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Structure, synthesis and application of azines: A Historical Perspective

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Structure, synthesis and application of azines: A Historical Perspective†

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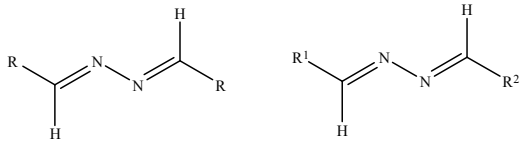
The present review provides a general survey of the chemistry of 2,3-diaza-1,3-butadienes (azines). We first briefly describe azines and then discuss the literature concerning the synthesis, properties, applications, and reactivity of these compounds. Finally, we illustrate their relevance and examine their organometallic chemistry. Such detailed survey of the broad chemical aspects of azine derivatives seems appropriate, as it has not previously been provided.

Contents

† Dedicated to the memory of Prof. R. Arshady & Prof. M. N. Sarbolouki

1. Introduction

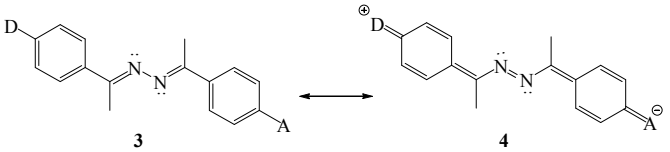
The term azine has two meanings in chemistry: In heterocyclic chemistry, azines are aromatic six-membered rings containing one (pyridine) to six N atoms (hexazine). In alicyclic chemistry, azines are compounds resulting from the reaction of two molecules of identical carbonyl compounds (symmetrical azines **1**) or, more commonly, from the reaction of two different carbonyl compounds (unsymmetrical azines **2**) with hydrazine (Figure 1). The compounds are called aldazines or ketazines depending on whether the carbonyl compound is an aldehyde or a ketone, respectively.[1]



1 **2**

Figure 1.

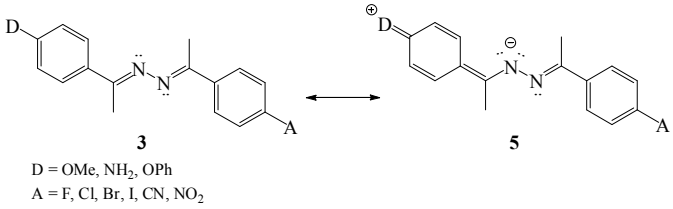
Azines that are N-N-linked diimines are 2,3-diaza analogs of 1,3-butadiene. They are a class of compounds with interesting chemical properties and undergo a wide variety of chemical processes.[2] The two imine bonds that form the azine moiety may be considered as polar acceptor groups oriented in opposite directions, as they include an N–N bond.[3] On the basis of their relationship to butadiene, electronic delocalization may be expected. Two resonance structures illustrating delocalization are represented by **3** and **4** (Scheme 1). However, crystallographic data, nuclear magnetic resonance (NMR) spectroscopic studies, and theoretical calculations provide little evidence for delocalization within the azine backbone. Thus, it was concluded that an azine bridge between two conjugated systems, termed as a "conjugation stopper", prevents delocalization, as shown by the resonance structure **5** (Scheme 2).[4]



3 **4**

D = OMe, NH_2, OPh
A = F, Cl, Br, I, CN, NO_2

Scheme 1.



Scheme 2.

During the past several years, one of the active areas of organic chemistry is the study of systems containing two conjugated double bonds. Within this general classification of compounds, three types of molecules that have attracted the most attention are 1,3-dienes **6**, enones **7**, and 1,2-diones **8** (Figure 2).[5]

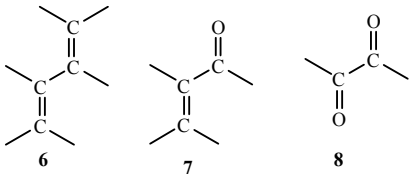


Figure 2.

In addition to the molecules mentioned above, azines **9**, enimines **10a** and 1**0b**, and 1,2-diimines **11a** and **11b** constitute several additional classes of compounds possessing two conjugated double bonds (Figure 3).[6,7]

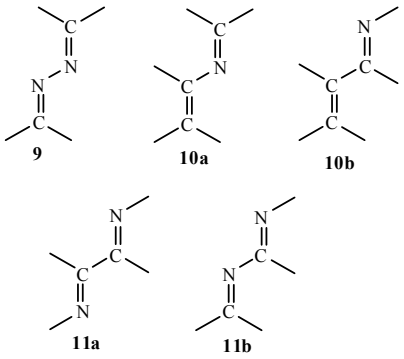
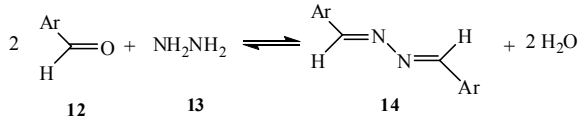


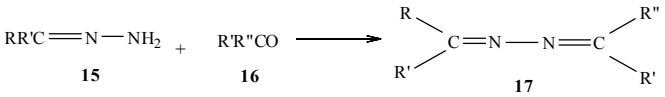
Figure 3.

In the mechanisms of addition of hydrazines to carbonyl compounds, the bifunctionality of hydrazine results in two types of complicated scenarios: First, the nucleophile not only can exist as a base, but also as mono- and diprotonated forms. Whereas the diprotonated form does not possess a nitrogen atom with a free electron pair, which is necessary for nucleophilic attack by amines, the monoprotonated and unprotonated forms of hydrazine can behave as nucleophiles. Second, formation of hydrazone from the reaction between the carbonyl compound and one molecule of hydrazine may be followed by a reaction with a second molecule of the carbonyl compound. This reaction results in formation of an azine of the type ArCH=N–N=CHAr **14** (Scheme 3).[8]



Scheme 3.

Formaldehyde azine, the simplest azine, was prepared in 1959 by Neureiter.[5] The rate of reaction of hydrazine with various carbonyl compounds decrease in the following order: aldehyde > dialkyl ketone > alkaryl ketone > diaryl ketone. Reaction of aldehydes and dialkyl ketones with hydrazine in water or alcoholic medium produce the hydrazone or azine.[9] Aldazines form more quickly than do ketazines. In fact, the reaction of hydrazones of aldehyde with a second molecule of aldehyde is faster than reaction with hydrazine itself; thus, aldazine is the normal product. On the other hand, ketazines require the presence of excess ketone together with acetic or formic acid as catalyst (Scheme 4).[10]



Scheme 4.

Azines are useful for the isolation, purification, and characterization of carbonyl compounds. They have several advantages as protective agents: 1) economic advantage due to low cost (only one-half equivalent of protective group is required), 2) easy isolation of the products due to their symmetrical structure and high melting points, and 3) easy identification of the products due to their fully conjugated and colorful structures.[11,12]

Unsymmetrical azines are particularly interesting because of their ability of their functionality to link two dissimilar groups in useful ways. For example, they can form steroidal opiate derivatives, which show very long opioid antagonist activity. This finding suggests that a new and general method for synthesizing unsymmetrical azines may greatly facilitate the development of other useful applications.[2,13] Generally, symmetrical azines are crystalline materials, facilitating their purification by recrystallization. Ease of purification and one-step synthesis with quantitative yield of the desired product are two main advantages of symmetrical azines. However, crystallinity is the key limiting factor in the application of various chromophores connected via azine linkage in optoelectronic devices. Unsymmetrical azines prepared from two different carbonyl compounds are more promising from this viewpoint, as their tendency for crystallization is significantly lower.[14]

2. Synthesis of azines

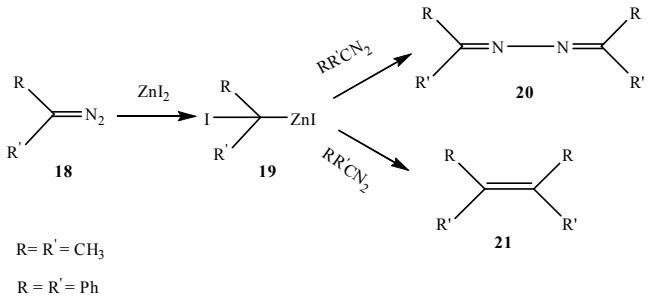
Different approaches for the synthesis of symmetrical and unsymmetrical azines are described in this review. Symmetrical azines are readily synthesized, directly or indirectly, by the reaction of hydrazine with excess aldehyde or ketone.[15,16] However, preparation of their unsymmetrical counterparts is

more challenging. Novel and selective methods for the synthesis of mixed azines have been reported.[17]

2.1. Synthesis of symmetrical azines

2.1.1. Synthesis from iodoalkylzinc iodide (19)

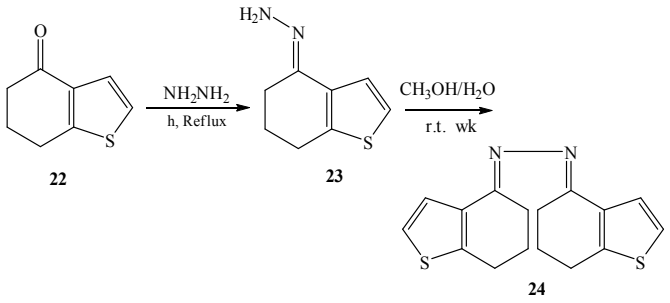
In 1962, Applequist and Babad used iodoalkylzinc iodide to synthesize symmetrical azines. Compound **19** was obtained by the reaction of a diphenyldiazomethane, 2-diazopropane, or both with ZnI_2. The iodoalkylzinc iodide then reacts rapidly with the diazo compound **17** to yield the azine **20** and the alkene **21** (Scheme 5).[6]



Scheme 5.

2.1.2. Synthesis by reaction of 4-oxo-4,5,6,7-tetrahydrothianaphthene (22) with hydrazine

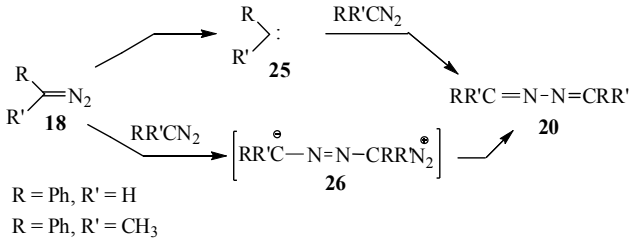
In 1987, Cook and coworkers prepared the crystalline azine **24** with a yield of 72% (Scheme 6). The reaction of **22** in refluxing hydrazine gave the hydrazone **23**. Compound **23** was then heated in refluxing ethanolic hydrogen chloride for several hours to obtain **24**.[18]



Scheme 6.

2.1.3. Synthesis by reaction of phenyldiazomethane with 1-diazo-1-phenylethane

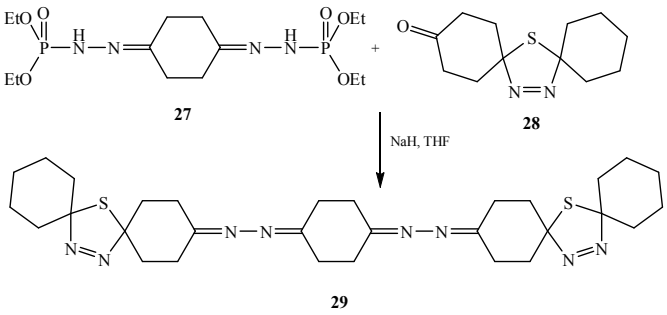
In 1989, Abelt and Pleier examined the bimolecular dimerization of phenyl diazomethane, 1-diazo-1-phenylethane, or both to prepare azines.[9] Azines often are the major products of thermal decomposition of diazo compounds.[19] They can result from the reaction of a carbene with a diazo compound and from the bimolecular reaction of two diazo compounds. The mechanism of reaction was found to involve nucleophilic attack of the carbon atom of the first diazo compound on the terminal nitrogen of the second compound. The resulting intermediate **26**, which contains groups of carbanion and diazonium, loses N_2, forming the azine **20** (Scheme 7).



Scheme 7.

2.1.4. Synthesis by treatment of a ketone (28) and bishydrazone (27)

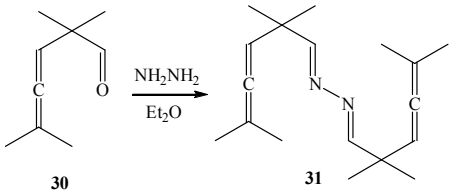
In 1995, Jenneskens and coworkers reported the synthesis of azine **29** from **28** and **27** (Scheme 8). Azines were used as precursors to prepare oligo(cyclohexylidenes) in this work.[20]



Scheme 8.

2.1.5. Synthesis by reaction of a homoallenylaldehyde (30) and hydrazine monohydrate

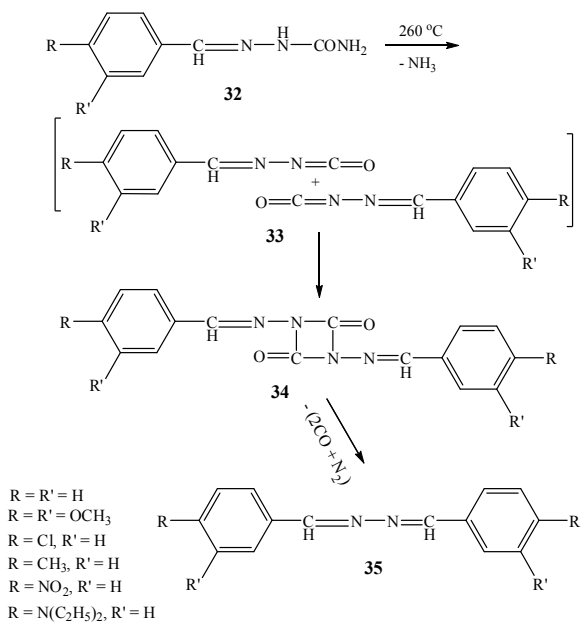
Marek prepared azine **31** from **30** in 1997 by adding an equivalent of hydrazine monohydrate and a catalytic amount of *p*-TSA in diethylether (Scheme 9). The product was purified by column chromatography on silica gel using CH_2Cl_2 to give compound **30** with 38% yield.[21]



Scheme 9.

2.1.6. Synthesis by thermolysis of aryl semicarbazones (32)

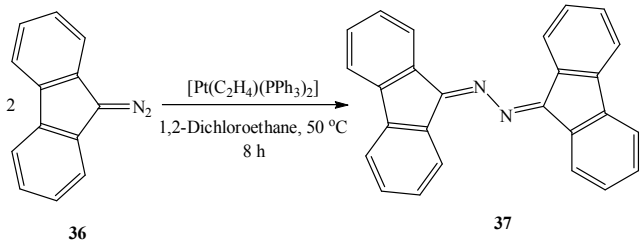
Shah and Chudgar reported in 2000 the thermolysis of **32** to azines **35**. This reaction occurs through reactive N-substituted isocyanate intermediates **33**, which can convert in situ to the unstable isocyanate dimer **34** by undergoing threefold extrusion (2CO, N_2) to give benzalazine **35** (Scheme 10).[12]



Scheme 10.

