe the effect of salt on extraction of nitro benzene and surfactant, monovalent NaCl and divalent CaCl₂ are selected. The concentrations of salts (NaCl and CaCl₂) have been chosen as 0.1, 0.2, 0.3, 0.4, 0.5 and 0.6 (M). The pH values of the solutions are adjusted to 2.0, 4.0, 6.0, 8.0 and 10.0 by adding hydrochloric acid and sodium hydroxide as appropriate.

Analysis

The concentrations of nitrobenzene and surfactant are determined by spectrophotometry (make: Perkin Elmer). Pure TX-100 and nitro benzene solutions are initially calibrated separately for different concentrations in terms of absorbance units, which are recorded at the wavelength of 226, and 268 nm respectively, at which maximum absorption takes place. Standard technique is used to find out the concentrations of both NB and surfactants.³

IIA.3. Results and discussions

The extent of extraction of nitro benzene and TX-100 is defined as,

$$\text{Extraction (\%)} = \left(1 - \frac{C_d}{C_0}\right) \times 100$$

where, C_0 and C_d are the feed and dilute phase concentration, respectively.

IIA.3.1. Extraction profile with surfactant concentration

For successful CPE of nitro benzene (NB), it is desirable to use minimum amount of surfactant for maximum extraction of NB. Figure IIA.3.1.1. shows the effect of concentration of TX-100 on the extraction of NB for different initial concentrations at 85 °C. It has been observed from the figure that for all NB concentration extraction of NB increases sharply when TX-100 concentration increases from 0.03 to 0.01(M). Beyond 0.01 (M), increase in extraction efficiency becomes gradual. For NB concentration of 100 mg/L, close to 99% extraction is possible with a TX-100 concentration of 0.25(M). For higher concentrations, e.g., 300 and 400 mg/L, about 97% and 94% extraction of NB

is achieved with 0.25(M) TX-100. It has also been observed that for a particular TX-100 concentration, percent extraction decreases with increase in the NB concentration. With increase in surfactant concentration, the volume of coacervate phase increases, as the concentration of surfactant in coacervate phase remains almost constant. This increase in coacervate phase volume renders higher solubilization of NB, which explains the higher extraction of NB at higher TX-100 concentration at constant temperature and initial NB concentration.

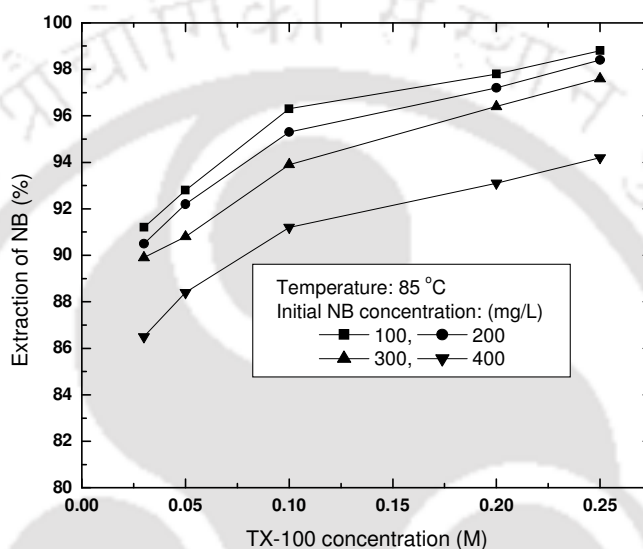


Figure IIA.3.1.1.: Variation of extraction of NB and TX – 100 with initial concentration of TX – 100 and NB. Temperature: 85 °C, pH: 6.0

IIA.3.2. Effects of initial nitro benzene concentration on TX-100 extraction

Variations of the extraction of TX-100 with feed NB and TX-100 concentration are shown in figure IIA.3.2.1. at 85 °C. It may be observed from the figure that extraction efficiency of the surfactant increases with initial surfactant concentration for all the NB concentrations. For example, at a feed surfactant concentration of 0.25(M), the surfactant is extracted in the coacervate phase in more than 99% for all the NB concentrations. Since, TX-100 concentration in the dilute phase remains almost constant (at lower surfactant concentration just above the CMC) at constant temperature and NB concentration, the extraction efficiency of TX-100 increases with increase in feed TX-100 concentration. Beyond a concentration of 0.2(M), the increase in extraction efficiency is gradual because of the fact that at higher surfactant concentration (>0.2 M), the surfactant concentration in

dilute phase increases with feed TX-100 concentration (>0.2 M). At constant surfactant concentration, TX-100 extraction increases with NB concentration. As more NB molecules are solubilized, inter micellar repulsion decreases, which increases the micellar size and hence the coacervate phase volume.

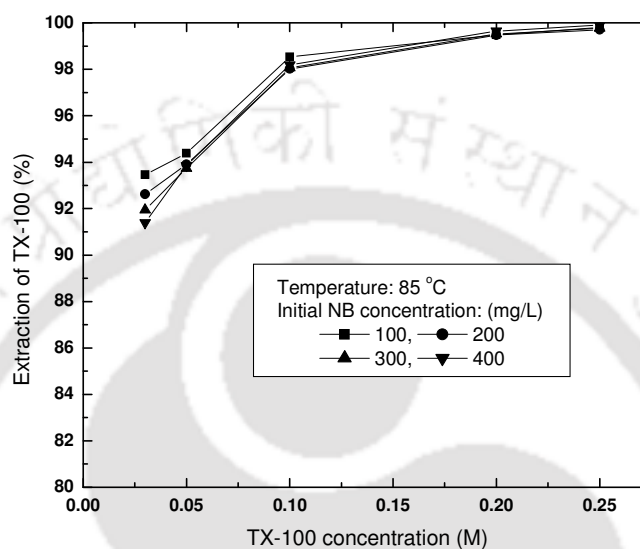


Figure IIA.3.2.1.: Effect of concentration of TX-100 on the CPE of TX-100 at different feed NB concentration at 85 °C

IIA.3.3. Effects of temperature on extraction

The effects of temperature on the efficiency of nitro benzene extraction are shown in figure IIA.3.3.1. for an initial nitro benzene concentration of 100 mg/L at 0.03, 0.05, 0.10, 0.20 and 0.25(M) of TX-100. It is clear from the figure that the extraction of nitro benzene increases with temperature and TX-100 concentration. It may be observed that the extraction of nitro benzene (for 100 mg/L of feed nitro benzene and 0.25 (M) of TX-100) increases from about 94 to 99%, when the temperature increases from 75 to 90 °C.

