Recent Advances in Oxidative Transformation of Oximes with Hypervalent Iodine (III) Reagents

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ABSTRACT

In the present book chapter, the fascinating chemistry of hypervalent iodine (III) reagents promoted various oxidation reactions of aldoximes and ketoximes have been described. When organo-iodine (III) reagents are reacted with aliphatic or aromatic aldoximes, they usually furnish nitrile oxides, which are useful synthetic intermediates. But in slightly different reaction conditions, hypervalent iodine (III) reagents oxidise the aldoximes to N-acetoxy amides or hydroxamic acids as the major isolable products instead of the anticipated nitrile oxide or its dimerized product oxadiazole-N-oxides. On the other hand, oxidation of ketoxime using hypervalent iodine (III) usually produces the parent ketone or it undergoes Beckmann Rearrangement. The synthetic utilities of these transformations have been summarized here.

Keywords: Hypervalent Iodine; Oxidation; Aldoxime; Ketoxime; Nitrile Oxide

INTRODUCTION

Currently, hypervalent iodine reagents, e.g., (diacetoxyiodo) benzene or **DIB**, (hydroxytosyloxyiodo) benzene or **HTIB**, iodosylbenzene, **IBX**, Dess-Martin Reagent, etc. (Figure-1) have gained the attention of experimental chemists. Recently, hypervalent iodine reagents have become an alternativeuseful synthetic reagent for very common organic transformations. This is because of their commercial availability, non-toxic and user-friendly nature. Due to their environmentally benign character, these reagents are valuable from the *Green Chemistry* point of view. The distinctive reactivity pattern of these non-metallic oxidizing reagents is revealed in their distinguishing nature in various organic transformations, which are very tough or sometimes unachievable using other oxidizing agents (Yoshimura & Zhdankin, 2016).
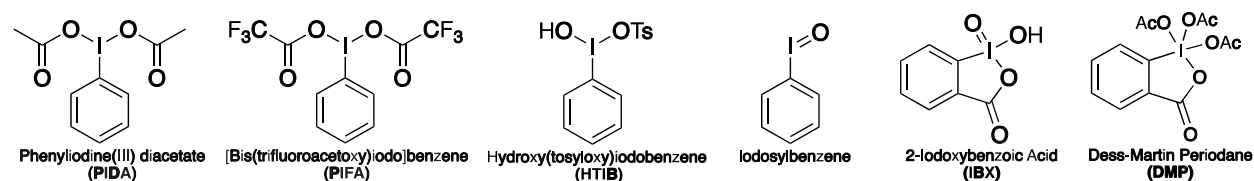

Figure 1: Frequently used hypervalent iodine reagents

The general reactivity relationship and stability of hypervalent iodine compounds can be explained through the character of the hypervalent bond of the compound. The hypervalent iodine compound contains the hypervalent bond, which is in fact a *3c-4e* (three-center-four-electron) bond in the apical orientation (Figure 2). The hypervalent bonds have a longer bond length than typical bonds. That is why, the hypervalent bonds can be easily cleaved. The cleavage causes iodine (III) species with 10 electrons to be reduced to iodine (I) with a stable 8 electron structure. Because of this, hypervalent iodine (III) can be used as a very good metal-free oxidizing agent in organic synthesis (Reed & Schleyer, 1990).
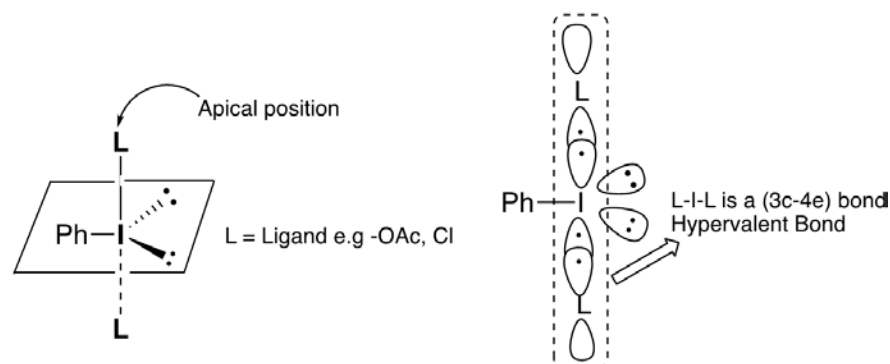
Figure 2: Bonding nature of Organo-iodine(iii) reagent

LITERATURE REVIEW

Iodine (III) compounds have been utilised for the oxidation of organic nitrogen compounds, e.g. hydrazones and acid hydrazides. On treatment with hypervalent iodine (III) reagents, various hydrazones and N', N'-dialkylhydrazides are cleaved to the corresponding parent ketones and carboxylic acids (Wuts & Goble, 2000). In the case of ketoxime, the oxidation product is either the deprotection of the parent ketone or a Beckmann Rearrangement product. But, in the case of aldoximes, the oxidation result is either deprotection of the parent aldehyde or oxidation to carboxylic acid or the formation of nitrile oxide. Here, the oxidation outcome depends on the hypervalent iodine agent employed and the reaction conditions chosen for the transformation (Yoshimura & Zhdankin, 2017).

