Chapter

Synthesis of Schiff Bases by Non-Conventional Methods

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Abstract

A Schiff base is a compound with the general structure $R_1R_2C=NR'$. They can be considered a subclass of imines. The term Schiff base is normally applied when these compounds are used as ligands to form coordination complexes with metal ions. Schiff bases can be synthesised from a primary aliphatic or aromatic amine and a carbonyl compound by nucleophilic addition forming a hemiaminal, followed by a dehydration to generate an imine. In other words, a Schiff base is a nitrogen analogue of a ketone or aldehyde where the carbonyl group has been replaced by azomethine or imine group. The imine group present in these compounds has been shown to be critical to their biological activities. Schiff bases have been frequently used in various fields such as medicine, pharmaceutical purposes due to their wide range of industrial applications. The unconventional methods of preparation of Schiff bases, compared with traditional methods, are more convenient, and reactions can be carried out in higher yield, shorter reaction time and milder conditions, without generation of pollution and safer to analyse.

Keywords: Schiff base, synthesis, imine, carbonyl, amine, condensation, solvent-free, natural catalysts

1. Introduction

Schiff bases are versatile C=N containing compounds possessing broad range of biological activities, and incorporation of metals in form of complexes show some degree of antibacterial, antifungal, antitumor, antiviral and anti-inflammatory properties [1]. Schiff bases are typically formed by the condensation of a primary amine and an aldehyde or ketone. Structurally, a Schiff base is a nitrogen analogue of an aldehyde or ketone in which the carbonyl group has been replaced by an imine or azomethine group. Schiff bases are some of the most widely used organic compounds. They are used as pigments and dyes, catalysts, intermediates in organic synthesis, and as polymer stabilisers [2]. They are fundamental materials for the synthesis of various ligands which can be used as chiral auxiliaries in asymmetric synthesis. Metal complexes of Schiff bases have also been used in oxidation reactions [3].

Imine or azomethine groups are present in various natural, natural-derived and non-natural compounds. The imine group present in such compounds has been shown to be critical to their biological activities (**Figure 1**) [4–6]. Schiff bases are

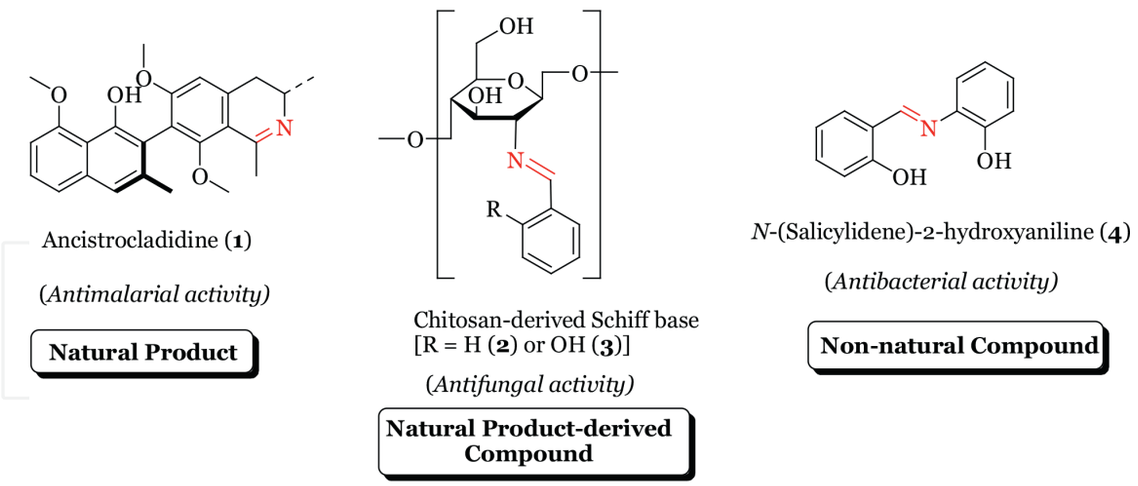


Figure 1.
Examples of bioactive Schiff bases.

represented by the general formula $R_3R_2C{=}NR_1$. The substituents R_2 and R_3 may be alkyl, aryl, heteroaryl or hydrogen while the substituent R_1 at the *N*-imino may be alkyl, aryl, heteroaryl, hydrogen or metallo (usually Si, Al, B, Sn).