2.1.7. Decomposition of diazo compounds catalyzed by platinum(0) complexes

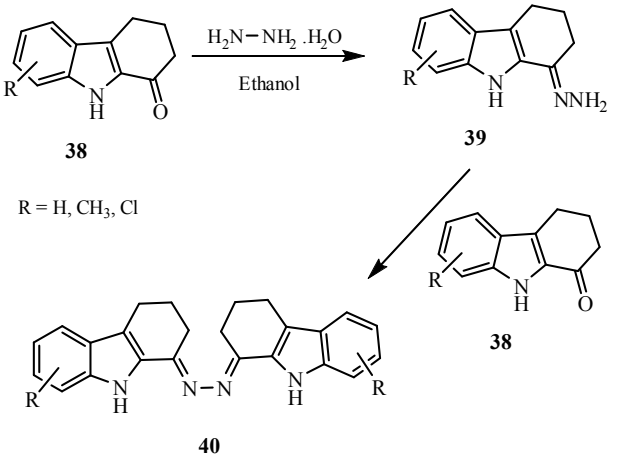
In 2002, Michelin et al. described the catalytic decomposition of 9-diazofluorene (**36**) in the presence of the platinum(0) complex $[Pt(C_2H_4)\text{-}(PPh_3)_2]$ (1% mol) to give difluoren-9-ylidene-hydrazine **37** in high yield (Scheme 11).[22]



Scheme 11.

2.1.8. Synthesis by treatment of 1-oxo-1,2,3,4-tetrahydrocarbazoles (38) with hydrazine hydrate

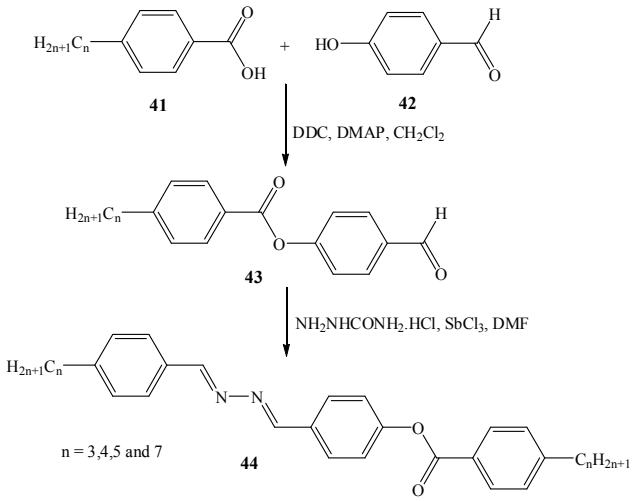
In 2004, Danish and Prasad reported the reaction of **38** with hydrazine hydrate in absolute ethanol, which afforded *N*,*N*-bis-carbazolylazine derivatives **40**. In the proposed mechanism, it is reasonable to assume that **38** forms hydrazone **39**. In other words, in situ condensation of **39** with **38** results in the formation of **40** (Scheme 12). However, their attempt to isolate **39** was unsuccessful. All compounds have great potential as antibacterial and antifungal agents because of the presence of the azine group. Particularly, product **40** with R = 6-Cl showed high antibacterial and antifungal activity because of the presence of chloro substituents.[23]



Scheme 12.

2.1.9. Synthesis by reaction of hydrazinecarboxamide with aldehydes

Yang et al. synthesized a series of symmetrical azine-type liquid crystals (LCs) **44** in 2007 (Scheme 13). These LCs had high clearing point (−320°C) and broad thermal range for the nematic phase (−154°C). They also found that the end groups of the LCs affect their mesomorphic properties. Compounds with propyl, butyl, and pentyl end groups had only nematic phases, and their clearing points increased with molecular length; whereas compounds with heptyl end groups showed nematic and smectic properties and lower clearing points.[24]

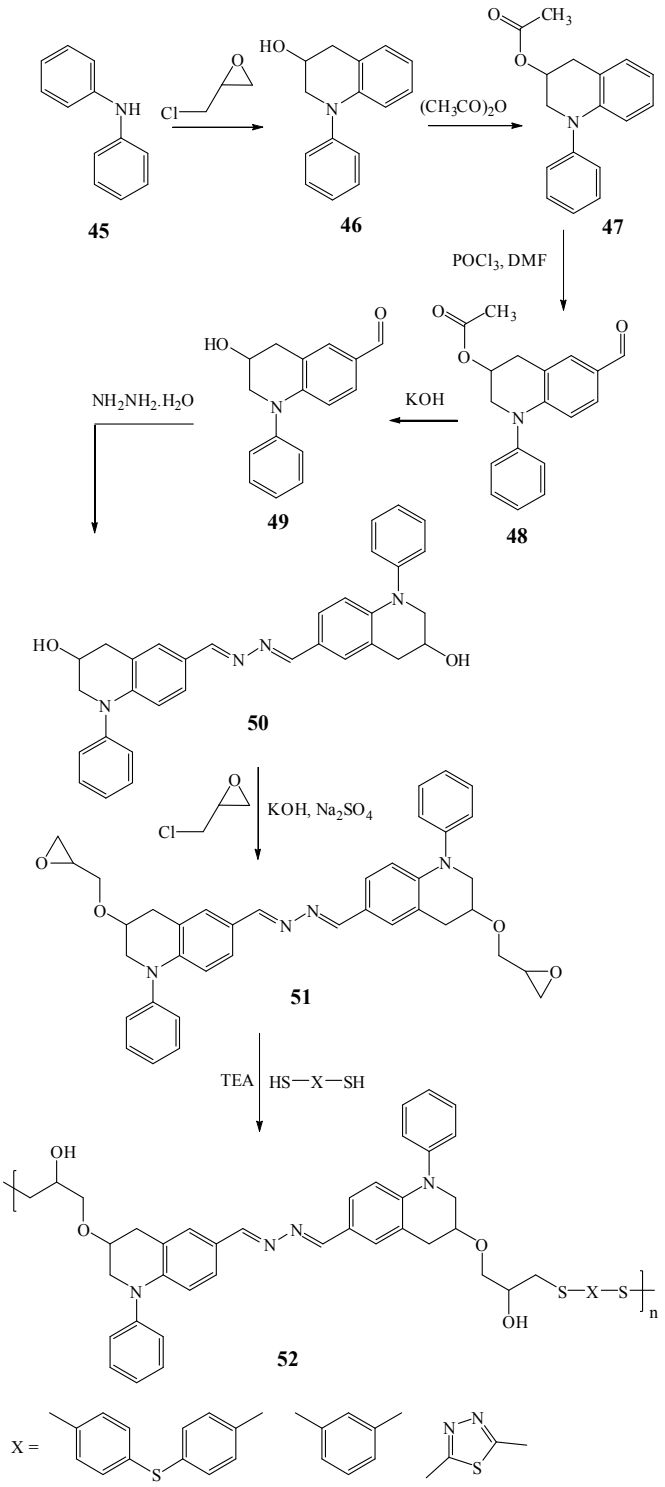


Scheme 13.

2.1.10. Synthesis from glycidyl-terminated azine and aromatic dimercapto compounds

Arlauskas and Getautis designed in 2011 a synthetic route yielding azine chromophore-containing monomers and polymers with charge-transport ability. They reported the synthesis and characterization of new photoconductive polymers containing symmetrical azine moieties (**52**) obtained by polyaddition of glycidyl-terminated 3-hydroxy-1-phenyl-1,2,3,4-tetrahydroquinoline-6-carbaldehyde azine

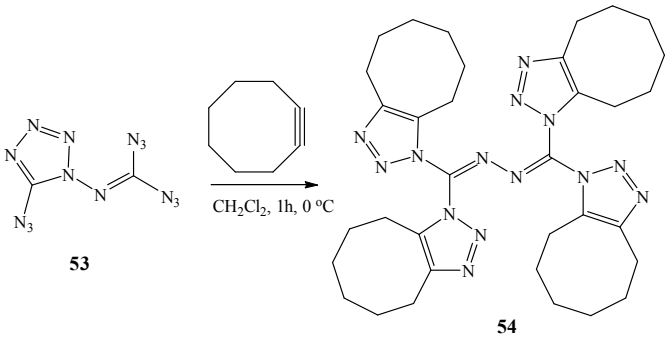
(**51**) and aromatic dimercapto compounds (Scheme 14). For the first time, the charge-drift mobility of azine polymers was investigated.[14]



Scheme 14.

2.1.11. Synthesis through reaction of tetrazole with excess cyclooctyne

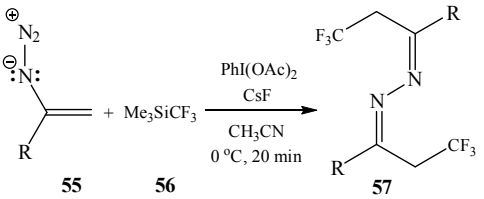
In 2013, Banert et al. demonstrated that treatment of tetrazole **53** with excess cyclooctyne afforded the cycloadduct **54** (Scheme 15), the structure of which was confirmed by NMR spectroscopy. Conversion of the electron-releasing azido groups into electron-withdrawing 1*H*-1,2,3-triazol-1-yl units shifted the tetrazole–azidoazomethine equilibrium [9*c*,19], liberating the fourth azido function, which reacted with cyclooctyne to produce **54**.[25]



Scheme 15.

2.1.12. Synthesis by radical trifluoromethylation of vinyl azides

In 2014, Chiba et al. developed $PhI(OAc)_2$-mediated radical trifluoromethylation of vinyl azides **55** using Me_3SiCF_3 to efficiently generate α-trifluoromethyl azines **57** (Scheme 16). Moreover, facile protocols were devised to convert α-trifluoromethyl azines into valuable fluorine-containing compounds. They expected that the radical trifluoromethylation of vinyl azides enables a new approach for the synthesis of biologically and medicinally important fluorine-containing molecules.[26]

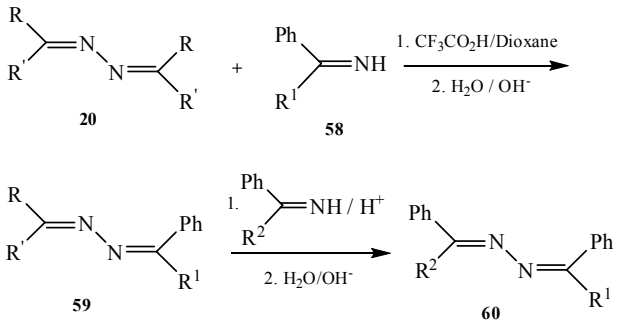


Scheme 16.

2.2. Synthesis of unsymmetrical azines

2.2.1. Synthesis by exchange of alkylidene group between azines and imines

Barluenga and coworkers reported in 1982 a new method to prepare unsymmetrical azines. It is based on the acid-catalyzed exchange of alkylidene group between azines and imines, as shown in Scheme 17. This method provides a simple route to prepare unsymmetrical azines of type **60**.[10]



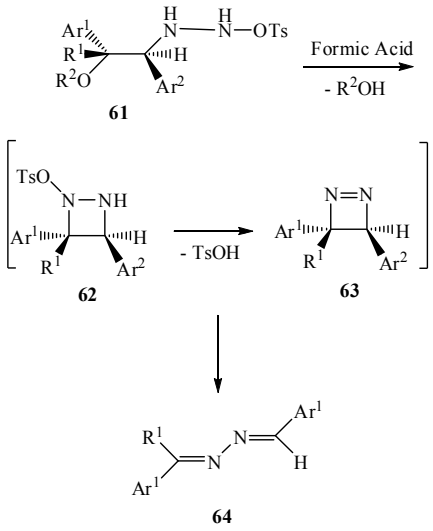
R' = H, Alkyl

R = R^1 = R^2 = Alkyl, Phenyl

Scheme 17.

2.2.2. Synthesis by treatment of *erythro*-1,2-diaryl-2-(2-tosylhydrazino)-ethan-1-ol derivatives (61) and formic acid

In 1983, Rosini and coworkers used another synthetic route to produce unsymmetrical azines (**64**). This procedure consists of treatment of **61** and formic acid. The reaction proceeds through a four-membered ring intermediate (Scheme 18).[1]



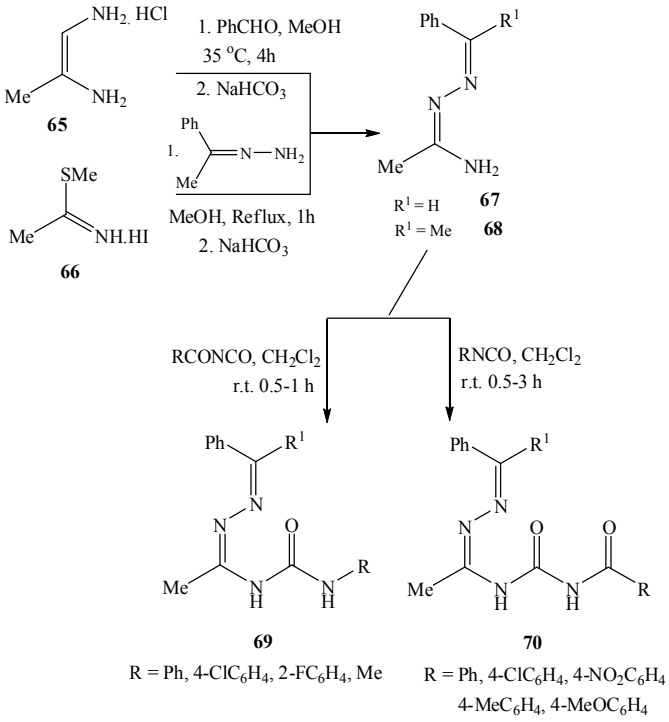
R^1 = R^2 = H, Alkyl

Ar^1 = Ar^2 = C_6H_5, 4-CH_3-C_6H_5, 4-OMe-C_6H_5

Scheme 18.

2.2.3. Synthesis from acetamidrazone hydrochloride (65) and/or *S*-methylthioacetamidate hydroiodide (71)

In 1995, Lee and coworkers reported the synthesis of azines **67** and **68** using **65** and benzaldehyde, as well as synthesis by reaction of acetophenone hydrazine with **71**. Uridoazines **69** and **70** were produced by the reactions of azines **67** and **68** with isocyanates in dichloromethane at room temperature (Scheme 19).[27]



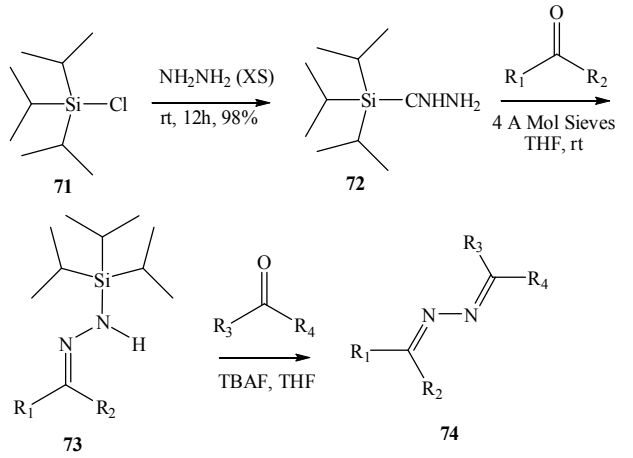
R = Ph, 4-ClC_6H_4, 2-FC_6H_4, Me

R = Ph, 4-ClC_6H_4, 4-$NO_2C_6H_4$ 4-MeC_6H_4, 4-$MeOC_6H_4$

Scheme 19.