At higher temperature, CMC of non-ionic surfactants decreases.⁴ Moreover, non-ionic surfactants appear relatively more hydrophobic at higher temperatures, due to an equilibrium shift that favors dehydration of the ether oxygens.⁵ This leads to an increase in the number concentration of micelles. Therefore, the solubilization capability of the micellar solution increases with temperature leading to an increase in the nitro benzene extraction. It is also evident from figure IIA.3.3.2. that the

volume of coacervate phase decreases with temperature. For example, at 100 mg/L of NB and 0.1(M) of TX-100, fractional volume of coacervate phase decreases from 0.14 to 0.103 when temperature is raised from 75 to 90 °C. At an elevated temperature, the interaction among the TX-100 micelles increases leading to dehydration from the external layers of micelles resulting into a decrease in volume of coacervate phase.⁵

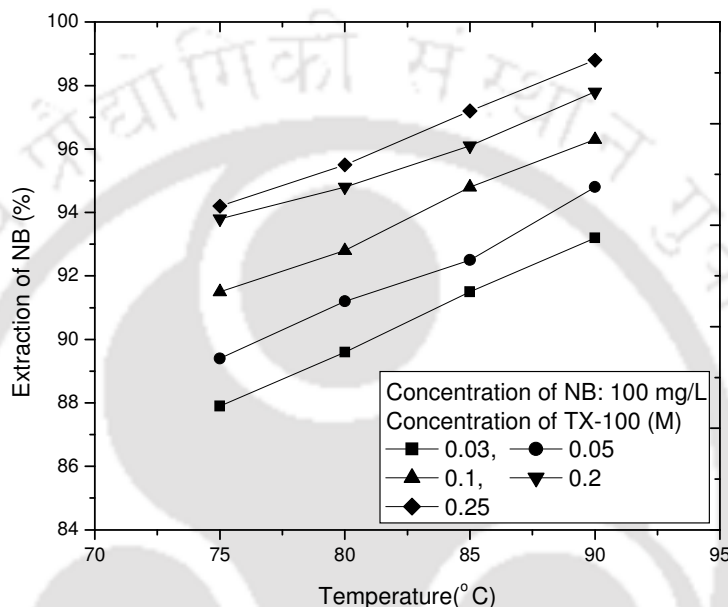


Figure IIA.3.3.1.: Effect of temperature on the extraction of NB. Initial concentration of NB: 100 mg/L, pH: 6.0

Figure IIA.3.3.2. shows the variation of fractional coacervate phase volume with temperature. It is evident from figure IIA.3.3.2. that the volume of coacervate phase decreases with temperature. For example, at 200 mg/L of nitro benzene, fractional volume of coacervate phase decreases from 0.180 to 0.132 when the temperature is raised from 75 to 95 °C. At elevated temperature, the interaction among the TX-100 micelles increases leading to dehydration from the external layers of micelles resulting into a decrease in volume of coacervate phase (refer section IA.10.1.). At a fixed temperature, fractional volume of coacervate phase increases with nitro benzene concentration. As nitro benzene concentration increases, more nitro benzene will be solubilized leading to an increase in coacervate phase volume.

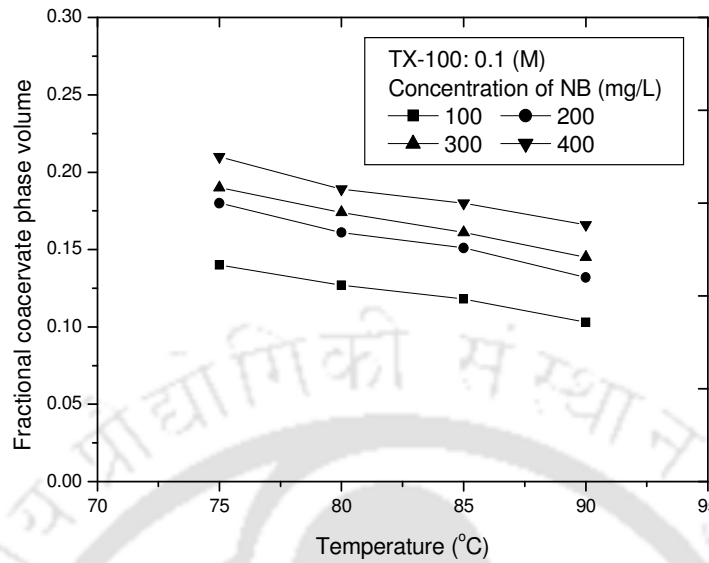


Figure IIA.3.3.2.: Change in coacervate phase volume fraction with temperature at different initial NB concentration. TX – 100: 0.1 (M), pH: 6.0

The variations of the extent of extraction of the surfactant with temperature are presented in figure IIA.3.3.3. for different feed surfactant concentration. It may be observed from the figure that the extraction of the surfactant increases with temperature and. For example, at 0.03 (M) surfactant concentration, the efficiency of extraction of surfactant increases from 91.8 to 93.1% when temperature is raised from 75 to 90°C. On the other hand, extraction efficiency increases with surfactant concentration. Beyond 0.2(M), the efficiency of TX-100 extraction is almost independent of temperature. The increasing extraction efficiency at higher temperature is due to the more micellar attraction as discussed in section IA.10.1. It may also be observed from figure that the extraction efficiency is more for higher feed TX-100 concentration. Since, all the feed TX-100 concentrations are much above the CMC and dilute phase remains slightly above the CMC, the ratio of the surfactant concentration of dilute phase to that of the feed decreases with increase in feed TX-100 concentration and hence extraction efficiency increases with feed surfactant concentration.

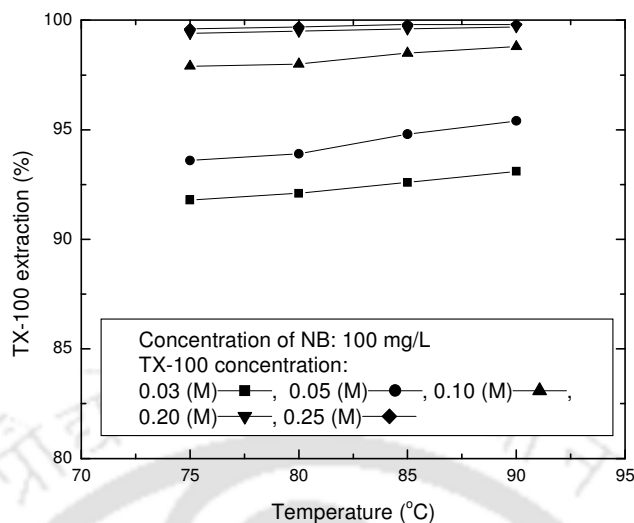


Figure IIA.3.3.3.: Variation of TX – 100 extraction with temperature. Initial concentration of NB: 100 mg/L, pH: 6.0

IIA.3.4. Effects of pH on extraction

The effects of pH of the solution on the extent of nitro benzene extraction are shown in figure IIA.3.4.1. for 100, 200, 300, and 400 mg/L of feed nitro benzene using 0.1(M) of TX-100 at 85 °C. Extraction of nitro benzene is less in acidic pH and increases with pH for all the cases. The lower extraction at acidic pH may be due to the increasing ionic character of oxy group of nonionic surfactant, which increases the CMC.⁴ This leads to a decrease in the micellar concentration and the aggregation number resulting in less solubilization of the nitro benzene. On the other hand, at basic pH, CMC is lowered due to increasing hydrophobicity of oxy groups that increase the size of the micelles as well as the aggregation number.¹ Therefore, nitro benzene solubilization is more at basic pH values leading to an increase in the nitro benzene extraction and lower fractional coacervate phase volume (Figure IIA.3.4.2.).