The general approaches to the synthesis of Schiff bases are described in this report. Some unconventional methods of preparation and efficient practical techniques like microwave irradiation, solid-solid condensation, ultrasound irradiation, water suspension medium, infrared irradiation and the use of natural product as catalysts are discussed.

2. Preparation of Schiff bases

The most common method for the preparation of imines is the original reaction reported by Hugo Schiff in 1864 [7–9]. It is usually formed by the condensation of an aldehyde or ketone **5** with a primary amine **6** and elimination of water molecule in a Dean Stark apparatus. The formation of a Schiff base **8** is a reversible reaction and the dehydration of carbinolamine **7** generally takes place under acid or base catalysis, or upon heating. Molecular sieves are then used to completely remove water formed in the system (**Figure 2**) [10].

Aliphatic ketones react with amines to form imines more slowly than aldehydes; therefore, higher reaction temperatures and longer reaction time are required. Acid catalysts and water removal from the reaction mixture can significantly increase the

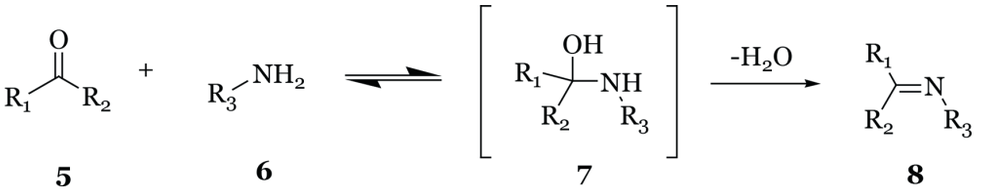


Figure 2.
Schiff reaction for the preparation of imines.

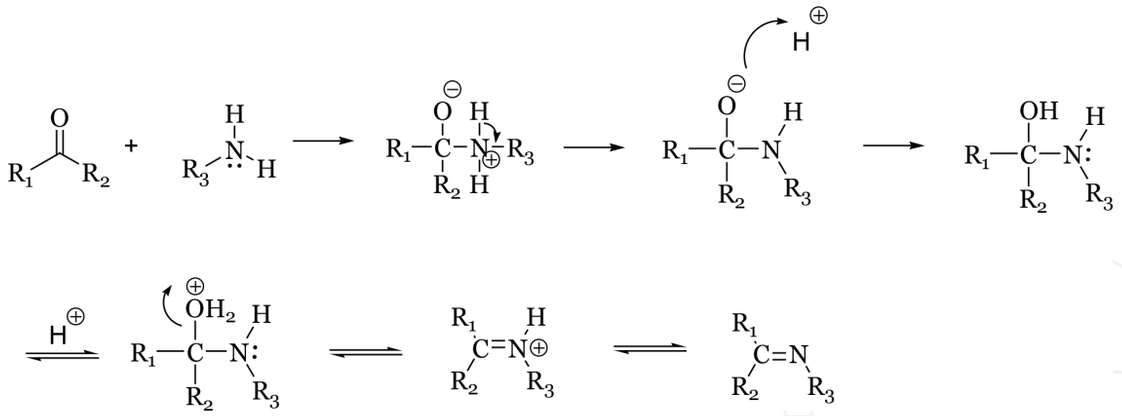


Figure 3.
Mechanism of formation of Schiff bases.

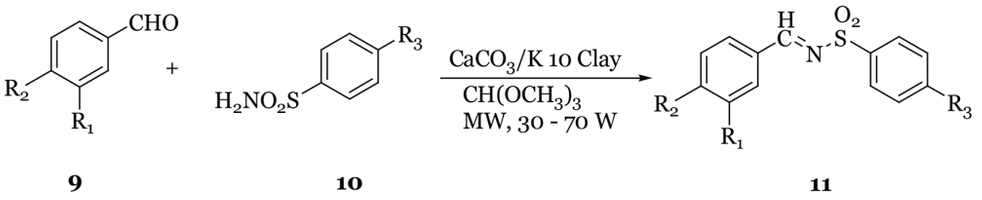
reaction yields. Aromatic ketones are less reactive than aliphatic ones and require harsh conditions to be converted into imines.

