iJRASET
International Journal For Research in
Applied Science and Engineering Technology

INTERNATIONAL JOURNAL
FOR RESEARCH
IN APPLIED SCIENCE & ENGINEERING TECHNOLOGY

**Volume:** 10 **Issue:** VIII **Month of publication:** August 2022

**DOI:** https://doi.org/10.22214/ijraset.2022.46194

International Journal for Research in Applied Science & Engineering Technology (IJRASET)
ISSN: 2321-9653; IC Value: 45.98; SJ Impact Factor: 7.538
Volume 10 Issue VIII August 2022- Available at www.ijraset.com

# A Capstone Review on Synthetic Methods and Applications of Schiffs Bases

Nilesh S. Kadu[1], Vijay H. Masand[2]
[1]Department of Chemistry, Bhartiya Mahavidyalaya, Amravati, Maharashtra, India
[2]Department of Chemistry, Vidya Bharati Mahavidyalaya, Amravati, Maharashtra, India

***Abstract: Different drugs, dyes, agrochemicals, a few to list, require to unify two or more structural features. A unique and easily feasible solution is to employ Schiff's bases. The ability of -C=N- part of Schiff's bases enhances flexibility of the molecules and acts as a bridge for joining two distinct structural features. The synthetic procedures for the preparation of Schiff's bases have been discussed with suitable examples. In addition, some useful applications of Schiff's bases have been reported in the present work. The work is an attempt to understand the synthesis of Schiff's bases and their uses.***

***Keywords: Synthesis, Applications, Schiff's bases***

## I. INTRODUCTION

Hugo Schiff, a German scientist, is credited with being the first to characterise the products of the reaction between primary amines and carbonyl compounds in 1864, giving rise to the phrase "Schiff's base" [1]. Schiff bases are a vast group of compounds considered by the existence of a double bond connecting the carbon and nitrogen atoms, the flexibility of which is produced in the several ways to combined with different alkyl or aryl substituents. This kind of compounds can be both found in nature and prepared in a laboratory [1].

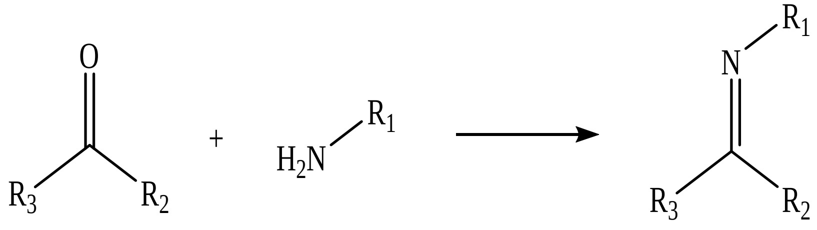
Schiff bases, also known as azomethines or imines, are compounds that in a broad sense possess the general formula $R_3R_2C=NR_1$. The substituents $R_2$ and $R_3$ may be alkyl, phenyl, heteroaryl, hydrogen. The substituent $R_1$ at the nitrogen of imino (C=N) may be an alkyl, phenyl, heteroaryl, hydrogen or a metal (mostly Si, Al, B, Sn). A Schiff base resulting from aniline, where $R_3$ is a phenyl or a substituted aryl, can be called an '*anil'*. Therefore, Schiff bases can be considered as a nitrogen equivalent of an aldehyde or a ketone in which the carbonyl group (C=O) has been substituted by an imine or azomethine group. The name "Organic Bases" first appeared in a German paper entitled "*Eine neue Reihe organischer Basen*" ("A New Series of Organic Bases") [2], though, they are not used as bases in the conventional sense, the designation of these compounds as bases, has persisted till this date.

The Schiff bases act as L-type ligands (like amines, amides, and phosphines) or ligands having two electron donors, which do not undergo electron modifications on their valence shells, in order to form co-ordination compounds with ions of transition elements [3]. The d-block metal ion forms coordination-bond by the electron-donating ligand atom during the coordination compound formation, which alters the metal's steric and electronic environment. As a result, reactivity of the ion of metal is stabilised and controlled, which is valuable for less stable ions at elevated oxidation states (O.S.) [3,4]. In the latter half of the 19th century, profound interest in applying transition metal complexes with different Schiff bases to medicinal and similar applications started to grow.

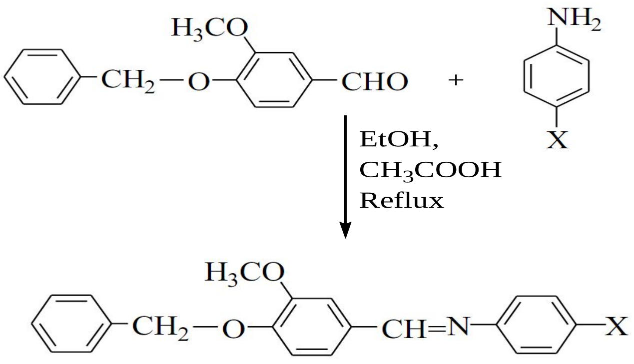
Schiff bases are referred to as auxiliary ligands because, unlike reactive ligands, they do not go through irreversible transformations themselves. Instead, they modify the structure and reactivity of the transition metal ion in the centre of the complex [3,4].

