

Newer Approaches to Schiff Bases

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ABSTRACT

Azomethine ($-C=N-$) group containing compounds were termed as Schiff base by Hugo Schiff. Schiff bases belong to the bigger class of compounds called imines. Schiff bases are important not only as intermediates but also as reagents, as fine chemicals, as catalysts etc.

The present paper covers newer approaches to Schiff bases.

Keywords: Azomethine, Schiff bases, Imines.

I. INTRODUCTION

Schiff bases have drawn much more attention of organic chemists as an intermediate/precursor for the development of various heterocycles of medicinal importance as well as an intermediate/precursor for metal complex formation etc.

These are the compounds with the structure $RC=NR'$ and contain azomethine ($-C=N-$) group.

They are generally formed by the reaction between primary amines and active carbonyl group bearing compounds. Schiff-base derivatives have been reported to serve many applications, for example, as medical substrates or fine chemicals, for analysis of metal ions present in environmental samples, for extracting metallic ions [1] etc. Schiff bases have been reported as effective catalysts for many reactions, such as, cyclopropanation and epoxidation reaction of alkenes [2] and several other reactions.

Schiff bases usually behave as tetradentate, tridentate, bidentate ligands and produce complexes having high stability with the transition metals. Schiff bases cannot form co-ordination complexes without presence of $-OH$ group in proximity of azomethine group because $-OH$ in the proximity of reaction site

enables Schiff bases to furnish a 5 or 6 membered ring structure when they are reacting with transition metal ions. The coordination metal complexes derived from Schiff base ligands are widely useful in industry as well as they have found numerous biological applications [3].

Schiff bases derived from aliphatic aldehydes bear low stability in comparison of those obtained from aromatic aldehydes and they tend to undergo polymerization easily.

Schiff bases derived from benzanoid amines & benzanoid aldehydes have found applications in different fields. For example, they have been used in electrochemical and optical sensors with very good sensitivity and selectivity [4, 5].

Schiff bases are also enormously useful in variety of analytical measurements, for example, their chelates are used in determination of amines and carbonyl compounds [6], here, Schiff bases are particularly useful due to their ability form the imine bond with carbonyl compounds. Schiff bases are also useful for determination of metal ions, because of their complex-forming ability with metal ions.

Schiff bases are also useful as reagents in analytical measurements, for example, P-dimethyl amino

cinnamaldehyde based imines were used for quantitative estimation of Sparfloxacin in bulk and pharmaceutical dosage forms [7].

In organic synthetic chemistry, Schiff bases are used for formation of carbon-nitrogen bond. Schiff bases also have applications in display systems and optical memory devices due to their properties of solid-state thermochromism & photochromism [8].

Schiff bases also play an important role in many physiological processes, for example, reaction between amino groups of the protein and aldehyde group of 11-cis-retinal give rise to Schiff base which is useful in the visualization process in human eye [9].

Schiff bases are also involved as an intermediate in the biochemical pathway for the formation of porphyrin from glycine. Schiff bases have also been reported as corrosion-inhibitors [10], for example, halogenated Schiff bases of benzidine with fluorinated aldehyde are reported to have been used as corrosion-inhibitors in steel [11]. Due to plethora of applications in different fields, Schiff bases have received great attention from researchers around the world.

The present paper reports brief overview of approaches to development of newer Schiff bases and their bioactivity profile.

II. ADVANCES IN THE DEVELOPMENT OF SCHIFF BASES

By removal of water under Catalysis:

The simplest method for formation of Schiff bases is the method very firstly shown by H. Schiff, which involves reaction between aldehyde or ketone and the amine with the removal of H₂O.

The process is facilitated by the adding the catalytic proportion of acid and by removing the H₂O simultaneously. The removal of H₂O is useful to

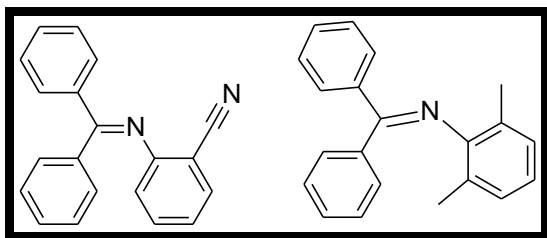
prevent the backward reaction due to the reaction being reversible. Further, longer reaction times are often needed to generate higher yield of the imine product.

The mechanism of imine formation comprises nucleophilic addition reaction of the amine to the carbonyl group of aldehyde/ketone. Firstly, there occurs formation of carbinolamine adduct by the addition reaction of amine to aldehyde/ketone. The carbinolamine is not stable and a water molecule is expelled under acid catalysis.

Thus, the removal of water molecule from the carbinolamine is the step which determines the rate of the imine formation reaction. The reaction takes place under acid catalysis. However, the amine can become protonated in presence of higher amount of acid. In case the amine becomes protonated (i.e., non-nucleophilic), the reaction equilibrium shifts to the left side. As a result, carbinolamine will not be formed. Therefore, synthesis of imines is accomplished at under mild acidic conditions.