Recently, a number of innovations and new techniques for the preparation of Schiff bases have been reported including solvent-free, clay, or microwave irradiation, solid-state synthesis, molecular sieves, liquid crystals, water suspension medium, infrared and ultrasound irradiation [11–15].

The mechanism of Schiff base formation is another variation of nucleophilic addition to the carbonyl group, where the nucleophile is the amine. The amine reacts with the carbonyl to give an unstable addition compound called carbinolamine. The carbinolamine loses water by either acid or base catalysed pathways. Since the carbinolamine is an alcohol, it undergoes acid catalysed dehydration (**Figure 3**) [16].

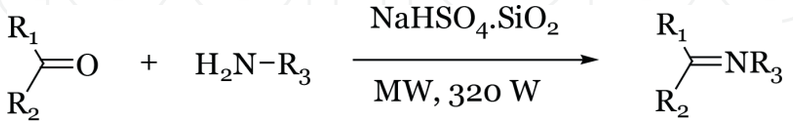
3. Synthesis of Schiff bases from various methods

The clay catalysed synthesis of imines and enamines under solvent-free conditions using microwave irradiation has been reported by Varma et al. [11] A synthetic procedure catalysed by montmorillonite K 10 clay was employed for the preparation of imines and enamines. An equimolar mixture of the carbonyl compound and amine was placed in an open glass container and irradiated in a microwave oven at full power for 3 minutes. The product was extracted into DCM and removal of the solvent under reduced pressure gave the imines/enamines in 75–98% yield. This approach eliminates the need for the large excess of support usually employed in solid phase reactions and reduces considerably the longer times and large quantities of aromatic solvents required in the conventional solution phase chemistry which entails the azeotropic removal of water using Dean-Stark apparatus. This method was also employed by Vass et al. [17] for the synthesis of *N*-sulfonylimines **11** (**Figure 4**). The one-pot and high-yielding protocol for the preparation of *N*-sulfonylimines from aryl aldehydes **9** and sulfonamides **10** provided a better alternative to the existing methods due to its shorter reaction time, simple reaction procedure and the formation of cleaner products that can be used for synthetic applications without further purification.



9 **10** **11**

Figure 4.
Microwave-assisted synthesis of N-sulfonylimines using calcium carbonate and K 10 clay.



5 **6** **8**

Figure 5.
Microwave-induced synthesis of imines using $NaHSO_4.SiO_2$ catalyst.

The synthesis of imines has been carried out efficiently using silica gel supported sodium hydrogen sulfate ($NaHSO_4.SiO_2$), a non-toxic and inexpensive catalyst, as a reusable heterogeneous catalyst in solvent-free conditions under microwave irradiation [18]. Several substituted imines were prepared by this method (**Figure 5**). The $NaHSO_4.SiO_2$ catalyst can be reused by simple washing with diethyl ether after each use followed by activation in an oven at 120°C for 1 h prior to use, thus rendering the process more economical. This constitutes a green and efficient alternative to the MW assisted method described by Varma et al. [11] using K-10 clay as catalyst and the use of DCM or diethylether, which are the commonly used solvents for this reaction. The use of $NaHSO_4.SiO_2$ catalysed nucleophilic attack on the carbonyl group by the amine and served as a dehydrating agent to facilitate the removal of water in the final step. This eliminates the environmental disadvantages of using toxic drying agents such as $TiCl_4$.

Schmeyers et al. [12] reported the solid-state synthesis of various kinds of benylideneaniline derivatives **14** without passing through liquid phases. The solid-solid reactions were performed by grinding together equimolar mixture of the pure aniline **12** and aldehyde **13** in a mortar at room temperature for 2 h (**Figure 6**). Twenty preparatively useful imines were quantitatively (100% yield at 100% conversion) obtained as hydrates. The water produced in the reaction was removed at 80°C under vacuum. These solid-solid condensations, unlike (acid catalysed) imine synthesis in solution, proceed waste-free.