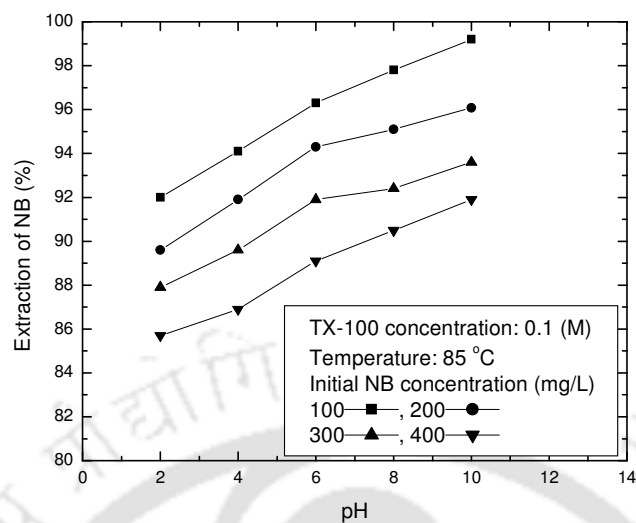


Figure IIA.3.4.1.: Variation of NB extraction with solution pH. Concentration of TX-100: 0.1 (M), Temperature: 85 °C

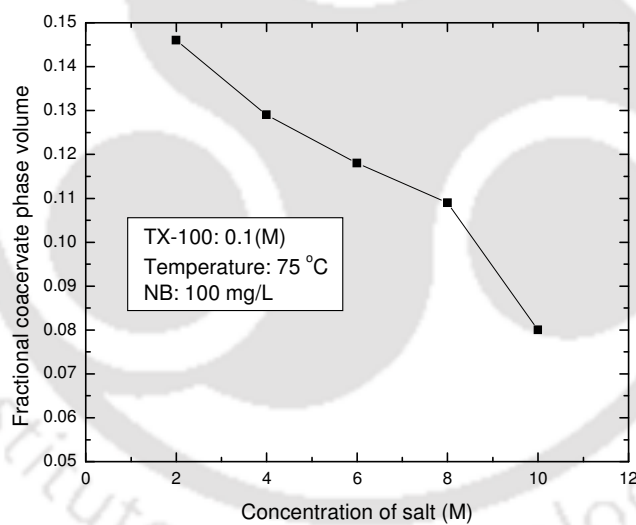


Figure IIA.3.4.2.: Variation of fractional coacervate phase volume with solution pH. Concentration of TX-100: 0.1 (M), Temperature: 85 °C

IIA.3.5. Effects of salt concentration on extraction

Figure IIA.3.5.1. shows the variation of extraction efficiency with salt (NaCl and CaCl₂) concentration. It may be observed from the figure that the extraction of nitro benzene increases from

about 95.4 to 99.7% when concentration of CaCl_2 increases from 0.1 to 0.6(M) at a fixed initial nitro benzene concentration (100 mg/L in this case) and TX-100 concentration (0.1(M)). Beyond 0.3(M) the increase in efficiency becomes gradual. Same trend of nitro benzene extraction has been observed with NaCl. The CMC of the non-ionic surfactants decreases in presence of electrolytes those are known to be capable of 'salting out', e.g. NaCl, KCl, CaCl_2 etc.⁴ Therefore, the number concentration and aggregation number of the micelles increases with the addition of NaCl and CaCl_2 . This enhances the amount of solubilized nitro benzene. Beyond a salt concentration of 0.3(M), the increase in extraction efficiency is marginal. This may be due to the marginal change of aggregation number beyond this condition. From Figure IIA.3.5.1., it may be noted that at the same concentration level of the salt, the nitro benzene extraction efficiency is more for CaCl_2 compared to NaCl. This is due to the fact that in presence of divalent calcium salt, the micellar aggregation is more because of the better salting out effect of CaCl_2 compared to NaCl.

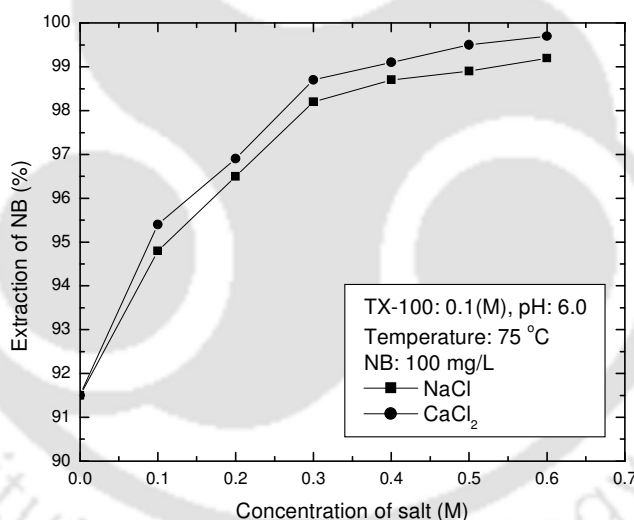


Figure IIA.3.5.1.: Variation of NB extraction with salt concentration. Concentration of TX-100: 0.1 (M), Temperature: 75 °C, pH: 6.0

The variations of fractional coacervate phase volume with NaCl and CaCl_2 concentration are shown in figure IIA.3.5.2. It is clear from the figure that the fractional coacervate phase volume decreases sharply (from 0.113 to 0.067 and 0.105 to 0.063 for NaCl and CaCl_2 , respectively) with increasing salt concentration from 0.1 (M) to 0.6 (M). It has also been found that at constant salt

concentration, fractional coacervate phase volume is more for NaCl. The decrease in fractional coacervate phase volume with increase in salt concentration is due to the decrease in intermicellar repulsion and increase in aggregation number. In case of CaCl₂, intermicellar repulsion is less than that of NaCl and hence decrease in fractional coacervate phase volume is also less.