2.2.4. Synthesis by reaction of triisopropylsilylhydrazine (72) with aldehydes and ketones

In 2000, Soderquist and coworkers introduced **72**, which they easily prepared from anhydrous hydrazine and chlorotriisopropylsilane, **71**. Compound **72** readily reacts with aldehydes and ketones, producing triisopropylsilyl hydrazones **73**. Desilylation of **73** with tetra-*n*-butylammonium fluoride in the presence of a second aldehyde or ketone produces the desired unsymmetrical azines, **74** (Scheme 20).[28]



R_1 = H, Me, Et, Cyclopentane, tBu-cyclohexane

R_2 = Et, Ph, Cyclopentane, tBu-cyclohexane

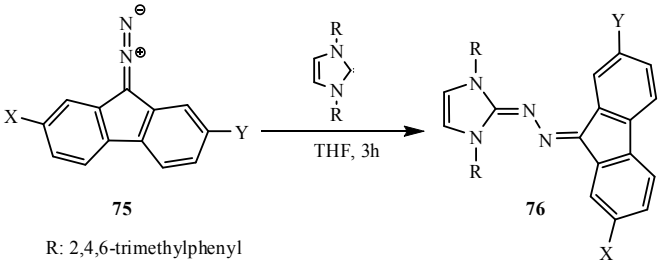
R_3 = H, Ph, Et, Cyclopentane, Furyl

R_4 = H, Et, Ph, Cyclopentane, Furyl

Scheme 20.

2.2.5. Synthesis by reaction of *N*-heterocyclic carbenes with diazoalkanes

Hopkins and coworkers developed in 2001 a very simple and convenient procedure to synthesize mixed azines. *N*-heterocyclic carbenes **75** react with diazoalkanes to yield the addition products, azines **76** (Scheme 21). This reaction is useful because it enables the formation of azines in a few steps. The substituent on both diazoalkane and carbine precursors can be varied to yield different substituted azines. This reaction occurs smoothly at room temperature and produces reasonable yields.[29]



R: 2,4,6-trimethylphenyl

X = Y = H

X = Y = Br

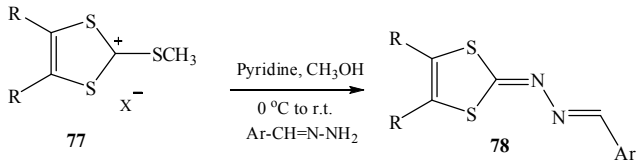
X = Y = Cl

X = F , Y = H

Scheme 21.

2.2.6. Synthesis by reaction of nitro-substituted (hetero)aromatic aldehydes with 2-methylthio-1,3-dithiolium salts (77)

In 2001, Moreno-Mañas and coworkers reported the synthesis and characterization of the first push–pull 1,3-dithiol-2-ylidene derivatives containing an azine spacer (Scheme 22). The azines **78** were prepared by reaction of nitro-substituted (hetero)aromatic aldehydes with **77**. Their electrochemical and second-order nonlinear optical (NLO) properties were investigated by electric field-induced second harmonic (EFISH) measurements.[30]



$R = SCH_3$, $X = BF_4$

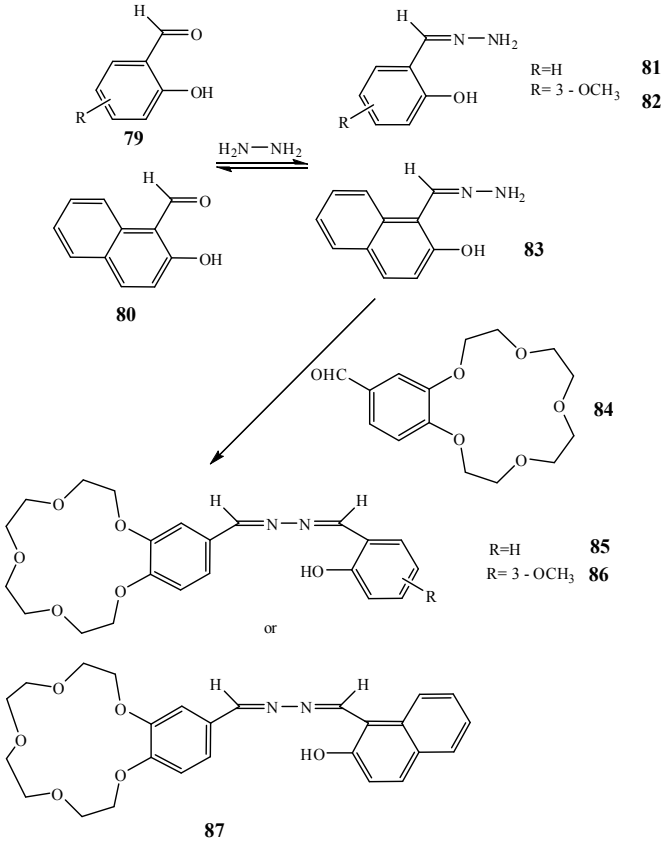
R = H, X= I

Ar = 4-$NO_2C_6H_5$, 2,4-$(NO_2)_2C_6H_4$, 5-NO_2-thiophene

Scheme 22.

2.2.7. Synthesis by Schiff condensation of hydrazone with 4-formyl-benzo-15-*crown*-5 ether (84)

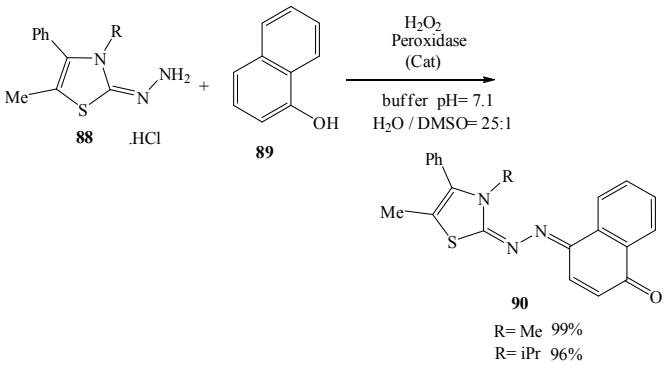
In 2003, Sousa and et al. reported the synthesis of Schiff base ligands functionalized with crown ethers containing a flexible spacer between the two subunits. In the first step, they prepared new unsymmetrical ligands functionalized with NH_2 groups (adducts **81**, **82**, and **83**) by Schiff condensation of hydrazine with an aldehyde. In the second step, the NH_2-functionalized compounds were reacted with **84**. Products of the second Schiff condensation are the original ligands with appended crown ether, namely, compounds **85**, **86**, and **87** (Scheme 23).[31]



Scheme 23.

2.2.8. Synthesis by oxidative coupling of 3-alkyl-2-hydrazono-4-thiazolines (85) and α-naphthol (86) catalyzed by horseradish peroxidase (HRP)

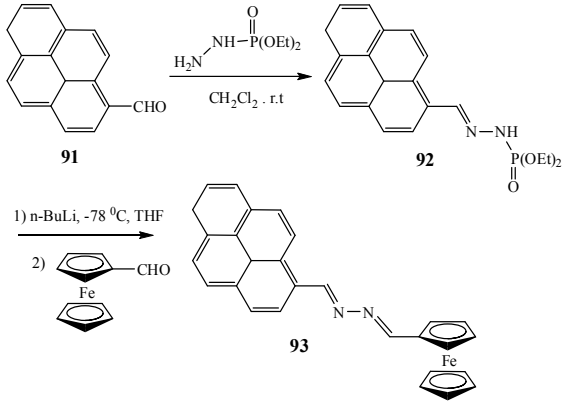
Pfeiffer and coworkers studied in 2005 the synthesis of azine pigments by HRP-catalyzed oxidative coupling of **85** and **86** in the presence of hydrogen peroxide. These transformations allow an environmentally benign synthesis of *p*-naphthoquinone-thiazol-2-on-azines **90** under mild conditions (Scheme 24).[32]



Scheme 24.

2.2.9. Synthesis by metallation of naphthaldehyde with butyllithium followed by reaction with ferrocene carboxaldehyde

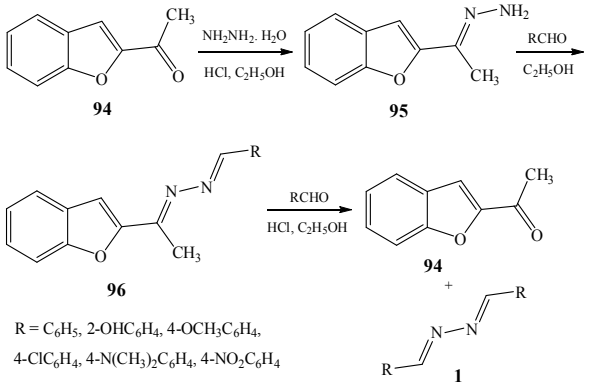
In 2006, Molina and coworkers reported the preparation of the dyad **93** through a modification of Zwierzak's synthesis of unsymmetrical azines. This procedure is based on the transfer of hydrazine to diethylhydrazidophosphate, which reacts with aldehydes to produce protected hydrazones. Preparation of the protected hydrazones is the first part of azine synthesis in Zwierzak's method.[33,34] Therefore, the procedure started with compound **92**, which was prepared through a 6 h condensation reaction between the amino group of diethyl phosphorohydrazidate and 1-pyrenecarboxaldehyde (**91**) in CH_2Cl_2 at room temperature. Indeed, protection was performed by applying Zwierzak's method. Metallation of **92** with butyl lithium in tetrahydrofuran (THF) at −78°C under N_2 followed by reaction with ferrocene carboxaldehyde led to the novel dyad **93** with an overall yield of 60% after recrystallization from CH_2Cl_2–Et_2O (Scheme 25).[35]



Scheme 25.

2.2.10. Reaction of 2-acetylbenzofuranhydrazone (95) with aromatic aldehydes

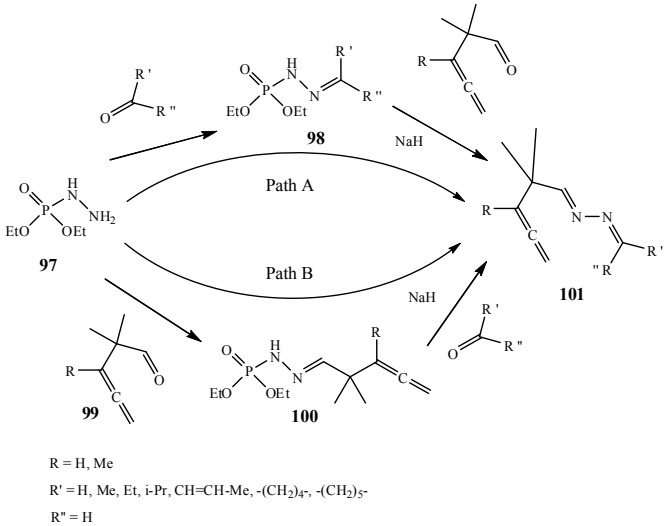
Regeneration of carbonyl compounds from hydrazine, *N*-substituted hydrazones, and semicarbazones is a significant aspect of organic chemical transformation. In 2007, Ujjinamatada and Agasimundin described the hydrolytic cleavage of **95** with aromatic aldehydes under acidic conditions (Scheme 26). Besides synthesis of aldzaines **96**, this method of C=N bond cleavage is a convenient way to regenerate the ketone **94** from **95**.[36]



Scheme 26.

2.2.11. Synthesis by treatment of hydrazone in the presence of sodium hydride and another carbonyl compound

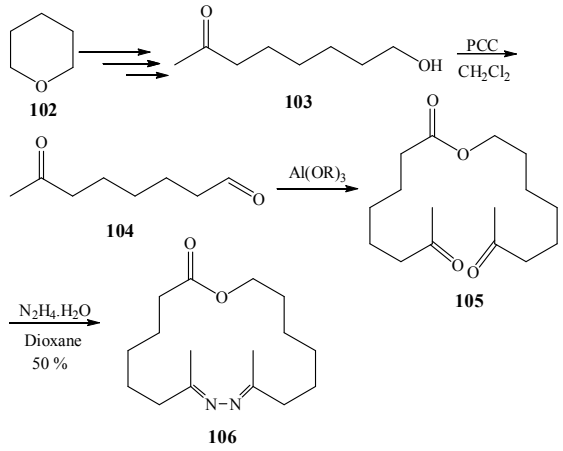
Preparation of new asymmetrical allenyl azines **101** with aliphatic and alicyclic substituents were described by Galeta et al. in 2009.[37] The method was adopted by Zwierzak to prepare unsymmetrical azines. In this method, the first step is protection of one of the nitrogen atoms of the hydrazine molecule by reaction with diethyl phosphite, forming diethyl hydrazidophosphate, **97**. The intermediate **97** was reacted with a carbonyl compound to form the protected hydrazones **98** or **100** in the usual manner. Treatment of the hydrazone in the presence of sodium hydride in dry ether with another carbonyl compound yielded the asymmetrical azine **101** (Scheme 27).



Scheme 27.

2.2.12. Synthesis from tetrahydropyran (102)

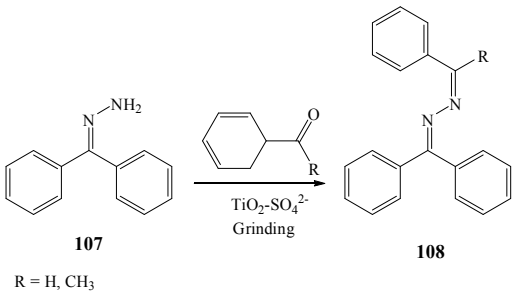
In 2009, Ishmuratov et al. synthesized a potentially useful 17-membered macrolide-containing azine group **106** from **102** via [1+1] condensation at room temperature (Scheme 28). This macrolide-containing azine functional group may exhibit complexing properties and biological activity. Ketoalcohol **103** was accessible from **102** in three steps. Corey oxidation of ketoalcohol **103** produced a ketoaldehyde, 7-oxooctanal (**104**). 7-Oxooctyl-7-oxooctanoate (**105**) was obtained via Tishchenko reaction using **104** with catalytic quantities of aluminum triisopropoxide. Finally, [1+1] condensation of **105** in dioxane at high dilution and room temperature with hydrazine hydrate produced macrolides with azine fragment **106** in good yields (40–50%).[38]



Scheme 28.

2.2.13. Synthesis from benzophenone hydrazone (107) and ketones or aldehydes

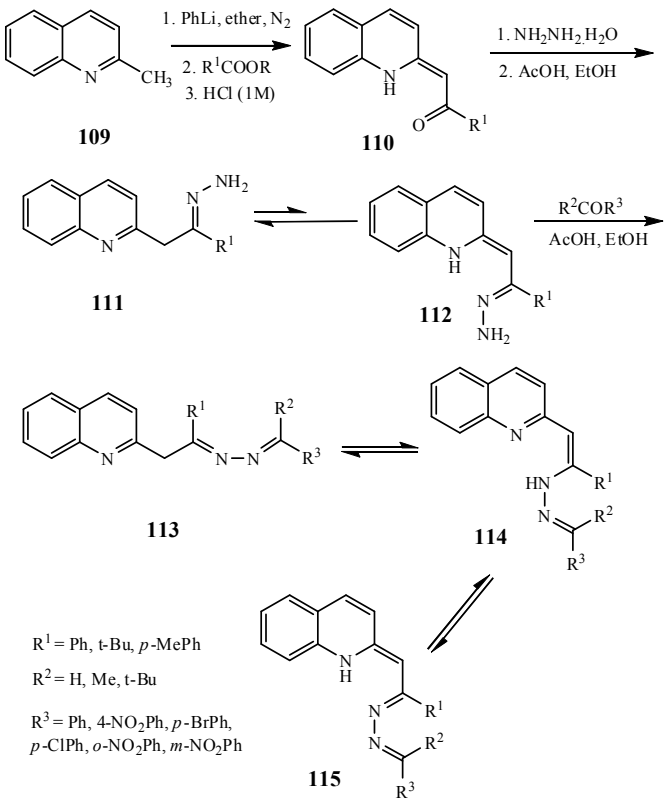
In 2011, Swaminathan and coworkers reported the synthesis of azine derivatives **108** from **107** and ketones or aldehydes by simple physical grinding in the presence of the solid acid catalyst, sulfated anatase titania (TiO_2–SO_4^{2-}) (Scheme 29). Sulfated titania is a good catalyst for the synthesis of azine derivatives at room temperature.[39]



Scheme 29.

