

CHAPTER-III

Solid phase synthesis of oxime derivatives

CHAPTER-III

SECTION-A

III.A. A brief review on oxime, synthesis and its applications

III.A.1.1. Oxime

An oxime is a chemical compound belonging to the imines, with the general formula $R_1R_2C=NOH$, where R_1 is an organic side-chain and R_2 may be hydrogen, forming an aldoxime, or another organic group, forming a ketoxime (**fig.III.A.1.**). O-substituted oximes form a closely related family of compounds.

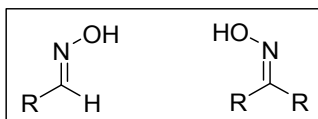


Fig.III.A.1. Example of aldoxime and ketoxime

Oximes are stable and highly crystalline materials and oximation is very efficient method for protection, characterization and purification of carbonyl compounds. These compounds not only represent a useful series of derivatives of carbonyl compounds but also may be used as intermediates for the preparation of wide spectrum of organic compounds and numerous functional group transformations. Among other synthesis applications, these compounds were successfully transformed into number of functional groups and nitrogen containing heterocyclic compounds in the presence of other reacting species. Recently oximes and their derivatives have drawn attention in medicinal research because of their significant bioactivity. In inorganic chemistry, oximes act as a versatile ligand. The Beckmann rearrangement of cyclohexanone oxime to ϵ -caprolactum is an industrially important reaction for the synthesis of Nylon-6. Moreover, oximes can be easily reduced to amines, which are further used in the manufacturing of dyes, plastics, synthetic fibres and pharmaceuticals. Oximes are used as anti-skinning agents in paint and blocking agents in the polymer industry.

III.A.1.2. Structure of oxime

Oximes exist as two geometric stereoisomers: a syn isomer and an anti isomer. Aldoximes, except for aromatic aldoximes, which exist only as anti isomers, and ketoximes can be separated almost completely and obtained as a syn isomer and an anti isomer.

III.A.2. Biological importance of oxime derivatives

Oxime functionality is also an important structural feature in several biologically active compounds. For example, perillartine (**1**), an oxime of perillaldehyde, is about 2000 times as sweet as sucrose and pralidoxime (**2**) and obidoxime (**3**) (**fig.III.A.2.**) are important antidotes for organophosphate poisoning. Recently, oxime ether derivatives have drawn much attention in medicinal research due to their significant bioactivity. Interestingly some oxime ether compounds exhibited not only excellent insecticidal activities but have also good plant growth regulatory activities.

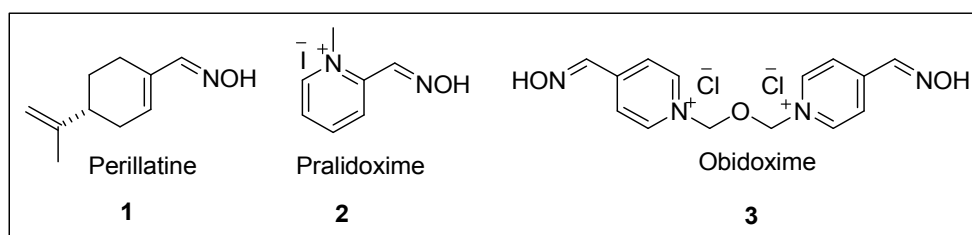


Fig.III.A.2. Biologically active oxime derivatives

The other biologically important oxime derivatives of various organic compounds are 5, 5'-substituted indirubin-3'-oxime derivatives found potent cyclin-dependent kinase inhibitors with anticancer activity (**fig.III.A.3.**).¹ Yeon Tae Jeong et al.² have reported in vitro antimicrobial activity against a panel of pathogenic bacteria and fungi from the oxime derivatives of substituted 2, 4, 6, 8-tetraaryl-3, 7-diazabicyclo[3.3.1]nonan-9-ones. The moderate antimicrobial properties of some homo- and heteronuclear Cu(II) and Ni(II) complexes of new oxime-type ligands against several pathogenic microorganisms is reported by Ahmet Colak et al.³ Alex W. White et al.⁴ have reported the biological evaluation of a novel series of pyrroloazepinone and indoloazepinone oximes which showed promising growth inhibition activity against four human cancer cell lines. Shaoshun Li et al.⁵ have reported the cytotoxic activity of alkannin and shikonin oxime derivatives against three kinds of tumor cells and a normal cell line and

found some oxime derivatives were more or comparatively effective to the lead compounds, especially their selective and excellent antitumor activities towards K562 cells with no toxicity in normal cells.

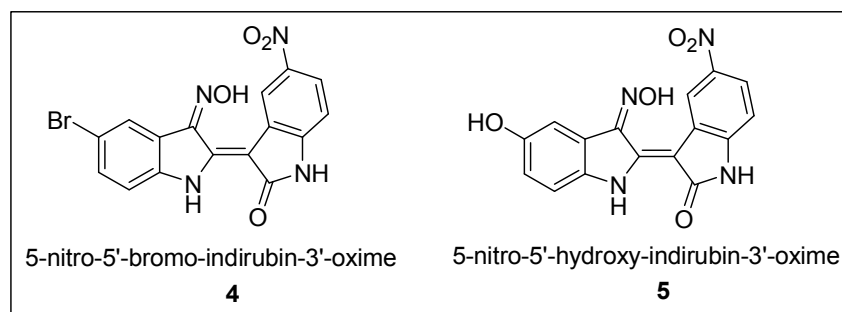


Fig.III.A.3. Biologically potent oxime derivatives

III.A.3. Application of oximes in organic transformations

III.A.3.1. Synthesis of amides, lactams and nitriles from oxime

Oximes are used extensively for the protection of carbonyl function. This compounds not only represents the series of derivatives of carbonyl compounds but also used as useful intermediate for the important organic synthesis and functional group transformations. Particularly, the manufacture of cyclohexanone oxime represents a key step in the sequence of the nylon 6 production. In spite of having a huge industrial and medicinal uses, the other important and interesting application of oximes is functional group transformations and synthesis of nitrogen containing heterocycles such as Beckmann rearrangement for the synthesis of amide from ketoxime which requires high temperature and strongly acidic dehydrating media. Recently reported advance methodologies for the preparation of amide from ketoximes includes, organocatalyst cyanuric chloride catalyzed Beckmann rearrangement of ketoximes into amides under mild condition with HCl and ZnCl₂ as effective cocatalyst and successfully achieved Beckmann rearrangement of six- to eight-membered cycloalkanone oximes,⁶ perfluoroalkylsulfonyl fluoride-mediated abnormal Beckmann rearrangement for the transformation of steroid 17-oximes to the corresponding alkene nitriles regioselectively,⁷ pivaloyl chloride/DMF a mild inexpensive and non-toxic system for the conversion of oximes to corresponding amides,⁸ triphosphazene (TAPC **fig.III.A.4.**) catalyzed Beckmann rearrangement of ketoximes to lactams,⁹ mercury-

catalyzed rearrangement of ketoximes into amides and lactams,¹⁰ ruthenium-catalyzed oxime to amide rearrangement.¹¹

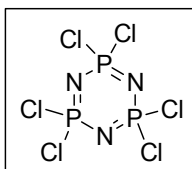
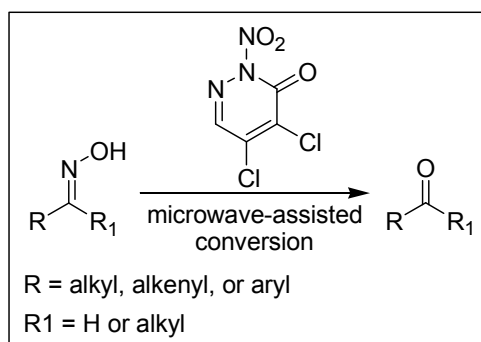


Fig.III.A.4. Triphosphazene (TAPC)

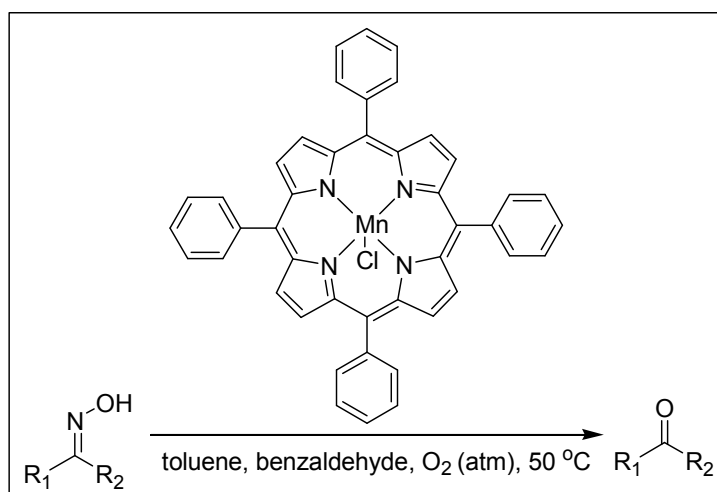
III.A.3.2. Regeneration of carbonyl function from oxime

Oximes are very useful for protecting carbonyl groups in organic synthesis.¹² Oximes can be prepared from carbonyl and non carbonyl compounds.¹³ Furthermore, their synthesis from non-carbonyl compounds provides an alternative way for preparation of aldehydes and ketones.¹⁴ Numerous methodologies have been developed for the regeneration of carbonyl compounds from oxime derivatives and synthesis of carbonyl compounds from non carbonyl compound via oxime formations. Bhushan M. Khadilkar et al reported the oxidative cleavage of oximes to corresponding carbonyl by silica supported chromium trioxide,¹⁵ photosensitized oxidative deprotection of oximes to their corresponding carbonyl compounds by platinum(II) terpyridyl acetylde complex,¹⁶ transformation of oxime to carbonyl compounds with 2-Nitro-4, 5-dichloropyridazin-3(2*H*)-one¹⁷ (**scheme.III.A.1.**),



Scheme.III.A.1. Transformation of oximes to carbonyl compounds in the presence of 2-Nitro-4, 5-dichloropyridazin-3(2*H*)-one

the regeneration of carbonyl functionalities of aromatic compounds in the presence of tetrapyrroline silver(II) peroxydisulfate in both acetonitrile and aqueous media,¹⁸ oxidative cleavage of oximes with NBS in the presence of β -cyclodextrin in water,¹⁹ oxidative deprotection of oximes to carbonyl compounds by 2, 6-Dicarboxypyridinium chlorochromate,²⁰ an aerobic oxidation of oximes to corresponding carbonyl compounds catalyzed by manganese porphyrin in the presence of benzaldehyde²¹ (**scheme.III.A.2**).