## II. SYNTHETIC STRATEGIES FOR SCHIFF BASES

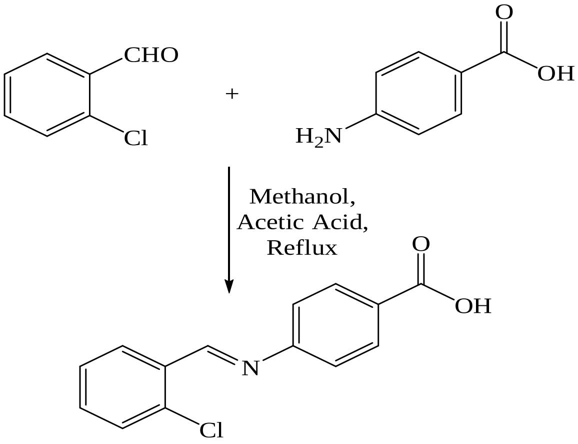
Hugo Schiff [2] first described the interaction of aniline with aldehydes in 1864, which is when the chemistry of Schiff's bases first emerged. The method involved Dean Stark apparatus for removal of water molecule to favour condensation to give imines.



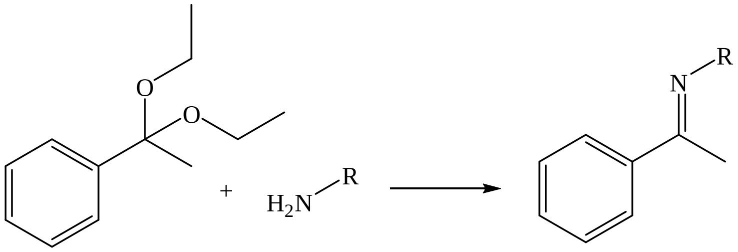
Hashim J. Aziz & Hiwa H. Ali [5] reported the synthesis of a series of Schiff bases from 4-benzyloxy 3-methoxy-benzaldehyde with substituted anilines in the presence of glacial acidic acid by using both traditional and the ultrasonic techniques.



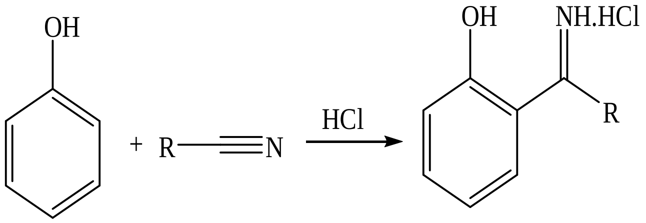
In 2005, Parekh *et al*. [6] reported the synthesis of some Schiff bases derived from 4-aminobenzoic acid.



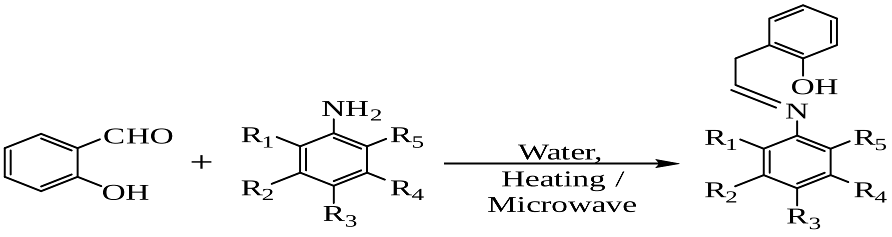
Claisen, in 1896 [7], described the synthesis of kitimine ($R_1R_2C{=}NR$). According to the study, aryl ketone, diethyl ketals and arylamines can be used to synthesis ketimine with high yields, whereas alkylamines produced relatively low yields.



Alkyl and aryl cyanides react effectively with phenols and their ether derivatives to produce Schiff's bases in extremely good yields in the presence of an acid catalyst reported by Houben and Fischer's [8] in 1929. By combining the cyanides with the proper phenol in ether and saturating the solution with HCl gas to produce, the reaction is carried out; however, $ZnCl_2$ must be employed with less reactive phenols.



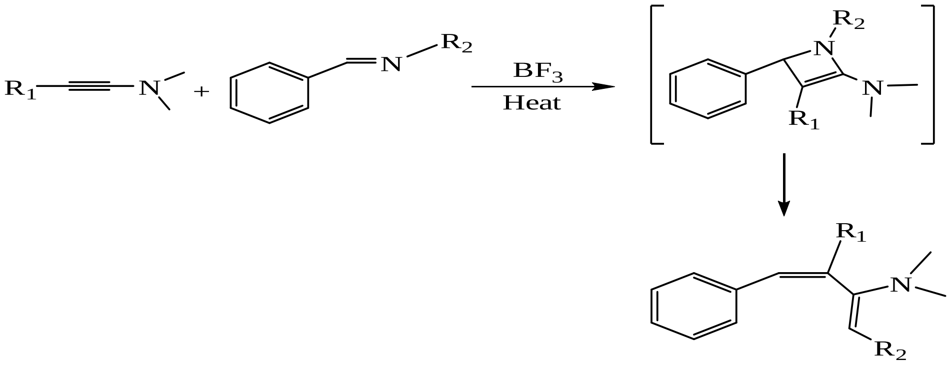
Bhagat *et al* [9], described a new efficient and environmentally friendly procedure for the synthesis of a series of salicylaldehyde-based Schiff bases under microwave irradiation. The study revealed that the choice of the solvent and reaction conditions allowed the final products to be generated in excellent yields in a one-step procedure, whereas experiments under thermal conditions led to lower yields with tedious work-up.