A mild and improved protocol for the preparation of imines by ultrasound irradiation has been developed by Guzen et al. [15] A wide range of aromatic and heteroaromatic aldehydes were employed and all imines were obtained in excellent yields. The reaction was very efficient on a large scale, with the advantage of a very simple work-up and short reaction time (10 min). However, the process involved the use of a catalyst for activation and reaction solvent (**Figure 7**).

A new, simple, efficient, and environmentally benign method for the preparation of substituted *N*-benzylideneaniline derivatives, via condensation of several benzaldehydes and anilines, by means of infrared irradiation under solvent-free conditions

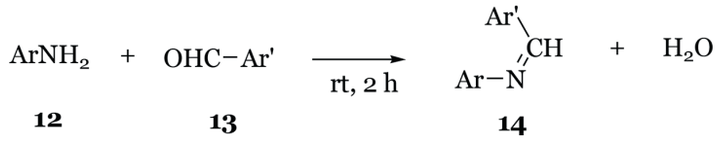


Figure 6.
Quantitative solid-solid synthesis of azomethines.

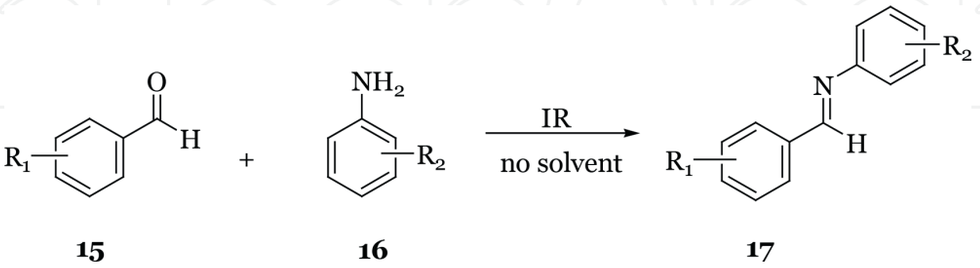


Figure 7.
Formation of N-benzylideneanilines by IR irradiation.

has been developed [19]. The reactions proceeded with good yields and in considerably shorter times than those previously reported under classical thermal conditions with additional advantages of lower cost, ease of work-up, and the fact that activation of the reaction by an acid catalyst was unnecessary.

The synthesis of various kinds of imines by a simple and green procedure was reported by Tanaka and Shiraishi [13]. The process involved the condensation reactions of aldehydes and amines in a water suspension medium at room temperature. Water is a non-toxic, safe, and cheap medium. The use of water as solvent allowed the formation of imines without the need for catalysis, the use of a large excess of aromatic solvents, or the azeotropic removal of water. The reactions were completed in short reaction times, high-yielding and the products were isolated by filtration.

This procedure was also employed by Rao et al. [20] for the synthesis of Schiff bases via the condensation of 1,2-diaminobenzene with various substituted aromatic aldehydes in aqueous medium (**Figure 8**). The method was experimentally simple, clean, high-yielding, with reduced reaction times. The product was purified by simple filtration followed by washing with water and drying processes.

4. Synthesis of Schiff bases using natural catalysts

A green method for the synthesis of Schiff bases using natural acids found in tamarind extract and lemon juice as a catalyst has been reported (**Figure 9**) [21]. The condensation of benzaldehyde **23** with aniline **24** and with urea **26** gave benzylidene aniline **25** and benzylidene urea **27** respectively. The products which were identified by various spectroscopic techniques showed significant antimicrobial and antioxidant activities. The role of tamarind extract and lemon juice as catalysts which are important for the formation of these Schiff bases was observed in that the reaction carried out in the absence of the catalysts gave no products. The method was economical and gave high yield of product.