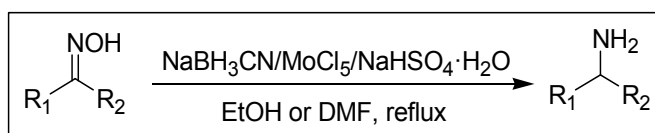


Scheme.III.A.2. Metalloporphyrins catalyzed oxidation of oximes to carbonyl compounds

III.A.3.3. Synthesis of amines from oxime

The conversion of carbonyl derivatives to amines via oxime is a useful transformation in the synthesis of numerous organic compounds and key intermediates in the biosynthesis of many pharmacological important compounds. Many synthetic routes have been reported for the facile synthesis of amines from oximes using various reductive systems such as, reduction of oximes to amines by catalytic transfer hydrogenation in the presence of magnesium powder and ammonium formate at room temperature,²² reduction with NaBH₄ in MeOH in the presence of MoO₃ or NiCl₂,²³ conversion of aldoximes and ketoximes into amines in the presence of zinc dust and ammonium formate,²⁴ reduction of oximes to amines with zinc borohydride in the form of (pyridine)(tetrahydroborato)zinc complex,²⁵ reduction of oximes to primary and secondary amines in the presence of sodium borohydride-copper

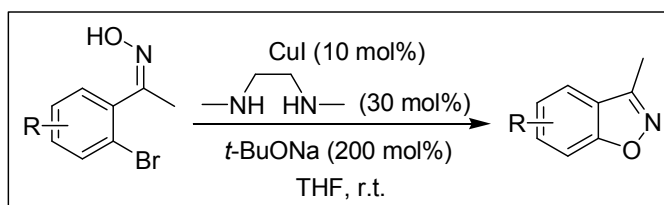
(II) sulphate in methanol,²⁶ NaBH₃CN/MoCl₅/NaHSO₄·H₂O system for the reduction of various aldoximes and ketoximes to the corresponding amines²⁷ (**scheme.III.A.3**).



Scheme.III.A.3. Synthesis of amines from oximes under reductive condition

III.A.3.4. Synthesis of heterocyclic compound from oxime

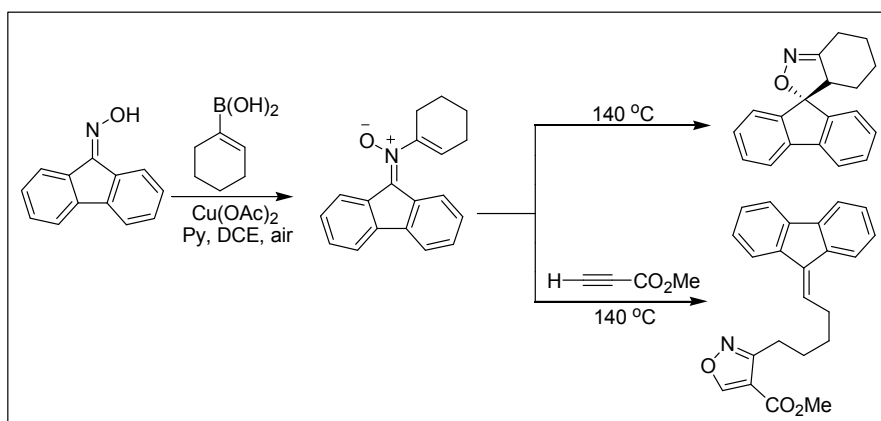
Not only functional group transformations but also oximes are equally useful for the synthesis of wide range of nitrogen containing heterocyclic compounds which contributes substructure of many bioactive natural products and structural motif of pharmaceutically important class of compounds. Literature review reveals the synthesis of large varieties heterocyclic compounds by taking oximes as starting material under different catalytic or reaction conditions such as the synthesis of variety of isoxazolines or isoxazoles from oximes and alkenes/alkynes in the presence of tert-butyl hypoiodite,²⁸ synthesis of annulated oxazoles by unprecedented cyclizations of α -oxo-oximes on heating with dimethyl sulfate, alkyl or aralkyl halides in DMF and in the presence of anhydrous potassium carbonate,²⁹ copper-catalyzed preparation of 3-methyl-1, 2-benzisoxazoles³⁰ (**scheme.III.A.4**), synthesis of isoquinolines by cationic ruthenium catalysts for alkyne annulations with oximes by C–H/N–O functionalizations,³¹ synthesis of polysubstituted, aluminisoxazoles and pyrazoles by a metalative cyclization.³²



Scheme.III.A.4. Copper-catalyzed cyclization of Z-oximes into 3-methyl-1,2-benzisoxazoles

Laura L. Anderson et al.³³ reported the synthesis of spiroisoxazolines and fluorene-tethered isoxazoles by copper-mediated coupling between fluorenone oxime and vinyl

boronic acids via nitron intermediate formation (**scheme.III.A.5**). Frank Glorius et al.³⁴ reported Rh(III) catalyzed synthesis of multisubstituted isoquinoline and pyridine N-oxides from oximes and diazo compounds exploring the application of oximes in heterocyclic synthesis.



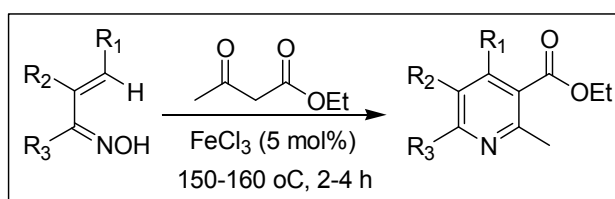
Scheme.III.A.5. Synthesis of spiroisoxazolines and fluorene-tethered isoxazoles by copper-mediated coupling between fluorenone oxime and vinyl boronic acids

There are numerous reports in the literature where oximes act as a starting material for the heterocyclic synthesis such as synthesis of quinoxalines by cyclization of α -arylimino oximes of α -dicarbonyl compounds,³⁵ rhodium catalyzed synthesis of isoquinolines and tetrahydroquinolines from ketoximes and alkynes by C-H bond activation,³⁶ solvent free synthesis of 2, 4, 6-triarylpyridines from acetophenone oximes and epoxy styrenes under neutral condition,³⁷ synthesis of isoindole from ortho-substituted aryl oximes sp^3 C-H activated cyclization,³⁸ synthesis of 5-substituted 1*H*-tetrazoles from various oximes and sodium azide (NaN_3) by using copper acetate as a catalyst³⁹ (**scheme.III.A.6.**), base promoted cyclocondensation of *C*-chloro oximes with cyclic 1, 3-diketones affords functionalized isoxazoles,⁴⁰ synthesis of 2, 4, 5-triaryl imidazoles from ketoximes via cyclization to the *N*-hydroxyimidazole and an unprecedented in situ thermal reduction of the N-O bond upon microwave irradiation at 200 °C,⁴¹ the synthesis of 1*H*-indazoles from *o*-aminobenzoximes by the selective activation of the oxime in the presence of the amino group. A variety of substituted *o*-aminobenzoximes using a slight excess of methanesulfonyl chloride and triethylamine

at 0-23 °C were presented.⁴² FeCl₃-catalyzed reaction of α , β -unsaturated oximes with ethyl acetoacetate to produce substituted nicotinic acid derivatives⁴³ (**scheme.III.A.7**).



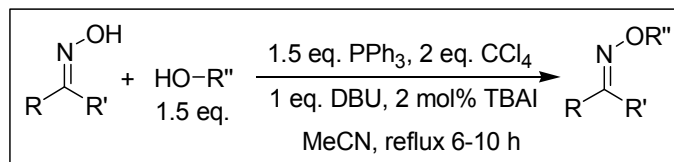
Scheme.III.A.6. Copper acetate catalyzed synthesis of 5-substituted 1*H*-tetrazoles from various oximes and sodium azide



Scheme.III.A.7. Synthesis of nicotinic acid derivatives from oximes

III.A.3.5. Synthesis of oxime ethers from oxime

Recently, oxime ether derivatives have drawn much attention in medicinal research due to their significant bioactivity.⁴⁴ Interestingly, Sun and co-workers found that some oxime ether compounds exhibited not only excellent insecticidal activities but have also good plant growth regulatory activities.⁴⁵ Such class of medicinally important compounds can be directly synthesized from oximes. Oximes are attractive synthetic reagents since they have both nitrogen and oxygen atoms as nucleophiles. Literature review reveals that numerous synthetic protocols have been developed to design and construct the oxime ethers of various compounds using oxime as a starting material such as Triphenylphosphine catalyzed synthesis of oxime ether by Michael addition of oximes onto activated olefins,⁴⁶ synthesis of oxime ethers by the treatment of alcohols with a mixture of triphenylphosphine, carbon tetrachloride, oxime, and DBU in the presence of catalytic amounts of tetrabutylammonium iodide in refluxing acetonitrile⁴⁷ (**scheme.III.A.8**), synthesis of 3-trifluoromethyl substituted pyrazole oxime ether derivatives containing a pyridyl moiety,⁴⁸ palladium catalyzed synthesis of allylated oxime ethers.⁴



Scheme.III.A.8. Synthesis of oxime ethers by the combination of oximes and alcohol

III.A.4. Synthesis of oxime derived ligands and its importance in organic synthesis

Oximes play an important role in the development of transition metal coordination chemistry due to their versatile bonding modes. Oximes and their metal complexes are of current interest for their various physicochemical properties, reactivity patterns and potential applications in many important chemical processes in medicine and catalysis. The aryl palladium complexes especially ortho functionalized aryl complexes have the numerous interesting applications in organic synthesis. Catalytic C–C or C–heteroatom coupling reactions are usually carried out in the presence of aryl palladium complexes with nucleophiles. Oxime based palladacycles have gained a special attention in modern organic synthesis due their ubiquitous use in variety of catalytic transformations, such as oxime palladacycle derived from 4, 4'-dichlorobenzophenone catalyzed Sonogashira reaction of aryl iodides and aryl bromides with terminal acetylenes⁵⁰ using 1 equivalent of tetrabutylammonium acetate in organic solvents generally in 1 h at 110 °C, 4-hydroxyacetophenone oxime-derived palladacycle catalyzed cross-coupling reaction of potassium aryltrifluoroborates with aryl and heteroaryl chlorides in refluxing aqueous media,⁵¹ *p*-hydroxyacetophenone oxime-derived palladacycle catalyzed Heck coupling reaction in refluxing water,⁵² fluorous oxime palladacycle catalyzed cross-coupling reaction (Suzuki-Miyaura, Sonogashira, Stille, Heck and Kumada) both in organic and aqueous media,⁵³ oxime-derived palladacycles with pyridine co-ligand catalyzed intramolecular Pauson–Khand reaction.⁵⁴

III.A.5. Classical method for preparation of oxime

Classically, oximes are prepared by refluxing an alcoholic solution of a carbonyl compound with hydroxylamine hydrochloride and pyridine. The method has multiple drawbacks such as low yields, long reaction time, toxicity of pyridine, and effluent pollution caused by the use of organic solvent. The condensation of aldehydes with

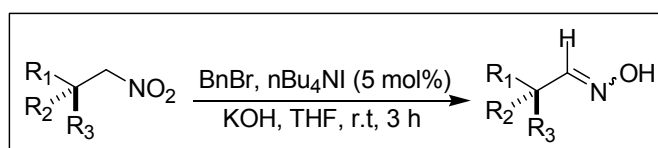
hydroxylamine gives aldoxime, and ketoxime is produced from ketones and hydroxylamine.

III.A.6. Modern methods for the synthesis of oxime from different functional groups

III.A.6.1. Synthesis of oxime from nitroalkanes

One of the preparatory methods of oximes is controlled reduction of nitro group. In the presence of strong reducing agents, nitro groups get converted into primary amines.

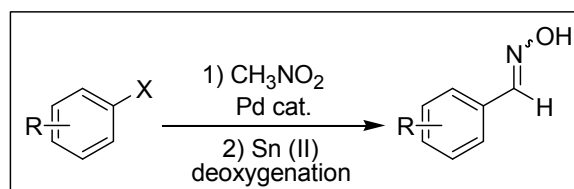
Erick M. Carreira et al.⁵⁵ have reported the synthesis of chiral adloxime from optically active nitro alkanes (**scheme.III.A.9.**) in the presence of benzyl bromide (BnBr), KOH, and *n*Bu₄NI in THF at room temperature.