Different researchers have tried various approaches to remove the water and to decrease the reaction time as well as for improving the yield. Dean-stark apparatus is mostly utilized method for removing H₂O. Use of molecular sieves has been shown [12].

Use of Si(OC₂H₅)₄ [tetraethyl orthosilicate] as a reaction medium has also been reported to prepare sterically hindered imines [13]. Also, the article depicts synthesis of sterically hindered benzophenone N-arylimines namely N-(diphenylmethylene)-2-cyanoaniline and N-(diphenylmethylene)-2,6-dimethylaniline using Si(OC₂H₅)₄, which resulted in the increase of yield and reaction time decreased to a considerable extent.



Use of common mineral acids (H_2SO_4 OR HCl) for Schiff base formation has been substituted by other organic acids. Fatiha et al. have used p-TSA (p-Toluene sulphonic acid) for the Schiff base formation from 3,3'-bithiophene-2,2'-dicarbaldehyde and aromatic amines [14].

Use of natural acid (lemon juice) instead of mineral acid has been reported by Patil S. et al. [15]. The reaction conditions employing lemon juice were studied for the reaction between a range of aromatic aldehydes and primary aromatic amines.

Kwang M. T. et al. has reported use of zinc chloride for Schiff base formation [16]. The article also reports use of hydrobromic acid as a catalyst and it was concluded that purification was much easier in case of using hydrobromic acid.

Use of other Lewis acids as catalyst has also been reported, for example BF_3 & TiCl_4 [17]. Use of TiCl_4 has drawbacks of requiring higher amounts of amine and formation of HCl as a by-product.

Yang Z. et al. has shown the formation of Schiff base formation from the reaction between 3,4,5-trimethoxybenzaldehyde and para-toluidine in the presence of magnesium sulphate [18].

Elevated temperatures and extensive reaction time are needed for the formation of Schiff bases of aliphatic ketones as aliphatic ketone does not easily react with amines and hence, the reaction is very slow. The reaction can be promoted by the acid

catalysts and water removal from the reaction mixture which can increase the yields. Aromatic ketones require drastic reactions conditions for reaction with amine to yield Schiff base due to their very low reactivity.

Conventional reported methodologies for the preparation of Schiff bases often involve difficult reaction or work-up procedures, humidity sensitive catalysts or reagents, use of high quantities of toxic solvents, use of expensive dehydrating agents or catalysts, elevated reaction temperatures, and higher reaction times. Further, many of these methods are suitable for the preparation of aldimines and formation of ketimines is not achievable through these methods.

Many research articles describing green chemistry preparations for Schiff base have been reported in the past decade. In contrast to conventional methodologies for Schiff base formation, these green chemistry approaches offer easy reaction and/or work-up procedures, shorter reaction time and improved yield.

Suresh P. et al. have reported a green method for synthesis of Schiff bases of different aromatic aldehydes with different substituted anilines using calcined eggshells as a green catalyst [19]. It was observed that lower yield was obtained in case of reaction of aromatic aldehyde having reduced electrophilicity of the carbonyl carbon by presence of the electron-donating substituent group. Similarly, lower yields were obtained in case of aromatic amines possessing strong electron-withdrawing substituent group which decrease its nucleophilicity e.g. 4-nitro group. It was also observed that if deactivating group was present in aldehyde or amine, longer reaction time was required.

El-faham A. et al. have reported preparation of novel imine derivatives of s-triazine under ultra-sonic irradiation [20] The imine derivatives were obtained in higher yields within low reaction time and with excellent purities as compared to conventional method of preparation.

H₃PO₄·12WO₃·xH₂O (PTA) catalyzed environment-friendly preparation of imines of benzimidazolyl naphthalene-2-amine has been reported [21] Use of PTA proved to be effective resulting in the improved yield and shorter reaction time..

Ancker T. et al. have reported preparation of bis-imine Schiff bases by the reaction of aliphatic diamines with aldehyde using poly(propyleneglycol) (PPG) as a green re-usable solvent [22]. Use of PPG resulted in simple reaction process giving high yield.

Use of silica-gel supported NaHSO₄.SiO₂ as a green and recyclable catalyst for the solvent-free microwave-assisted preparation of imines have been reported [23] The catalyst can be recycled simply by washing with ether and can be used upto 10 times which makes the reaction process more cost-effective.

Taj T. et al. have accomplished synthesis of Schiff bases using magnesium perchlorate as a catalyst [24]. The reaction was successful in producing Schiff bases in excellent yields in comparatively shorter reaction times.

By Oxidation:

Formation of Schiff base from the amines and alcohols via the oxidation has been reported by many researchers.