(A) Oxidative transformation of aldoximes using Organo-Iodine(III) reagents:

The oxidation of aldoximes using organo-iodine(III) reagents can generate various products such as nitrile oxide, the parent aldehyde or carboxylic acid (Figure 3). The outcome of the reaction depends on the reaction conditions and iodine(III) species chosen as the oxidant.
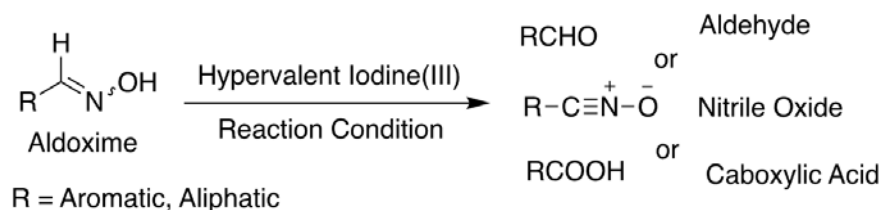

Figure 3: Hypervalent Iodine(III) induced oxidation of aldoximes

Among all these products, nitrile oxide is the most valuable synthetic intermediate. The chemistry of nitrile oxide is attractive because of its immense biological and synthetic importance. Nitrile oxide is the main precursor for the synthesis of the compound 5-aminoisoxazoles, which are of vast biological interest. 5-aminoisoxazole has fungicidal, anthelmintic, and bactericidal properties, and these are also useful for the treatment of various cerebrovascular disorders (Saad, Vaultier, & Derdour, 2004). Nitrile oxides are an important class of synthetic intermediates because of their ability to undergo l,3-dipolar cycloaddition reactions with alkenes or alkynes, giving heterocyclic compounds, mainly isoxazolines and isoxazoles (Figure 4). Organo-iodine (III) reagents are considered to be the best reagents of choice for the generation of nitrile oxides from aldoximes (Yoshimura *et al.*, 2020).
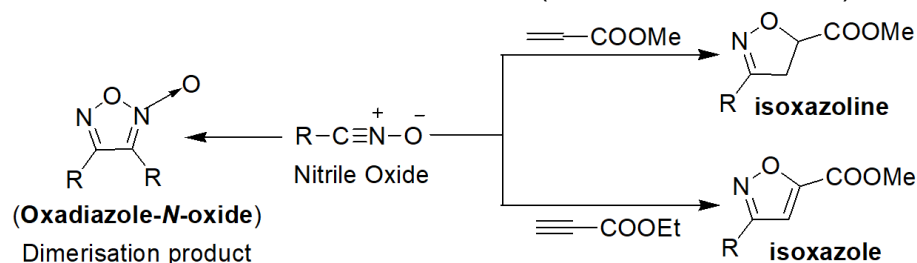

Figure 4: l,3-Dipolar additions reaction of nitrile oxide

Yoshimura *et al.* (2013) reported a novel strategy for the cyclization reaction of aldoxime and an alkene or alkyne (Figure 5). They have used a catalytic amount of organo-iodine (III) reagent in the presence of stoichiometric oxone as a terminal oxidant in hexafluoroisopropanol (HFIP) and an aqueous methanol solvent mixture. Initially, a nitrile oxide intermediate is formed in this reaction. Then, the nitrile oxide reacts with various alkenes and alkynes in a 1.3-dipolar cycloaddition reaction fashion, to produce theisoxazolines and isoxazoleskeletons, respectively (Figure 5).
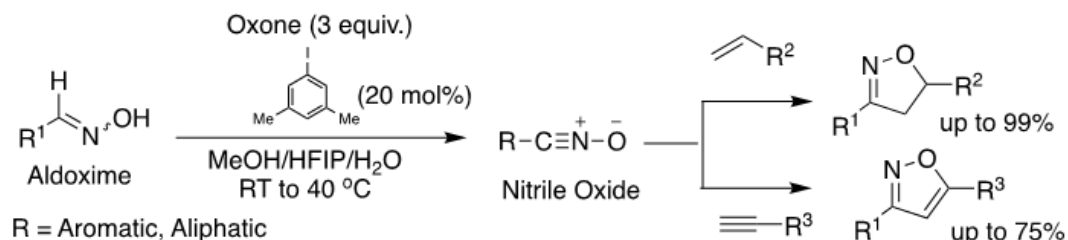