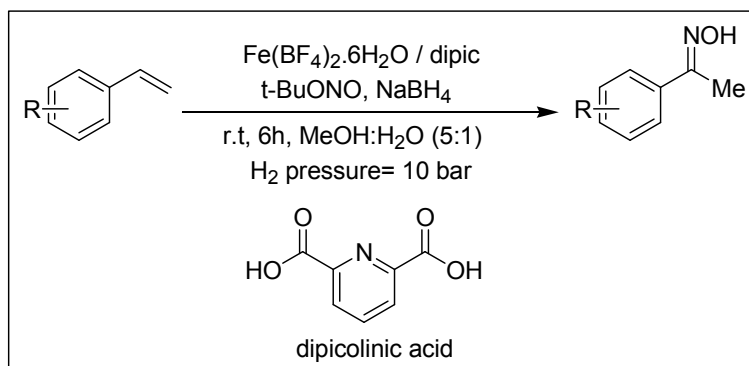
Scheme.III.A.9. Transformations of chiral nitroalkanes into chiral oximes

III.A.6.2. Miscellaneous methods for the preparation of oxime

The other methods include palladium catalyzed cross-coupling reaction of aryl halides and nitromethane under Nef conditions⁵⁶ (**scheme.III.A.10.**), Fe(BF₄)₂·6H₂O/ 2, 6-pyridinedicarboxylic acid catalyzed a selective synthesis of oximes in the presence of *t*-BuONO/NaBH₄ under H₂ pressure (10 bar) in MeOH–H₂O (5 : 1) from styrene derivatives⁵⁷ (**scheme.III.A.11.**), gold catalysts chemoselective route to synthesize oximes by hydrogenation of α , β -unsaturated nitrocompounds with H₂.⁵⁸

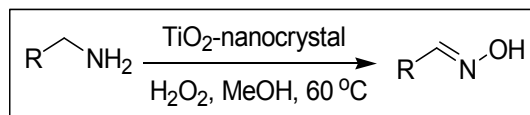


Scheme.III.A.10. Palladium catalyzed synthesis of oximes by cross-coupling between aryl halide and nitro alkane under reductive condition

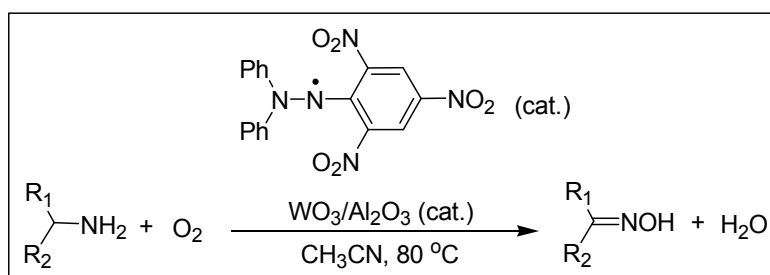


Scheme.III.A.11. Iron catalyzed synthesis of oximes from alkenes

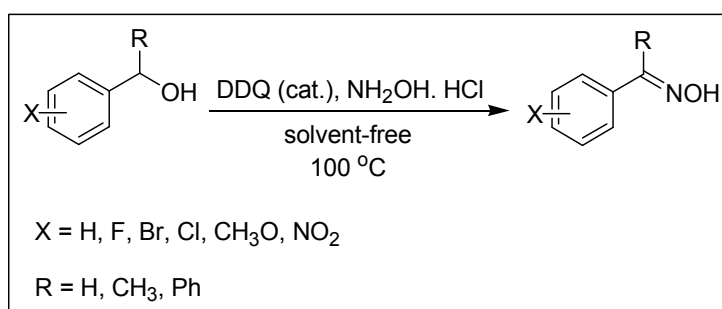
Oxime can also be directly synthesized from primary amine by mild oxidation. Jack K. Crandall et al.⁵⁹ reported the oxidation of primary amines where several primary amines have been oxidised with dimethyldioxirane under variety of conditions, selective catalytic oxidation of benzylic and allylic amines to oximes with H_2O_2 over TS-1 (titanium silicalite) is reported by A. Sudalai et al.⁶⁰ The similar type of synthesis preparation of oximes by oxidation of Primary aliphatic amines with α - hydrogen atoms in the presence of hydrogen peroxide as oxidant and catalytic quantities of titanium silicalite molecular sieves to corresponding oximes is reported by J. Sudhakar Reddy et al.⁶¹ The recent literature report for the conversion of amines to oximes include oxidation of aliphatic and aromatic amines into corresponding oximes using heterogenous nanocrystalline titanium (IV) oxide as catalyst and H_2O_2 as oxidising agent⁶² (**scheme.III.A.12.**), oxidation of primary amines to oximes with molecular oxygen using 1, 1-Diphenyl-2-picrylhydrazyl and $\text{WO}_3/\text{Al}_2\text{O}_3$ as catalysts⁶³ (**scheme.III.A.13.**), synthesis of aldoximes and ketoximes from primary and secondary benzyl alcohol in the presence of hydroxylamine hydrochloride and catalytic amount of 2, 3-dichloro-5, 6-dicyanobenzoquinone (DDQ) under solvent free condition⁶⁴ (**scheme.III.A.14.**), synthesis of oximes by benzylic C-H functionalization of azaarenes by its nucleophilic addition to nitroso compound⁶⁵ (**scheme.III.A.15.**), one-pot conversion of methyl arenes into aryl oxime with N-bromo succinamide (NBS), benzoyl peroxide, hydroxylamine hydrochloride and a base triethylamine in pyridine/DMF at reflux conditions.⁶⁶



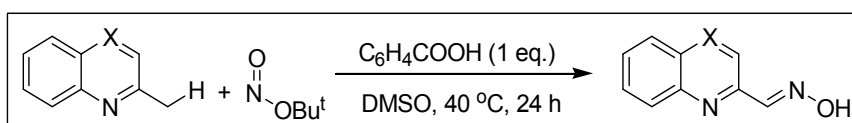
Scheme.III.A.12. Nanocrystalline titanium (IV) oxide catalyzed synthesis of oximes from amines



Scheme.III.A.13. Transformation of primary amines to oximes



Scheme.III.A.14. Synthesis of oximes from benzylic alcohols

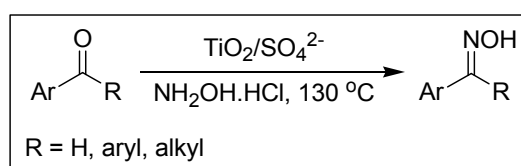


Scheme.III.A.15. Synthesis of oximes by benzylic C-H functionalization

III.A.6.3. Synthesis of oxime from carbonyl compounds

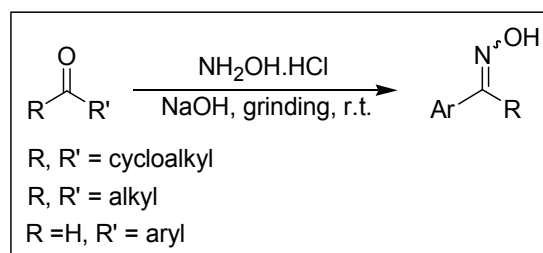
The drawbacks of classical method for the preparation of oxime which include pyridine in alcoholic solution of carbonyl compounds and hydroxylamine hydrochloride at elevated temperature; there was a need for the improvement of the complex classical method to simple one. Many improvements regarding the classical method have been done in the past years such as preparation of oximes on silica in the presence of sodium hydroxide,⁶⁷ microwave assisted solvent free synthesis of oximes from aldehydes or

ketones on hydroxylamine hydrochloride impregnated wet basic alumina,⁶⁸ synthesis of aromatic oximes by reaction of aromatic aldehydes and ketones with hydroxylamine hydrochloride catalyzed by $\text{TiO}_2/\text{SO}_4^{2-}$ solid superacid⁶⁹ (**scheme.III.A.16.**), preparation of cyclohexanone oxime from cyclohexanone and aqueous hydroxylamine in recyclable reaction media ionic liquid (bmiBF_4) at room temperature without any other additives.⁷⁰



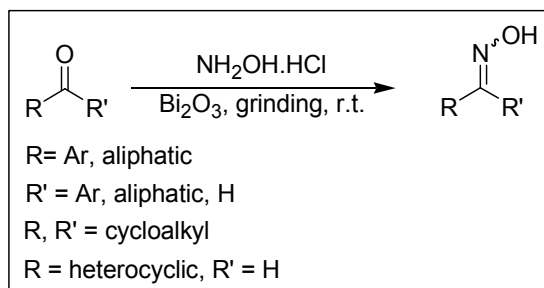
Scheme.III.A.16. $\text{TiO}_2/\text{SO}_4^{2-}$ catalyzed synthesis of aromatic oximes from carbonyl compounds

The conversion of alicyclic, aliphatic and aromatic aldehydes into the corresponding oximes by simple grinding the aldehydes, hydroxylamine hydrochloride and sodium hydroxide without solvent at room temperature was also successfully made. However, this procedure was unsuccessful in the case of aromatic ketones. In this case it was necessary to add silica gel as a catalyst⁷¹ (**scheme.III.A.17.**).

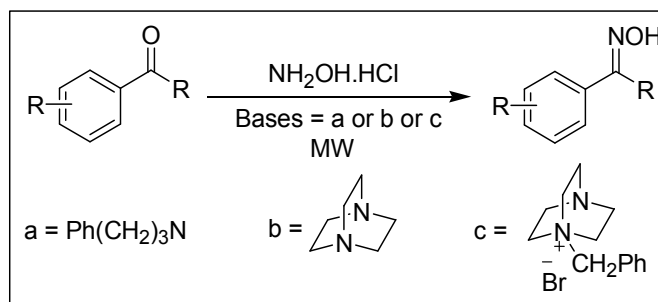


Scheme.III.A.17. Synthesis of oximes from carbonyl compounds in the presence of sodium hydroxide as base

Ashim Jyoti Thakur et al.⁷² recently reported the solvent-free conversion of carbonyl compounds into corresponding oximes by simply grinding the reactants in the presence of Bi_2O_3 (**scheme.III.A.18.**). A. R. Hajipour et al.⁷³ reported the chemoselective method for the preparation of aldoximes using microwave irradiation in the presence of tribenzylamine or 1, 4-diazabicyclo[2.2.2]octane or 1-benzyl-4-aza-1-azoniabicyclo[2.2.2]octane bromide as bases (**scheme.III.A.19.**).



Scheme.III.A.18. Conversion of carbonyls into oximes in presence of Bi_2O_3



Scheme.III.A.19. Synthesis of oximes from carbonyls under microwave irradiation

III.A.7. Conclusion

As oxime derivatives have enormous applications in the area of pharmaceutical as well as organic transformation. The substantial amount of methodologies for the oxime preparation from different functionality and under different catalytic conditions is reported in the literature. Most of the reported methodologies are not straight-forward, green and selective. Therefore, based on the above literature, it appeared that there is still a demand of green, selective, and easy reaction protocol for the synthesis of oxime derivatives.