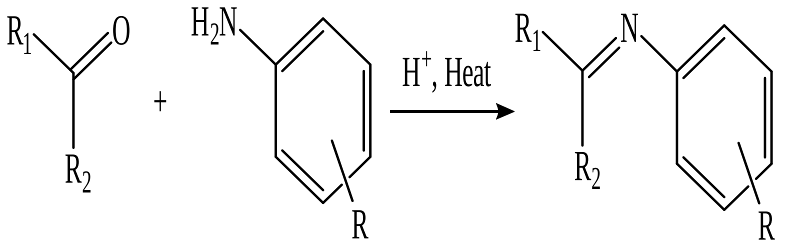
3(a-e)

(3a) $R_1 = F, R_2 = H, R_3 = F, R_4 = H, R_5 = H$
(3b) $R_1 = H, R_2 = H, R_3 = Cl, R_4 = H, R_5 = H$
(3c) $R_1 = F, R_2 = F, R_3 = F, R_4 = F, R_5 = H$
(3d) $R_1 = H, R_2 = H, R_3 = Br, R_4 = H, R_5 = H$
(3e) $R_1 = H, R_2 = H, R_3 = F, R_4 = H, R_5 = H$

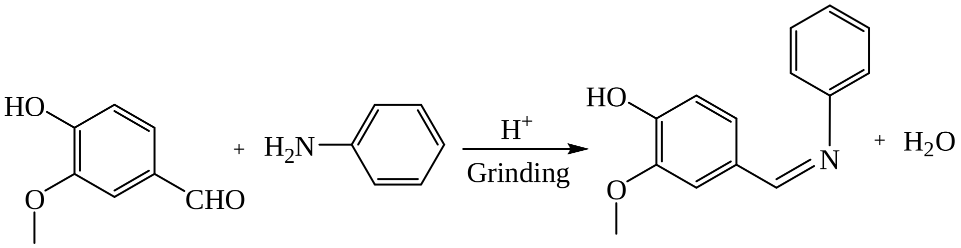
Viehe *et al* [10] reported the condensation of alkynyl amines with Schiff's bases in presence of $BF_3$ as catalyst. The mechanism of reaction involves cycloaddition reaction to form via azetines.



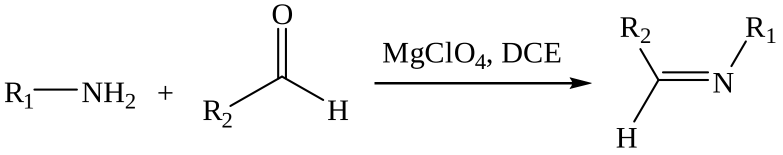
The synthesis of sterically hindered Schiff's bases was investigated by Love and Ren [11]. The study includes using substituted aromatic amines to treat the sterically hindered ketonic group of chemicals, such as camphor, bornanone, benzophenone, etc.



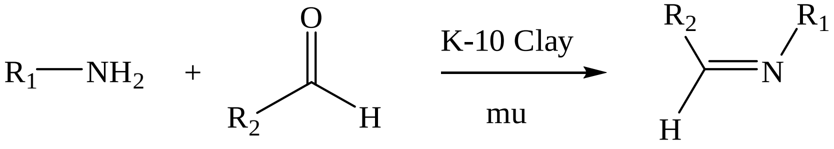
Abdurrafi *et al* [12], reported the synthesis of Schiff bases from vanillin and aniline with volume variations using natural acid catalysts from Belimbing Wuluh (Averrhoa Blimbi L.) using grindstone method.



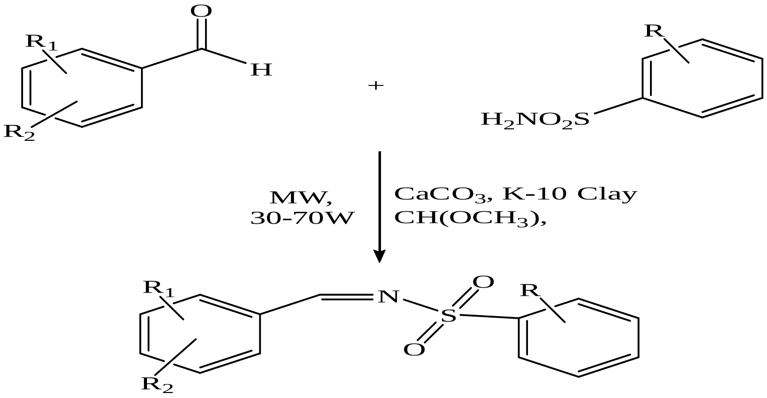
According to Chakraborti *et al* [13], magnesium perchlorate acts as a catalyst to produce imines from carbonyl compounds and amines in a quick and efficient manner at room temperature. Imines were produced in excellent yields when less electrophilic carbonyl compounds were combined with weakly nucleophilic amines.