Figure 5: Use of catalytic hypervalent iodine for oxidative cyclization reaction

Hou, Lu and Liu (2013)demonstrated theiodobenzene diacetate (DIB) mediated synthesis of benzo[d]isoxazole-4,7-diols through [3+2] cycloaddition reaction in aqueous mediumand *one-potmethodology* (Figure 6). In this transformation, nitrile oxide and benzoquinone are found to be formed as the intermediates. This method was also extended to synthesize another three types of compound e.g. benzodiisoxazole-4,8-diols, isoxazolo[5,4-a]phenazines, and indazole-4,7-diols.
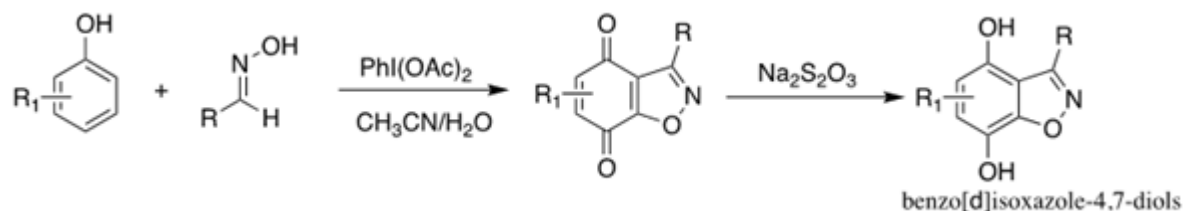

Figure 6:Preparation of Benzo[d]isoxazole-4,7-diols through [3 + 2] cycloadditive reaction

Aplausible mechanism of this conversion involves the intermediate formation of nitrile oxide and *para*-benzoquinone by DIB promoted oxidation in one-potand subsequent [3+2] cycloadditionreaction among them (Figure 7).
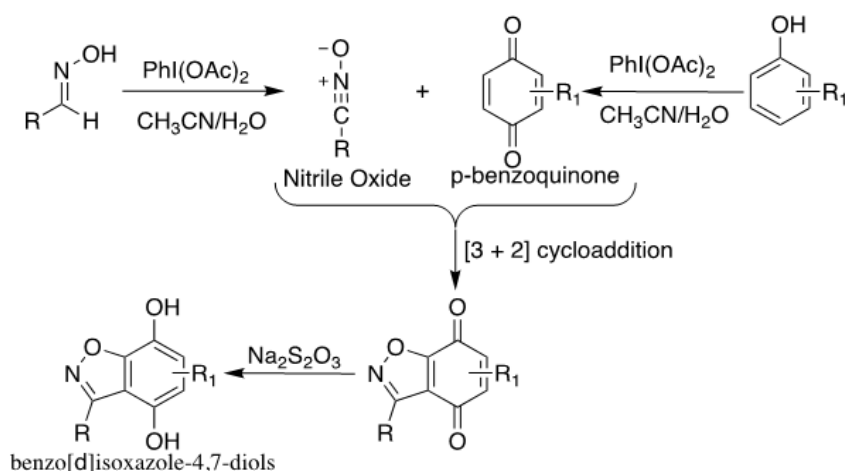

Figure 7: Mechanism of formation of Benzo[d]isoxazole-4,7-diols through [3 + 2] cycloaddition reaction

In a report by Yoshimura *et al.* (2017), they have demonstrated an efficient synthesis of a heterobicyclic scaffold fused with an isooxazoline moiety through an oxidative [3+2] cycloaddition reaction using

HTIB as the mild oxidant (Figure 8). Aldoximes and sulfur and phosphorus-containing heterocyclic alkenes were taken as the starting materials. This oxidative cyclization reaction proceeds via initially formed nitrile oxides intermediate from aldoximes mediated by HTIB reagent. Then, the nitrile oxides intermediateundergoes intermolecular 1,3-dipolar cyclization reaction with 1-propene-1,3-sulfone or cyclic pholene-oxideto furnish the respective isoxazoline-ring fusedheterobicyclic scaffolds in satisfactory yields (Figure 8).
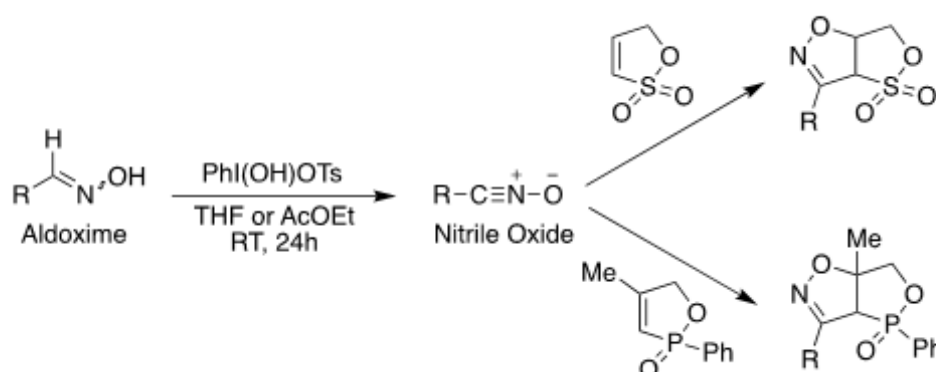