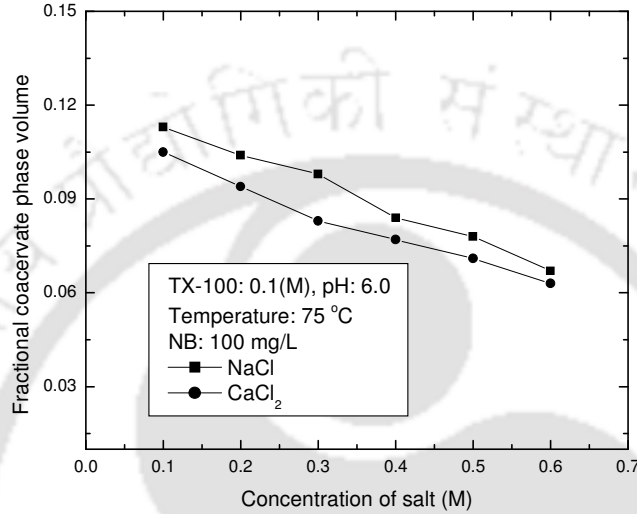


Figure IIA.3.5.2.: Effect of salt concentration on fractional coacervate phase volume

IIA.3.6. Determination of thermodynamic parameters

Change in the values of ΔG^0 , ΔS^0 and ΔH^0 during the CPE of NB with different operating condition is elaborated briefly in this section. The variation of the extraction of NB using TX-100 with temperature at different initial NB concentration has been discussed earlier sections. It is observed that the solubilization capacity increases significantly with temperature. The thermodynamic parameters ΔG^0 , ΔS^0 and ΔH^0 for this extraction process are determined by using the following equations,⁶

$$\Delta G^0 = \Delta H^0 - T\Delta S^0 \quad (\text{IIA.3.6.1.})$$

$$\log(q_e / C_e) = \frac{\Delta S^0}{2.303R} + \frac{-\Delta H^0}{2.303RT} \quad (\text{IIA.3.6.2.})$$

where, q_e is the mole of NB solubilized per mole of non-ionic surfactant. C_e is equilibrium concentration of NB (moles/L) before the completion of two phases and T is temperature in Kelvin. q_e/C_e is called the solubilization affinity. Here, it may be noted that the experimental data considered for the calculation of thermodynamic parameters, namely, ΔG^0 , ΔS^0 and ΔH^0 are in the linear range of q_e versus C_e plot. The values of Gibbs free energy (ΔG^0) have been calculated by knowing the enthalpy of solubilization (ΔH^0) and the entropy of solubilization (ΔS^0). ΔS^0 and ΔH^0 are obtained from a plot of $\log(q_e/C_e)$ versus $\frac{1}{T}$, from equation (IIA.3.6.2.). Once these two parameters are obtained, ΔG^0 is determined from equation (IIA.3.6.1.). The values of ΔG^0 , ΔH^0 and ΔS^0 are calculated at different experimental conditions and reported systematically.

IIA.3.6.1 Variation of Gibbs free energy (ΔG^0) during CPE of NB

Variations of ΔG^0 with temperature at four different surfactant concentration and at constant NB concentration (3.94×10^{-4} mole/L) are shown in figure IIA.3.6.1.1. It may be noted from the figure that the value of ΔG^0 increases linearly with temperature and decreases with TX-100 concentration. The negative values of ΔG^0 indicate that the NB solubilization process is spontaneous and thermodynamically favorable. The increase in negative values of ΔG^0 with temperature imply the greater the driving force of solubilization which is confirmed by the greater extent of NB extraction with increase in temperature (IIA.3.6.1.1.). The decrease in $-\Delta G^0$ values with the increase of surfactant concentration is due to decrease in amount of NB solubilization (moles of NB solubilized per mole of surfactant).

Change of ΔG^0 with initial NB concentration is shown in figure IIA.3.6.1.2. It may be found from the figure IIA.3.6.1.2. that the value of ΔG^0 decreases with NB concentration at constant temperature and surfactant concentration. This is due to the fact that with the increase of NB concentration CMC values of surfactant decreases resulting greater surfactant concentration in micellar phase which again decreases the amount of NB solubilization per mole of surfactant micelle.

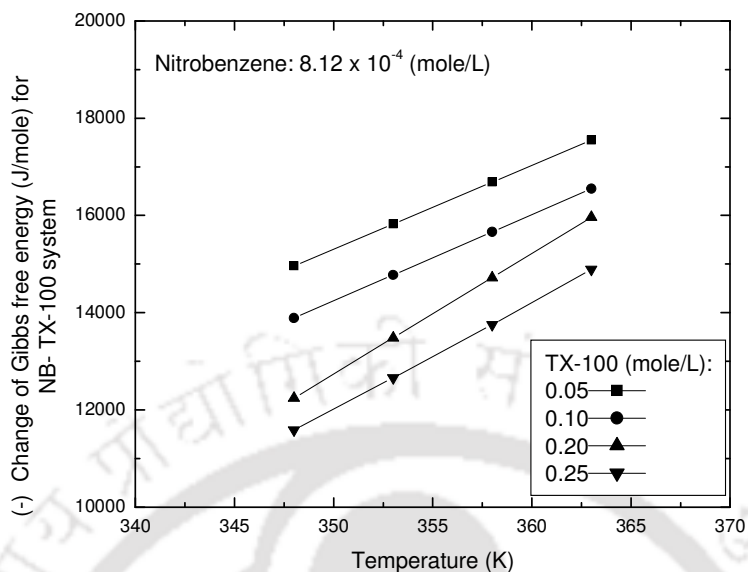


Figure IIA.3.6.1.1.: Variation of Gibbs free energy change (ΔG^0) with temperature at constant Nitrobenzene concentration and at four different TX-100 concentration

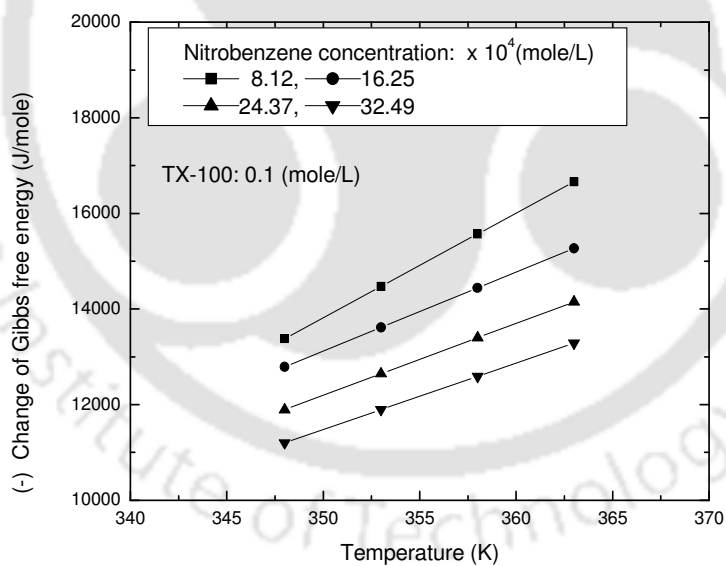


Figure IIA.3.6.1.2.: Variation of Gibbs free energy change (ΔG^0) with temperature at constant surfactant concentration and at four different Nitrobenzene concentrations