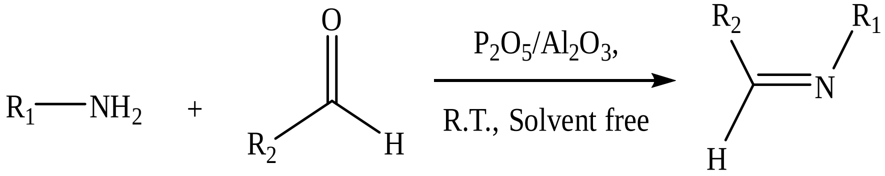
Clay was used to catalyse the synthesis of Schiff's bases via microwave irradiation, according to Varma *et al* [14]. The addition-elimination phases of the condensation reaction of primary amines with aldehydes include the addition of the basic nitrogen of the amine to the carbonyl carbon and the elimination of a water molecule to produce Schiff bases.



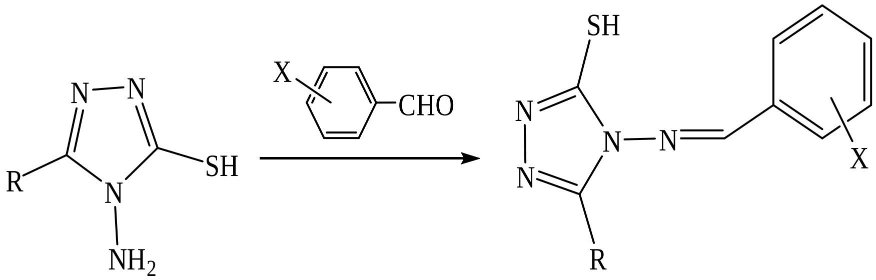
In 1999, Varma *et al* [15] used microwave thermolysis of aldehydes and sulfonamides in the presence of environmentally friendly reagents, calcium carbonate, and montmorillonite K-10 clay to quickly manufacture N-Sulfonylimines.



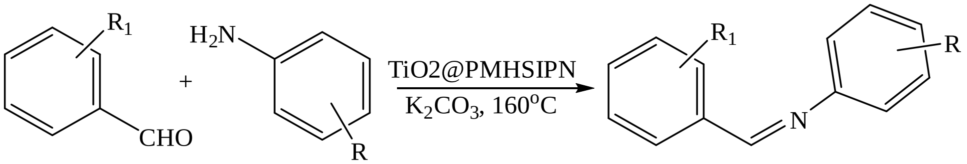
Naeimi *et al* [16] in 2006, reported that $P_2O_5/Al_2O_3$ effectively catalysed the synthesis of Schiff's bases from primary amines and carbonyl compounds in solvent-free environments.



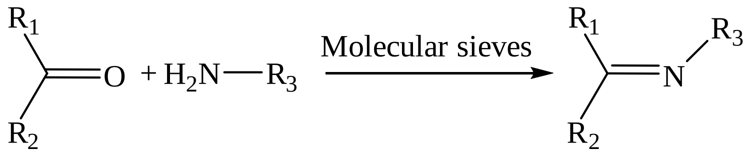
Sun *et al* [17] reported the synthesis of Schiff’s bases using 3-alkyl-4-amino-1,2,4-triazole-5-thione and substituted benzaldehyde as starting materials.



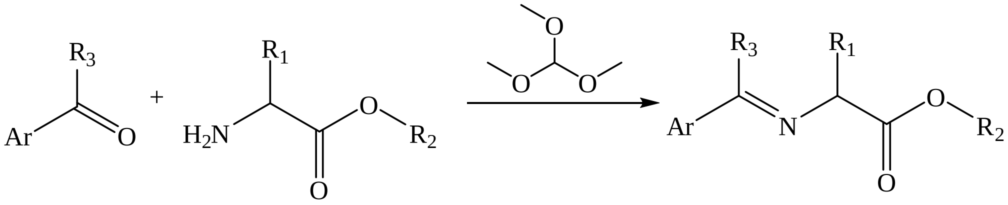
For the effective synthesis of Schiff's bases in good to exceptional high yields, Wang *et al* [18] used catalytic dehydrogenation and tandem transformation of aromatic alcohols, including oxidative coupling of alcohols with amines, utilising a catalytic quantity of organosilicon supported titania (TiO2@PMHSIPN).



