

Chapter III

3, 5 Di-nitrobenzoic Acid Derived Copper II Complex Catalyzed One pot multi components Synthesis of 2, 4, 5-trisubstituted Imidazoles Under solvent-free conditions

Section A

(General introduction and synthetic background of imidazole)

III. A. 1. A general introduction of imidazole:

III. A. 1. 1. Imidazole:

Imidazole is colourless and water soluble organic diazole compound with molecular formula $C_3H_4N_2$. It is an aromatic heterocyclic compound and belongs to the alkaloid family. The imidazole substructure serves an important building block for many biological important moieties such as histidine.

III. A. 1. 2. Structure:

Imidazole has a planar 5-membered ring structure in two equivalent tautomeric forms (due to the dislocation of N-H proton on either of the two N-atoms). It is a highly polar compound having dipole moment of 3.61D. Besides, the presence of a sextet of π -electrons, make imidazole an aromatic compound. The resonating structures of imidazole are as follows (Fig. III. A. 1):

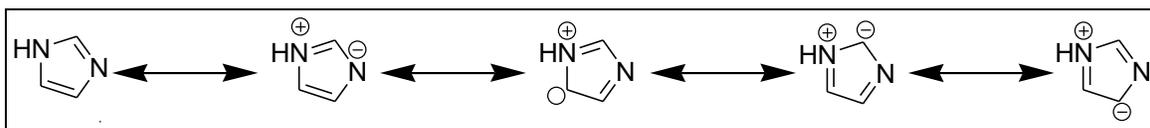


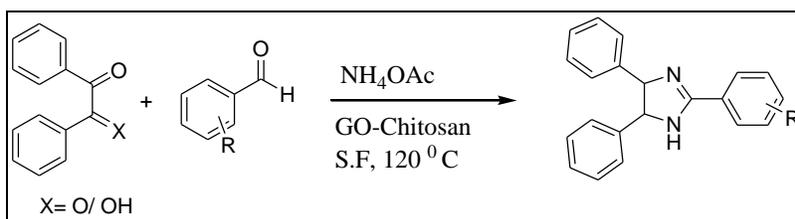
Fig. III. A. 1: Resonating structure of imidazole.

III. A. 2. Synthetic background of Imidazole:

III. A. 2. 1. Classical method for the preparation of imidazole:

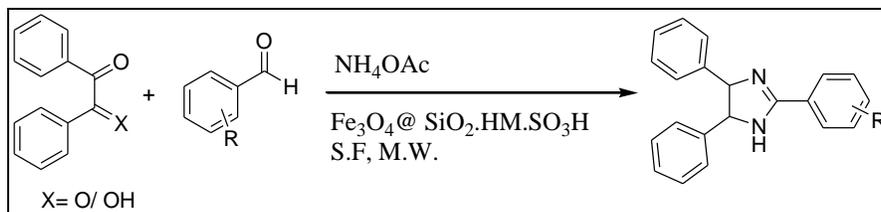
Heinrich Debus, in 1858¹ firstly synthesized imidazole by using a dicarbonyl compound, an aldehyde and ammonia. He used glyoxal as the dicarbonyl precursor and formaldehyde as the aldehyde (scheme. III. A. 1).

Heravi et al.⁸ used $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ and E. Rafiee et al.⁹ used Fe_3O_4 as their potential catalyst for synthesis of tri-substituted imidazole). Besides this some solid supported catalyst are also used for the preparation. Just like, Ali Maleki et al. (scheme. III. A. 3)¹⁰ synthesized trisubstituted imidazole by the reaction of 1,2-diketone/ α -hydroxy ketone, substituted aldehyde and NH_4OAc using graphene oxide-chitosan bio-nanocomposite as a potential catalyst under solvent free condition. The protocol was equally applicable for both electron donating/ withdrawing group substituted aldehydes.



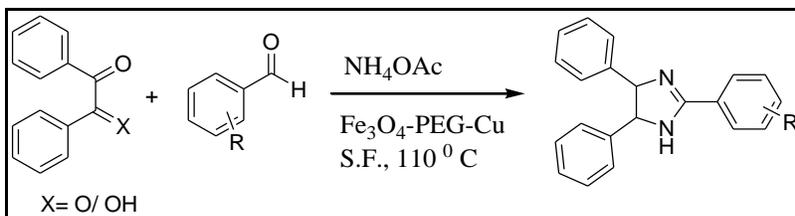
Scheme III. A. 3. GO-Chitosan catalysed preparation of trisubstituted imidazole.

Hossein Naeimi et al. (scheme III. A. 4)¹¹ used $\text{Fe}_3\text{O}_4\text{-SiO}_2\text{.HM.SO}_3\text{H}$ as a heterogenous catalyst for preparation of trisubstituted imidazole under solvent free condition.