IIA.3.6.2. Effect of initial NB and surfactant concentration on the change of enthalpy (ΔH^0) of the CPE process

The variations of enthalpy change (ΔH^0) during CPE of NB have been presented in figures IIA.3.6.2.1.– IIA.3.6.2.2. Effects of concentration of TX-100 and NB on the change of enthalpy have been shown in figures IIA.3.6.2.1.and IIA.3.6.2.2., respectively. From the figures it may be seen that the value of ΔH^0 increases with the TX-100 concentration but decreases with the NB concentration. The positive values of ΔH^0 indicates that the solubilizations of NB is endothermic in nature. The endothermic nature is also indicated by the increase in the amount of solubilization with temperature (Figure IIA.3.6.2.2.). The increase in ΔH^0 value with initial surfactant concentration is due to the increase in solubilization capacity. The decrease in ΔH^0 value with increasing NB concentration at a fixed surfactant concentration is because of decrease in the amount of NB solubilization per mole of surfactant as discussed in preceding section.

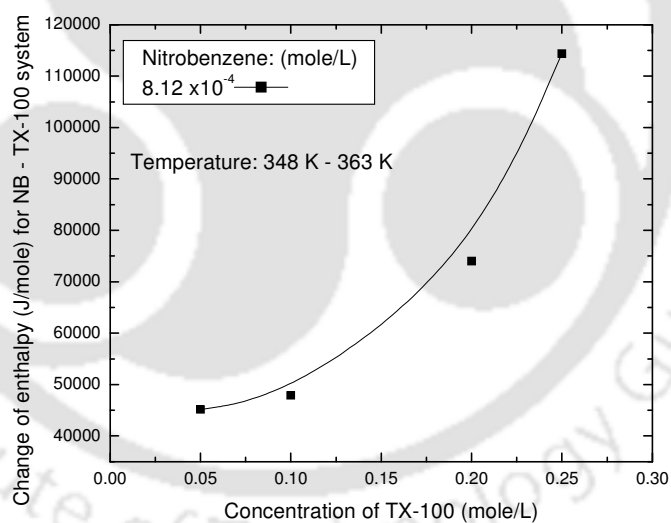


Figure IIA.3.6.2.1.: Variation of enthalpy change (ΔH^0) with TX-100 concentration for CPE of Nitrobenzene

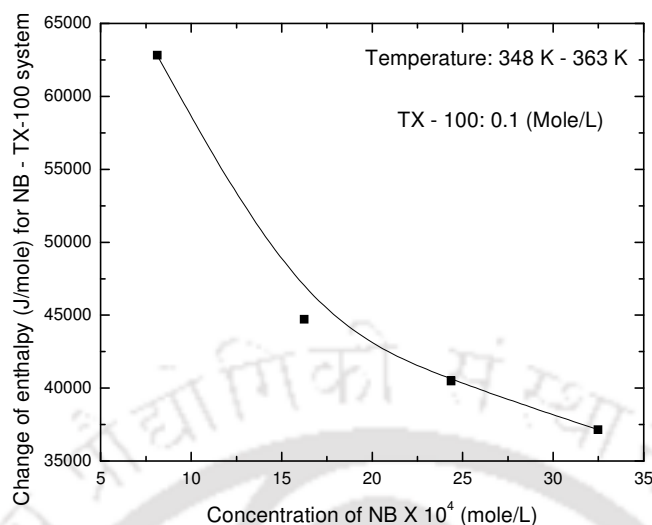


Figure IIA.3.6.2.2.: Variation of enthalpy change (ΔH^0) with NB concentration for CPE of Nitrobenzene

IIA.3.6.3. Effect of initial NB and surfactant concentration on the change of entropy (ΔS^0) of the CPE process

Figures IIA.3.6.3.1. and IIA.3.6.3.2. represents the variation of entropy change (ΔS^0) with TX-100 concentration and NB concentrations, respectively. For all the cases entropy changes are positive that reflects good affinity of NB molecules towards surfactant micelles. Entropy depends on unsolubilized NB molecule and free surfactant molecules in the CPE system. The entropy depends mostly on the surfactant molecules, since the concentration of surfactant is much higher than NB in the solution, as in the case of variation of ΔH^0 , the values of ΔS^0 also increases with surfactant concentration and decreases with NB concentration for all the cases. The number concentration of surfactant molecule increases in dilute phase with the increase of initial surfactant concentration. The increase in ΔS^0 value with initial surfactant concentration is due to the increase of free surfactant molecule in the dilute phase. On the other hand, CMC of surfactant molecule decreases with increase in NB concentration at a fixed surfactant concentration. This reduces the number of surfactant molecule in the dilute phase causing decrease in ΔS^0 value (Figure IIA.3.6.3.2.).

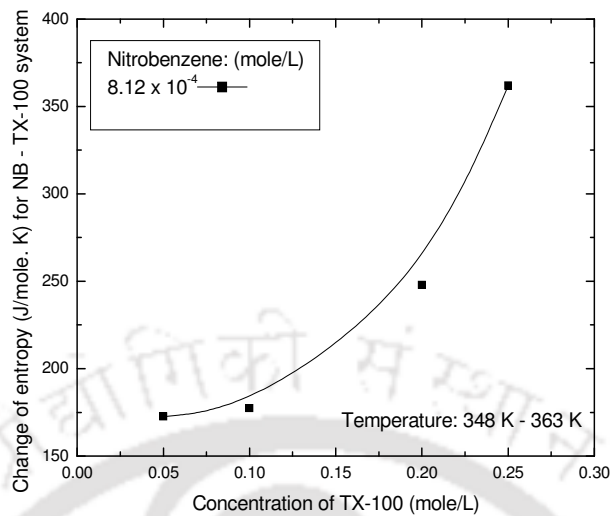


Figure IIA.3.6.3.1.: Variation of entropy change (ΔS^0) with TX-100 concentration for CPE of Nitrobenzene