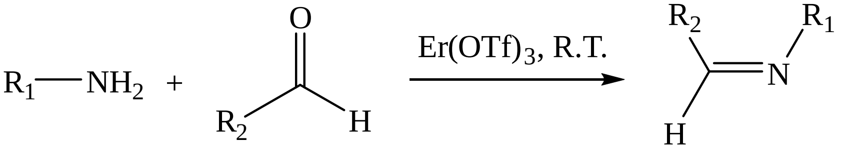
Molecular sieves were used by Taguchi and Westheimer [19] to synthesise Ketimines (Schiff's bases) from aryl/cyclic ketones. The approach is practically exhaustive and works well even with somewhat hindered compounds like camphor and medium-sized ring ketones.



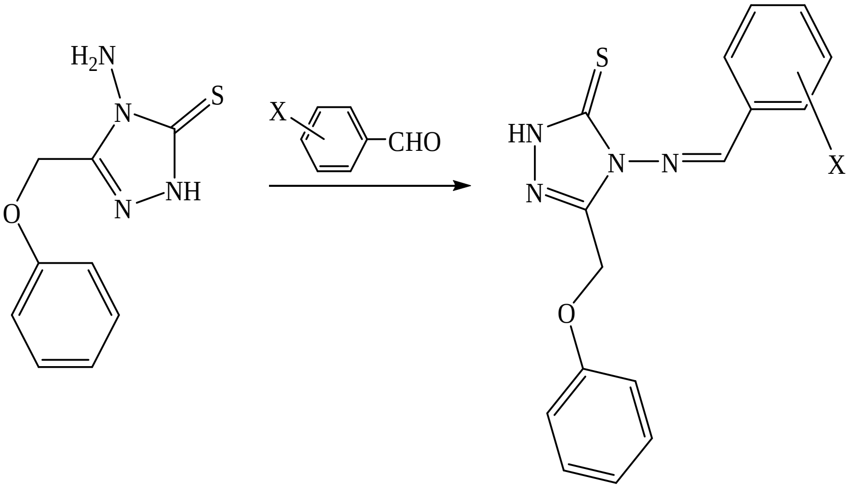
Look *et al* [20] synthesized Schiff’s bases from trimethyl orthoformate as a solvent. They found that trimethyl orthoformate is an effective dehydrating solvent for the formation of Schiff’s bases, in the solid and solution phases.



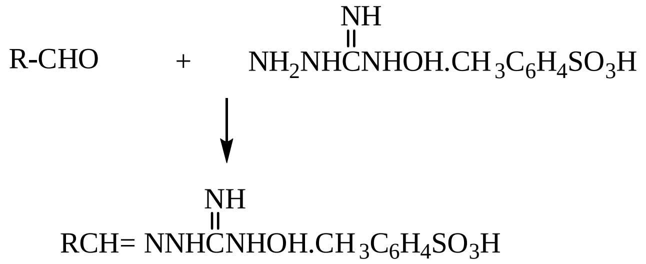
Erbium (III) Triflate was suggested by Dalpozzo *et al* [21] as a helpful catalyst for the synthesis of Schiff's bases. In order to produce high yields of Schiff's bases, carbonyl compounds and amines were treated in the reaction at room temperature.



4-amino-4,5-dihydro-3-(phenoxy-methyl)-1H-1,2,4-triazole-5-thione and substituted benzaldehydes were employed for the preparation of Schiff’s bases [22].



Wang *et al* [23] described the synthesis of substituted Schiff's bases of 1-Amino-3-hydroxyguanidine tosylate by reacting l-amino-3-hydroxyguanidine tosylate with different aromatic or heterocyclic aldehydes.

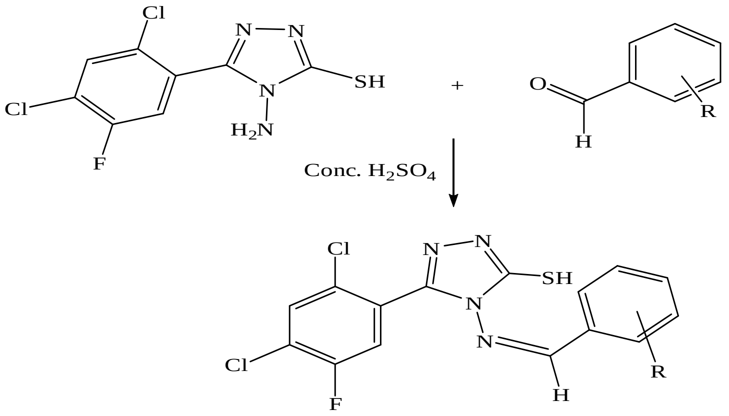


$$\text{R-CHO} \quad + \quad \text{NH}_2\text{NH}\overset{\overset{\text{NH}}{\|}}{\text{C}}\text{NHOH.CH}_3\text{C}_6\text{H}_4\text{SO}_3\text{H}$$

$$\downarrow$$

$$\text{RCH= NNH}\overset{\overset{\text{NH}}{\|}}{\text{C}}\text{NHOH.CH}_3\text{C}_6\text{H}_4\text{SO}_3\text{H}$$