III.A.8. References

1. Choi, S-J.; Lee, J-E.; Jeong, S-Y.; Im, I.; Lee, S-D.; Lee, E-J.; Lee, S. K.; Kwon, S-M.; Ahn, S-G.; Yoon, J-H.; Han, S-Y.; Kim, J-I.; Kim, Y-C. *J. Med. Chem.* **2010**, *53*, 3696.
2. Parthiban, P.; Kabilan, S.; Ramkumar, V.; Jeong, Y. T. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6452.
3. Colak, A.; Terzi, Ü.; Col, M.; Karaoglu, Ş. A.; Karaböcek, S.; Küçükdumlu, A.; Ayaz, F. A. *Eur. J. Med. Chem.* **2010**, *45*, 5169.
4. White, A. W. Carpenter, N.; Lottin, J. R. P.; McClelland, R. A.; Nicholson, R. I. *Eur. J. Med. Chem.* **2012**, *56*, 246.
5. Wang, R.; Zhang, X.; Song, H.; Zhou, S.; Li, S. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 4304.
6. Furuya, Y.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2005**, *127*, 11240.
7. Gui, J.; Wang, Y.; Tian, H.; Gao, Y.; Tian, W. *Tetrahedron Lett.* **2014**, *55*, 4233.
8. Narahari, S. R.; Reguri, B. R.; Mukkanti, K. *Tetrahedron Lett.* **2011**, *52*, 4888.
9. Hashimoto, M.; Obora, Y.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2008**, *73*, 2894.
10. Ramalingan, C.; Park, Y-T. *J. Org. Chem.* **2007**, *72*, 4536.
11. Owston, N. A.; Parker, A. J.; Williams, J. M. *J. Org. Lett.* **2007**, *9*, 3599.
12. Corey, E. J.; Hopkins, P. B.; Kim, S.; Yoo, S.; Nambiar, K.P.; Falk, J.R. *J. Am. Chem. Soc.* **1979**, *101*, 7131.
13. Barton, D. H. R.; Beaton, J. M.; Geller, L. E.; Pechet, M. M. *J. Am. Chem. Soc.* **1961**, *83*, 4076.
14. Kabalka, G. W.; Pace, R. D.; Wadgaonkar, P. P. *Synth. Commun.* **1990**, *20*, 2453.
15. Bendale, P. M.; Khadilkar, B. M. *Tetrahedron Lett.* **1998**, *39*, 5867.
16. Yang, Y.; Zhang, D.; Wu, L-Z.; Chen, B.; Zhang, L-P.; Tung, C-H. *J. Org. Chem.* **2004**, *69*, 4788.
17. Kim, B. R.; Lee, H-G.; Kim, E. J.; Lee, S-G.; Yoon, Y-J. *J. Org. Chem.* **2010**, *75*, 484.
18. Hakimi, M.; Feizi, N.; Hassani, H.; Vahedi, H.; Thomas, P. S. *Synth. Commun.* **2010**, *40*, 725.
19. Reddy, M. S.; Narender, M.; Rao, K. R. *Synth. Commun.* **2004**, *34*, 3875.

20. Hosseinzadeh, R.; Tajbakhsh, M.; Niaki, M. Y. *Tetrahedron Lett.* **2002**, *43*, 9413.
21. Zhou, X-T.; Yuan, Q-L.; Ji, H-B. *Tetrahedron Lett.* **2010**, *51*, 613.
22. Abiraj, K.; Gowda, D. C. *Synth. Commun.* **2004**, *34*, 599.
23. Demir, A. S.; Tanyeli, C.; Şeşnoğlu, O.; Demic, Ş. *Tetrahedron Lett.* **2007**, *37*, 407.
24. Abiraj, K.; Gowda, D. C. *J. Chem. Res.* **2003**, *6*, 332.
25. Zeynizadeh, B.; Zahmatkesh, K. *J. Chin. Chem. Soc.* **2005**, *52*, 109.
26. Rao, H. S. P.; Bharathi, B. *Ind. J. Chem.* **2002**, *41B*, 1072.
27. Kouhkan, M.; Zeynizadeh, B. *Bull. Korean Chem. Soc.* **2011**, *32*, 3323.
28. Minakata, S.; Okumura, S.; Nagamachi, T.; Takeda, Y. *Org. Lett.* **2011**, *13*, 2966.
29. Katritzky, A. R.; Wang, Z.; Hall, C. D.; Akhmedov, N. G.; Shestopalov, A. A.; Steel, P. J. *J. Org. Chem.* **2003**, *68*, 9093.
30. Udd, S.; Jokela, R.; Franzén, R.; Tois, J. *Tetrahedron Lett.* **2010**, *51*, 1030.
31. Kornhaas, C.; Li, J.; Ackermann, L. *J. Org. Chem.* **2012**, *77*, 9190.
32. Jackowski, O.; Lecourt, T.; Micouin, L. *Org. Lett.* **2011**, *13*, 5664.
33. Mo, D-L.; Wink, D. A.; Anderson, L. L. *Org. Lett.* **2012**, *14*, 5180.
34. Shi, Z.; Koester, D. C.; Bouladakis-Arapinis, M.; Glorius, F. *J. Am. Chem. Soc.* **2013**, *135*, 12204.
35. Xekoukoulotakis, N. P.; Hadjiantoniou-Maroulis, C. P.; Maroulis, A. J. *Tetrahedron Lett.* **2000**, *41*, 10299.
36. Parthasarathy, K.; Cheng, C-H. *J. Org. Chem.* **2009**, *74*, 9359.
37. Mahernia, S.; Adib, M.; Mahdavi, M.; Nosrati, M. *Tetrahedron Lett.* **2014**, *55*, 3844.
38. Savarin, C. G.; Grisé, C.; Murry, J. A.; Reamer, R. A.; Hughes, D. L. *Org. Lett.* **2007**, *9*, 981.
39. Patil, U. B.; Kumthekar, K. R.; Nagarkar, J. M. *Tetrahedron Lett.* **2012**, *53*, 3706.
40. Bode, J. W.; Hachisu, Y.; Matsuura, T.; Suzuki, K. *Org. Lett.* **2003**, *5*, 391.
41. Richard B. Sparks, Andrew P. Combs. *Org. Lett.* **2004**, *6*, 2473.
42. Counciller, C. M.; Eichman, C. C.; Wray, B. C.; Stambuli, J. P. *Org. Lett.* **2008**, *10*, 1021.

43. Chibiryaev, A. M.; Kimpeb, N. D.; Tkachev, A. V. *Tetrahedron Lett.* **2000**, *41*, 8011.
44. (a) Rossello, A.; Bertini, S.; Lapucci, A.; Macchia, M.; Martinelli, A.; Rapposelli, S.; Herreros, E.; Macchia, B. *J. Med. Chem.* **2002**, *45*, 4903; (b) Park, H. J.; Lee, K.; Park, S. J.; Ahn, B.; Lee, J. C.; Cho, H. Y.; Lee, K. I. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3307; (c) Ramalingan, C.; Park, Y. T.; Kabilan, S. *Eur. J. Med. Chem.* **2006**, *41*, 683.
45. Sun, R. F.; Lü, M. Y.; Chen, L.; Li, Q. S.; Song, H. B.; Bi, F. C.; Huang, R. Q.; Wang, Q. M. *J. Agric. Food Chem.* **2008**, *56*, 11376.
46. Bhuniya, D.; Mohan, S.; Narayanan, S. *Synthesis*, **2003**, 1018.
47. Rad, M. N. S.; Khalafi-Nezhad, A. A.; Karimitabar, F.; Behrouz, S. *Synthesis*, **2010**, 1724.
48. Dai, H.; Yu, H-B.; Liu, J-B.; Li, Y-Q.; Qin, X.; Zhang, X.; Qin, Z-F.; Wang, T-T.; Fang, J-X. *ARKIVOC.* **2009**, 126.
49. Miyabe, H.; Yoshida, K.; Reddy, V. K.; Matsumura, A.; Takemoto, Y. *J. Org. Chem.* **2005**, *70*, 5630.
50. Alonso, D. A.; Nájera, C.; Pacheco, M. C. *Tetrahedron Lett.* **2002**, *43*, 9365.
51. Alacid, E.; Nájera, C. *Org. Lett.* **2008**, *10*, 5011.
52. Botella, L.; Nájera, C. *Tetrahedron Lett.* **2004**, *45*, 1833.
53. Susanto, W.; Chu, C-Y.; Ang, W. J.; Chou, T-C.; Lo, L-C.; Lam, Y. *J. Org. Chem.* **2012**, *77*, 2729.
54. Wanga, X-R.; Lu, F-H.; Song, Y.; Lu, Z-L. *Tetrahedron Lett.* **2012**, *53*, 589.
55. Czekelius, C.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 612.
56. Walvoord, R. R.; Berritt, S.; Kozlowski, M. C. *Org. Lett.* **2012**, *14*, 4086.
57. Ray, R.; Chowdhury, A. D.; Maiti, D.; Lahiri, G. K. *Dalton Trans.* **2014**, *43*, 38.
58. Corma, A.; Serna, P.; Garcia, H. *J. Am. Chem. Soc.* **2007**, *129*, 6358.
59. Crandall, J. K.; Reix, T. *J. Org. Chem.* **1992**, *57*, 6759.
60. Joseph, R.; Ravindranathan, T.; Sudalai, A. *Tetrahedron Lett.* **1995**, *36*, 1903.
61. J Reddy, S.; Jacobs, P. A. *Perkin Trans. I.* **1993**, 2665.
62. Kidwai, M.; Bhardwaj, S. *Synth. Commun.* **2011**, *41*, 2655.
63. Suzuki, K.; Watanabe, T.; Murahashi, S-I. *J. Org. Chem.* **2013**, *78*, 2301.
64. Aghapour, G.; Mohamadian, S. *Bull. Korean Chem. Soc.* **2012**, *33*, 1209.
65. Gao, X.; Zhang, F.; Deng, G.; Yang, L. *Org. Lett.* **2014**, *16*, 3664.

66. Chandrappa, S.; Umashankara, M.; Vinaya, K.; Kumar, C. S. A.; Rangappa, K. *S. Tetrahedron Lett.* **2012**, *53*, 2632.
67. Hajipour, A. R.; Mohammadpoor-Baltork, I.; Nikbaghat, K.; Imanzadeh, G. *Synth. Commun.* 1999, *29*, 1697.
68. Kad, G. L.; Bhandari, M.; Kaur, J.; Rathee, R.; Singh, J. *Green Chem.* **2001**, *3*, 275.
69. Guo, J-J.; Jin, T-S.; Zhang, S-L.; Li, T-S. *Green Chem.* **2001**, *3*, 193.
70. Ren, R. X.; Ou, W. *Tetrahedron Lett.* **2001**, *42*, 8445.
71. Damljanović, I.; Vukićević, M.; Vukićević, R. D. *Monatshefte für Chemie.* **2006**, *137*, 301.
72. Saikia, L.; Baruah, J. M.; Thakur, A. J. *Org. Med. Chem. Lett.* **2011**, *1:12*, 1.
73. Hajipour, A. R.; Rafieea, F.; Ruoho, A. E. *J. Iran. Chem. Soc.* **2010**, *7*, 114.