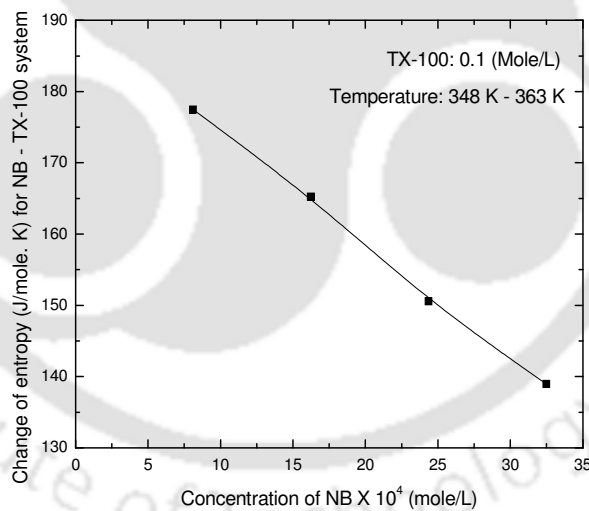


Figure IIA.3.6.3.2.: Variation of entropy change (ΔS^0) with NB concentration at constant surfactant concentration

IIA.3.7. Determination of design parameters for cloud point extraction of NB using TX-100

Cloud point extraction has been successfully used for the removal of NB using TX-100 as the non-ionic surfactant. In the present study, various design parameters of a CPE process have been estimated by developing correlations for NB solubilization and fractional coacervate phase volume with the operating conditions, namely, temperature, feed surfactant and NB concentration. A method is presented to calculate the feed surfactant concentration required for the removal of NB up to a level of 1.0 mg/L (8.12×10^{-6} mol/L). The developed correlations may be useful to design a cloud point extractor of a desired efficiency.

Solubilization isotherm

In order to determine NB solubilization capacity of TX-100 at different temperatures, the experimental data are used to calculate the solubilization isotherms. These isotherm data are the basic requirements for the design of CPE system.

Figure IIA.3.7.1. shows the isotherm at different temperatures, for NB-TX-100 system. The Freundlich isotherm model has been used to explain the solubilization of NB in TX-100. The Equation IIA.3.7.1. gives the expression of the well known Freundlich model.

$$q_e = aC_e^b \quad (\text{IIA.3.7.1.})$$

where, q_e is the moles of NB solubilized per mole of surfactant. C_e is the dilute phase equilibrium concentration of the NB. The constant a and b are the isotherm constants signifying the solubilization energy and measure of intensity of solubilization, respectively.⁷ Values of a and b for each operating temperatures are evaluated by regression analysis using the experimental data. The variations of a and b with temperature are fitted to a quadratic model as shown in figure IIA.3.7.2. The expressions of a and b as function of temperature are given below:

$$a = 22.56 - 0.434 T + 2.28 \times 10^{-3} T^2 \quad (r^2 = 0.992) \quad (\text{IIA.3.7.2.})$$

$$b = 0.093 + 0.017 T - 1.4 \times 10^{-4} T^2 \quad (r^2 = 0.996) \quad (\text{IIA.3.7.3})$$

where, T is the temperature in °C.

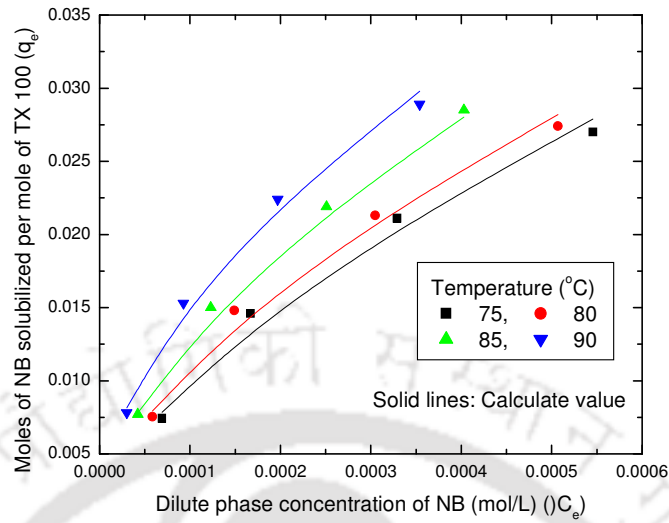


Figure IIA.3.7.1.: Solubilization isotherm for NB at different temperature using TX-100

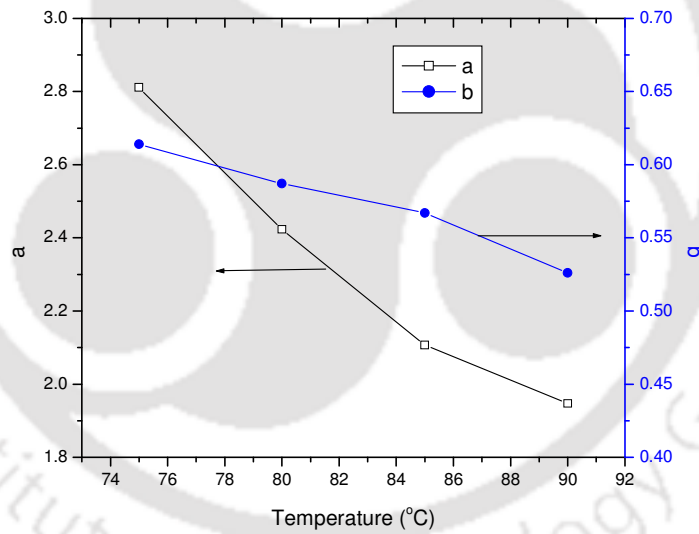


Figure IIA.3.7.2.: Variation of the values of a and b with temperature for solubilization of NB in TX-100

Variation of fractional coacervate phase volume

In order to calculate the performance of a CPE process, the variation of the fractional coacervate phase volume with concentration of the feed surfactant and the operating temperature

needs to be studied. In this regard, the following correlation for the fractional coacervate phase volume with the feed surfactant concentration is proposed.

$$F_c = PC_s^Q \quad (\text{IIA.3.7.4.})$$

where, F_c is the fractional coacervate volume and C_s is the molar concentration of the feed surfactant solution. As mentioned in the experimental section, a wide range of feed surfactant concentration and NB concentration is used in the experiments at various operating temperatures. F_c is thereby correlated with C_s using equation IIA.3.7.4.) The values of P vary within 0.472 to 0.485 for the temperature and NB concentration range under taken in this work. An average value of 0.478 is considered for further calculation of P . The values of Q varies linearly with temperature as

$$Q = R + S T$$

The parameters R and S are evaluated for various feed NB concentrations. The value of S varies from -0.038 to -0.052. Therefore, an average value of S considered is -0.045. Typical variations of the parameters R with feed NB concentration is expressed by the following correlation.

$$R = 4.28 + 3.42C_0 + 4.651 \times 10^{-9} \frac{1}{C_0^2} \quad (r^2 = 0.987) \quad (\text{IIA.3.7.5.})$$

IIA.3.8. Determination of surfactant requirement for the removal of NB to a desired level without using salts

Using the developed correlations (equations IIA.3.7.1. - IIA.3.7.3 and IIA.3.7.4. - IIA.3.7.5.), a calculation procedure is outlined to determine the amount of surfactant required for the removal of NB up to a desired level. The solubilization isotherm is defined as,

$$q_e = \frac{\text{Moles of NB solubilized}}{\text{Moles of TX - 100 used}} = \frac{A}{X} \quad (\text{IIA.3.8.1.})$$