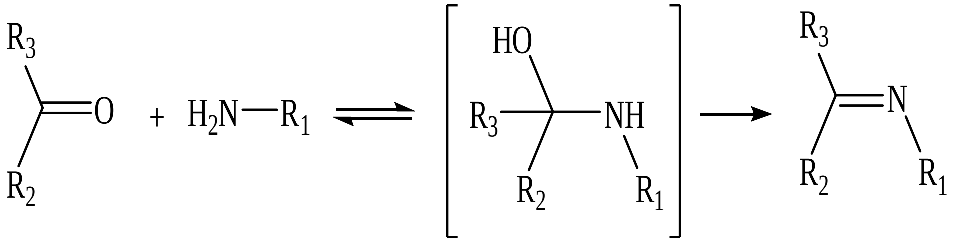
Karthikeyan *et al* [24] synthesized Schiff's bases from 4-amino-3-(2,4-dichloro-5-fluorophenyl)-5-mercapto-1,2,4-triazole and aldehyde.



## III. METHODS OF PREPARATION OF SUBSTITUTED SCHIFF'S BASES

### A. *Reaction of Aldehydes or Ketones with Amines*

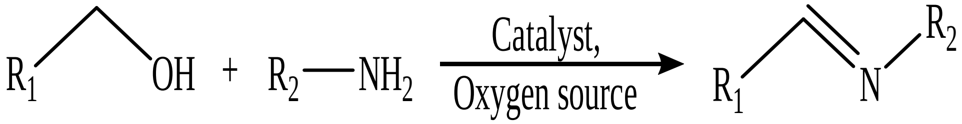
The initial reaction reported by Hugo Schiff in 1864 [2] is still the most comprehensive and often used technique for synthesizing imines. The procedure essentially entails the reaction of an aliphatic or aromatic aldehyde (or ketone) with a primary amine (aliphatic/aromatic), with the removal of one water molecule.



Aryl ketone, diethyl ketals and arylamines can be used to produce ketimine in higher yields while alkylamines only produce low yields [25, 26].

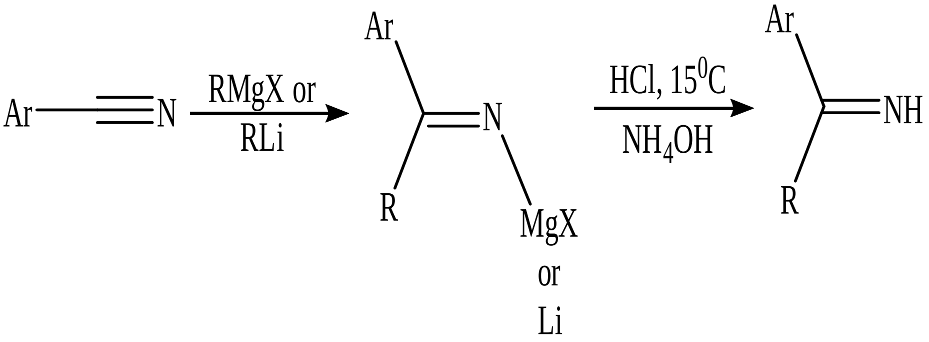
### B. *Aerobic Oxidative Synthesis between Alcohols and Amines*

Tandem oxidative synthesis from amines and alcohols is a relatively new technique for the generation of Schiff's bases [36, 37]. Since aldehydes and ketones are typically created from similar alcohols using an oxidative process, it has been discovered that producing imines simply through this technique is quite effective.



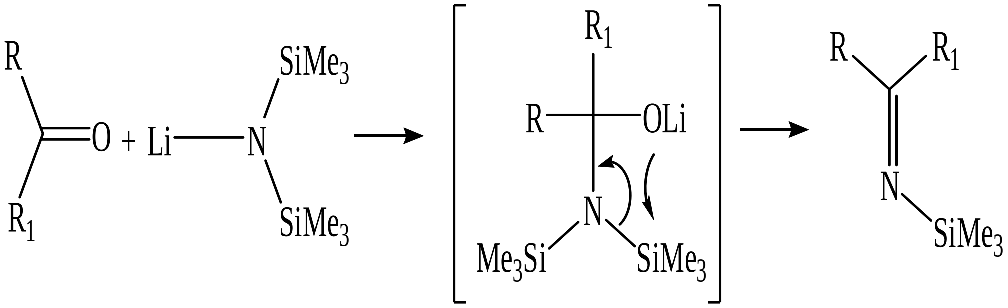
### *C. Addition of Organometallic Reagents to Cyanides*

Organometallic compounds have been used to create unsubstituted Schiff's bases [27, 28]. According to the hydrolysis conditions employed to breakdown the metallo-imine intermediate, the reaction of Grignard or organolithium reagents with aryl/alkyl cyanides has been optimised to yield imine, which can be developed to the corresponding ketones [27-28].