2.2.14. Synthesis from 2-ketomethylquinolines (110) and hydrazine

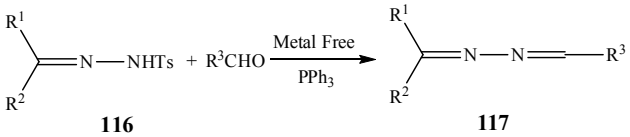
In 2013, Loghmani-Khouzani and coworkers investigated the synthesis of new azines in three steps. At first, a series of compounds **110** were prepared. Tautomerism in this group of compounds has been elucidated by several investigators. In the next step, **110** was reacted with hydrazine in ethanol solution in the presence of a drop of acetic acid (catalyst) to produce 2-ketomethylquinolinehydrazones **111** and **112** in good to high yields. In the third step, **111** and **112** were treated with different aldehydes and ketones in ethanol solution and in the presence of a drop of acetic acid catalyst to give unsymmetrical azines **113** (Scheme 30).[40]



Scheme 30.

2.2.15. Synthesis by reaction of aldehydes with ketone-derived *N*-tosylhydrazones

Wei et al. developed in 2013 an efficient one-pot method to synthesize unsymmetrical azines. Under metal-free conditions, triphenylphosphine captured the diazo compounds generated in situ. The corresponding unsymmetrical azines **117** were formed in good yields (Scheme 31).[41]



116 **117**

61-86 %

R^1= Ph, 4-Cl-C_6H_4, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 4-CNC_6H_4, 4-$MeCO_2C_6H_4$, 4-$MeCONHC_6H_4$, 4-MeC_6H_4, 1-Naphtyl

R^2 = Me, Et, Ph

R^3= Ph, 4-Cl-C_6H_4, 4-$MeOC_6H_4$, 4-$Me_2NC_6H_4$, 4-$NO_2C_6H_4$, 2-$NO_2C_6H_4$, 2-Thienyl

Scheme 31.

3. Properties of azines

3.1. Delocalization

Delocalization occurs in compounds containing bonding orbitals that are not confined to two atoms but rather spread out over three or more atoms. As previously mentioned, the extent of localization in azines has been the subject of many studies. It is well known that one of the prerequisites for maximum conjugation in a system is planarity.[42] Glaser examined the bond lengths in an attempt to find evidence for conjugation. Selected bonds were identified by studying possible resonance structures of the symmetric and asymmetric acetophenone azines with significant conjugation. However, extensive X-ray analyses of conformational properties about the N–N and Ar–C bonds, bond length analysis, and theoretical studies showed no evidence of conjugation. Overall, Glaser concluded that the azine unit is in fact a "conjugation stopper", at least in the solid state, although the C=N–N=C spacer appears to have the necessary structural elements to function as a good conjugation bridge.[11,43] The lack of strong conjugative interaction is consistent with the conclusions reached from X-ray crystallography of azines. Newer data are analogous to Glaser's results and show that solid-state azines have gauche geometries around the >C=N–N=C< moiety and that the bond lengths are inconsistent with any extended conjugation (for example, it has no significant –N=N– character).[44]

3.2. NLO properties

Attention to organic NLO materials has increased because of their characteristics such as very short response time, lower electric constants, and easier processing relative to those of traditional inorganic solids. NLO materials have various applications in telecommunication, optical computing, and lasers.[45–51]

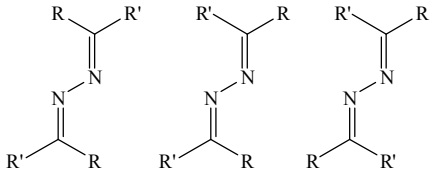
Azines have recently attracted interest because of their NLO properties. A macroscopic dipole moment established with suitable donor or acceptor substituents on the azine may make them suitable candidates for NLO materials.[52] The two imine bonds making up the azine moiety can be considered polar acceptor groups oriented in opposite directions, since they include a N–N bond. This characteristic of azines bound to two aryl rings containing a donor and an acceptor group makes them ideal candidates for NLO materials.[53]

3.3. LC properties

Some azines that are Liquid crystal (LC) compounds were also investigated.[54–57] They have been studied for their possible application in twisted-nematic displays.[58] However, most studies on azines focused mainly on the analysis of their crystal structures and their dipolar properties because these issues are crucial in the design and understanding of NLO-active molecules.[58]

3.4. Isomerization

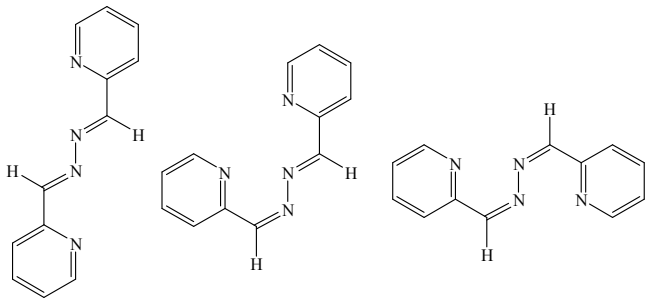
Aldazines and ketazines may occur as three configurational isomers: (*E*,*E*) (*E*,*Z*), and (*Z*,*Z*) isomers (**118**, **119**, and **120**, respectively; Figure 4).[3,59] Azines undergo photochemical E/Z isomerization of the C=N bonds to produce (*E*/*Z*) and (*Z*/*Z*) isomers from the thermodynamically most stable (*E*/*E*) form.[56]



118 **119** **120**

Figure 4.

The conformation of aromatic azines is controlled by a chain of four atoms: C=N–N=C. Almost all studied aromatic azines exist in the preferred (*E*,*E*) configuration in which the large groups attached to the C=N bonds are trans to the N–N bond (Figure 5).[60] The stereochemistry with respect to the N–N bond of the azines is determined by the τ_1 angle. For the s-trans conformation, τ_1 = 180°C, and for the gauche conformation, $\tau_1 \neq 180°C$. Conjugation of two halves of azine is maximal in the s-trans conformation.[61]



121 **122** **123**

Figure 5.

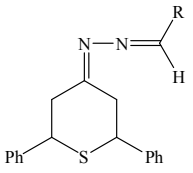
4. Applications of azines

4.1. Chemical applications

Azines have special applications in chemistry. The use of azines as starting materials in organic synthesis is well documented.[31] These readily available compounds have been widely used as substrates in the synthesis of substituted hydrazones[62] and heterocyclic compounds[37] such as pyrazoles, purines, and pyrimidines.[63–66] As dipolarophils, they can undergo 1,3-cycloadditions and thus provide an efficient route to afford 1,5-diazabicyclo[3.3.0]octanes by crisscross addition.[67–69] Not only can they be used as good synthons for heterocyclic synthesis,[70] but they can also be employed in certain useful synthetic transformations. Furthermore, azines have received much interest for their potential in reactions involving bond formation.[71,72] They have also been evaluated for their possible use in analytical and synthetic chemistry.[73]

4.2. Biological applications

Azines constitute an important class of stereochemically significant nitrogen donor ligands in organometallic complexes with pharmacological and biological activity.[74] The specific role of azine ligands as binding molecules or modulators of biological receptors makes them suitable candidates for drug development.[75] The molluscacidal activity displayed by azines of certain *p*-benzoquinones was largely attributed to their parent quinines.[76–78] The biological activity of some novel *N*(1)-arylidene-*N*(2)-*cis*-2,6-diphenyltetrahydrothiopyran-4-one azine derivatives **124** is well-known. Their antibacterial activities against *Streptococcus faecalis*, *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*, as well as their antifungal activities against *Candida*-6, *Candida*-51, *Aspergillus niger*, and *Aspergillus flavus* were evaluated (Figure 6).[79]

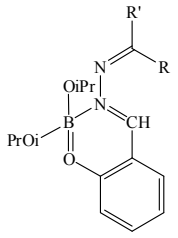


124

R = 2-NO_2-Ph, 4-OMe-Ph, 2-OH-Ph

Figure 6.

Azines were also studied for their use as antimalarial and therapeutic agents.[80] Some heterocyclic azines inhibit tumor growth[81] in murine models. Mixed azines synthesized from opioid antagonists and steroidal ketones[82] show various biological effects, including ultralong opioid antagonist activity.[83] Some unsymmetrical azines have antibacterial properties.[73] Furthermore, diazines (N–N-linked diimines) have recently attracted attention because of their biological properties as anticonvulsant, antidepressant, anti-inflammatory, antiviral, or antitumor agents.[84] Some boron derivatives of mixed azines 1**25** have been reported to be effective bactericides, fungicides, and trichomonacides. Organoboranes used as insecticides and plant growth regulators have also been described. Boron complexes have inhibition properties more potent than those of their free ligands. The increased biological activity after complexation may be explained on the basis of chelation theory (Figure 7).[62]



125

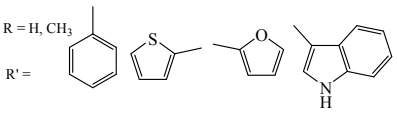
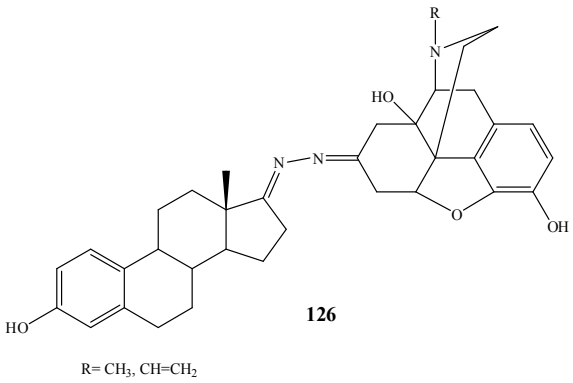


Figure 7.

Mixed azines **126** formed from estrone and naloxone, novel non-peptide selective opiate antagonists, were also discovered (Figure 8).[2]

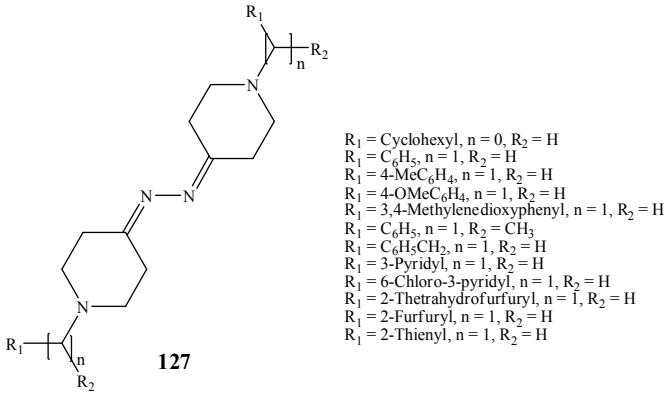


126

R= CH_3, $CH{=}CH_2$

Figure 8.

A series of novel symmetrical *trans*-bis-Schiff bases (azines) **127** were designed and prepared as novel anticancer analogs. The potential analogs showed anti-leukemic activity half maximal inhibitory concentration (IC_{50}) = 6.35 μg/mL) higher than that of the drug 5-fluorouracil (IC_{50} = 8.48 μg/mL) (Figure 9).[85]



127

Figure 9.

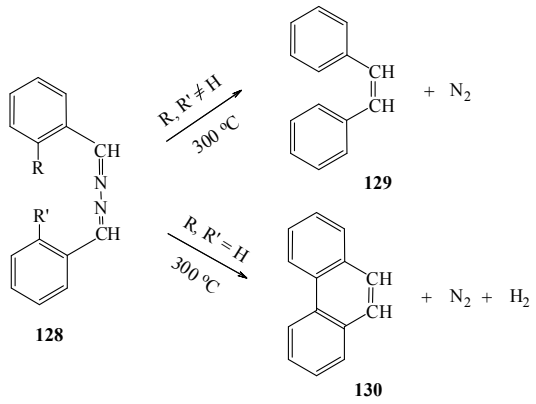
4.3. Physical applications

Asymmetric azines with donor and acceptor groups at the terminal of the π-conjugated backbone were introduced as novel organic NLO materials.[86] Azines are used as ion-selective optical sensors,[87,88] conducting materials,[70] dye lasers, image recording materials,[89] and in supramolecular chemistry[90,91] and in applications of materials.[92–95] Conjugated polyazines may be doped with iodine to give conducting materials.[96] Azines with aromatic and various heterocyclic substituents are photochromic and undergo thermal isomerization and photochemical E–Z isomerization about the C=N double bond. The photochromic properties of organic substances can be used to fabricate dosimeters for ultraviolet radiation, screens for protecting the eyes, and optical devices against powerful sources of light (for example, nuclear explosions).[97] Substituted aromatic azines such as *ortho*-hydroxyacetophenone azine have gained considerable interest for their lasing properties and for useful applications in coloring and dyeing processes.[98] Some unsymmetrical azines are used as organic luminophores, and others are used to synthesize unsymmetrical diarylethylenes.[73] In 1959, a series of azine-type LCs were synthesized and were found to exhibit high clearing points.[99] A series of salicylaldehyde azine derivatives were found to exhibit interesting characteristics of aggregation-induced emission enhancement.[100] In addition, 1,4-disubstituted 2,3-diaza-1,3-butadienes bearing two redox ferrocene groups, a photoactive pyrene group, and a *p*-methoxyphenyl group were introduced for use in two new sensors exhibiting higher sensitivity and selectivity for Hg^{2+} in aqueous environments.[101] Additionally, 1,4-bis(4-pyridyl)-2,3-diaza-1,3-butadiene was introduced as a new ligand for solid-phase extraction of mercury. The photoluminescence properties of this complex in the solid state were studied.[102] Symmetrical azine-based polymers possessing 1-phenyl-1,2,3,4-tetrahydroquinoline moieties were used as materials for optoelectronics. Symmetrical azines tend to crystallize because of the presence of numerous aliphatic fragments, their good ionization potential, and their sufficient charge drift mobility. Reducing this tendency makes them suitable for application as hole-transport materials in optoelectronic devices.[14]

5. Reactions of azines

5.1. Formation of a stilbene derivative with evolution of nitrogen on heating

In 1953, Clark found that aryl azines are not readily degraded. Thus, heating at 300°C led to evolution of nitrogen and formation of a stilbene derivative, **128**. Aryl azines with free ortho positions were found to yield phenanthrenes **130** (Scheme 32).[103]

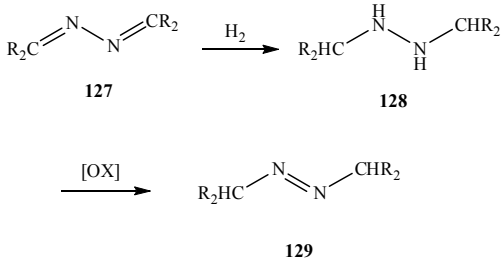


128 **129** **130**

Scheme 32.