Figure 8: Synthesis of Isoxazoline-fused heterobicyclic compound

Nakamura *et al.* (2018) disclosed a mild and eco-friendly synthetic technique for oxidative transformation of aldoximes to carboxylic acids using the hypervalent iodide(III) reagent HTIB (Figure 9). They have shown that treatment of a series of substituted aldoximes with 2.2 equivalent of PhI(OH)OTs as an oxidant in DMSO-H_2O solvent mixture furnishes the corresponding carboxylic acid in excellent yield.
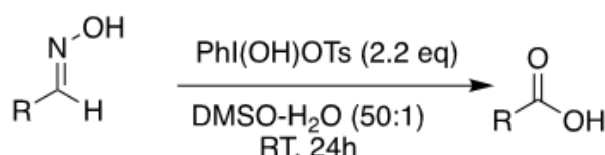

Figure 9: HTIB mediated synthesis of carboxylic acids from aldoximes

They have established the mechanism of this conversion by performing a few controlled experiments. The intermediate of this transformation is hydroxamic acid, which undergoes ligand exchange with tosylate ligand on HTIB. After that, liberation of iodobenzene and water from the intermediate provided the acyl-nitroso compound, which ultimately undergoes hydrolysis to produce carboxylic acid (Figure 10).
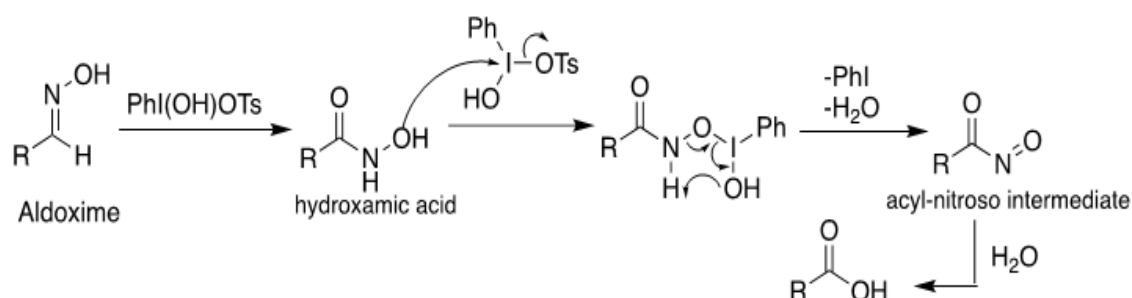

Figure 10: Mechanism of formation carboxylic acids from aldoximes promoted by HTIB

Professor Patel's research group found out a different outcome during the studies of organo-iodine(III) induced oxidation reaction of aldoximes (Patel & Ghosh 2010). They have detected the generation of N-acetoxy benzamide from aromatic aldoximes [Figure 11, (a)]on reaction with(diacetoxyiodo)benzene. When they performed the same reaction with Koser's reagent (HTIB),

the product isolated was N-hydroxy benzamide or hydroxamic acid [Figure 11, (b)].
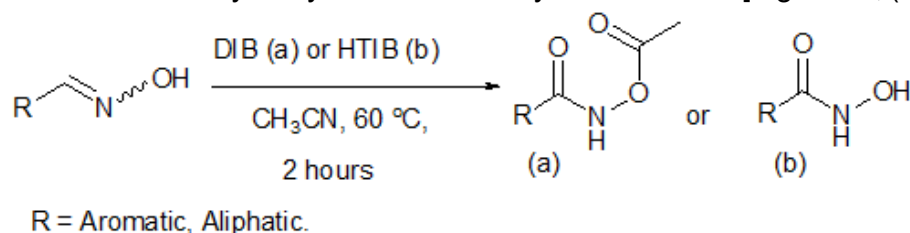

Figure 11: DIB and HTIB mediated oxidation of aldoximes

When 1 equivalent of benzaldehyde oxime was treated with 1.1 equivalent of (diacetoxyiodo)benzein acetonitrile solvent at a temperature of 60 °C, N-acetoxy-benzamide was isolated in 78% yield as the final product. It should be mentioned here that, in this reaction condition, neither the benzonitrile oxide nor its dimerised adduct were isolated from the reaction mixture. This observation contradicts an earlier report (Das *et al.*, 2004) where in CH₂Cl₂ reaction solvent and in the lack of any added alkenes, a nitrile oxide dimerised adduct (oxadiazole-N-oxides) is reported to be formed. The only difference between the earlier report by Das *et al.* and the present method by Patel and Ghosh (2010) is the use of the solvent acetonitrile instead of dichloromethane.