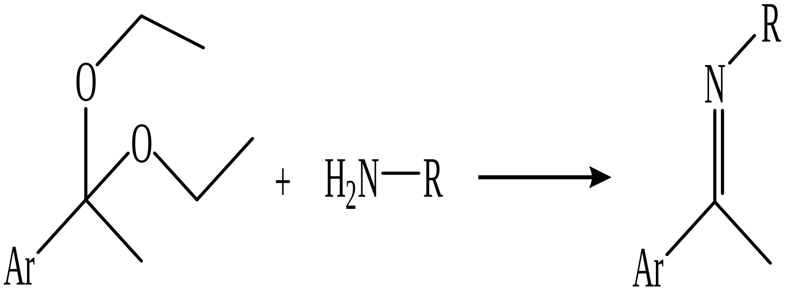
### *D. Addition Of Lithium Hexamethyldisilazide To Aldehydes Or Ketones*

According to Hart et al. [29], N-silylimines were formed by a reaction of lithium bis(trimethylsilyl)amide with aldehydes or ketones. The reaction occurs by an addition-elimination process that leads in the synthesis of an intermediate addition compound that, most likely through a four centres cyclic transition state, produces N-silylimines.



### *E. Synthesis Of Ketimines From Ketals*

In 1896 [7], Claisen described a reaction between ketals and amines to prepared ketimine. According to the study, aryl ketone, diethyl ketals and arylamines can be used to synthesis ketimines with high yields, whereas alkylamines produce low yields.



## IV. CONCLUSIONS

The present work is an attempt to highlight the importance of Schiff's bases and their applications. The synthetic protocols mostly involve dehydration using an amine with an appropriate aldehyde or ketone. Organometallic reagents and molecular sieves have appeared as attractive alternatives with improved yields. Further, Schiff's bases are largely used as a part pharmacophore for different drugs, as the group enhances flexibility and allows the introduction of novel groups or rings. In majority of drugs, the -C=N- moiety of Schiff's bases acts as a bridge or linker to club two different structural features. The work could be beneficial to organic and synthetic chemists.

## REFERENCES

[1] Raczuk, E., Dmochowska, B., Samaszko-Fiertek, J., & Madaj, J. (2022). Different Schiff Bases—Structure, Importance and Classification. Molecules, 27(3), 787. doi: 10.3390/molecules27030787.

[2] Schiff, H. (1864). Mittheilungen aus dem Universitätslaboratorium in Pisa: Untersuchungen ü das Chinolin. Annalen der Chemie und Pharmacie, 131(1), 112-117. doi: 10.1002/jlac.18641310112.

[3] Lundgren, R.L.; Stradiotto, M. (2016). Ligand Design in Metal Chemistry: Reactivity and Catalysis; Key Concepts in Ligand Design: An Introduction, John Wiley & Sons, Ltd.: Chichester, UK; Hoboken, NJ, USA, 1–13.

[4] Fryzuk, M.D.; Haddad, T.S.; Berg, D.J.; Rettig, S.J. (1991). Phosphine complexes of the early metals and the lanthanoids, Pure Appl. Chem., 63, 845–850.

[5] Hashim J. Aziz, H. H. A. (2010). Synthesis of a New Series of Schiff Bases Using Both Traditional and the Ultrasonic Techniques. Tikrit Journal of Pure Science, 15(3), 70-74.

[6] Parekh, J., Inamdhar, P., Nair, R., Baluja, S., & Chanda, S. (2005). Synthesis and antibacterial activity of some Schiff bases derived from 4-aminobenzoic acid. Journal of the Serbian Chemical Society, 70(10), 1155-1162. doi: 10.2298/jsc0510155p.

[7] Claisen, L. (1896). Ueber eine eigenthümliche Umlagerung. Berichte der deutschen chemischen Gesellschaft, 29(3), 2931-2933. doi: 10.1002/cber.189602903102.

[8] Houben, J., & Fischer, W. (1929). Formation of aromatic nitriles by basic hydrolysis of trichloromethyl aryl ketimines. Acidic hydrolysis yields ketones. Journal für Praktische Chemie, 123(1), 262-275. doi: 10.1002/prac.19291230117

[9] Bhagat, S., Sharma, N., & Chundawat, T. S. (2013). Synthesis of Some Salicylaldehyde-Based Schiff Bases in Aqueous Media. Journal of Chemistry, 2013, 1-4. doi: 10.1155/2013/909217.

[10] Viehe, H. G., Buijle, R., Fuks, R., Merényi, R., & Oth, J. M. F. (1967). Acylation, Alkylation, and Protonation of Alkynylamines. Angewandte Chemie International Edition in English, 6(1), 77-78. doi: 10.1002/anie.196700771.

[11] Love, B. E., & Ren, J. (2002). Synthesis of sterically hindered imines. The Journal of Organic Chemistry, 58(20), 5556-5557. doi: 10.1021/jo00072a051.

[12] Abdurrafi, F. F. H., Hanapi, A., & Ningsih, R. (2020). Synthesis of schiff base compound from vanillin and aniline volume variations of acid catalyst from Belimbing Wuluh using grindstone method. IOP Conference Series: Earth and Environmental Science, 456(1), 012018. doi: 10.1088/1755-1315/456/1/012018.

