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A Review of Chemistry and Biological Importance of Schiff Base

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ABSTRACT

Schiff bases are synthesized from the condensation of an amino compound with carbonyl compounds. These compounds and their derivatives play an important role in various biological systems, polymers, dyes and medicinal and pharmaceutical fields. This article fully based on literature review, summarizing the applications of Schiff bases and their various derivatives and complexes.

KEYWORDS: Schiff bases; synthesis; biological applications.

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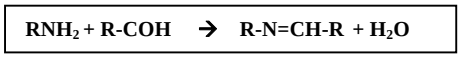
1. INTRODUCTION

Schiff bases named after Hugo Schiff (1964), are aldehyde- or ketone like compounds in which the carbonyl group is replaced by an imine or azomethine group[1]. Schiff bases are typically formed by the condensation of a primary amine and an aldehyde. Schiff bases are important intermediates for the synthesis of various bioactive compounds. Furthermore, they are reported to show a variety of biological activities including antibacterial, antifungal, anti cancer and herbicidal activities [2-6]. On the other hand, they are fundamental material for synthesis of various Schiff base ligands which used as chiral auxiliaries in asymmetric synthesis. Metal complex Schiff bases have also been used in oxidation reactions[7].In view of these facts we can clear about that Schiff base are important not only in medical chemistry, but also in food industry, dye industry, analytical chemistry, catalysis, fungicidal, agrochemical and biological activities[8].In this paper, we will explain which the simple methods to synthesize Schiff bases and importance of Schiff bases.

2. SYNTHESIS



Several of methods for the synthesis of imines were reported [8].The classical synthesis reported by Schiff involves the condensation of a carbonyl compound with an amine (scheme-1) under azeotropic distillation[9]. Molecular sieves are then used to completely remove water formed in the system[10].In the 1990s, in situ method for water elimination was developed, using dehydrating solvents such as tetra methyl orthosilicate or trimethyl orthoformate [11,12].

In 2004, Chakraborti[13] demonstrated that the efficiency of these methods is dependent on the use of highly electrophilic carbonyl compounds and strongly nucleophilic amines. They proposed as an alternative the use of substances that function as Bronsted-Lowry or Lewis acids to activate the carbonyl group of aldehydes, catalyze the nucleophilic attack by amines, and dehydrate the system, eliminating water as the final step[13].

The starting material for the synthesis of various new Schiff's and Mannich base derivatives was isatin (1H-indole- 2, 3-dione) which in turn was prepared from substituted isonitrosoacetanilide using aniline[14] (scheme-3).

In the past 12 years a number of innovations and new techniques have been reported, including solvent-free/clay/micro- wave irradiation, solid-state synthesis, K-10/microwave, water suspension medium, BF_4/molecular sieves, infra- red irradiation/no solvent, $NaHSO_4$ÆSiO_2/microwave/solvent- free, solvent-free/CaO/microwave, and silica/ultrasound irradiation [15-27].

On the formation of imines in water- a comparison study [28], Synthesis of 4-amino-5-substituted-4*H*-1,2,4-triazole-3-thiol[29] & Synthesis of 3-(4-substitutedphenyl)-1*H*-pyrazole-4-carbaldehyde[30] -The compounds were synthesized according to previously reported procedure. A highly atom economic one pot synthesis of tetrahydropyridines was achieved by l-proline/TFA catalyzed multi component reaction of β-keto-esters, aromatic aldehydes and anilines[31].

Among these innovations, microwave irradiation has been extensively used due to its operational simplicity, enhanced reaction rates, and great selectivity[26]. Microwave irradiation is less environmentally problematic than other methods because it abolishes the excessive use of aromatic solvents and the Dean-Stark apparatus for azeotropic removal of water. Another feature of this technique is that the reactions achieve high efficiency in a shorter period of time.

Examples

2.1 Scheme.1

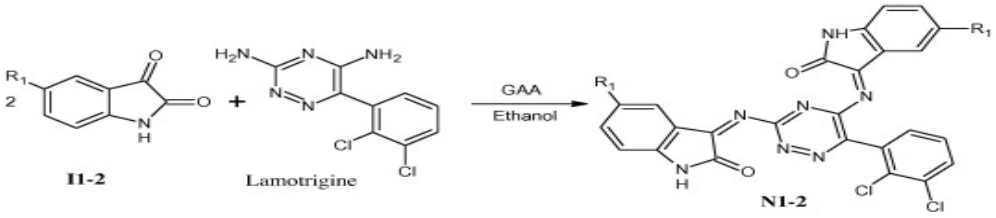
A solution of aniline and aldehyde in absolute ethanol [27], at 40^o- 50^{o}C, refluxed for 2 hours. white or yellow white imines with cold water, then recrystallised using ethanol to obtain the compound (83%) as a white crystal.