The proposed mechanism for this transformation is shown in Figure-12. First, benzonitrile oxide (X) (Figure 12), which is expected to be the intermediate for this kind of transformation, is formed from the aldoximes. Then, the nitrile oxide intermediate (X) is attacked by the insitu liberated acetate anion from (diacetoxyiodo)benzene, providing a C-acylated intermediate (Y). Finally, the intermediate (Y) undergoes intramolecular rearrangement to give the expected N-acetoxy-arylamide (Figure 12).
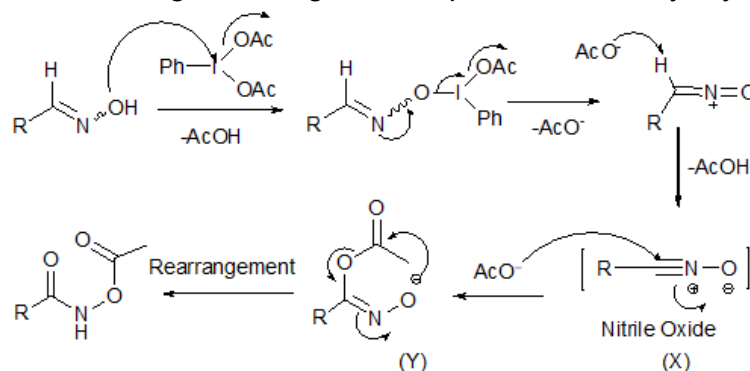

Figure 12: Mechanism of N-Acetoxy amides formation promoted by DIB

A few controlled experiments were carried out to establish the proposed reaction mechanism. The reaction was conducted in the presence of propionic acid (1 equivalent) in the standardised reaction condition. Surprisingly, formation of *N-propionyloxy*-benzamide was observed along with *N-acetoxy*-benzamide in the ratio of 40:60 (Figure 13). From this experiment, the authors were able to establish two of their arguments: (1) benzonitrile oxide is formed as the intermediate and (2) acetate or propionate attack the intermediate benzonitrile oxide in an inter-molecular pathway (Figure 13).
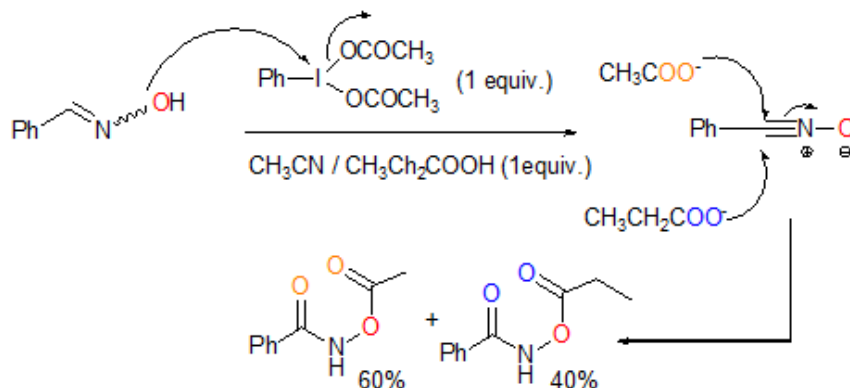

Figure 13: Inter molecular nature of the mechanism

Oxidative Transformation of Oximes

Professor Tanaka's research group demonstrated that iodosylarene (PhIO) oxidises aldoxime to oxadiazole-*N*-oxide, which is actually the dimerised adduct of intermediate nitrile oxide. They isolated oxadiazole-*N*-oxide from the reaction mixture and characterised it (Figure 14, Path-B) (Tanaka *et al.*, 2002). Therefore, it can be understood that in the absence of a suitable alkene or nucleophile, the intermediate nitrile oxide undergoes dimerisation to form oxadiazole-N-oxide.. But, in the presence of an appropriate external nucleophile, e.g.AcO- or OH- group, the intermediate nitrile oxides produce the corresponding N-acetoxy-benzamides or N-hydroxy-benzamides through an oxidative rearrangement process (Figure 14, Path-C). In that case, no dimerised product formation was observed. The reactivity pattern of nitrile oxide has been summarised below (Figure 14, Path-A, B, C).
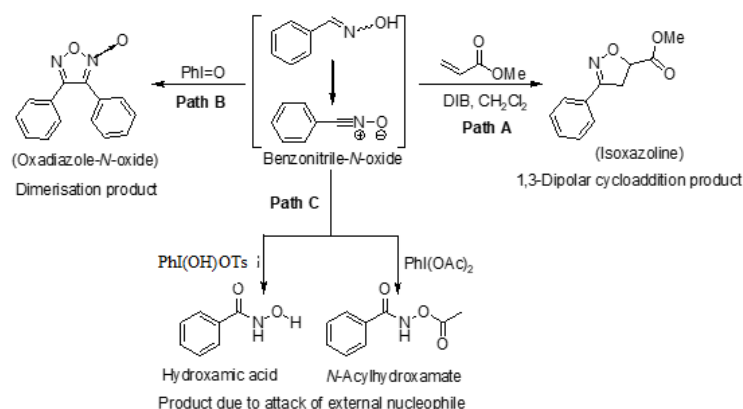