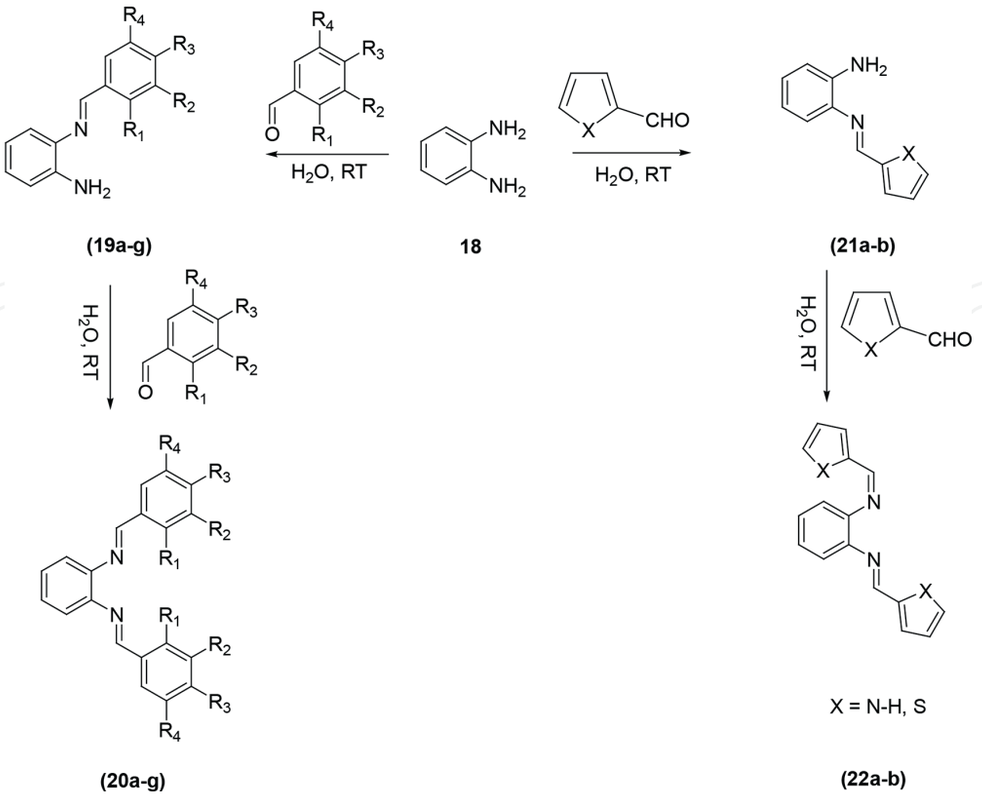


Figure 8.
Synthesis of Schiff bases in aqueous medium.

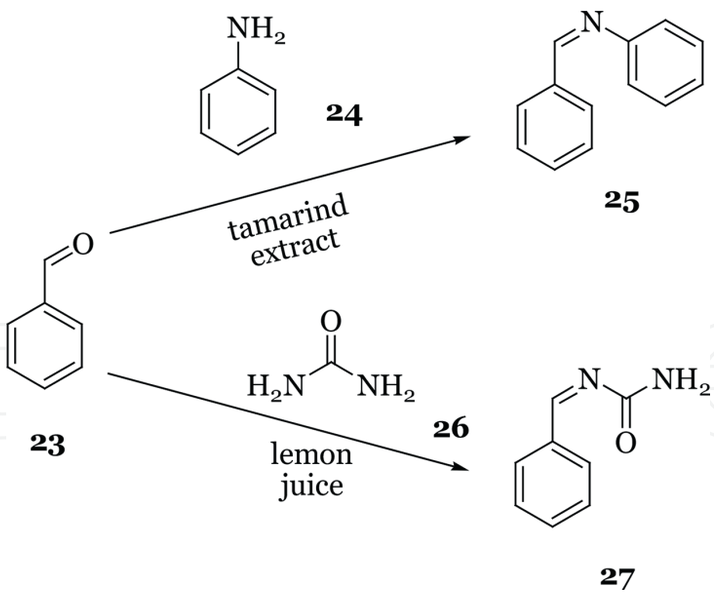


Figure 9.
Synthesis of Schiff bases catalysed by natural products.

5. Conclusion

Some non-conventional methods of preparation of Schiff bases have been extensively discussed. These methods are environment friendly, free from organic solvents and without the drawbacks of long reaction time, special apparatus and cost of dehydrating agent.

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