2.2Scheme.2

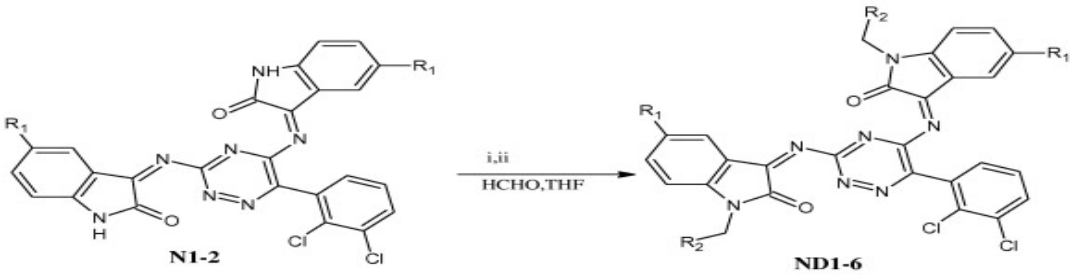
A mixture of 4,4'-diaminodiphenyl ether **1** (1mol) and o-vanillin **2** (1mol) [32] in methanol (40 mL) is stirred at room temperature for one hour to give an orange precipitate and after filtration and washing with methanol to give the pure Schiff base **3** .

2.3 Scheme.3

Step 1: Synthesis of Schiff's bases (imines) from Lamotrigine & substituted isatin.



Step 2: Synthesis of Mannich bases of synthesized Schiff's bases.



Where

i = Ethanol, GAA(Glacial Acetic Acid);

ii = THF, HCHO, (Dimethylamine, Diethylamine, Morpholine)

R_1 = -H, -Cl

R_2 = $-N(CH_3)_2$, $-N(C_2H_5)_2$, -N(morpholino)

3. CHEMISTRY AND BIOLOGICAL APPLICATIONS OF SCHIFF BASES.

- Schiff bases have a large number of synthetic uses in organic chemistry. Acylation of Schiff bases initiated by attack at the nitrogen atom and leads to net addition of the acylating agent to the carbon-nitrogen double bond. Reactions of this type have been put to good use in natural product synthesis.
- Schiff bases appear to be an important intermediate in a number of enzymatic reactions involving interaction of an enzyme with an amino or a carbonyl group of the substrate.
- One of the most important types of catalytic mechanism is the biochemical process which involves the condensation of a primary amine in an enzyme usually that of a lysine residue, with a carbonyl group of the substrate to form an imine, or Schiff base.
- Schiff bases enhance research activity in the field of coordination chemistry leading to very interesting conclusions. The carbon-nitrogen double bond of Schiff bases like the carbon-oxygen double bond is readily reduced by complex metal hydrides.

3.1 Biological activities

A considerable number of Schiff-base has potential biological interest, being used as more or less successful models of biological compounds[33]. Not only have they played a seminal role in the development of modern chemistry, but also they can also be found at key points in the development of inorganic biochemistry, catalysis, optical materials and other field [34]. Anti bacterial activities of substituted Schiff bases like nitro & phenyl derivatives possess more active but activity was lesser than the standard drug