5.2. Exchange of the =N–N= group with an azo group

Exchange of the =N–N= group with an azo group (–N=N–) may be performed by reduction of an azine (**127**) over palladium or platinum catalyst at 50 lb/in^2 pressure to give the hydrazine compound **128**. This compound could be readily oxidized to the required azohydrocarbon **129** by using cupric salts,[104] oxygen,[105] or hydrogen peroxide (Scheme 33).[106]

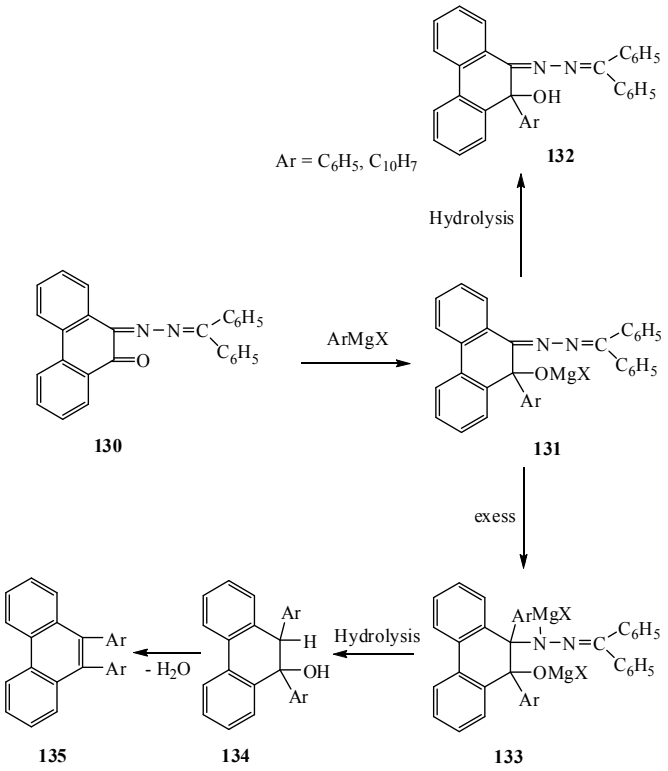


127 **128** **129**

Scheme 33.

5.3. Action of Grignard reagents on phenanthrenequinone benzophenone azine

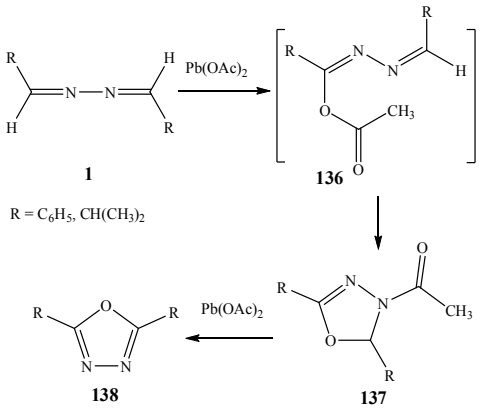
Awad et al. investigated in 1960 the action of Grignard reagents on phenanthrenequinone benzophenone azine (**130**). Aryl magnesium halides preferentially added to the carbonyl group of **130**. When excess Grignard reagent was used, cleavage–condensation reaction took place with the formation of 9,10-diarylphenanthrene (**135**). However, excess phenyl or anisyl magnesium bromide afforded 9,10-diphenyl or 9,10-dianisylphenanthrene, respectively, as a final product in moderate yield (Scheme 34).[107]



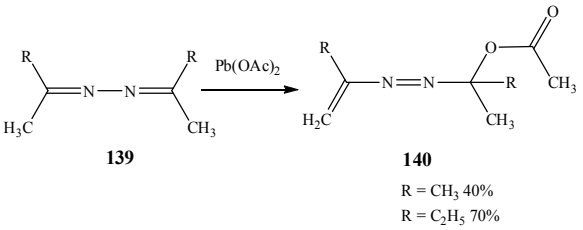
Scheme 34.

5.4. Oxidation of azines by lead tetraacetate

In 1967, Gillis and Lamontagne reported the oxidation of aldazines and ketazines with lead tetraacetate. 1,3,4-Oxadiazolines **137** could be converted to 1,3,4-oxadiazole **138** upon further oxidation with lead tetraacetate (Scheme 35). When ketazines were treated with 1 equiv of lead tetraacetate, the α,β-unsaturated azo acetate **140** was isolated (Scheme 36). Aromatic ketazine failed to react with lead tetraacetate.[7]



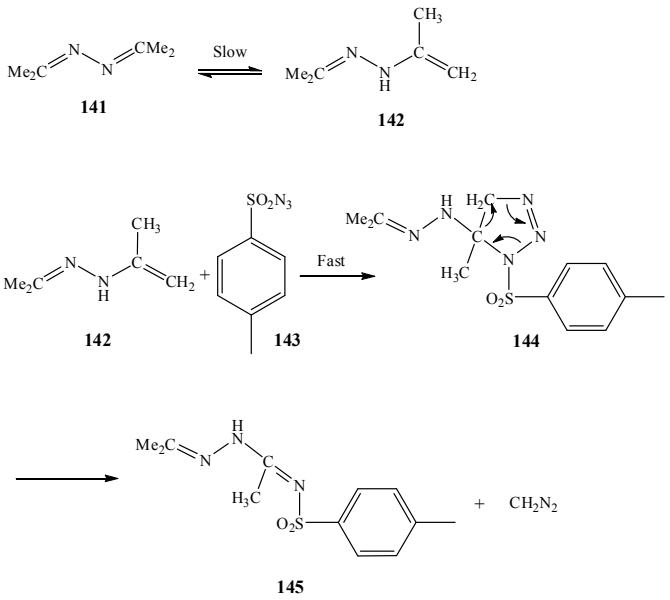
Scheme 35.



Scheme 36.

5.5. Reaction of acetone azine with *p*-toluenesulfonyl azide (143)

Acetone azine reacts with **143**, producing compound **144** after 1,3-dipolar cycloaddition by diazomethane extrusion. The product was assigned the structure of *N*-[l-(isopropylidenehydrazino)ethylidene]*p*-toluenesulfonamide (**145**; Scheme 37). Hartzler suggested this reaction in 1971. The reaction occurred very slowly under reflux in tetrahydrofuran solution, producing **145** at 12% yield after 7 days. The reaction proceeded approximately at the same rate at which deuterium (from D_2O) was incorporated into the azine. NMR spectroscopy confirmed the structure of **145**, showing the absorption by four different methyl groups. Infrared spectroscopy, which showed the absorption by the NH group, as well as ultraviolet absorption spectroscopy, also confirmed the structure.[8]

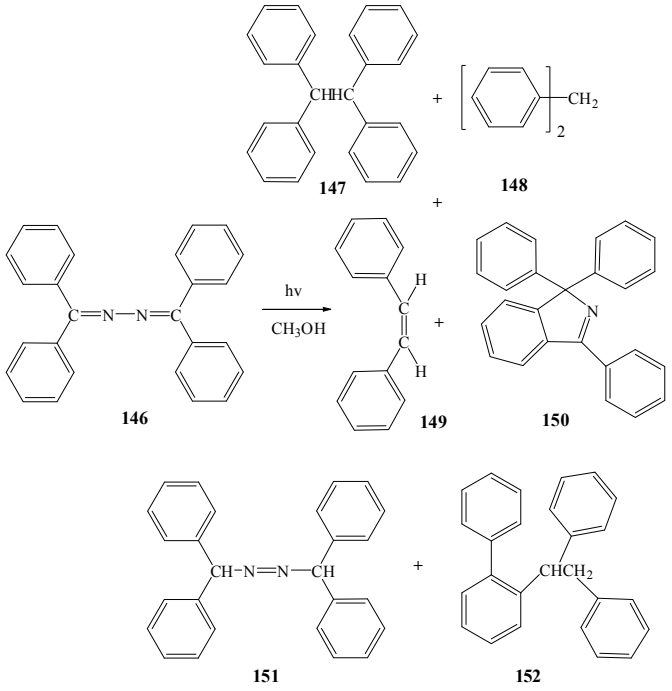


Scheme 37.

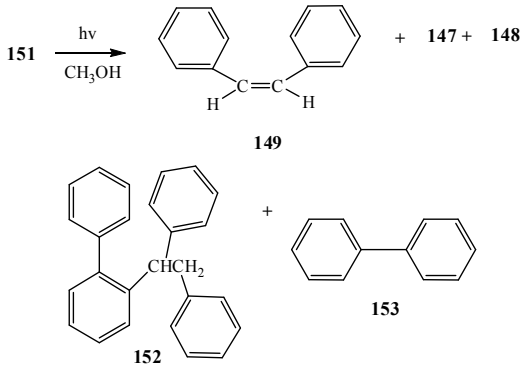
5.6. Photochemical reactions of benzophenone azine

Binkley and coworkers described in 1972 their findings related to two photochemical reactions of benzophenone azine, **146**. The photochemical reaction of **146** has several unique aspects. Compound **146** was found to be the starting point for two different photochemical reactions. The first reaction is molecular rearrangement leading to 1,3,3-triphenylisoindole **150**, and the second is photoreduction forming l,l,l',l'-

tetraphenylazomethane **151** (Scheme 38). Compound **151** is photochemically unstable, yielding l,l-(*Z*,*Z*)-tetraphenylethane (**147**) and diphenylmethane (**148**). Compound **147** had been previously shown to decompose by photolysis to *cis*-stilbene (**149**), 1-(2-biphenylyl)-1,2-diphenylethane (**152**), and biphenyl (**153**) (Scheme 39). All of these compounds were isolated from the photolysis of benzophenone azine.[108]



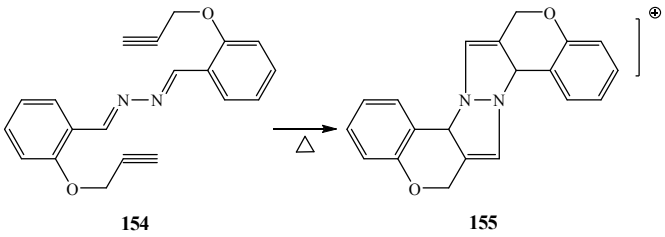
Scheme 38.



Scheme 39.

5.7. Rearrangement of the azine of salicylaldehyde propargyl ether (154)

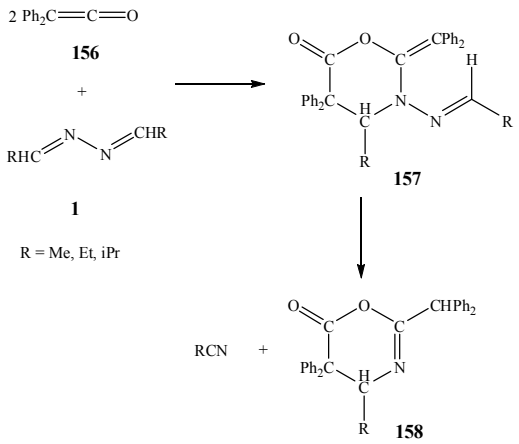
In 1917, two papers by Bailey et al. provided the first report on crisscross addition.[109] The first article describes the cycloaddition of cyanic acid to benzalazine.[109a] The second explains the cycloaddition of cyanic acid, isothiocyanic acid, and phenyl isocyanate with aromatic aldazines prepared from benzaldehyde, 3-nitrobenzaldehyde, cinnamaldehyde, and furfuraldehyde.[109b] In 1975, Suschitsky et al. prepared dihydropyrazolopyrazole (**155**) by rearrangement of the azine of **154** in refluxing diethylaniline (Scheme 40).[110]



Scheme 40.

5.8. Reaction of ketenes and ketene precursors with azines

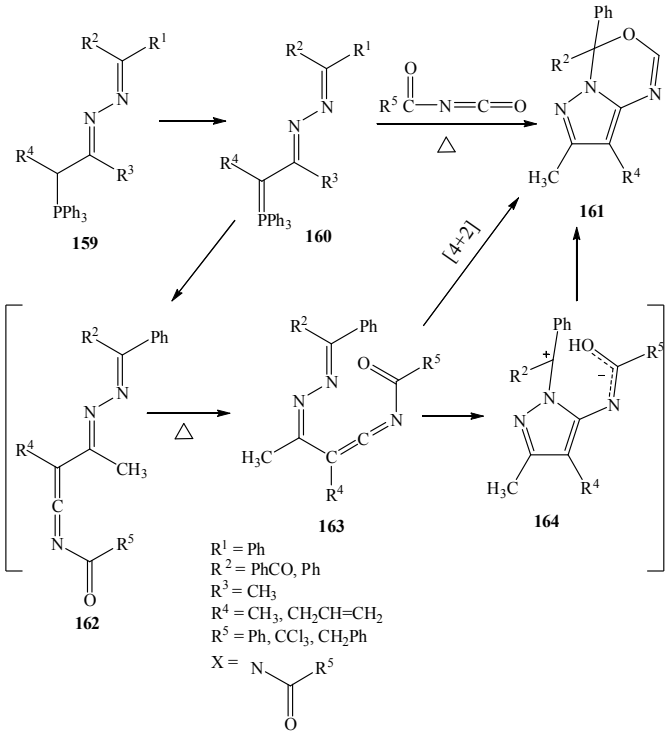
Satsumabayashi et al. reported in 1976 some cycloaddition reactions of 2,2-diphenylethenone (**156**) with aldehyde azines **1**. The reaction of **156** with **1** was carried out in refluxing ether for 5 h, and a white, crystalline product was obtained with good yield. On the basis of elemental analysis and spectroscopy, the product was assumed to be 4-methyl-5,5-diphenyl-2-diphenylmethyl-4,5-dihydro-1,3-oxazin-6-one (**158**). This product was formed by elimination of 2, 1, and 1 moles of acetonitrile from adducts of **156**, **1**, and **157**, respectively. The expected cycloadduct **157** was obtained at lower temperature (−20°). Compound **157** was unstable and decomposed to **158** in acetonitrile on heating at ~100°C or upon refluxing in ether (Scheme 41).[9]



Scheme 41.

5.9. Treatment of acyl isocyanates with azine phosphoranes (160)

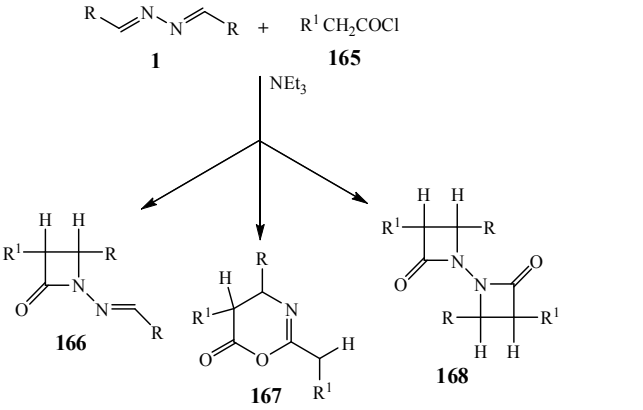
In 1987, Schweizer and Lee extended the usefulness of azines as synthons to prepare fused pyrazolo species by synthesizing 4*H*-pyrazolo[l,5-*c*] [1,3,5]oxadiazines **161** (Scheme 42). The compounds were prepared by reacting acyl isocyanates with **160**. Compounds **161** were synthesized by ring closure via the zwitterionic species **164**. However, **161** were found to form directly via [4+2] intramolecular cycloaddition of **163**.[111]



Scheme 42.