Scheme. III. A. 4. Synthesis of trisubstituted imidazole using $\text{Fe}_3\text{O}_4\text{-SiO}_2\text{.HM.SO}_3\text{H}$ as a heterogenous catalyst

Moreover, Cu-nanoparticle supported on Fe_3O_4 -polyethelene glycol nanocomposite as reported by J. Safari et al. severs well for substituted imidazole synthesis (scheme. III. A. 5)¹².



Scheme. III. A. 5. Synthesis of substituted imidazole using $\text{Fe}_3\text{O}_4\text{-PEG-Cu}$ nano-composite

Beside this, there also other solid supported catalysts have reported for the 2, 4, 5-trisubstituted imidazole synthesis are e.g. Cu (NO₃)₂-zeolite¹³, silica-H₂SO₄¹⁴, mercaptopropyl silica¹⁵ and SBA-15/TFE¹⁶ etc.

Along with those catalytic processes there are some other techniques also available just as the microwave irradiation technique as reported by Scott E. Wolkenberg et al.¹⁷ for the synthesis of tri- substituted imidazole.

III. A. 3. Uses of Copper salts as a catalyst:

The easy accessibility of Cu into various oxidation state (such as: Cu⁰, Cu^I, Cu^{II} and Cu^{III}) allowing it to follow both radical pathways as well organometallic- intermediating bond-forming pathway similar that of palladium catalyst. Alongside with the change in oxidation state allowing copper to attached with different functional group through π - coordination or Lewis acids interaction. Thus, copper easily can conduct a number of different type chemical reactions.

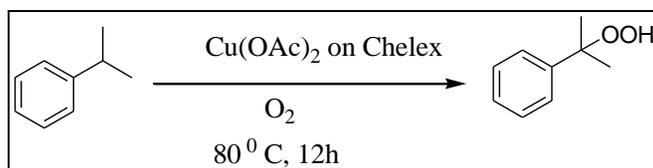
III. A. 3. 1. Copper catalysed oxidation reaction of benzylic, alkane, alkene, alkyne and arene C-H bond:

Suitable Copper catalysts are useful for oxidation of classes of hydrocarbons such as alkyl, alkynyl, benzylic, aryl and alkenyl.

III. A. 3. 1. 1. Benzylic C-H oxidation:

This type of reactions involves the oxidation of weaker C-H bond (e.g. X. Song et al. in their work reported the mild and highly efficient oxidation method for acidic benzylic compounds to their corresponding acids using Cu-phthalocyanine as a catalyst).¹⁸ Besides there are other reported process are also available in which oxidation of a compound having benzylic hydrogen occurs using copper catalyst. Such as, Allara in 1972 reported the selective oxidation of fluorene to fluorenone.¹⁹ Besides, Garcia et al. described the Cu(II)-1,3,5-benzenetricarboxylate a metal-organic framework catalysed oxidation of Xanthene, also they used the same catalyst for oxidation of fluorene.²⁰ Besides the oxidation of reactive benzylic substrates, there also examples of oxidation of non-reactive benzylic substrate are present (e.g. Cheng and co-workers reported oxidation of cumene to per oxo-cumene using Cu(OAc)₂ on chelex without using of any

radical initiator with maximum selectivity, scheme. III. A. 6).²¹ Again, Zhang et al. describe the oxidation of toluene to corresponding acid through the use of CuCl_2 and a radical initiator HPPDO.²² Moreover, recent literature reveals that by using suitable copper catalyst a benzylic substrate can also oxidized to their corresponding nitriles (e.g. Cu-impregnated zeolites catalysed conversation of toluene or its derivative to their nitriles as reported by Beschmann et al.).²³



Scheme. III. A. 6. Oxidation of cumene using Cu (II)-catalyst

III. A. 3. 1. 2. Oxidation of alkane:

Higher C-H bond strength, lack of regioselectivity and formation of over oxidized product are the common issue for oxidation of alkane. Thus, several researches are developed to achieve a well-accepted protocol for this oxidation process using copper catalyst. Such as Sir Derek Barton and coworkers reported the use of Cu(II) chelates catalyst along with TBHP and O_2 for oxidation of saturated hydrocarbon.²⁴ Later, Komiya et al. reported the addition of crown ether to Cu (II) catalyst enhanced the selectivity of oxidation towards the required product.²⁵ Recently, Glatz et al. shown the use of modified Cu- SiCN ceramics can oxidized cyclo-alkanes to their corresponding ketones with a better yield.²⁶