CHAPTER III

SECTION-B

Solid phase synthesis of oxime derivatives

III.B. Present Investigation

III.B.1. Background of the present investigation

Oximes are highly valuable organic molecules considering their numerous applications for polymers,¹ fungicides,² biochemicals,³ fragrances.⁴ Oximation is very efficient method for characterization and purification of carbonyl compounds. The manufacture of cyclohexanone oxime represents a key step in the sequence of the Nylon 6 production. Synthesis of oximes is considered as an important reaction in organic chemistry because these compounds not only represent a series of useful derivatives of carbonyl compounds but also considered as a versatile organic intermediate for the synthesis of wide range of heterocyclic compounds such as quinoxaline,⁵ imidazole,⁶ oxadiazole,⁷ oxazole,⁸ oxazoline.⁹ Besides these, oximes are used for the ample of functional group transformation which comprises conversions into nitriles,¹⁰ nitro compounds,¹¹ nitrones,¹² amines.¹³ Oximes act as a versatile ligand for several metal catalyzed organic synthesis.¹⁴

Oximes play an important role as ligands for transition metals. Oxime based palladacycles have gained a special attention in modern organic synthesis due to their ubiquitous use in variety of catalytic transformations. Catalytic C–C or C–heteroatom coupling reactions are usually carried out in the presence of aryl palladium complexes with nucleophiles such as oxime palladacycle derived from 4, 4'-dichlorobenzophenone catalyzed Sonogashira reaction,¹⁵ oxime-derived palladacycle catalyzed cross-coupling reaction of potassium aryltrifluoroborates with aryl and heteroaryl chlorides,¹⁶ *p*-hydroxyacetophenone oxime-derived palladacycle catalyzed Heck coupling reaction,¹⁷ fluorinated oxime palladacycle catalyzed cross-coupling reaction (Suzuki-Miyaura, Sonogashira, Stille, Heck and Kumada),¹⁸ oxime-derived palladacycles with pyridine co-ligand catalyzed intra-molecular Pauson–Khand reaction.¹⁹

Classically, oximes were prepared by refluxing an alcoholic solution of a carbonyl compound with hydroxylamine hydrochloride and pyridine. The method has multiple

drawbacks such as low yields, long reaction time, toxicity of pyridine, and effluent pollution caused by the use of organic solvent.

In recent years, solvent free reactions have drawn considerable interest and popularity²⁰ not only from the environmental aspect but also for the synthetic advantages in terms of yield, selectivity and simplicity of the reaction procedure. Several procedures for the preparation of oximes exist, but, most of them have not addressed the green chemistry issue. They are associated with generation of pollutants, requirement of high reaction temperature, low yields, and waste of metal salts in the environment. Over the last decades, several protocols have been developed for the synthesis of oximes from carbonyl compounds. A. R.Hajipour et al.²¹ reported the solid phase synthesis of oximes from carbonyl compounds and hydroxylamine hydrochloride in the presence of sodium hydroxide. The use of strong base has reduced its application as a green and selective protocol. The a number of reagent and catalyst have been used for the transformation of carbonyl compounds into oximes such as preparation of oximes from aldehydes or ketones and hydroxylamine hydrochloride impregnated wet alumina under microwave irradiation,²²

TiO₂/SO₄²⁻ solid superacid catalyzed synthesis of aromatic aldoximes and ketoximes under solvent free condition,²³ preparation of cyclic ketoximes using aqueous hydroxylamine in ionic liquids (bmiBF₄),²⁴ solvent free synthesis of alicyclic, aliphatic carbonyl compounds and aromatic aldehydes into the corresponding oximes by grinding the carbonyl compounds, hydroxylamine hydrochloride and sodium hydroxide,²⁵ synthesis of oximes from carbonyl compounds in the presence of Bi₂O₃ by simple grinding the reactants,²⁶ synthesis of aldoximes under microwave irradiation using *in situ* generated ionic liquids.²⁷

Synthesis of oximes provides not only reaction intermediates but also the preparation of carbonyl compounds from non carbonyl compounds. There is substantial report in literature of the synthesis of oximes from non carbonyl compounds such as reduction of nitro alkane to oximes in the presence of benzyl bromide, KOH, and *n*Bu₄NI in THF at room temperature,²⁸ palladium catalyzed cross-coupling reaction of aryl halides and nitromethane under Nef conditions,²⁹ oxidation of aliphatic and aromatic amines into corresponding oximes using heterogenous nanocrystalline titanium (IV) oxide as catalyst and H₂O₂ as oxidising agent,³⁰ synthesis from primary and secondary benzyl

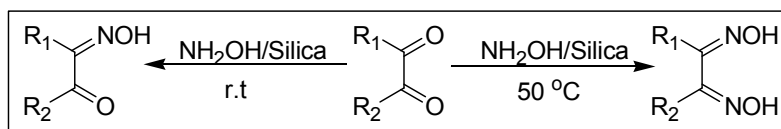
alcohol in the presence of hydroxylamine hydrochloride and catalytic amount of 2, 3-dichloro-5, 6-dicyanobenzoquinone (DDQ) under solvent free condition.³¹

Such a huge application of oximes and also the associated drawback of traditional method of its preparation such as no selectivity, use of hazardous chemicals, high cost, poor chemical yields, requirements of long reaction time and tedious work-up procedures, has limit their use under the aspect of chemical selectivity as well as environmentally benign process. Reports are still scanty towards the development of a simple, selective and greener protocol for the preparation of such an important class of derivatives.

Sustainable development can be defined as the ability to meet the needs of the current generation while preserving the ability of future generations to meet their needs. Green chemistry is one way to achieve it. Several ways are known through which a reaction can be said to be clean and green. There is a need for a process that involves multiple chemical transformations in a single-pot with minimal work up and less waste generation.

In recent years, silica gel have attracted intensive interest for their being a possible replacement of traditional solvents for organic synthesis, particularly in the area of green chemistry, due to their advantageous properties, including non toxic medium for organic reactions, high thermal and chemical stability. Hence, there is a demand for developing an efficient, convenient, and non-polluting or less polluting alternative method for the preparation of oximes. So, the development of easy and clean procedures for obtaining this oxime results in high interest.

It was therefore felt necessary to develop selective, easy, safe and green procedure for oxime synthesis. In view of the above and in continuation our studies towards the development of greener methodology for organic transformation,³² In this chapter, we have reported a very simple, highly selective and green protocol for oxime preparation from carbonyl compounds. The beauty of the protocol has been its selectivity that can be applied either for exclusively monoxime or dioxime preparation from symmetrical 1, 2 dicarbonyl system or from 1, 2 unsymmetrical dicarbonyl systems by regioselective pathway (**scheme.III.B.1**).



Scheme.III.B.1. Selective synthesis of mono and dioxime from 1, 2 dicarbonyl compounds

III.B.2. Results and discussion

To cope up with the growing demand towards the development of greener protocols for organic transformation, our laboratory has devoted a significant effort to develop efficient protocols for the preparation of a diverse collection of organic derivatives from common intermediates following simple and greener methodologies. The present investigation has developed a clean and selective method for the synthesis of oxime derivatives from a wide variety of carbonyl compounds.

A model study with benzil on silica – $\text{NH}_2\text{OH}\cdot\text{HCl}$ at room temperature (*vide infra*) gave an excellent yield of the monoxime and at elevated temperature gave excellent yield of dioxime. Since no selective protocol is being reported so far either for exclusive formation of monoxime or dioxime from a 1, 2 dicarbonyl compounds, a change in reaction temperature and in the molar proportion of the reactants (**table.III.B.1**) induces selectivity in the protocol towards monoxime and/or dioxime formation from 1, 2 dicarbonyl system. For example, benzil and hydroxyl amine hydrochloride in the mol ratio of 1:1.2 afforded only the monoxime (97%), at room temperature and 1:2.2 mol ratio of the same combination yielded exclusively the dioxime at 50 °C (**entries 1-2, table.III.B.1**). Similar result was also obtained with phenyl glyoxal (**entry 3-4, table.III.B.1**) as a dicarbonyl compounds. Among the two different carbonyl groups in phenyl glyoxal only aldehyde function takes part in the formation of monoxime following regioselective pathway.

Table.III.B.1

Selective synthesis of mono and dioxime from 1, 2 dicarbonyl system

Entry	R ₁	R ₂	Mol ratio ^a	Temp (°C)	Time (h)	Yield (%) ^b	
						Monoxime	Dioxime
1	Ph	Ph	1:1.2	r.t	6	97	nil
2	Ph	Ph	1:2.2	50	5	nil	95
3	H	Ph	1:1.2	r.t	3	97	nil
4	H	Ph	1:2.2	50	4.3	nil	96

^aMol ratio of 1, 2 dicarbonyl and hydroxyl amine.^bIsolated yield.

Several experiments were then carried out with a wide variety of aromatic monocarbonyl compounds to explore the potential of the newly developed method as a general protocol for synthesis of oximes (**scheme.III.B.2.**) (**table.III.B.2.**). In deciding the best reaction condition for the above transformation, aromatic aldehydes having electron withdrawing (**entries 1-4, table.III.B.2.**) as well as electron donating group (**entries 5-9, table.III.B.2.**) were tried in comparison to the unsubstituted substrate (**entry 10, table.III.B.2.**) in the above protocol and the transformation was found independent on the nature of substituent (**scheme.III.B.2.**). The study also indicated that aromatic carbonyl compounds with electron withdrawing substituents mostly at *ortho*- or *para*- position gave best results at room temperature and those having electron releasing substituents needed a higher temperature (50 °C) to yield the maximum product (**entries 7, 8, 9, 11, 12, table.III.B.2.**).

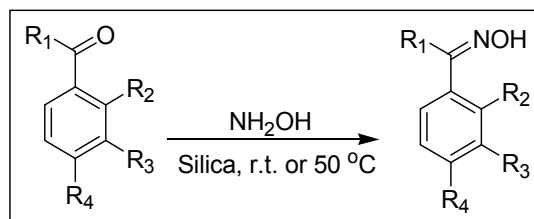
**Scheme.III.B.2.** Synthesis of oxime from aromatic monocarbonyl compounds

Table.III.B.2.

Synthesis of oxime from aromatic monocarbonyl system

Entry	R ₁	R ₂	R ₃	R ₄	Time (h)	Temp (°C)	Yield (%) ^b
1	H	NO ₂	H	H	1.2	r.t	94
						50	96
2	H	H	NO ₂	H	3	r.t	91
						50	97
3	H	H	H	NO ₂	1.2	r.t	95
						50	98
4	H	H	H	F	4	r.t	94
						50	98
5	H	OH	H	H	5	r.t	90
						50	92
6	H	H	H	OH	5	r.t	91
						50	92
7	H	OH	OMe	H	6.3	r.t	18
						50	86
8	H	H	OMe	OH	6	r.t	24
						50	89
9	H	H	H	NMe ₂	5	r.t	28
						50	84
10	H	H	H	H	5	r.t	92
						50	93
11	Me	H	H	H	4.3	r.t	nil
						50	97
						r.t	nil

12	Ph	H	H	H	2.3	50	96
----	----	---	---	---	-----	----	----

In order to establish the general applicability, we applied this present procedure on alicyclic carbonyl compounds, cyclohexanone (**entry 1, table.III.B.3**). Although yields are comparatively less, large molecule like steroidal ketone also showed identical result (**entry 4 table.III.B.3**).

However, alicyclic 1, 2 and 1, 3 dicarbonyl (**entry 2 and 3, table.III.B.3**) does not show the selectivity rather they only form the dioxime at room temperature as well as at elevated temperature.

Table.III.B.3

Synthesis of alicyclic and steroidal oximes

Entry	Carbonyls	Temp (°C)	Time (h)	Yield (%) ^b	
				Monoxime	Dioxime
1	Cyclohexanone	r.t	3	95	Nil
		50	4	97	Nil
2	Cyclohexa-1,2 dione	r.t	3	Nil	72
		50	3	Nil	94
3	Dimedone	r.t	3	Nil	62
		50	4	Nil	91
4	16-DPA	r.t	8	18	Nil
		50	6	42	Nil

III.B.3. Experimental

III.B.3.1. Chemicals

All the chemicals which were used for the present investigation are listed in the **table.III.B.4**. The details of the chemicals regarding their source and purity are summarised in **table.III.B.4**.