Shiraishi et al. have reported formation of Schiff base from photo-reaction of amine and alcohol in the

presence of TiO₂ loading Pt nanoparticles [25]. The formation of Schiff base was accomplished via UV-assisted oxidation of alcohols in presence of Pt to give corresponding aldehydes which then react with amines on the surface of TiO₂.

Yung-Syuan L. et al. have reported formation of Schiff bases from benzyl alcohols and amines via oxidative coupling in presence of a dicopper complex [26]. The reaction was also successful for reaction of diamines with benzylic alcohols leading to formation of dimines. The dicopper complex catalyst was prepared by the reaction of 2,7-bis(2-pyridyl)-1,8-naphthyridine with Cu₂O using HCOOH as reaction medium.

Lan J. et al. have developed an efficient protocol for the formation of Schiff base from alcohols and amines in the presence of low-loading palladium catalyst [27]. The reaction can be performed at ambient temperature without any special reaction arrangements in the open air.

Many researchers have also reported the synthesis of Schiff bases from primary amines by oxidative process.

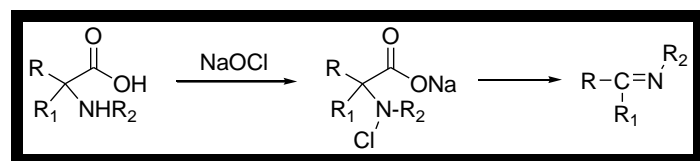
Girrane A. et al. have reported use of TiO₂ supported gold nanoparticles for the imine formation from variety of amines [28]. It was observed that N-benzylidene-benzylamine was obtained in the presence of TiO₂ supported gold nanoparticles having 3.5 nm size, however, 25 nm particle size Au/TiO₂ could not facilitate the reaction and did not give the product N-benzylidene-benzylamine. They also performed experiment using gold supported on active carbon (0.8% Au/C) which was found to be increasing magnitude of reaction rate as compared to the TiO₂ supported gold nanoparticles. Further, gold supported on active carbon was proved to be efficient for the conversion of broad range of substrates

including heterocyclic amines such as (pyridin-2-yl)methanamine and (thiophen-2-yl)methanamine. Au/C was also effective for coupling of benzylamines and amines lacking α -hydrogen atoms.

Rajendra D. P. has reported solvent-free oxidation of variety of amines using copper (I) catalyst [29]. The catalyst is cheap, easily available and was effective for oxidation of wide range of amines including benzylic, aliphatic, cyclic secondary, heteroaromatic amines. Cross-coupled imines were also accessible by the reaction of benzylamines with different anilines, however, low selectivity was observed in such cases and N-benzylidene-benzylamine was obtained as a major product. The plausible mechanism for the formation of homocoupled imines was also proposed that firstly the formation of a Cupric complex from oxidative addition of Copper iodide to the amine occurs, followed by the oxidation of cupric complex resulting in the methanimine intermediate $RCH=NH$.

III. OTHER MISCELLANEOUS FORMATION

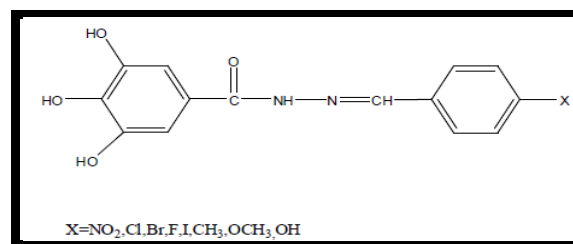
Aryl ketone diethyl ketals upon reaction with aromatic amines furnish ketimins. While very low reactivity is observed in case of reaction of Aryl ketone diethyl ketals with aliphatic amines.



An efficient and green synthetic protocol was developed for the preparation of 4-hydroxy-6-methyl-3-(1-(arylimino)ethyl)-2H-pyran-2-one derivatives [30]. The imine derivatives were prepared by the reaction of dehydroacetic acid with appropriate amines under ultrasound waves. The reaction protocol was advantageous over the conventional synthesis in terms of improved yield,

reduced reaction time and convenient work-up procedure.

Bodade V. et al. have reported microwave-assisted environmentally benign synthesis of Schiff bases of 3,4,5-trihydroxy-benzohydrazide with different substituted aldehydes [31].



IV. CONCLUSION

Newer approaches to Schiff bases have led to formation of diversely functionalized Schiff bases in an efficient way. Further, these newer approaches have also improved the older reaction protocols for Schiff bases by using novel strategies. Future developments by applying these newer approaches will yield diverse libraries of Schiff bases which can be used for wide-spread applications.

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Cite this article as :

Jayanti S. Rajora , "Newer Approaches to Schiff Bases", International Journal of Scientific Research in Science and Technology (IJSRST), Online ISSN : 2395-602X, Print ISSN : 2395-6011, Volume 6 Issue 4, pp. 473-478, July-August 2019.
Journal URL : <https://ijsrst.com/IJSRST12545>