III. A. 3. 1. 3. Alkene oxidation:

III. A. 3. 1. 3. 1. Oxidation at allylic position:

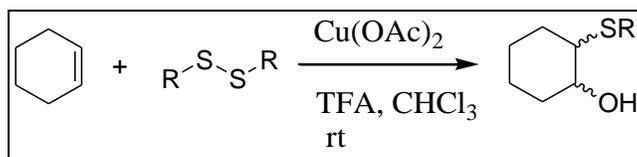
Presence of unsaturation, make the oxidation of allylic position of an alkene more difficult and need much milder condition than that for alkane or benzylic system. But using of copper catalyst for the process makes it more suitable in aspect of yield and selectivity. Such as Pozzi and co-workers reported the oxidation of allylic position of cyclohexene to corresponding ketone by the use of copper catalyst.²⁷

III. A. 3. 1. 3. 2. Epoxidation of alkene:

As epoxides play an important role in chemical industry, selective epoxidation of alkenes thus gains an attraction in recent years. Copper catalytic epoxidation thus plays an important role in this regard. Just like Karandikar et al. reported the use of copper perchloro phthalocyanine complex on HSi-MCM-41 molecular sieves give promising result during the reaction.²⁸

III. A. 3. 1. 3. 3. Oxidative di-functionalization of alkenes:

Oxidative di-functionalization is quite useful technique for insert heteroatom to hydrocarbons. There are several methods are present for the di functionalization (e.g. Bewic et al. reported the $\text{Cu}(\text{OAc})_2$ catalysed hydroxy-sulfenylation of alkenes; scheme. III. A. 7)²⁹



Scheme. III. A. 7. Hydroxy-sulfenylation of alkenes

III. A. 3. 1. 4. Alkyne oxidation:

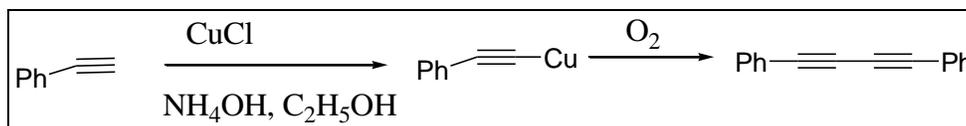
Aerobic oxidation of propargylic substances is quite complex in terms of overoxidation and alkyne reaction pathways. But literature survey reveals some useful methods using copper as a catalyst by which we can easily overcome those problems (e.g. oxidation of propargylic substrate to their corresponding ketones by using $\text{Cu}(\text{II})$ catalyst-in combination with NHPI as reported by Sakaguchi et al.).³⁰

III. A. 3. 1. 5. Oxidation of arenes (Hydroxylation):

Hydroxylation of arenes is quite challenging due to stronger C-H bond and also in term of selectivity. Just like direct conversion of benzene to phenol gives hydroquinone, catechol etc. are also formed during the reaction as side product. Here copper catalyst provides a good alternative way for the reaction. For this reaction $\text{Cu}(\text{I})$ catalyst serves well (e.g. Sasaki and co-workers reported the direct conversion of benzene to phenol by using CuCl as a catalyst)³¹ Besides, Orita et al. carry the same conversation using CuSO_4 and ascorbic acid.³²

III. A. 3. 2. Copper Catalysed coupling reaction:

Another useful reaction for the functionalization of organic compound that is catalysed by copper is coupling reaction. Copper can catalyse both C-C and C-hetero (C-N, C-S or C-O) type coupling reaction. It was 1869 when Carl Glaser prepared Cu (I) salt of phenylacetylene which further exposure on air produced homo-coupled 1, 3-diyne product (scheme. III. A. 8)³³



Scheme. III. A. 8. Homo-coupling reaction of copper product

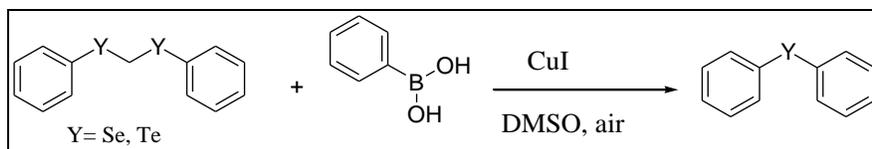
From then a number of modified methodologies are developed for this type of coupling reactions. Such as, Beifuss and co-workers have made a study of the effect of ligand and base on the above coupling reaction and find that TMEDA as the ligand of choice.³⁴ Besides, presence of other cocatalyst such as Ni (0)³⁵, iron³⁶ or palladium³⁷ enhance the rate of reaction during the homocoupling as well as for hetero-coupling of terminal alkynes. Again, in effort to find a greener alternative for the reaction methodologies Chen et. al., reported the solvent free technique for the coupling reaction³⁸. Cadot-Chodkiewicz have reported the coupling of unsymmetrical di-ynes successfully³⁹. Besides this cross-coupling reaction of alkynes with non-alkynyl substrate has also been reported (e.g. cross-coupling reaction of terminal alkynes with trifluoromethyl anion from CF₃-TMS)⁴⁰. Recently, Stahl et. al., has reported the cross coupling of terminal alkynes with amides catalysed by CuCl₂⁴¹.