Table.III.B.4.
Chemicals used for the present investigation

Entry	Chemical	Source	Purity (%)
1	Benzil	SRL	98
2	Phenyl glyoxal	Sigma-Aldrich	97
3	2-Nitrobenzaldehyde	LOBA Chemie	>99
4	3-Nitrobenzaldehyde	LOBA Chemie	98
5	4-Nitrobenzaldehyde	LOBA Chemie	99
6	4-Fluorobenzaldehyde	Fisher Scientific	>98
7	2-Hydroxybenzaldehyde	S.D Fine	99
8	4-Hydroxybenzaldehyde	S.D Fine	98
9	2-Hydroxy-3-methoxybenzaldehyde	ACROS	99
10	3-Methoxy-4-hydroxybenzaldehyde	S.D Fine	99
11	N,N-dimethyl-4-aminobenzaldehyde	Sigma-Aldrich	99
12	Benzaldehyde	Sigma-Aldrich	>99.5
13	Acetophenone	SRL	99.5
14	Benzophenone	SRL	99
15	Cyclohexanone	Alfa Aesar	>99
16	Cyclohexane-1, 2-dione	Sigma-Aldrich	97
17	Cyclohexane-1, 3-dione	Alfa Aesar	98
18	16-Dehydropregnenolone	-	-
19	Hydroxylamine hydrochloride	Fisher Scientific	96
20	Sodium sulphate anhydrous	SRL	99.5
21	Petroleum ether	Thomas Baker	98
22	Ethyl acetate	Thomas Baker	99
23	Diethyl ether	SRL	99.5

24	Silica gel 60-120 mesh	SRL	-
25	Silica gel for TLC	SRL	-
26	Potassium bromide for IR	Merck	99
27	CDCl ₃ for NMR	ACROS	99.8
28	DMSO-d ₆ for NMR	SRL	99.8

Entry 18 was prepared in the laboratory by reported protocol; the protocol is given in chapter II experimental.

III.B.3.2. Reaction procedure and purification

2g/mol silica gel (60-120 mesh) was taken on motor, mixed finely with carbonyl compound, add 1.2 mol of hydroxylamine hydrochloride for monoxime and 2.2 mol for dioxime and then mixed thoroughly with pestle. The reaction mixture was then allowed to stir at room temperature or at 50 °C as the case may be on a magnetic stirrer using oil bath. The completion of reaction was monitored by TLC. The product was extracted with ether, washed with water (30ml x 3), dried over anhydrous Na₂SO₄ and purified by column chromatography using neutral active alumina.

III.B.3.3. Spectroscopic measurements

IR spectra were recorded on KBr disks and nujol in the range 4000-400 on Perkin Elmer FT IR spectrometer. ¹H NMR were recorded on 300 MHz and ¹³C NMR were recorded on 75 MHz Bruker Avance FT NMR spectrometer using TMS as internal standard.

III.B.4. Conclusion

In conclusion, we have developed a highly selective, green, mild and highly efficient protocol for the synthesis of oximes from 1, 2 dicarbonyl compounds and wide varieties of aldehydes and ketones.

III.B.5. Spectroscopic data

The compounds were characterized by IR, ¹H NMR, ¹³C NMR and comparing the melting point with authentic samples (**table.III.B.4**).

III.B.5.1. Benzil monoxime

IR (cm⁻¹, KBr): 3238, 1674, 1593. ¹H NMR (300 MHz, CDCl₃): δ, 7.24-7.64 (m, 8H), 7.96-7.99 (m, 2H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ, 126.4, 128.2, 128.4, 128.9, 129.1, 129.4, 130.3, 130.5, 130.9, 134.6, 157.1, 194.2 ppm.

III.B.5.2. Benzil dioxime

IR (cm⁻¹, KBr): 3180, 1649, 1498. ¹H NMR (300 MHz, DMSO-d₆): δ, 7.36-7.38 (m, 6H), 7.48-7.49(m, 4H), 11.49 (s, 2H) ppm. ¹³C NMR (75 MHz, DMSO-d₆): δ, 125.9, 129.1, 129.7, 133.2, 151.1 ppm.

III.B.5.3. Phenylglyoxal monoxime

IR (cm⁻¹, KBr): 3419, 1701, 1651, 1598. ¹H NMR (300 MHz, DMSO-d₆): δ, 7.49-7.54 (m, 1H), 7.61-7.67 (m, 1H), 7.14-7.98 (m, 2H), 8.03 (s, 1H), 12.70 (s, 1H) ppm. ¹H NMR (75 MHz, DMSO-d₆): δ, 128.8, 130.0, 133.6, 136.5, 148.2, 189.5 ppm.

III.B.5.4. Phenylglyoxal dioxime

IR (cm⁻¹, KBr): 3421, 1618, 1511. ¹H NMR (300 MHz, DMSO-d₆): δ, 6.31 (s, 1H), 7.46-7.51 (m, 3H), 7.81-7.89 (m, 3H), 9.14 (s, 1H) ppm. ¹³C NMR (75 MHz, DMSO-d₆): δ, 128.4, 129.2, 131.4, 134.5, 147.3, 151.6 ppm.

III.B.5.5. 2-Nitro benzaldoxime

IR (cm⁻¹, KBr): 3390, 1662 1522. ¹H NMR (300 MHz, CDCl₃): δ, 7.52-7.55 (m, 1H), 7.63-7.64 (m, 1H), 7.91-7.92 (m, 1H), 8.91 (s, 1H), 8.11-8.19 (m, 1H), 8.28 (s, 1H) ppm.

III.B.5.6. 4-Nitro benzaldoxime

IR (cm⁻¹, KBr): 3396, 1667. ¹H NMR (300 MHz, DMSO-d₆): δ, 7.83-7.87 (m, 2H), 8.23-8.30 (m, 3H), 11.97 (s, 1H), ppm. ¹³C NMR (75 MHz, DMSO-d₆): δ, 123.9, 127.3, 139.4, 146.7, 147.4 ppm.

III.B.5.7. 4-Fluoro benzaldoxime

IR (cm⁻¹, KBr): 3262, 1512, 1321. ¹H NMR (300 MHz, CDCl₃): δ, 7.11-7.24 (m, 2H), 7.52-7.61 (m, 2H), 8.13 (s, 1H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ, 115.7, 116.1, 128.6, 128.7, 149.1, 162.3, 165 ppm.

III.B.5.8. 2-Hydroxy benzaldoxime

IR (cm⁻¹, KBr): 3336, 1656, 1523. ¹H NMR (300 MHz, CDCl₃): δ, 6.90-6.98 (m, 2H), 7.16-7.31 (m, 2H), 7.92 (s, 1H), 8.22 (s, 1H), 10.01 (s, 1H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ, 116.4, 116.6, 119.8, 130.7, 131.3, 152.9, 157 ppm.

III.B.5.9. 2-Hydroxy-3-methoxybenzaldoxime

¹H NMR (300MHz, CDCl₃): δ, 3.92 (s, 3H), 6.81-6.94 (m, 3H), 8.96 (s, 1H), 8.24 (s, 1H), 9.98 (s, 1H) ppm. ¹³C NMR (75MHz, CDCl₃): δ, 56.1, 113.2, 116.6, 119.5, 122.2, 146.8, 148, 152.5 ppm.

III.B.5.10. 4-Hydroxy-3-methoxy benzaldoxime

¹H NMR (300 MHz, DMSO-d₆): δ, 3.72 (s, 3H), 6.68 (d, 1H, J=8.1 Hz), 6.89 (m, 1H), 7.12 (d, 1H, J=2 Hz), 7.88 (s, 1H) ppm. ¹³C NMR (75 MHz, DMSO-d₆): δ, 55.6, 108.2, 115.1, 120.3, 124.2, 147.6, 147.8, 148.1 ppm.

III.B.5.11. 4-*N,N*-Dimethylaminobenzaldoxime

IR (cm⁻¹, KBr): 3241, 3127, 2976, 1609, 1554. ¹H NMR (300 MHz, CDCl₃): δ, 2.96 (s, 6H), 6.71(d, 2H, J=8.8 Hz), 7.39 (d, 2H, J=8 Hz), 7.89 (s, 1H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ, 41, 112.1, 121.4, 127.8, 149, 151.4

III.B.5.12. Benzaldoxime

IR (cm⁻¹, KBr): 3355, 1656, 1436. ¹H NMR (300 MHz, CDCl₃): δ, 7.21-7.32 (m, 3H), 7.41-7.47 (m, 1H), 7.75-7.79(m, 1H), 8.11 (s, 1H), 8.31 (s, 1H), ppm. ¹³C NMR (75 MHz, CDCl₃): δ, 127, 128.8, 130.1, 131.8, 150.4.

III.B.5.13. Acetophenone oxime

IR (cm⁻¹, KBr): 3248, 1447, 1371. ¹H NMR (300 MHz, CDCl₃): δ, 2.31 (s, 3H), 7.20-7.48 (m, 3H), 7.51-7.82 (m, 2H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ, 12.3, 126.2, 128.5, 129.2, 136.5, 156.1 ppm.

III.B.5.14. Benzophenone oxime

IR (cm⁻¹, KBr): 3214, 1557, 1377. ¹H NMR (300 MHz, DMSO-d₆): δ, 7.08-7.13 (m, 1H), 7.32-7.38 (m, 2H), 7.50-7.62(m, 3H), 7.77-7.80 (m, 2H), 7.94-7.97 (m, 2H), 10.26 (s, 1H) ppm. ¹³C NMR (75 MHz, DMSO- d₆): δ, 120.8, 124.1, 128.1, 128.8, 129.0, 132, 135.4, 139.6, 166 ppm.

III.B.5.15. Cyclohexanone oxime

IR (cm⁻¹, KBr): 3291, 1665. ¹H NMR (300 MHz, CDCl₃): δ, 1.48-1.69 (m, 6H), 2.11 (d, 2H, *J*=8Hz), 2.29 (t, 2H, *J*=8 Hz), 6.51 (s, 1H), ppm. ¹³C NMR (75 MHz, CDCl₃): δ, 23.8, 24.3, 24.9, 27.5, 33.2, 158.2 ppm.

III.B.5.16

Some of the known oximes were characterized by comparing their melting point with authentic samples **table.III.B.5**.

Table.III.B.5.