[13] Chakraborti, A. K., Bhagat, S., & Rudrawar, S. (2004). Magnesium perchlorate as an efficient catalyst for the synthesis of imines and phenylhydrazones. Tetrahedron Lett, 45(41), 7641-7644. doi: 10.1016/j.tetlet.2004.08.097.

[14] Varma, R. S., Dahiya, R., & Kumar, S. (1997). Clay catalyzed synthesis of imines and enamines under solvent-free conditions using microwave irradiation. Tetrahedron Lett, 38(12), 2039-2042. doi: 10.1016/s0040-4039(97)00261-x.

[15] Vass, A., Dudás, J., & Varma, R. S. (1999). Solvent-free synthesis of N-sulfonylimines using microwave irradiation. Tetrahedron Lett, 40(27), 4951-4954. doi: 10.1016/s0040-4039(99)00867-9.

[16] Naeimi, H. S., F.; Rabiei, K. (2006). Mild and convenient one pot synthesis of Schiff bases in the presence of $P_2O_5/Al_2O_3$ as new catalyst under solvent-free conditions. Journal of Molecular Catalysis a Chemical, 260(1), 100-104(105).

[17] Sun, X.-H., Tao, Y., Liu, Y.-F., Chen, B., Jia, Y.-Q., & Yang, J.-W. (2008). Synthesis and Biological Activities of Alkyl Substituted Triazolethione Schiff Base. Chinese Journal of Chemistry, 26(6), 1133-1136. doi: 10.1002/cjoc.200890202.

[18] Wang, H., Zhang, J., Cui, Y.-M., Yang, K.-F., Zheng, Z.-J., & Xu, L.-W. (2014). Dehydrogenation and oxidative coupling of alcohol and amines catalyzed by organosilicon-supported TiO2@PMHSIPN. RSC Advances, 4(65), 34681. doi: 10.1039/c4ra06685e.

[19] Westheimer, F. H., & Taguchi, K. (2002). Catalysis by molecular sieves in the preparation of ketimines and enamines. The Journal of Organic Chemistry, 36(11), 1570-1572. doi: 10.1021/jo00810a033.

[20] Look, G. C., Murphy, M. M., Campbell, D. A., & Gallop, M. A. (1995). Trimethylorthoformate: A mild and effective dehydrating reagent for solution and solid phase imine formation. Tetrahedron Lett, 36(17), 2937-2940. doi: 10.1016/0040-4039(95)00442-f.

[21] R. Dalpozzo, A. D. N., M. Nardi, B. Russo, A. Procopio. (2006). Erbium (III) Triflate: A Valuable Catalyst for the Synthesis of Aldimines, Ketimines, and Enaminones. Synthesis, 7, 1127-1132.

[22] Sun, Q., Zheng, F., Sun, X., & Wang, W. (2009). Construction of a dinuclear silver(I) coordination complex with a Schiff base containing 4-amino-1,2,4-triazole ligands. Acta Crystallogr Sect E Struct Rep Online, 65(Pt 3), m283-284. doi: 10.1107/S1600536809004760.

[23] Wang, P. H., Keck, J. G., Lien, E. J., & Lai, M. M. C. (2002). Design, synthesis, testing, and quantitative structure-activity relationship analysis of substituted salicylaldehyde Schiff bases of 1-amino-3-hydroxyguanidine tosylate as new antiviral agents against coronavirus. Journal of Medicinal Chemistry, 33(2), 608-614. doi: 10.1021/jm00164a023.

[24] Karthikeyan, M. S., Prasad, D. J., Poojary, B., Subrahmanya Bhat, K., Holla, B. S., & Kumari, N. S. (2006). Synthesis and biological activity of Schiff and Mannich bases bearing 2,4-dichloro-5-fluorophenyl moiety. Bioorganic & Medicinal Chemistry, 14(22), 7482-7489. doi: 10.1016/j.bmc.2006.07.015.

[25] Langheld, K. (1909). Über das Verhalten von α-Aminosäuren gegen Natriumhypochlorit. Berichte der deutschen chemischen Gesellschaft, 42(2), 2360-2374. doi: 10.1002/cber.190904202134.

[26] Reddelien, G. (1920). Über die Zersetzung von Anilen. (Über die katalytische Wirkungsweise von Halogenwasserstoffsäuren bei Kondensationen, II). Berichte der deutschen chemischen Gesellschaft (A and B Series), 53(2), 355-358. doi: 10.1002/cber.19200530233.

[27] Pickard, P. L., & Young, C. W. (1951). Ketimines. III. ι-Cyclohexylalkyl Alkyl Type1. Journal of the American Chemical Society, 73(1), 42-43. doi: 10.1021/ja01145a016.

[28] Pickard, P. L., & Tolbert, T. L. (1961). An Improved Method of Ketimine Synthesis. The Journal of Organic Chemistry, 26(12), 4886-4888. doi: 10.1021/jo01070a025.

[29] Hart, D. J., Kanai, K., Thomas, D. G., & Yang, T. K. (2002). Preparation of primary amines and 2-azetidinones via N-(trimethylsilyl)imines. The Journal of Organic Chemistry, 48(3), 289-294. doi: 10.1021/jo00151a002.