5.10. Reaction between acid chloride and azine

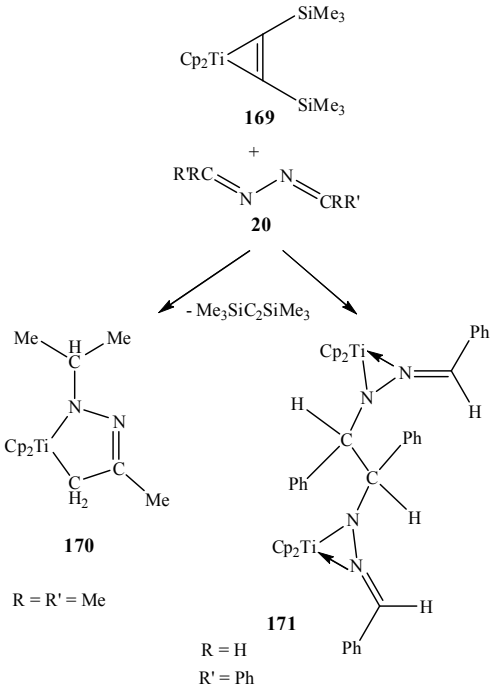
In 1994, Alcaide reported a general study of the reaction between alkoxy-substituted acetyl chlorides with a wide variety of azines derived from aliphatic, aromatic, and α,β-unsaturated aldehydes and from ketones in the presence of triethyl amine (Et_3N) (Scheme 43). This reaction may be carried out according to three possible routes. These routes form *N*-imino-β-lactams (**166**), 3,4,5-dihydro-1,3-oxazin-6-one derivatives (**167**), or *N*,*N*-bis-β-lactams (**168**). The thermal reaction of diphenyl ketene and azines **1** derived from *p*-substituted benzaldehydes yields **167**, whereas aliphatic azines form **168**. The C=N group of **166** is unreactive toward second cycloaddition, but azines **1** derived from α,β-unsaturated aldehydes could react with benzyloxyacetyl chloride under standard conditions (2:1 acid chloride/azine ratio) to produce considerable amounts of bis-β-lactams **168**.[112]



Scheme 43.

5.11. Reactions of titanocene with azines

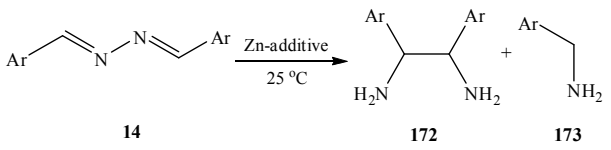
In 1998, Ohff and coworkers demonstrated reactions of azines **20** with titanocene [bis(trimethylsilyl)acetylene-titanocene] (**169**; Scheme 44). Depending on the azine substituents, either C–H activation or C–C coupling was observed. These reactions led to the formation of complexes **170** or the binuclear complex **171**, respectively.[113]



Scheme 44.

5.12. Reductive coupling of aromatic azines to 1,2-diamines using ZnMsOH or $ZnTiCl_4$

In 2001, Kise and Ueda performed reduction of aromatic azines **14** with Zn in the presence of MsOH or $TiCl_4$, affording N,N'-unsubstituted 1,2-diamines **172** in one step (Scheme 45). Aromatic azines were effectively transformed to the corresponding N,N'-unsubstituted 1,2-diaryl-1,2-diamines **172** by reductive coupling with Zn in the presence of MsOH or $TiCl_4$. The use of MsOH as an additive selectively led to *meso*-1,2-diamines, whereas that of $TiCl_4$ led to DL-1,2-diamines.[114]



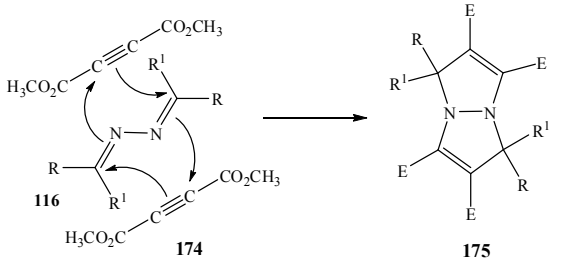
14 **172** **173**

Ar = Ph, *p*-MeC_6H_4, *p*-$MeOC_6H_4$, *p*-ClC_6H_4, *p*-NCC_6H_4, *p*-$Me_2NC_6H_4$, 1-Furyl, *m*-BrC_6H_4

Scheme 45.

5.13. Crisscross cycloaddition of acetylene derivatives with aldazines and ketazines

This reaction was reported by El-Alali and coworkers in 2002. The prepared aldazines and ketazines reacted as dipoles with 2 moles of the acetylene derivative **174**, a dipolarophile. The initially formed products were heterocyclic compounds with two fused membered rings, including pentalene azine derivatives **175** (Scheme 46).[115]



174 **175**

R = Alkyl or Aryl

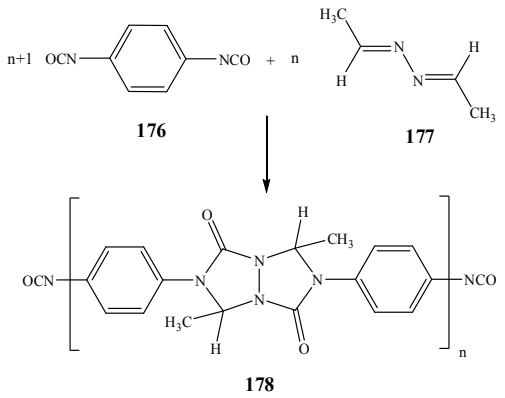
R^1 = H , CH_3 , or alkyl

E = CO_2CH_3

Scheme 46.

5.14. Polymerizability of alkyl aldehyde azines

Hashidzume et al. studied in 2006 the polymerization of C=N compounds, especially aldehyde azines and azastyrene derivatives. In their work on the reactivity and polymerizability of alkyl aldehyde azines, they observed that acetaldehyde azine (AcAz; **177**), a simple alkyl aldehyde azine, underwent crisscross addition with 1,4-phenylene diisocyanate ($Ph(IC)_2$); **176**) under mild conditions. This is the first example of crisscross addition of alkyl aldehyde azines. Using crisscross addition of AcAz, they obtained polymeric products **178** from AcAz and 1,4-phenylene diisocyanate at high yield (80%) (Scheme 47).[116]



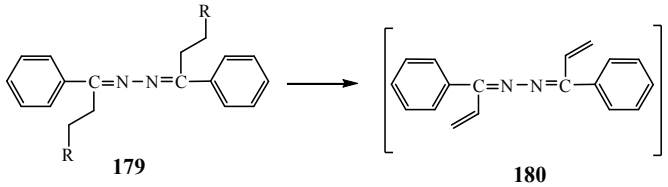
176 **177**

178

Scheme 47.

5.15. Reaction of aryl azine with 2-mercaptoethanol

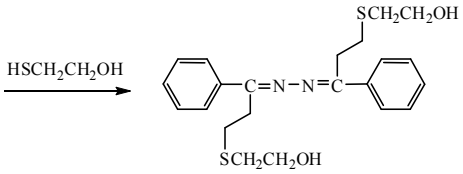
In 2007, Dimmock and coworkers reported that the reaction of azine **179** with 2-mercaptoethanol led to the isolation of the corresponding thiol adduct **181** in 54% yield (Scheme 48). Thus, formation of the intermediate **180** seems likely although the thiol could react with the electron-deficient methylene carbon atom adjacent to the quaternary ammonium nitrogen atom.[117] Compound **179** was designed as a candidate prodrug of the putative bifunctional alkylation agent, **180**, which was found to be capable of reacting with cellular thiols.[118] A number of thiol alkylators act as anti-neoplastic agents by sensitizing tumor cells, and others reverse drug resistance.



179 **180**

R = $\overset{\oplus}{N}(CH_3)_3\,\overset{\ominus}{I}$

R = $N(CH_3)_2$. HCl

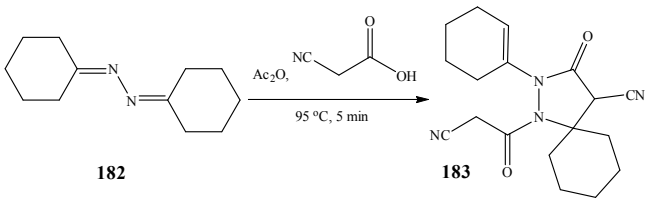


181

Scheme 48.

5.16. Reaction of cyclohexanone azine with cyanoacetic acid acetic anhydride

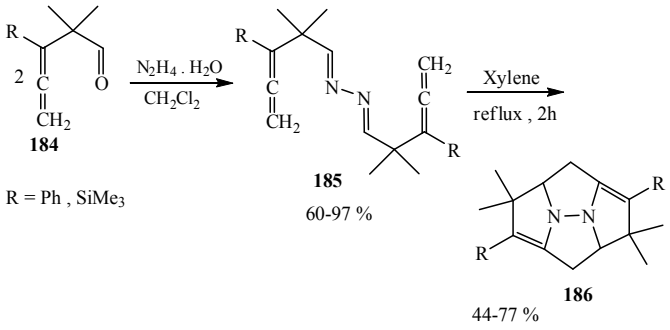
In 2008, Bergman et al. performed the reaction of cyclohexanone azine **182** with cyanoacetic acid and acetic anhydride under heating, producing a highly substituted dihydropyrazolone, **183** (Scheme 49).[119] The azine of cyclohexanone **182** was selected because this molecule was known to be convertible into the hexahydroindazole derivative by reaction with oxalic acid.[120]



Scheme 49.

5.17. Intramolecular crisscross cycloaddition of homoallenyl azines

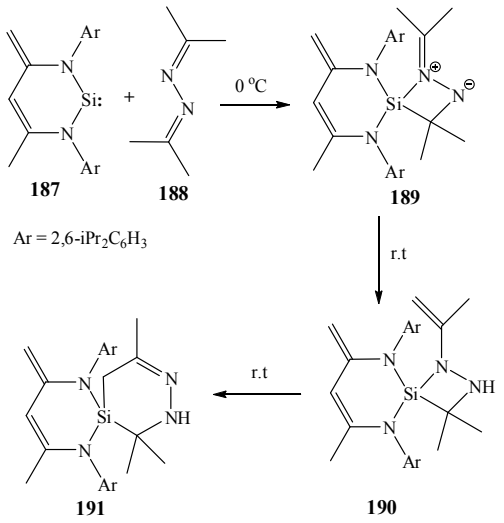
In 2009, Zachová and coworkers performed the intramolecular crisscross cycloaddition of 3-substituted symmetrical homoallenyl azines **185** by heating in xylene. This reaction leads to interesting fused heterocyclic systems (**186**) consisting of four five-membered rings with two nitrogen atoms in the skeleton (Scheme 50). Compounds **186** were found to be sensitive to attack by alkyl halides. Their presence depends on the reaction conditions.[70]



Scheme 50.

5.18. Cycloaddition reactions of thermally stable N-heterocyclic silylene (187) with acetone azine

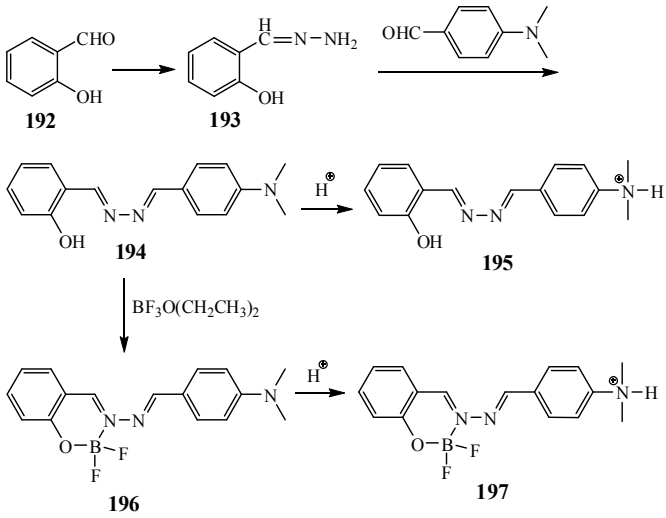
Driess and et al. described this reaction in 2010. They probed cycloaddition reactions of the thermally stable compound **187** with acetone azine (1,1,4,4-tetramethyl-2,3-diazabuta-1,3-diene; **188**) and other derivatives of 1,3-butadiene. Unexpectedly, acetone azine **188** undergoes a unique [3+1] cycloaddition to give the 1-sila-2,3-diazacyclobutane (**189**) and its 1-sila-2,3-diazacyclobutane isomer, **190**. The latter rearranges to decrease ring strain, affording the corresponding 1-sila-4,5-diazacyclohex-3-ene, **191** (Scheme 51).[121]



Scheme 51.

5.19. Synthesis from hydrazone and synthesis of the corresponding boron complex

This work concerns the synthesis of a novel azine dye, **195**, and its corresponding boron complex, **196**, which was carried out by Kim and coworkers in 2010 (Scheme 52). Boron complexes characteristically display strong peaks for absorption and sharp peaks for emission at high quantum yield. Colors of the dyes were achieved through protonation and deprotonation processes. The observed effects of pH on the color of dyes were interpreted in terms of electron density distribution and intramolecular charge transfer.[122]

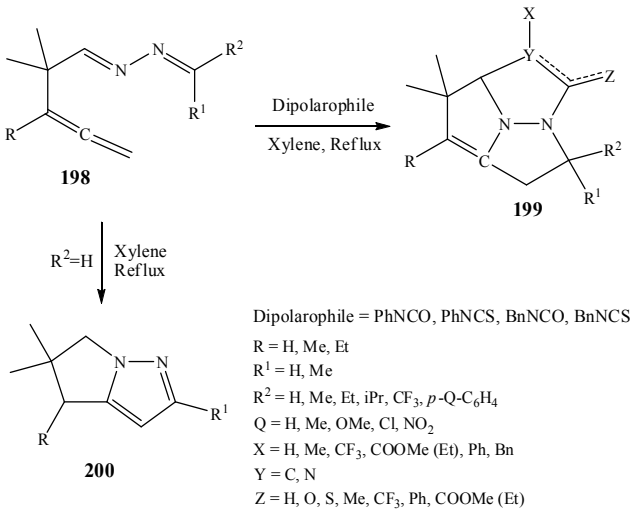


Scheme 52.

5.20. Intramolecular cycloaddition of unsymmetrical homoallenyl azines

Potáček et al. reported in 2011 simple intermolecular crisscross cycloadditions involving two molecules of a dipolarophile reactant with one molecule of azine. Unsymmetrical allenyl azines **198** reacted with various dipolarophiles, generating products that are either tricyclic heterocycles **199** or, in the case of thermal stress without any dipolarophile, fused bicyclic

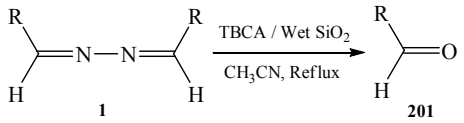
products **200** (Scheme 53).[123] The broad usefulness of such reaction is consistent with its diverse substitution products. The investigators demonstrated possible applications of molecules bearing polycyclic aromatic systems in fluorescent labeling and even as DNA intercalators.[124]



Scheme 53.