Melting point comparison of known prepared oximes with authentic samples

Entry	Mp of prepared oxime (°C)	Mp of authentic sample (°C)
1	4-hydroxy benzaldoxime (83-86)	85
2	3-nitro benzaldoxime	123
3	Cyclohexane 1,2-dione-dioxime (190-193)	192
4	Dimedone-dioxime (172-175)	173
5	16-DPA oxime (222-225)	223-227

III.B.6. Supporting spectra

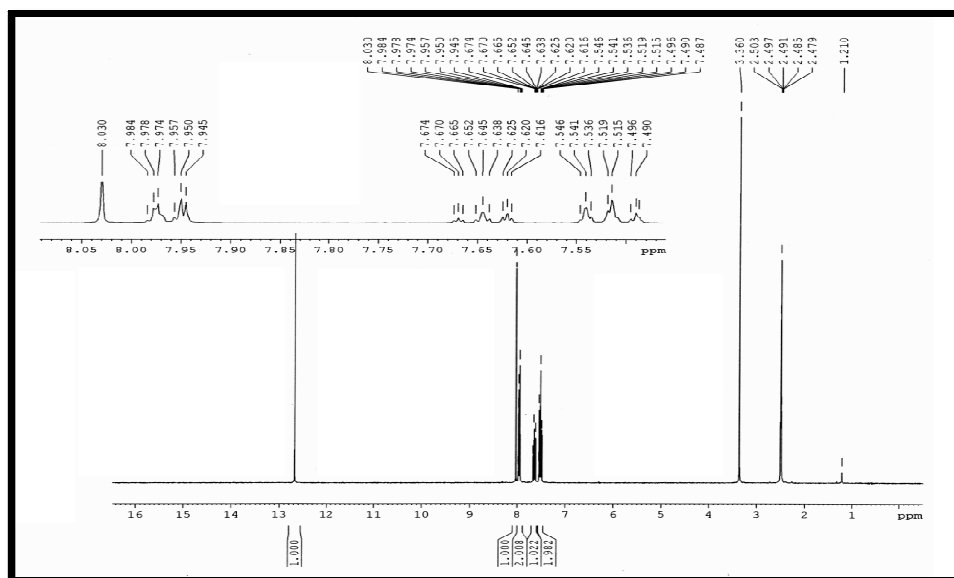


Fig.III.B.1. ^1H NMR spectrum of phenylglyoxal monoxime

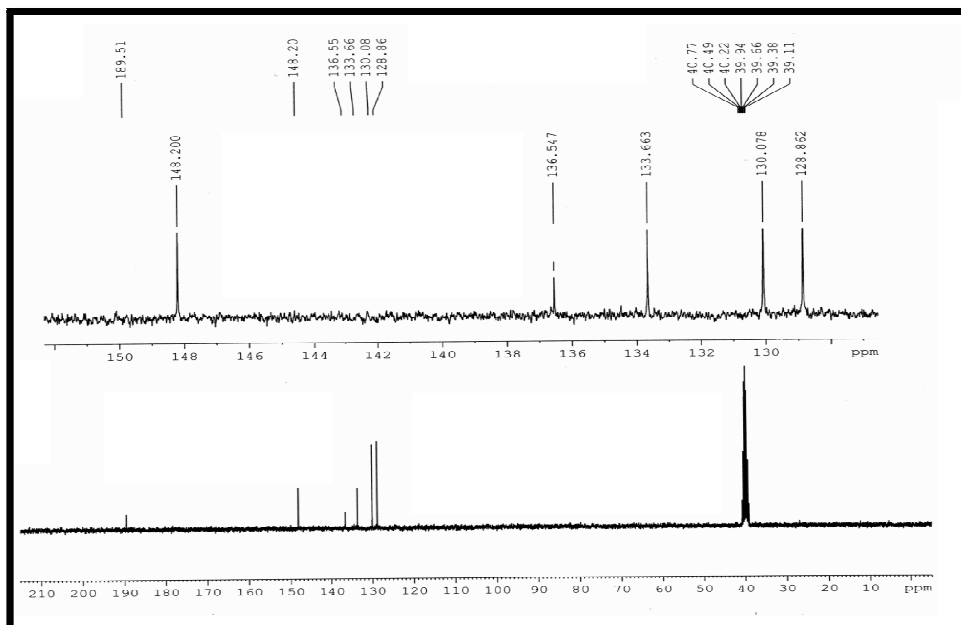


Fig.III.B.2. ^{13}C NMR spectrum of phenylglyoxal monoxime

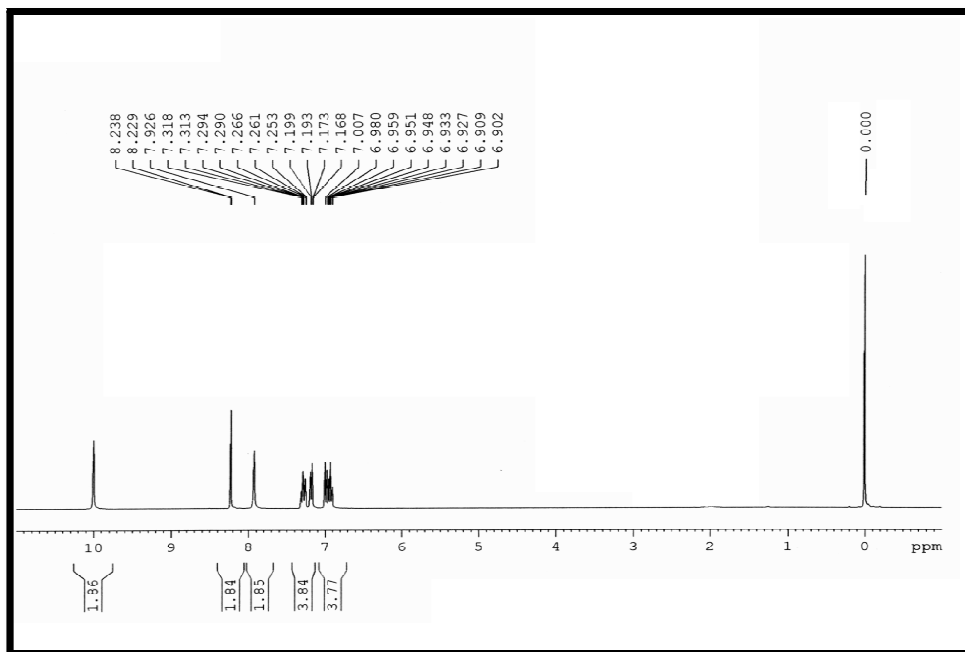


Fig.III.B.3. ^1H NMR spectrum of 2-Hydroxy benzaldoxime

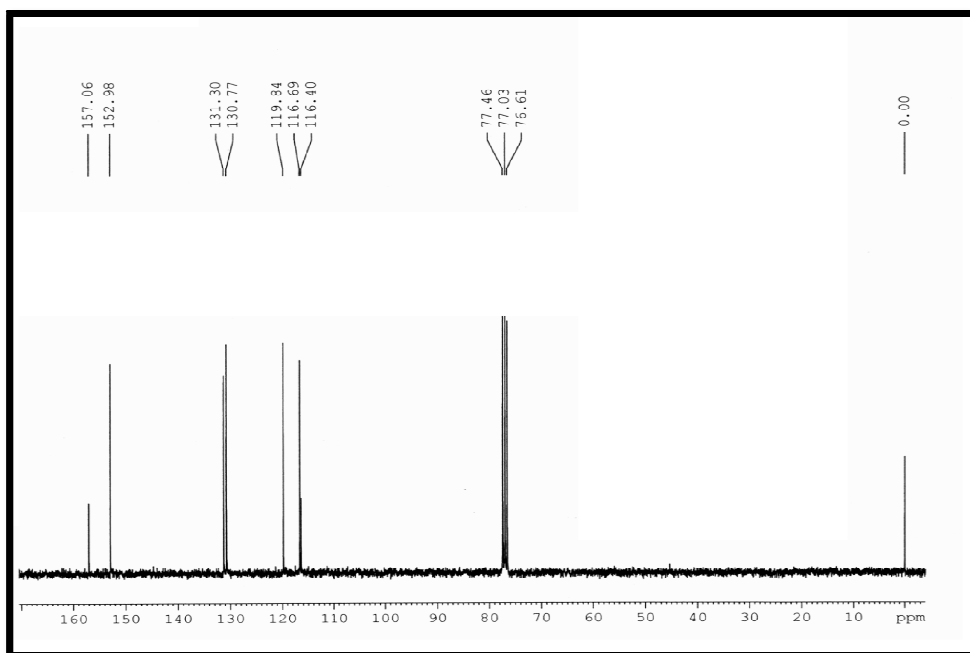


Fig.III.B.4. ^{13}C NMR spectrum of 2-Hydroxy benzaldoxime

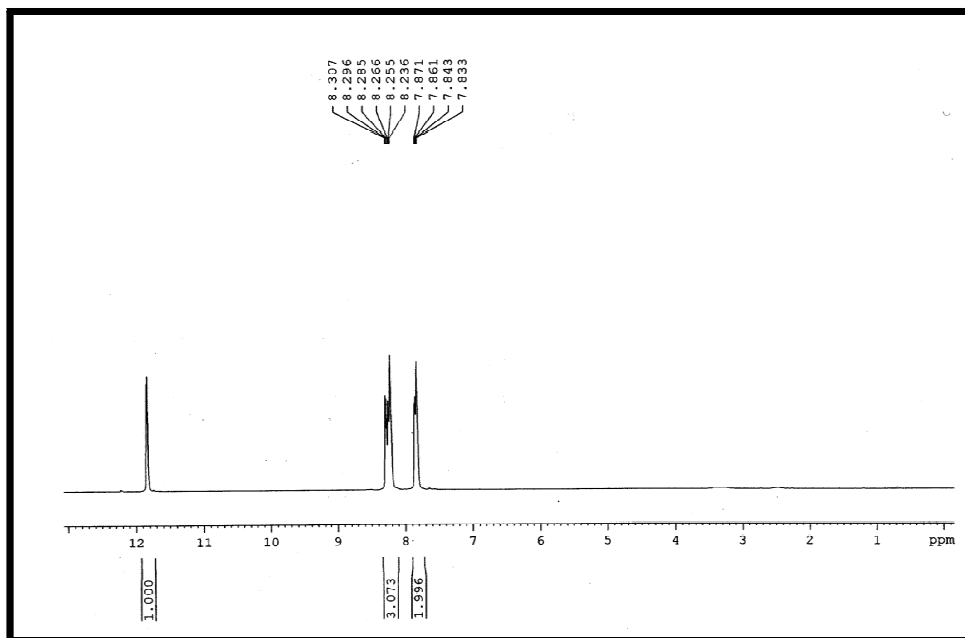


Fig.III.B.5. ^1H NMR spectrum of 4-Nitro benzaldoxime

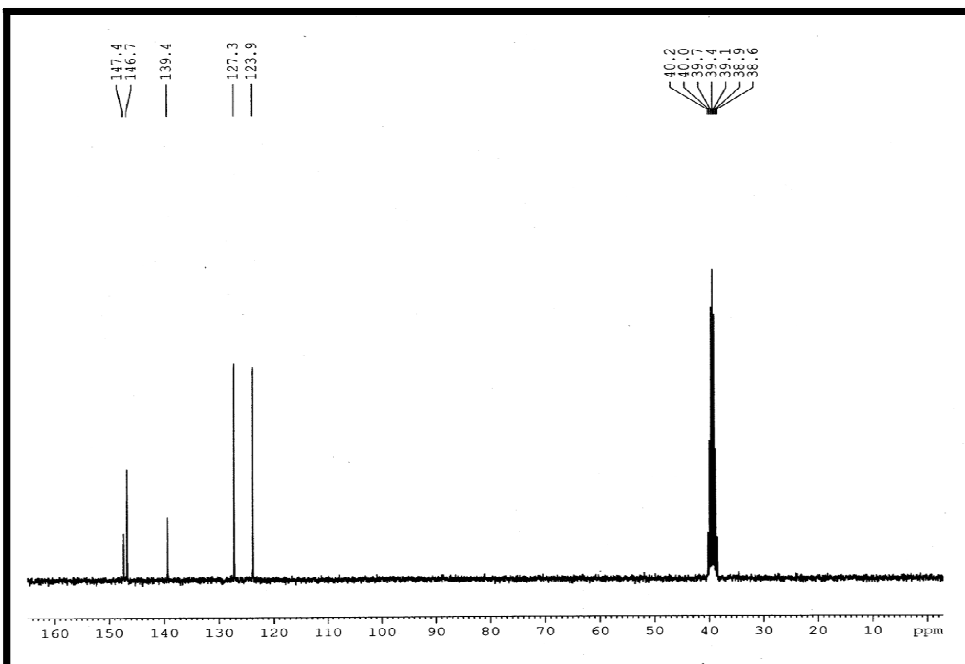


Fig.III.B.6. ^{13}C NMR spectrum of 4-Nitro benzaldoxime

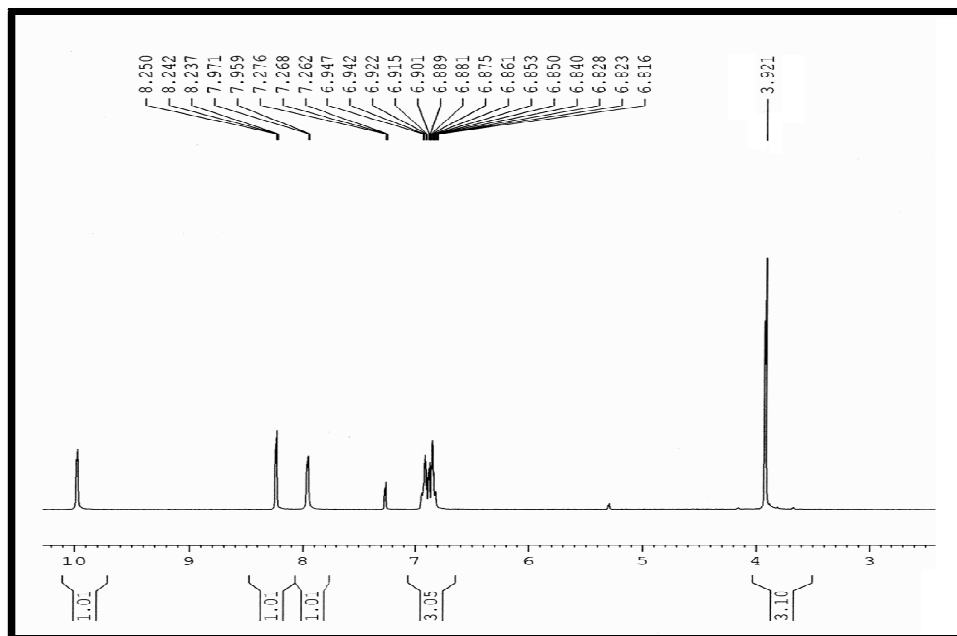


Fig.III.B.7. ^1H NMR of 2-Hydroxy-3-methoxy benzaldoxime

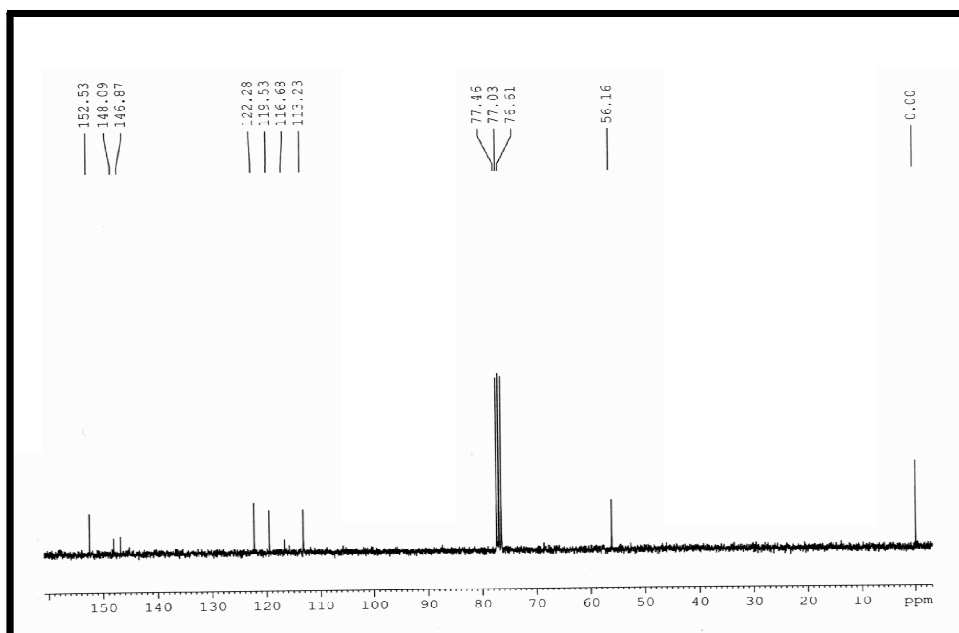


Fig.III.B.8. ^{13}C NMR of 2-Hydroxy-3-methoxy benzaldoxime

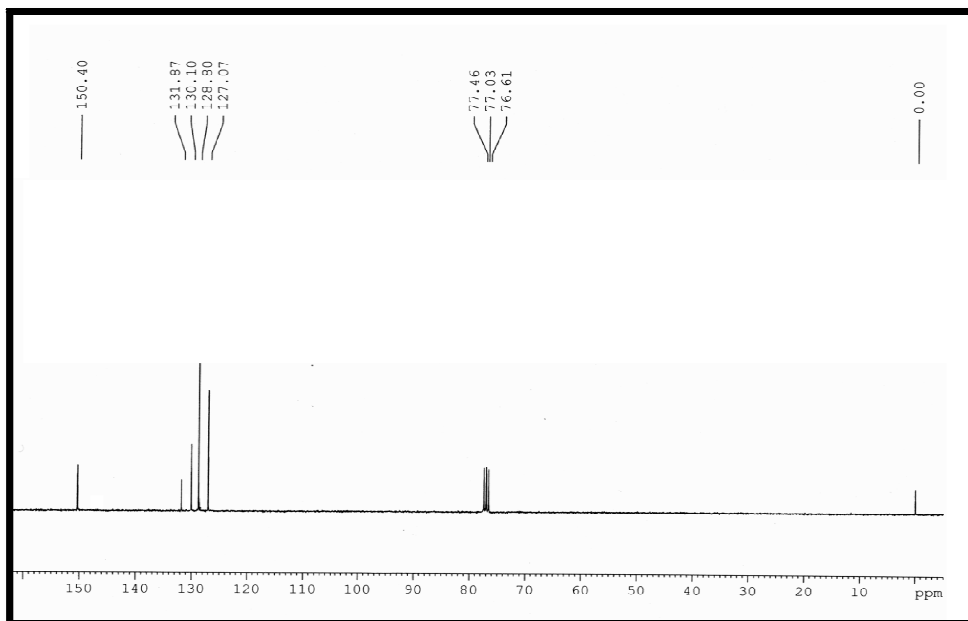


Fig.III.B.9. ^{13}C NMR of benzaldoxime

III.B.7. References

1. Mokaya, R.; Poliakoff, M. *Nature*. **2005**, *437*, 1243.
2. Fawcett, C. H. *Nature*. **1964**, *204*, 1200.
3. (a) Park, J.; Pei, D. *Biochemistry*. **2000**, *43*, 15014. (b) Gergely, A.; Gyimesi-Forrás, K.; Horvath, P.; Hosztafi, S.; Koekoesi, J.; Nagy, P. I.; Szasz, Gy.; Szentesi, A. *Curr. Med. Chem.* **2004**, *11*, 2555.
4. Fehr, C.; Delay, F. Firmenich & Cie. U.S. Patent US5521151, **1996**.
5. Ahmad, S.; Ali, M. *Chin. J. Chem.* **2007**, *25*, 818.
6. Sparks, R. B.; Combs, A. P. *Org. Lett.* **2004**, *6*, 2473.
7. Ali, K.; Niknam, E.; Bijan, R.; Hossien, N-M. *Synth. Commun.* **2007**, *37*, 2753.
8. Wipf, P.; Fletcher, J. M.; Scarone, L. *Tetrahedron Lett.* **2005**, *46*, 5463.