Figure 14: Difference in reactivity of nitrile oxide in various conditions

N-acetoxy amide is a highly significant organic scaffold. So, the authors applied the developed methodolgy to various aldoximes for the synthesis of a wide array of N-acetoxy amides. The authors reported the preparation of N-acetoxy amides with electron donating substituents as well as electron withdrawing substituents in the aromatic moiety (Figure 15). All the products were reported to be formed with DIB reagent in acetonitrile medium at 60o C within 2 hours in good yields.
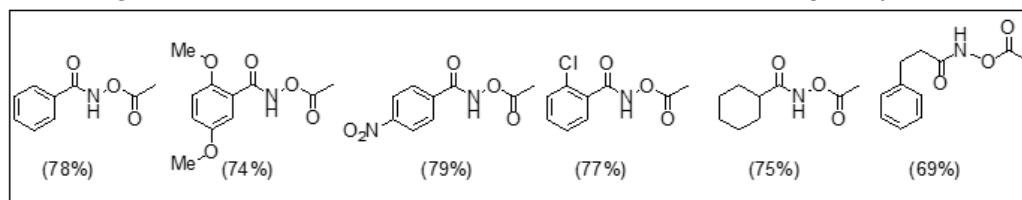

Figure 15: Various N-Acetoxy amides prepared

Aldoximes with both electron donating (e.g. Me, OMe) and electron withdrawing (e.g. Cl, NO_2) substituents in the aromatic moiety react well with DIB. In a competing reaction, when an equimolar mixture of two aldoximes with different electronic natures, e.g. 4-methyl-benzaldehyde oxime and 4-nitro-benzaldehyde oxime, were reacted with one equivalent of DIB, the ratio of the corresponding acetoxy product formed after two hours was found to be 3: 1. This demonstrate the higher reactivity for the substrates having an electron donating substituentin comparasion to the substrates having an electron withdrawing substituent in the aromatic moiety (Figure 16).
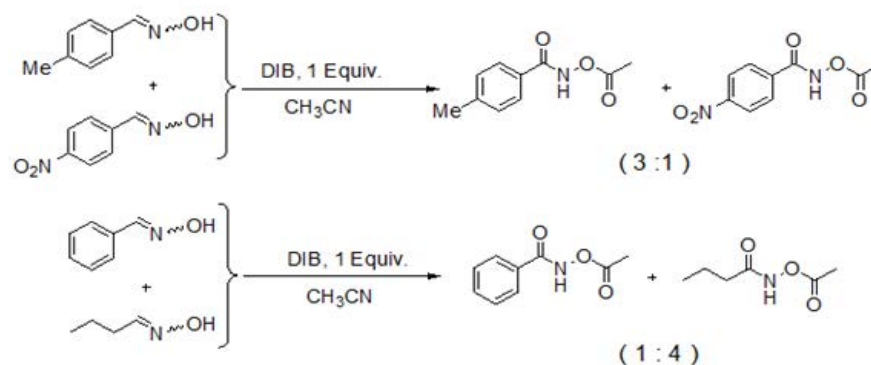

Figure 16: The reactivity difference of aliphatic and aromatic aldoximes

The most interesting reactivity difference was observed when a competing reaction was performed with a (1:1) mixture of aliphatic and aromatic aldoxime. Benzaldehyde and n-butyl aldehyde aldoxime were used for this purpose (Figure 16). The proportion of the corresponding acetoxy product produced after two hours was analysed as (4:1). This observation proves that the aliphatic aldoxime has faster reactivity compared to the aromatic aldoxime.

HTIB or Koser's Reagent, was also tested for the oxidation of benzaldehyde oxime. The product isolated was *N-hydroxybenzamide*, or hydroxamic acid. The authors proposed that the–OH nucleophile, which is generated from the Koser's Reagent, reacts with the intermediate nitrile oxide, generating *N*-hydroxy benzamide (Figure 12). Chloroform was found to be better than acetonitrile as a solvent for the preparation of N-hydroxy amide.
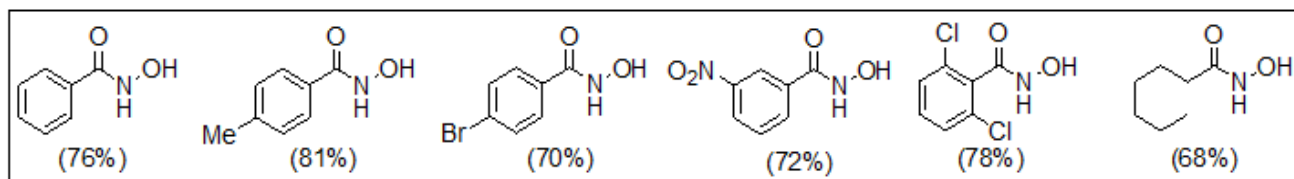

Figure 17: N-Hydroxy amides prepared

Various N-hydroxy amide havingelectron donating or withdrawing substitutents in the aromatic ring can be successfullysynthesized from the respectivestarting material oximes, in satisfactory yield as shown in Figure 17.