5.21. Selective conversion of azines to their corresponding carbonyl compounds

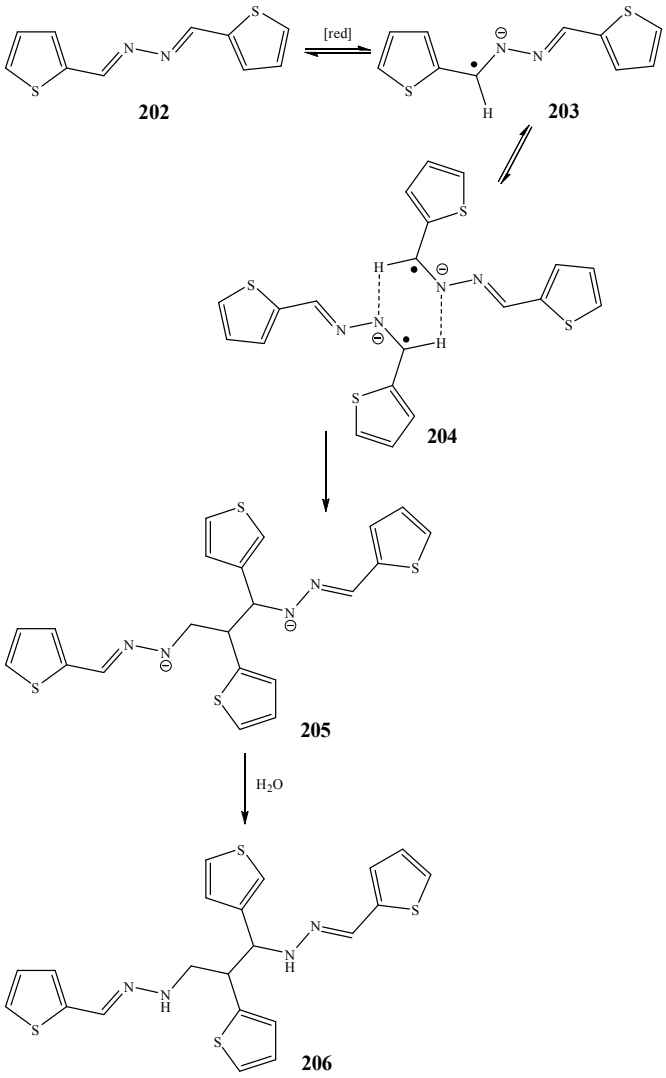
In 2012, Habibi et al. used a tribromoisocyanuric acid/wet SiO_2 system to convert azines **1** to their corresponding carbonyl compounds **201** (Scheme 54). The interesting feature of this system is that the C=N bond in azines with conjugated or unconjugated C=C bonds selectively changes to the relevant C=O bond while the conjugated or unconjugated C=C bond remains intact.[125]



Scheme 54.

5.22. Dimerization of azines

In 2014, Vercelli showed that radical anions of azines in organic media could dimerize, but 1,4-dimethyl-substituted azines undergo successive reduction to their radical anion and then to their dianion. In cases in which there was no acidic azine proton, formation of the radical anion was completely reversible. The suggested mechanism of dimerization involving acidic methine protons is shown in Scheme 55. The radical anion **203** formed by reduction undergoes free rotation along the newly formed C–N bond. This rotation allows two radical anions to form a face-to-face adduct in which the acidic methine protons face the negatively charged nitrogen atoms. In the resulting six-membered ring, the negative charges are partially shielded, thus lowering the electrostatic repulsion and affording radical–radical dimerization of **204**. Methyl capping clearly eliminates such stabilization, thus stabilizing the monomeric form of the radical anion. Dimerization is the rate-determining step, after which further protonation by proton donors (typically water) in the medium lead to the final product, the dimeric hydrazine **206**.[126]



Scheme 55.

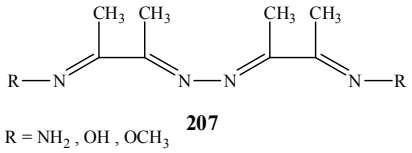
6. Complexes of azine

Utilizing the advantage of reactivity of transition-metal complexes has attracted considerable interest to develop new systems in organic synthesis.[127] Because of their ability to donate two to eight electrons via lone pairs of the N atom and the C=N p-orbital electrons, azines show versatile properties of coordination in binding to metal centers.[128] Furthermore, N–N bond activation is important in various types of organic ligands, especially in catalysis and in organic synthesis in general.[129]

6.1. Synthesis of two new tetrafunctional azine ligands and study of their complexing ability

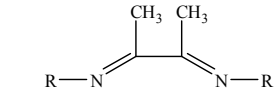
As part of a continuing study of tetrafunctional azine ligands, Stratton and et al. reported in 1970 the synthesis of new ligands related to **207** and a brief study of their complexion ability.

Biacetyl oxime azine (**207**, R = OH) is of interest because of its structural relationship to the well-known nickel reagent, dimethylglyoxime (**208**, R = OH; Figure 10). **208** forms a highly stable 2:1 neutral complex with nickel(II), [Ni(DMG_2)] **209**. This compound was shown to be planar, with two hydrogen bonds between its ligands. It is diamagnetic, typical of square-planar d^8 ions (Figure 11). Biacetyl oxime azine (**207**, R = OH) is potentially capable of forming hydrogen bonds and bridging two metal ions.[130]



207

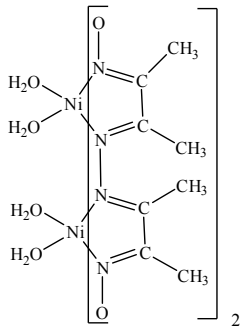
R = NH_2 , OH , OCH_3



208

R = OH , NH_2

Figure 10.

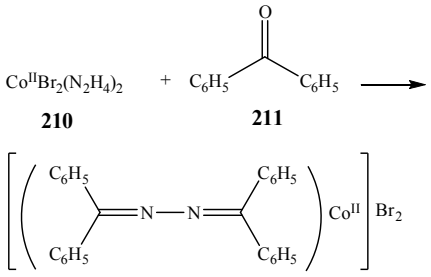


209

Figure 11.

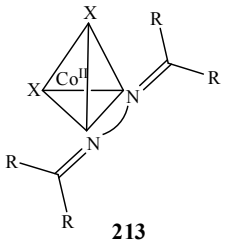
6.2. Synthesis of complexes of cobalt(I1) halides with hydrazine derivatives

Stapfer and D'Andrea described in 1971 novel complexes of cobalt(II) halides with hydrazine derivatives and some of their chemical properties. A benzophenone azino complex of cobalt(II) bromide **212** was obtained by refluxing a suspension of the bishydrazinate **210** in 2 equiv of benzophenone (**211**) (Scheme 52). In this case, the hydrazine condensed with the solvent prior to displacement of one of the ligands, which was probably due to steric crowding. This compound could not be obtained by direct reaction of benzophenone azine with cobalt(II) bromide. This seemed to prevent a two-step reaction involving decomposition of the bishydrazinate followed by chelation of the metal halide with the benzophenone azine formed by condensation of the ketone with free hydrazine. As azinocobalt(II) halides exist in monomeric form, it is reasonable to believe that the azinates can adopt a bidentate chelate structure similar to that of **213** (Figure 12).[131]



210 **211** **212**

Scheme 52.

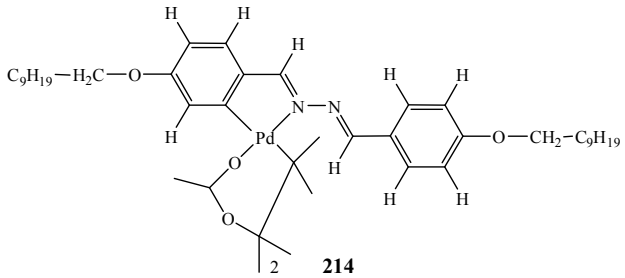


213

Figure 12.

6.3. Study of the optical activity of complexes of azine by replacement of the bridging acetate with (*R*)-2-chloropropionate

Synthesis of LCs based on organometallic or coordination compounds opens new perspectives in the design of mesogenic molecules. In this regard, Espinet and coworkers reported in 1990 the unexpected finding of mesogenic behavior of book-shaped ortho-palladated dimers.[132] The presence of a metal atom enables synthesis of derivatives through very simple coordination chemistry, which may be an advantage over the usually more tedious procedures requiring related molecules. Thus, the investigators showed how optical activity could easily be introduced into the aforementioned complexes by simply replacing the bridging acetate with (*R*)-2-chloropropionate (Figure 13).[133]

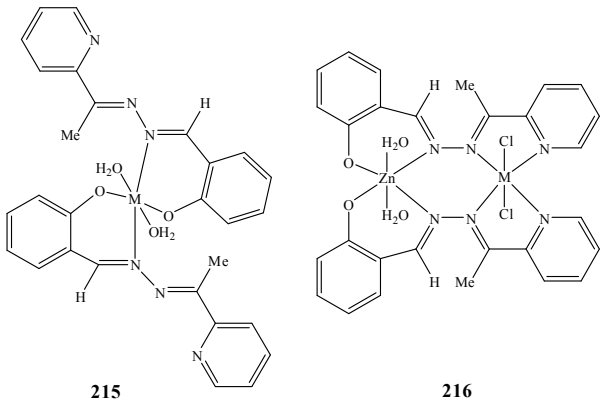


214

Figure 13.

6.4. Synthesis of bimetallic azine-bridged complexes

In 1996, Singh and Srivastav prepared a novel unsymmetrical tetradentate azine, 2-acetylpyridinesalicylaldazine (Haps), by condensing salicylhydrazone with 2-acetylpyridine. This ligand reacted with Mn, Co, Ni, Cu, and Zn acetates to yield deprotonated $M(aps)_2(H_2O)_2$ complexes, **215**. Subsequent reaction of the mononuclear unit $Zn(aps)_2(H_2O)_2$ with $MC1_2$ gave homonuclear $[ZnC1_2Zn(aps)_2(H_2O)_2]$ and heterobinuclear $[MC1_2Zn(aps)_2(H_2O)_2]$-type azine-bridged complexes **216**. These complexes were characterized through analytical data, molecular weight data, conductivity measurements (solid and solution), magnetic susceptibility measurements, electronic data, Electron Spin Resonance (ESR) spectroscopy, Infra-Red (IR) spectroscopy, and X-ray powder diffraction data. On the basis of chemical composition and physicochemical studies, an octahedral geometry of the complexes was proposed (Figure 14).[134]



215 **216**

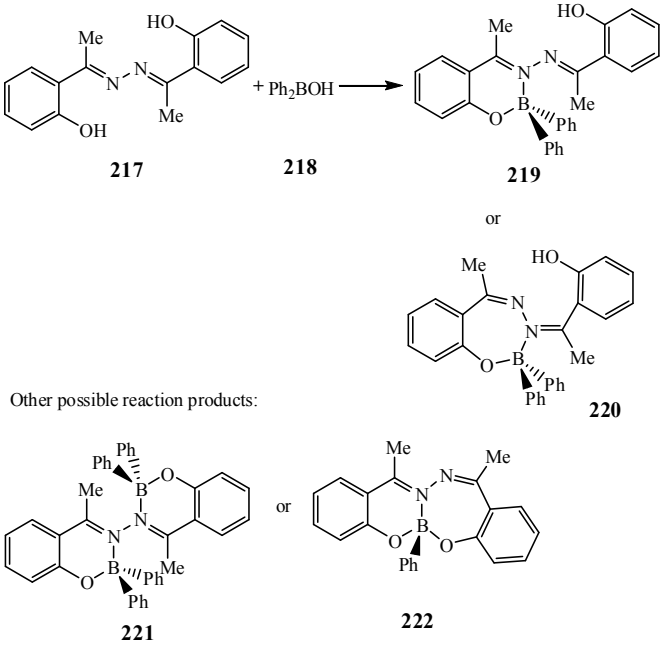
$M(aps)_2(H_2O)_2$
M = Mn^{II}, Co^{II}, Cu^{II} and Zn^{II}

$MCl_2Zn(aps)_2(H_2O)_2$
M = Mn^{II}, Co^{II}, Ni^{II}, Cu^{II} and Zn^{II}

Figure 14.

6.5. Synthesis of boron chelates of salicylaldehyde and 2α-hydroxyacetophenone azomethines

Boron chelates obtained from salicylaldehyde and 2α-hydroxyacetophenone azines are colored compounds with potential applications in analytical chemistry. Boron chelates of salicylaldehyde and 2α-hydroxyacetophenone azomethines were synthesized for the first time in 1965 and in 1973, respectively.[135] Particular interest in the formation and properties of these chelates is related to their analytical application in the separation and identification of primary alkylamines by high-performance liquid chromatography.[136] Therefore, in 1998, Höpfl et al. prepared boron chelates from 2α-hydroxyacetophenone azines **217** and diphenylborinic acid (**218**) through one-step synthesis.[137] Different possibilities of chelate formation are shown in Scheme 56. Because of their color-deepening effect, boron complexes obtained from 2α-hydroxyacetophenone azines could be important for the quantitative determination of chelate components.[138]



217 **218** **219**

or

220

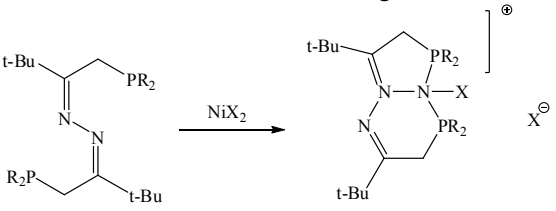
Other possible reaction products:

221 **222**

Scheme 56.

6.6. Preparation of nickel(II) complexes of azine diphosphine ligands

Nickel(II) complexes of azine diphosphine ligands **223** were prepared by Čermák et al. for the first time in 2002 by reactions of anhydrous NiX_2 (X = Cl, Br, I) with ligands **223**. The azine diphosphines **223** are coordinated terdentately in (*E*,*Z*) configuration and form a bicyclic ligand frame **224** (five- and six-membered rings) with diphosphine bite angles of 160–165°C (Scheme 57). The investigators proposed a balance of stereoelectronic factors governing square-planar coordination and tetrahedral coordination of the ligands.[105]



223 **224**

R=Ph, But, Pri, C_6H_{11}

Scheme 57.

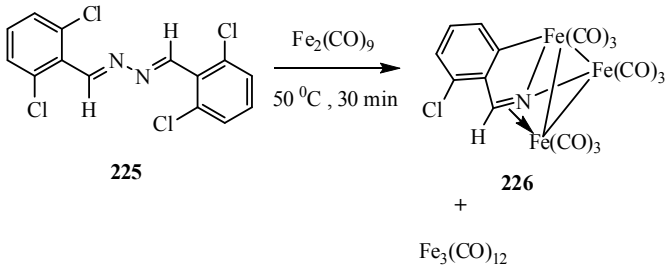
6.7. Treatment of azine ligands derived from hydrazine and benzaldehyde derivatives bearing halogen with $Fe_2(CO)_9$

In 2004, Dönnecke and coworkers reported that upon treatment with $Fe_2(CO)_9$, azine ligands bearing halogen substituents in the ortho position undergo two typical reactions with respect to the carbonyl function. One is the symmetrical cleavage of the N–N bond of azine to yield either dinuclear (**229** and **231**) or trinuclear (**226**, **228**, and **230**) iron carbonyl compounds, each showing two arylidenimido moieties. The other is formation of a trinuclear iron carbonyl cluster compound exhibiting a tetrahedral Fe_3N cluster core, **232**. Scheme 58 shows the reaction of azine **225** with $Fe_2(CO)_9$ in heptane solvent.