9. Chowdhury, P.; Das, A. M.; Goswami, P. *Steroids*. **2005**, *70*, 494.
10. Dewan, S. K.; Singh, R.; Kumar, A. *Arkivoc.* **2006**, 41.
11. Dave, P. R.; Forshar, F. *J. Org. Chem.* **1996**, *61*, 8897.
12. Smith, P. A. S.; Gloyer, S. E. *J. Org. Chem.* **1975**, *40*, 2508.
13. Negi, S.; Matsukura, M.; Mizuno, M.; Miyake, K.; Minami, N. *Synthesis*. **1996**, 991.
14. Alonso, D. A.; Nájera, C.; Pacheco, M. C. *Tetrahedron Lett.* **2002**, *43*, 9365.
15. Alonso, D. A.; Nájera, C.; Pacheco, M. C. *Tetrahedron Lett.* **2002**, *43*, 9365.
16. Alacid, E.; Nájera, C. *Org. Lett.* **2008**, *10*, 5011.
17. Botella, L.; Nájera, C. *Tetrahedron Lett.* **2004**, *45*, 1833.
18. Susanto, W.; Chu, C-Y.; Ang, W. J.; Chou, T-C.; Lo, L-C.; Lam, Y. *J. Org. Chem.* **2012**, *77*, 2729.
19. Wanga, X-R.; Lu, F-H.; Song, Y.; Lu, Z-L. *Tetrahedron Lett.* **2012**, *53*, 589.
20. (a) Metzger, J. O. *Angew Chem. Int. Ed.* **1998**, *37*, 2975; (b) Tanaka, K.; Toda, F. *Chem. Rev.* **2000**, *100*, 1025.
21. Hajipour, A. R.; Mohammadpoor-Baltork, I.; Nikbaghat, K.; Imanzadeh, G. *Synth. Commun.* **1999**, *29*, 1697.
22. Kad, G. L.; Bhandari, M.; Kaur, J.; Rathee, R.; Singh, J. *Green Chem.* **2001**, *3*, 275.
23. Guo, J-J.; Jin, T-S.; Zhang, S-L.; Li, T-S. *Green Chem.* **2001**, *3*, 193.
24. Ren, R. X.; Ou, W. *Tetrahedron Lett.* **2001**, *42*, 8445.

25. Damljanović, I.; Vukićević, M.; Vukićević, R. D. *Monatshefte für Chemie*. **2006**, *137*, 301.
26. Saikia, L.; Baruah, J. M.; Thakur, A. J. *Org. Med. Chem. Lett.* **2011**, *1:12*, 1.
27. Hajipour, A. R.; Rafieea, F.; Ruoho, A.E. *J. Iran. Chem. Soc.* **2010**, *7*, 114.
28. Czekelius, C.; Carreira, Erick M. *Angew. Chem. Int. Ed.* **2005**, *44*, 612.
29. Walvoord, R. R.; Berritt, Simon.; Kozlowski, M. C. *Org. Lett.* **2012**, *14*, 4086.
30. Kidwai, M.; Bhardwaj, S. *Synth. Commun.* **2011**, *41*, 2655.
31. Aghapour, G.; Mohamadian, S. *Bull. Korean Chem. Soc.* **2012**, *33*, 1209.
32. Ghosh, P.; Mandal, A. *Cat. Commun.* **2011**, *11*, 744.