Moles of NB solubilized can be obtained from mass balance,

$$A = V_0 C_0 - V_d C_e \quad (\text{IIA.3.8.2.})$$

where, V_0 and V_d are the volume of the feed solution and that of the dilute phase after CPE. C_0 and C_e are the molar NB concentration in the feed and that remaining in the dilute phase after CPE. Hence, C_e is the desired concentration level of the NB for which the CPE is to be performed. In terms of fractional coacervate phase volume (F_c), equation (IIA.3.8.2.) can be written as,

$$A = V_0 [C_0 - C_e (1 - F_c)] \quad (\text{IIA.3.8.3.})$$

Using equations (IIA.3.7.4.), (IIA.3.8.1.) and (IIA.3.8.3.), the moles of surfactant required can be expressed as,

$$X = \frac{V_0}{q_e} [C_0 - C_e (1 - PC_s^Q)] \quad (\text{IIA.3.8.4.})$$

If C_s is the concentration of surfactant initially in the feed, X in equations (IIA.3.8.4.) can be expressed as,

$$X = C_s V_0 \quad (\text{IIA.3.8.5.})$$

Equating equations (IIA.3.8.4.) and (IIA.3.8.5.), the following governing equation of C_s is obtained,

$$C_s = \frac{1}{q_e} [C_0 - C_e (1 - PC_s^Q)] \quad (\text{IIA.3.8.6.})$$

Expressing q_e in terms of C_e from equation (IIA.3.7.1.), the expression of C_s is obtained as,

$$C_s = \frac{[C_0 - C_e (1 - PC_s^Q)]}{aC_e^b} \quad (\text{IIA.3.8.7.})$$

With the knowledge of feed NB concentration (C_0), the desired level of NB concentration in the dilute phase (C_e), isotherm constants a , b and design parameters P , Q , equation (IIA.4.5.6) can be solved by trial and error to obtain C_s . Solving equation (IIA.3.8.7.) using some typical temperature conditions and fixing the desired concentration level of NB in the dilute phase as 1.0 mg/L (8.12×10^{-6}

mol/L), the surfactant concentrations required for various feed NB concentrations are calculated and plotted in figure IIA.3.8.1. It may be observed from the figures that the required surfactant concentration increases with feed NB concentration and is less at higher temperatures. Higher operating temperature requires higher energy input to the system. Therefore, there exists a trade off between the feed surfactant dose and the operating temperature with respect to the feed NB concentration to effect a desired level of NB removal.

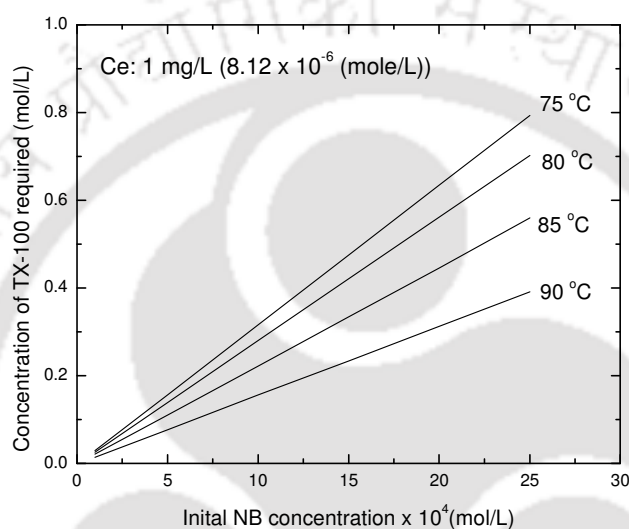


Figure IIA.3.8.1.: Variation of the requirement of TX-100 concentration for different initial NB concentration at three different temperatures to bring down its dilute phase concentration to 1 mg/L (8.12×10^{-6} (mole/L)).

IIA.3.9. Surfactant recovery by solvent extraction (SE)

To meet the environmental standards and the economy of the CPE process, it is necessary to recover the surfactant from both the coacervate and aqueous phase. Unlike ionic surfactant, precipitation method is not applicable for nonionic surfactant. For volatile solute, it is easy to recover surfactant from the coacervate phase by vacuum, steam, or gas stripping.⁸ But problem arises for non volatile solute like nitro benzene, which is used in the present case. Although regeneration of surfactant from coacervate phase is not studied in this work, efficacy of SE is explored here to recover surfactant from the dilute phase.

The experimental investigation on separation of TX-100 at 30 °C from aqueous solution is performed using heptane and hexane as extracting medium. All SE experiments are conducted in a cylindrical vessel. The composition of each set of experiment is prepared by adding different volume (5, 10, 15, 20, 25 and 30 ml) of heptane to a fixed volume (50 ml) of TX-100 solution of 178, 248, 1024 and 3546 mg/L. Nitro benzene concentration is zero, since the concentration of nitro benzene in the dilute phase is almost zero for a wide range of feed nitro benzene-TX-100 system. The mixture of TX-100 solution and heptane and hexane is vigorously shaken separately for 20 minutes using a stirrer (Type-RQ-123, Remi Motors Ltd., India) at 450 rpm to achieve equilibrium. After that, the mixture is transferred into a separating funnel and kept for 3 hours for complete separation of two phases. The volume and concentration of aqueous and non-aqueous phase are measured. The experiments are conducted in batch mode.

The results are presented in figure IIA.3.9.1. It is clear from the figure that for a fixed TX-100 concentration (e.g., 178 mg/L), the surfactant recovery increases sharply from 42.29 to 88%, when the ratio of heptane to dilute phase increases from 0.067 to 0.5. With further increase of the above ratio upto 0.833, the surfactant recovery reaches up to 88%. On the other hand, at the same ratio, extraction efficiency decreases with increase in feed TX-100 concentration. The increase in recovery with the solvent to dilute phase volume ratio is due to more distribution of TX-100 molecule in the heptane phase. The concentration distribution of the surfactant in both the solvent and dilute phase is constant at a fixed temperature (room temperature of 30 ± 2 °C). Therefore, keeping the volume ratio of solvent to dilute phase fixed, increase in feed surfactant concentration results into lower recovery of surfactant. Similar result is observed when hexane is used as solvent as shown in figure IIA.3.9.2. The extraction efficiency is 2-3% less for hexane. This is may be due to the lower hydrophobic nature of hexane compared to heptane.