Based on the above results, Professor Patel's Research Group developed a simple and eco-friendlymethodologytoconstructvarious aromatic amine viaa reaction of aromatic aldoxime with HTIB in an alkaline sodium hydroxide mediumand DMSO solvent (Ghosh *et al*., 2011). They were successful to conduct the whole process in one-pot (Figure 13).
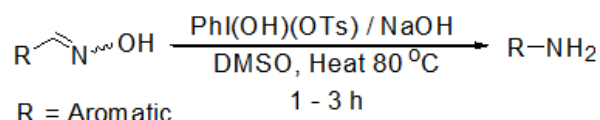

Figure 18: Preparation of amine from aldoxime in one-pot

At first, Koser's reagent converts the aldoxime to the intermediate N-hydroxy amide (hydroxamic acid) as described earlier. Then,the hydroxamic acid undergoes base (sodium hydroxide) mediated Lossen rearrangement which generate corresponding amineas the desired product (Figure 19). Variousaromatic amines,which are challengingsubstrate to be synthesised by the reduction methodfrom the corresponding nitro compounds, can be prepared using the present methodolgy.
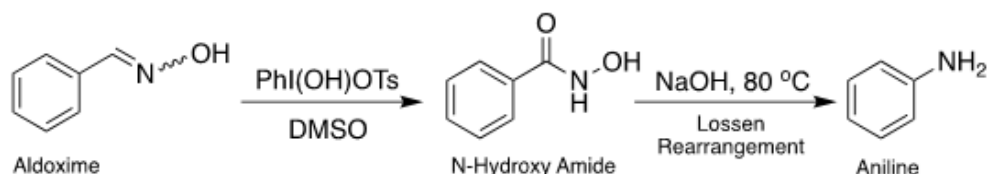

Figure 19: Synthesis of aniline from aldoxime in one-pot using HTIB reagent

In a standard reaction procedure, 1.4 equivalents of Koser's reagent were poured into a stirring mixture of 1 equivalent of benzaldehyde oxime and dimethylsulfoxide solvent. The resultant mixture was stirred at ambient temperature for 30 minutes. Then, the reaction mixture was heated at 80oC for one hour to generate the hydoxamic acid. Finally, 1.5 equivalents of sodium hydroxide were mixed into the reaction mixture and heating was continued for another 1.5 hours to produce the aniline (Figure 19). The authors found out that DMSO was the best solvent among all the solvents examined to achieve optimumconversion for the product.
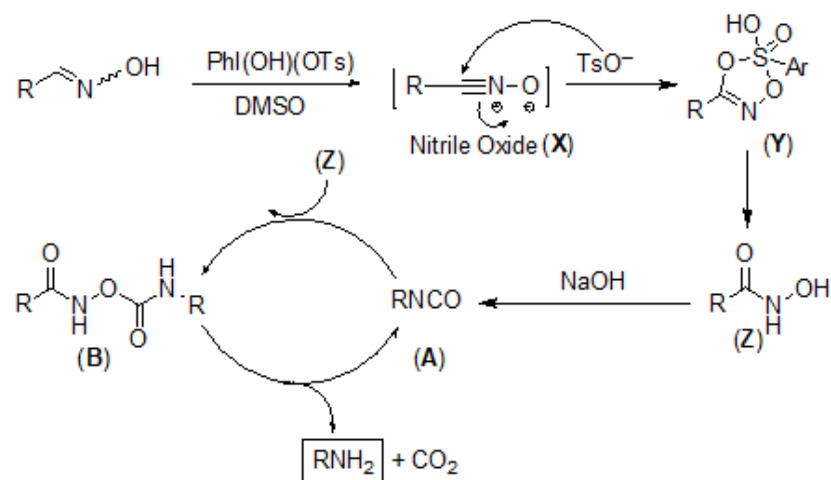
Figure 20: Plausible mechanism for formation of the amine from aldoxime

Generation of the aromatic amine from aromaticaldehydeoxime can be justified through the above plausible reaction mechanism (Figure 20).

The usefulness of the developed methodology have been demonstrated by synthesising various aromatic amines (Figure 21). Substituted amine which contain allyloxy- and propargyloxy- group is difficult to prepare using usual reduction method from nitro arene, because allyloxy- or propargyloxy- group does not tolerate the nitration condition or reduction condition.
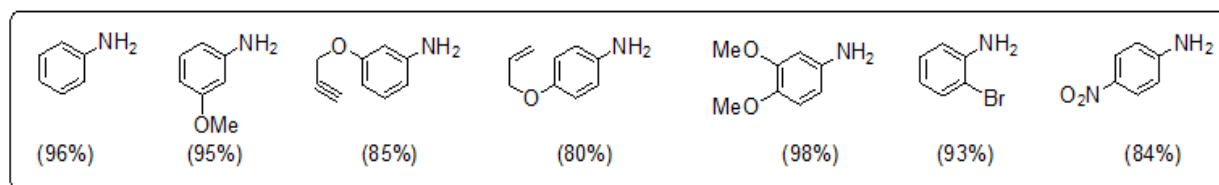

Figure 21: Various amine derivative synthesized

(B) Hypervalent Iodine Mediated Oxidation of Ketoximes:

In Moriarty, Prakash and Vavilikolanu (1986) studied the oxidation reaction of ketoxime with iodosobenzene diacetate (Moriarty, Prakash & Vavilikolanu, 1986). They found out that hypervalent iodine cleaved ketoxime and produced the corresponding ketones under neutral conditions in good yields.
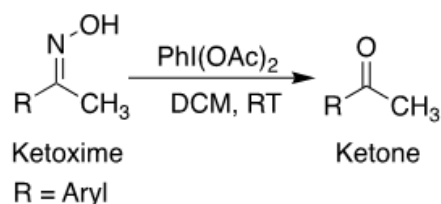

Figure 22: Oxidation reaction of ketoxime with iodosobenzene diacetate

The authors noticed evolution of N_2 gas during the reaction. Based on this observation, they proposed a probable mechanism for this organic conversion where generation of a nitroso intermediate was suggested (Figure 23).
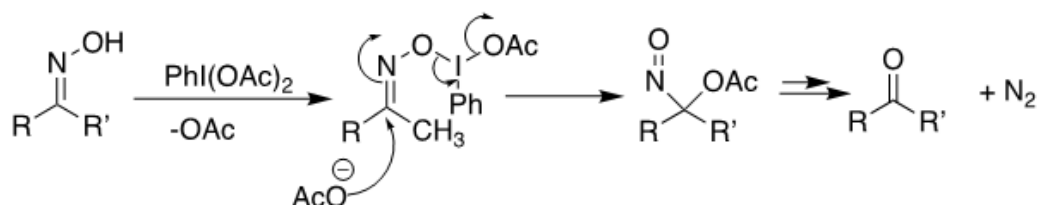

Figure 23: Mechanism of cleavage ketoxime with iodosobenzene diacetate

Very recently, Oishi *et al*. reported a novel Beckmann rearrangement reaction employing PhI(OAc)₂ and BF₃·Et₂O starting from various aliphatic and aromatic ketoximes (Figure 24). In this methodology, the Lewis acid BF₃·Et₂O was used for the pre-activation of organo-iodine (III) species.
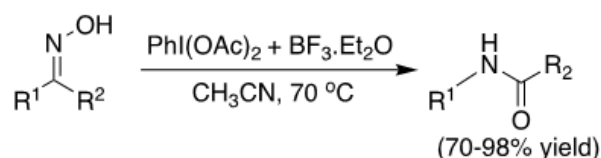

Figure 24: Beckmann rearrangement mediated by hypervalent Iodine(iii) reagent

The authors proposed a plausible reaction mechanism for this transformation. First, a pre-activation of the reagent, diacetoxy iodobenzene, occurs by the Lewis acid. Then, the activated diacetoxy iodobenzene triggers the hydroxy group of the ketoxime by substitution with an acetoxy group. Finally, the intermediate (X) (Figure 25) undergoes rearrangement with the elimination of iodosobenzene and the acetoxy group to generate the cation which subsequently reacts with H₂O to afford the amide.
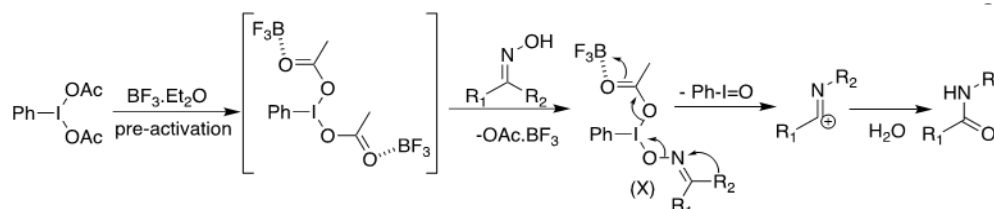

Figure 25: The mechanism of beckmann rearrangement initiated by iodine(iii) reagent

CONCLUSION

The oxidation results of various aldo/ketoximes induced by organo-iodine(III) reagents have been summarised in this book chapter. Aldoximes are oxidised with iodine(III) species to create nitrile oxide intermediate which a vital synthon that undergoes 1,3-dipolar cycloaddition reaction to producea series of valuable organic scaffolde.g.isoxazolines and isoxazoles. Hypervalent iodine (III) reagents DIB or HTIB oxidise both aromatic and aliphatic aldoximes toproduce the corresponding *N*-acetoxy or N-hydroxy amides in satisfactory yield instead of the anticipated nitrile oxides or its dimerised adduct. Hydroxamic acid can be generated using hypervalent iodine(III) reagent HTIB in DMSO solvent. The *in situ* generated hydroxamic acids undergoes a alkali initiated rearrangement process to affordvarious aromatic amines in *one-pot*. Oxidation of ketoxime with hypervalent iodine(III) reagent regenerate the parent ketone in normal reaction condition. But in the presence of Lewis acid activator, the ketoxime undergoes Beckmann Rearrangement while reacting with hypervalent iodine(III) reagent. So, in conclusion oxidation of oxime compounds using organo-iodine(III) reagents leads to many interesting results and it is expected this specific reactivity of these reagents will lead to many more fascinatingorganic transformations in future.

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