Along with this homo or hetero coupling of alkyne's there also other coupling reactions involving arenes and catalysed by Copper are available. Such as, cross-coupling reaction of arylboronic acid with arenes catalysed by Cu (OCOCF₃)₂⁴² is reported. In addition, with this homocoupling of alkyl and vinylic substrate can also be catalysed by copper salts⁴³.

Another major utility of copper catalysed coupling reaction is the formation of C-N, C-O or C-S bonds using boronic acid derivatives/aryl halides, which offer new milder method with broad generality for C-hetero bond forming reactions. Such as, Collman and co-workers reported the N-arylation of imidazoles with arylboronic acid using copper (I) catalyst^{44a}, besides, Buchwald

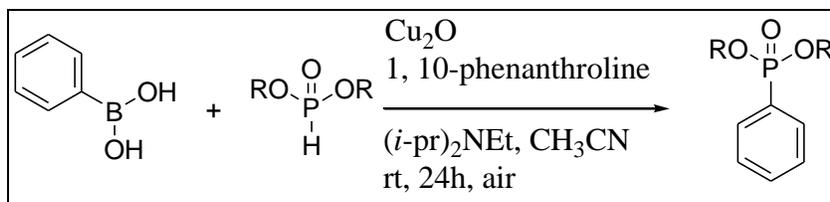
et. al. stated the N-arylation of indoles by the reaction of substituted indoles with aryl halide using CuI as the catalyst ^{44b} whereas that of for pyrazoles is reported by Taillefer et. Al. ^{44d} Again, CuCl in presence of DIPEA can enables easy aryl transfer to nitro enamines from hypervalent iodonium salts ^{44c}. With the realization of C-N bond formation, the next attempt was made for the oxidative coupling between -OH groups and arylboronic acid/aryl halides for C-O bond formation ⁴⁵. Like C-N or C-O bond forming reaction C-S bond forming reaction face the drawback related to poor yield due to the tendency of copper catalyst to oxidized thiol. This is overcome by the usage of oxidized sulphur species. Just like cross coupling of boronic acid derivative with sulfinate salt catalysed by Cu(OAc)₂ ^{46a}, whereas recently Feng et. al. successfully overcome the drawback regarding to oxidation of thiol and reported the S-arylation of thiols at room temperature using CuSO₄ as the potent catalyst ^{46b}. Sometimes using disulfides instead of thiol gives the better yield ^{47a, b}. Again, formation of diaryl thio-ethers can also possible by copper mediated reactions ^{47 c}.

Another emerging uses of copper catalysed coupling reaction is the formation of organo selenium or tellurium product. Huang and coworkers described the cross coupling of boronic acid derivatives with aryl ditellurides and diselenides species to get respective organo compounds using CuI as a catalyst (scheme. III. A. 9) ⁴⁸.



Scheme. III. A. 9. Copper catalysed formation of organo selenides and organo tellurides.

Other examples regarding to this C-hetero bond formation by using diverse boronic acid or selenium or tellurium species in presence of copper catalyst are available ⁴⁹. Further exploration of copper mediated coupling reactions led to the formation of C-P heteroatomic bond formation. Zhuang et. al., firstly reported the H-phosphonate diesters cross coupled with aryl boronic acid gives phosphonates (scheme. III. A. 10) ⁵⁰.



Scheme. III. A. 10. C-P bond formation catalysed by copper

III. A. 3. 3. Other reactions catalysed by copper:

Suitable copper salt can also help to functionalized heterocyclic moiety through coupling reaction. Just as, demonstrating by coupling reaction of various amines⁵¹/ thiols⁵² with azoles at 2-position catalysed by Cu (II) salt. In addition to this C-C coupling in azoles at 2-position are also offered. Such as cross coupling of terminal alkynes with 1, 3, 4-oxadiazoles using Cu (II)-chloride under an oxygen atmosphere⁵³. Along with this cross coupling, homocoupling of azoles can also carried out by application of copper catalyst⁵⁴.

III. A. 4. Conclusion:

Literature survey reveals that there are number of methodologies available for the synthesis of tri-substituted imidazole. But, harsh reaction conditions, tedious work up procedure, highly acidic medium, oxidizing environment, prolonged time period and uses of expensive reagents are the major disadvantages of the existing methods. Thus, to fulfill the insufficiency and to strengthen the synthetic methodologies and also influenced by the applicability of copper as a catalyst, author felt the necessity to develop a novel method for the synthesis of substituted imidazole using an polymeric Cu (II) complex prepared by us.