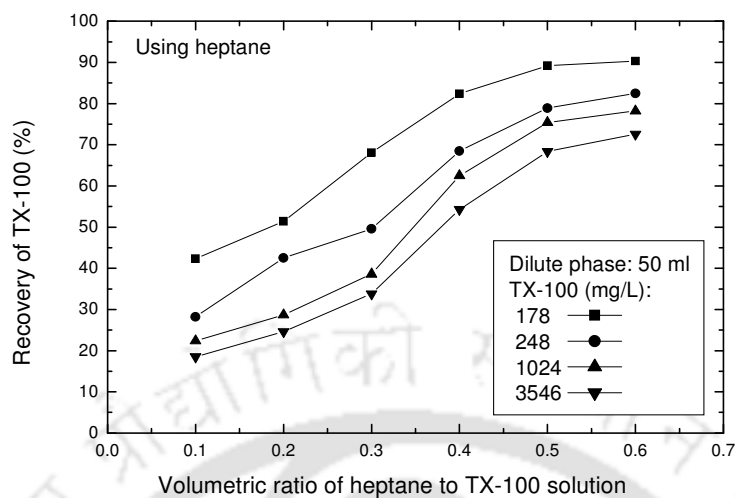


Figure IIA.3.9.1.: Variation of TX-100 recovery with heptane volume at different TX-100 concentration

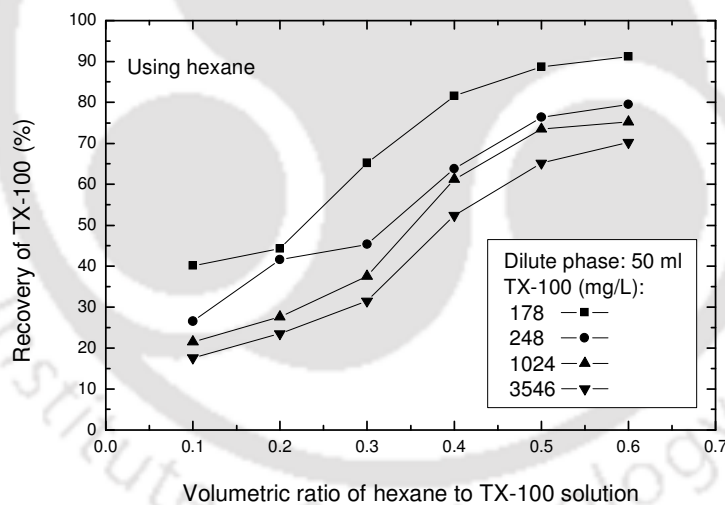


Figure IIA.3.9.2.: Variation of TX-100 recovery with hexane volume at different TX-100 concentration

In conclusion cloud point extraction is successfully used to remove nitrobenzene from synthetic wastewater using TX-100 as non-ionic surfactant. The effects of pH, temperature, concentrations of salts, surfactants and nitro benzene on the extraction of nitro benzene have been

studied in detail. It is observed that the extraction efficiency increases with temperature, surfactant and salt concentration.

It is observed that for 100 mg/L of nitrobenzene, the optimum TX-100 dose is about 0.1(M) for 92% extraction at 75°C. Nitro benzene extraction increases significantly with temperature (from 75 °C to 90 °C). The optimum operating pH for both the surfactants is about 9.0. The addition of electrolytes enhances the extraction. Nitro benzene extraction is more in the presence of calcium chloride compared to sodium chloride. The optimum salt concentration is found to be about 0.3(M).

Thermodynamic parameters are determined during cloud point extraction of NB – TX-100 system. The effects of temperature, concentrations of surfactants and NB on the change in Gibbs free energy (ΔG^0), enthalpy (ΔH^0) and entropy (ΔS^0) of NB extraction have been studied in detail. The changes in Gibbs free energy increases with temperature and decreases with both surfactant and NB concentration. The change in enthalpy and entropy of extraction decreases with NB concentration but increases with surfactant concentration. The spontaneity of the NB extraction is governed by the negative value of ΔG^0 . The positive values of ΔS^0 indicate that the solubilized NB molecules are organized in more random fashion on the mantle of aqueous hydrophilic chain. The extraction processes is endothermic in nature that is also proven by the positive value of ΔH^0 .

Solubilization isotherms are developed from the CPE data. Temperature dependency of the constants of the isotherms is also evaluated. From the experimental results, a correlation has been developed to quantify the variation of fractional coacervate phase volume at different operating conditions. An approach to design a cloud point extractor has been proposed to estimate TX-100 requirement for a known temperature, initial and desired nitro benzene concentration.

Finally, solvent extraction technique has been adopted using heptane and hexane as organic solvents to make the CPE process more economical. From the dilute phase, 88 % surfactant can be recovered using a volume ratio of heptane to dilute phase of 1:1.2.

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List of Publications

1. "A one-pot preparation of cyanamide from dithiocarbamate using molecular iodine"
Jayashree Nath, B. K. Patel, L. Jamir, U. B. Sinha, K. V. V. V. Satyanarayana, *Green Chemistry*, **2009**, 11(10), 1503-1506.
2. Molecular Iodine Mediated Preparation of Isothiocyanates from Dithiocarbamic Acid Salts"
Jayashree Nath, Harisadhan Ghosh, Ramesh Yella, B. K. Patel, *European Journal of Organic Chemistry*, **2009**, (12), 1849-1851.
3. "Phosphate impregnated Titania: An efficient reusable heterogeneous Catalyst for *aza*-Michael reactions under solvent-free condition"
Jayashree Nath and Mihir K. Chaudhuri, *Catal. Lett.* **2009**, 133, 388-393.
4. "Boric acid catalyzed bromination of a variety of organic substrates: an eco-friendly and practical protocol"
Jayashree Nath, Mihir K. Chaudhuri, *Green Chemistry Letters and Reviews* **2008**, 1(2-4), 223-230.
5. "Improved procedure for the preparation of isothiocyanates via iodine-mediated desulfurization of dithiocarbamic acid salts"
Jayashree Nath, Latonglila Jamir, Bhisma K. Patel, (*Green Chemistry Letters and Reviews* **2010**, Accepted for publication).
6. "Cloud point extraction of nitrobenzene using TX-100"
Aparajita Goswami, **Jayashree Nath**, Mihir K. Purkait, (Submitted, *Water Research*).
7. "Determination of design parameters for the cloud point extraction of nitrobenzene"
Aparajita Goswami, **Jayashree Nath**, Mihir K. Purkait, (Manuscript under preparation for the journal *Hazardous Material*).

Patent

1. "A clean process for the preparation of alkyl and aryl isothiocyanates", B. K. Patel, **Jayashree Nath**, Patent application No. 2138/KOL/2008, Dated: 11-12-2008.

Boric Acid Catalyzed Bromination of a Variety of Organic Substrates: An Eco-friendly and Practical Protocol

The work described in this Section has been published in *Green Chemistry Letters and Reviews* **2008**, 1(2-4), 223-230.