- Nitro and halo derivatives of Schiff bases are reported to have antimicrobial and antitumor activities [35].Antimicrobial and antifungal activities of various Schiff bases have also been reported [36].
- Fungi toxicity of some Schiff bases has investigated by Sahu[37]. Gawad et al. reported high antimicrobial activities of some Schiff bases [38].
- Many Schiff bases are known to be medicinally important and are used to design medicinal compounds [39].
- The order of increasing activities is ligand < MeSnL < PhSnL < BZ3SnL, the results matched with the previously reported data for the biological activity of organotin complexes [40].
- Two bidentate Schiff base ligands 2- (2-hydroxy-3, 5-dichloro/dibromo) benzaldehyde-[4- (3-methyl-3-mesitylcyclobutyl)-1, 3-thiazol-2- yl]hydrazone, L^1H, L^2H and their metal complexes were tested against a yeast-like fungus *C.albicans* [41]. The fungicidal effect of salicylaldimine containing formaldehyde and piperazine moity and its metal polychelates were determined against two yeast *Candida albicans, Aspergillus*.
- Copper (II) complexes containing Schiff bases derived from S-benzyldthiocarbazate and saccharinate showed anticancer properties[42].
- Schiff bases of gossypol show high antiviral activity [43]. Silver complexes in oxidation state I showed inhibition against Cucumber mosaic virus; glycine salicylaldehyde Schiff base Ag(I), gave effective results up to 74% towards C.mosaic virus[44].
- Several Schiff bases possess anti – inflammatory, allergic inhibitors reducing activity radical scavenging, analgesic and anti-oxidative action[45]. Thiazole derived Schiff bases[46] show analgesic and anti-inflammatory activity. Schiff base of chitosan and carboxymethyl-chitosan shows an antioxidant activity such as superoxide and hydroxyl scavenging.

3.2Catalyst

Co(II), Fe(III) and Ru(III) complexes of Schiff bases derived from hydroxy benzaldehyde are used in oxidation of cyclohexane into cyclohexanol and cyclohexanone in presence of hydrogen peroxide are more efficient catalyst in oxidation reactions[47,48]

3.3 *Dye*

Chromium azomethine complexes, cobalt complex Schiff base[49], unsymmetrical complex 1:2 chromium[50] , Azo groups containing metal complexes[51] give fast colours to leathers, food packages, wools etc. Schiff bases possess excellent light resistance and storage ability and do not degrade even in acidic gases (CO_2). Novel tetra dentate Schiff base acts as a chromogenic reagent for determination of Ni in some natural food samples [52].

3.*4 Corrosion inhibitor*

- An interesting application of Schiff bases is their use as an effective corrosion inhibitor which is based on their ability to spontaneously form a monolayer on the surface to be protected [53]. Schiff bases have been found to posses more inhibitor efficiency than their constituent carbonyls and amines [54].
- Some authors have attributed these considerably stronger inhibition efficiencies to the presence of unoccupied π*- orbital in the Schiff base molecules, which enable electron back donation from the metal d-orbital and thereby stabilize the existing metal-inhibitor bond, which is not possible with the constituent amines [55-57].

3.5 Miscellaneous applications

- Schiff base polymers with a system of conjugated –C=C- and –C=N- bonds in their main chain are of considerable interest due to their thermal stability similar to polyamides and their using as solid stationary phase for gas chromatography [58],properties [59], and useful catenation ligand, where the coordination polymeric Schiff bases are extensively studies [60].
- Schiff base polymers are produced by the poly condensation of diamines with various dicarbonyl compounds [61-70]. Due to various applications of silver(I) complexes, for example as reagents in organic and inorganic synthesis [71], in photography or electrochemical silver plating [72], and as free

radical scavengers in industrial processes [73-76], these complexes have received considerable attention in recent years [77-85].

- Jarrahpour et al. have synthesized the 1-(2-aminopyridine)-4-phenyl-1,3-diene and 1-(3-aminopyridine)-4-phenyl-1,3-diene as heterodynes for iron carbonyl complexes [86]. Knölker et al. have reported that (η4 efficient for the transfer of the tricarbonyliron fragment [87].
- Cyclometallation reactions are well-established for many of the metals in the periodic table, especially where the metallation has occurred at an aromatic carbon atom [88-91]. However examples involving cyclometallation of sp2carbon atoms from non-aromatic substrates are much less common.
- Morshedi et al. have designed and prepared tetra dentate N_2S_2 donor Schiff base ligand with using of cinnamaldehyde. They have studied the coordination chemistry of their copper(I) complexes [92].
- Transition metal complexes with 1, 10-phenanthroline and 2, 2-bipyridine are used in petroleum refining. Popova and Berova reported that copper is good for liver function, its level in blood and urine has influence in pregnancy disorders, nephritis hepatitis, leprosy, anemia and leukemia in children [93].
- Baker's yeast contains a benzofuran derivative which acts as an antioxidant preventing haemorrhagine liver necrosis in rats and haemolysis of red cells in vitamin E eficiency[94].
- Macrocyclic Schiff bases of Dithiocarbazic acid have many fundamental biological functions, such as photosynthesis and transport of oxygen in mammalian and other respiratory system[95].

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