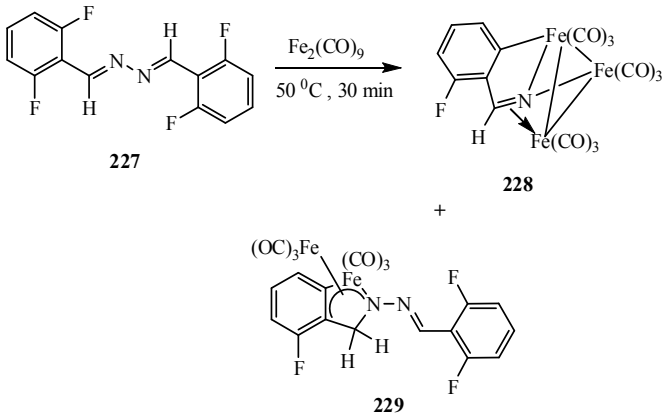
Chromatographic workup of the reaction mixture showed that it mainly consisted of unreacted **225** and $Fe_3(CO)_{12}$. In addition, the trinuclear cluster compound **226** was produced in small yields.

Scheme 59 shows the products **228** and **229** produced by activation of a carbon fluorine bond in **227**. The trinuclear iron carbonyl cluster **228** is an isomer of **226**, which has a fluoro substituent instead of a chloro group.

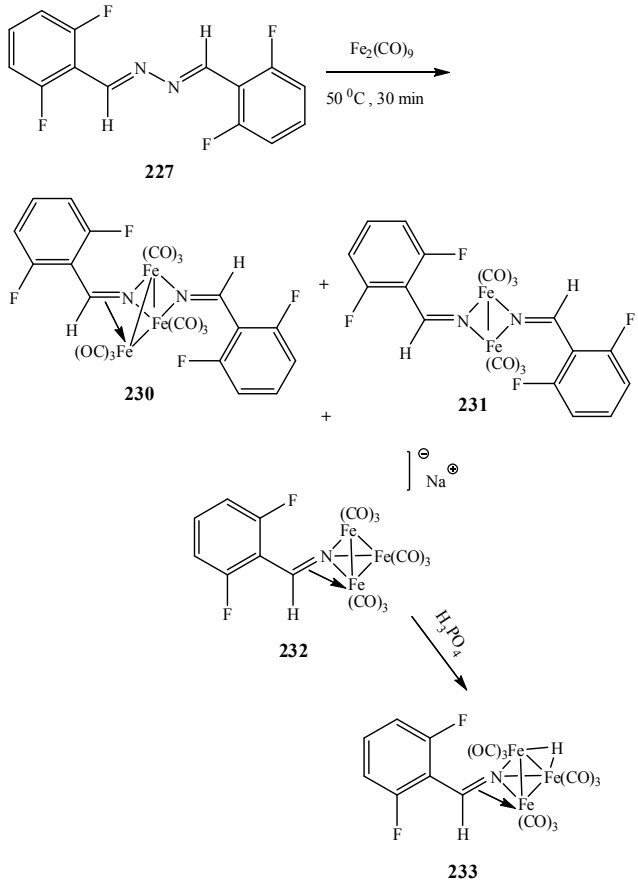
Scheme 60 shows all iron carbonyl compounds formed from the reaction of **227** with $Fe_2(CO)_9$ via cleavage of the central N–N bond of the ligand. The trinuclear cluster **232**, an ionic compound, is quantitatively converted into **233** upon treatment with phosphorous acid. All new iron carbonyl compounds were characterized by means of X-ray crystallography.[139] Additional material on the structure analyses is available from the Cambridge Crystallographic Data Centre by mentioning the deposition number CCDC-228279 (226), CCDC-228280 (228), CCDC-228281 (229), CCDC-228282 (231) and CCDC-228284 (232).



Scheme 58.



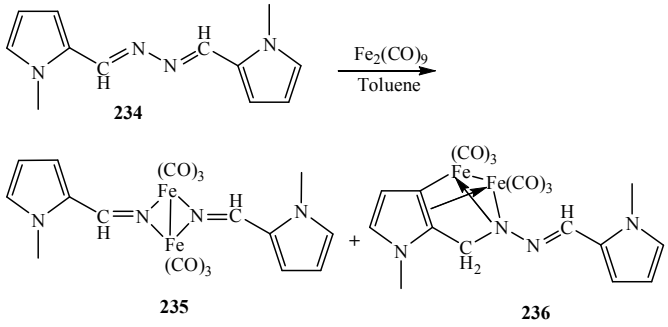
Scheme 59.



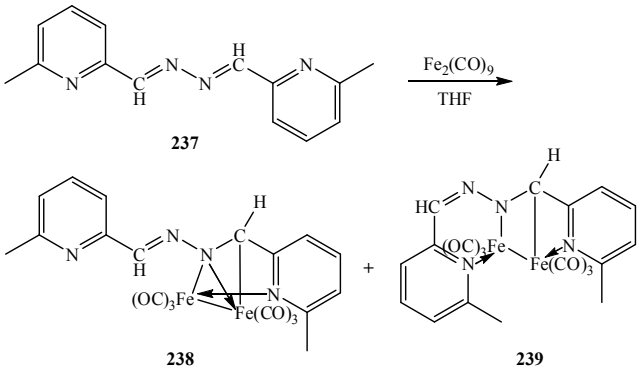
Scheme 60.

6.8. Synthesis of various types of hexacarbonyl diiron complexes with five different coordination modes

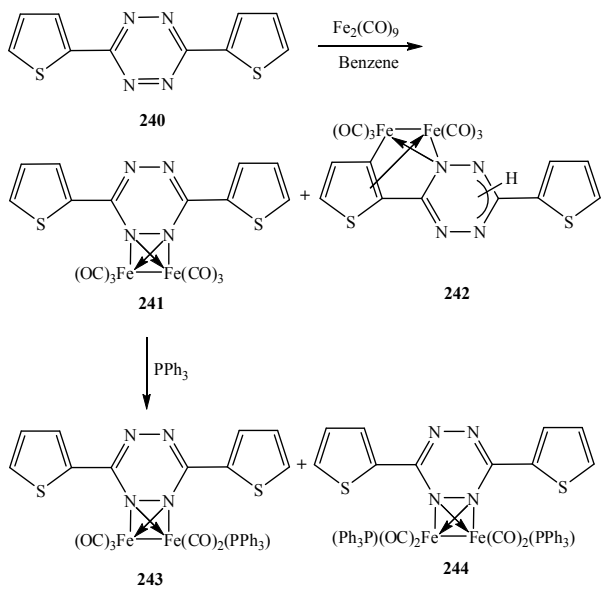
In 2006, Hwang et al. reported the reactions of 1,4-di-(*N*-methyl-2′-pyrrolyl)-2,3-diaza-1,3-butadiene (**234**), 1,4-di-(6-methyl-2′-pyridyl)-2,3-diaza-1,3-butadiene (**237**), and 3,6-di-(2′-thienyl)-1,2,4,5-tetrazine (**240**) with $Fe_2(CO)_9$ in toluene, THF, and benzene, respectively. These reactions yielded various types of hexacarbonyl diiron complexes with five different coordination modes: a complex with two 2-pyrrolylmethylideneamido bridging ligands (**235**), which resulted from N–N bond cleavage of the ligand **234**; a cyclometallated complex (**235**); an acyclometallated complex (**242**); a diaza-bridged complex (**241**); and imine-bridged complexes **237** and **238** (Schemes 61–63). The molecular structures of the ligands **234** and **239** and of the complexes **235**, **238**, and **244** were determined by single-crystal X-ray crystallography.[140] Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Center, CCDC No. 277567 for 234, 277569 for 235, 277570 for 238, 277568 for 240, 277571 for 241 and 277572 for 243.



Scheme 61.



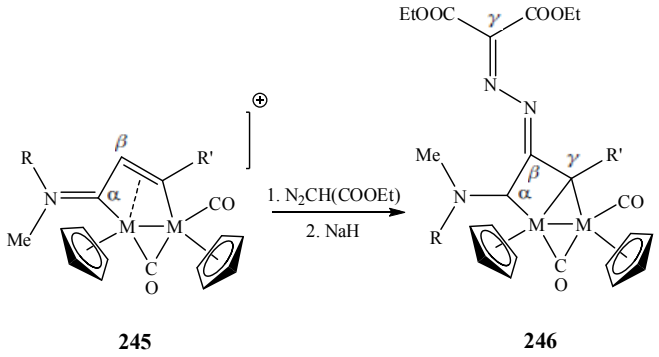
Scheme 62.



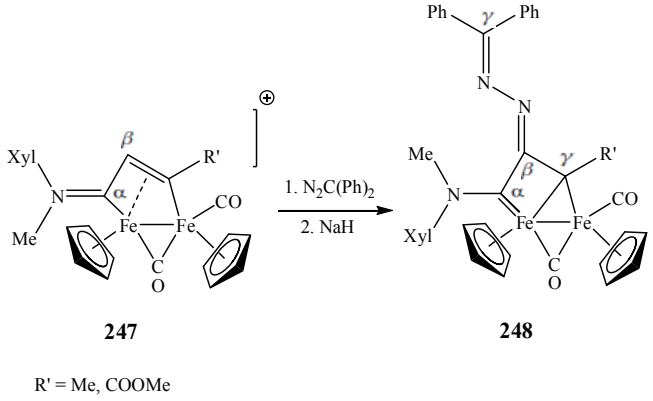
Scheme 63.

6.9. Synthesis of novel dinuclear azine-bis(alkylidene) complexes (246)

Zanotti and coworkers reported the reactions of diazo compounds with μ-vinyliminium ligands. The vinyliminium complexes **245** reacted with ethyl diazoacetate in the presence of NaH, affording **246** in 70–77% yields (Scheme 64). Analogous reactions with N_2CPh_2 led to the formation of **248** (Scheme 65). To extend the reaction to other diazo reagents, the complexes **247** were treated with diphenyldiazomethane in the presence of NaH. Similarly, addition of the diazo reagent occurred at the β-carbon of the bridging ligand, affording **248**.[141]



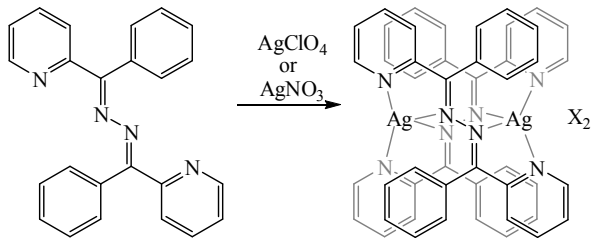
Scheme 64.



Scheme 65.

6.10. Preparation of Ag complexes of the azine-based ligand, phenyl-2-pyridyl ketone azine (249)

The extended structure of Ag complexes of the azine-based ligand **249** (L1) was reported by Hwang and et al. in 2008. By using $AgNO_3$ and $AgClO_4$ salts in acetonitrile as starting materials for this ligand, they observed the formation of the dinuclear complexes $[Ag_2(L1)_2](NO_3)_2$ (**250a**) and $[Ag_2(L1)_2]$-$(ClO_4)_2$ (**250b**) (Scheme 66).[142]



249

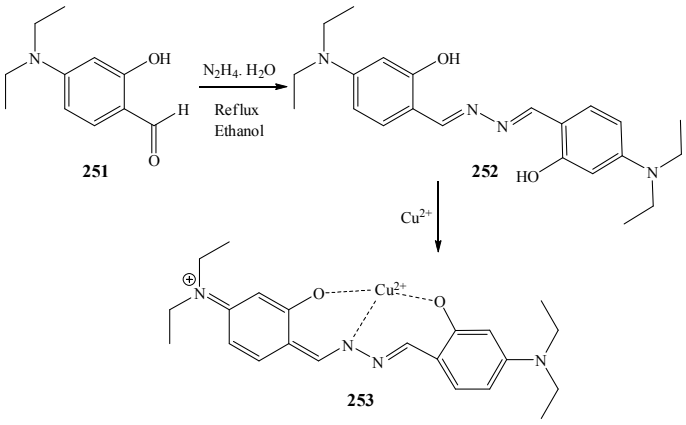
X = NO_3 **250 a**

X = ClO_4 **250 b**

Scheme 66.

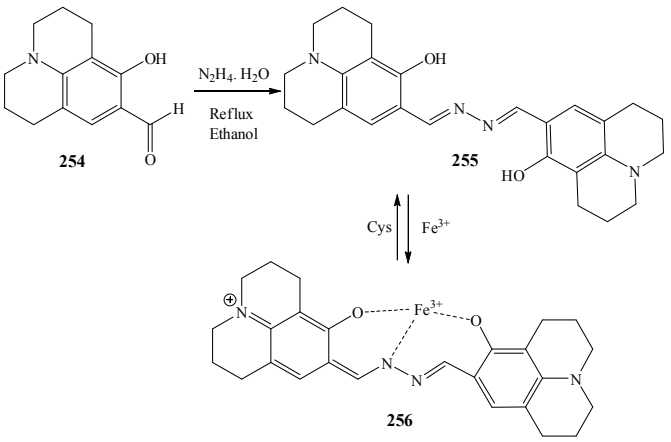
6.11. Synthesis of novel aldazine-based colorimetric chemosensors by complexation with Cu^{2+} and Fe^{3+}

In 2012, Govindaraju et al. developed novel aldazine-based colorimetric chemosensors for Cu^{2+} and Fe^{3+}. The aldazine ligands were synthesized by simple condensation of 4-diethylamino-salicylaldehyde (**251**) and 8-hydroxyjulolidinal (**254**) with hydrazine (Schemes 67 and 68). Interestingly, the ligands (4-diethylamino)salicylaldehyde azine (SA; **252**) and 8-hydroxyjulolidinal azine (JA; **255**) showed high selectivity and sensitivity toward Cu^{2+} and Fe^{3+} over other alkali ions and transition-metal ions, respectively. These ligands sense Cu^{2+} and Fe^{3+}, respectively, via double deprotonation and twisted-plane intramolecular charge transfer. In the presence of Cu^{2+}, the absorption band of SA at 425 nm redshifted to 545 nm. In the presence of Fe^{3+}, the absorption band of JA at 445 nm redshifted to 575 nm. The color of SA solution changed from pale yellow to purple upon binding to Cu^{2+}, and that of JA solution changed from pale yellow to violet on complexation with Fe^{3+}. The aldazine platform presented here can be used to develop colorimetric sensors for other heavy transition-metal cations.[143]



251 252 253

Scheme 67.

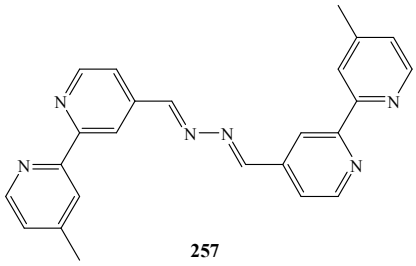


254 255 256

Scheme 68.

6.12. Synthesis of new tetradentate azine complexes of Re and Ru

Katz and coworkers synthesized in 2014 the novel tetradentate ligand, 1,4-bis[4-(40-methyl)-2,20-bipyridyl]-2,3-diaza-1,3-butadiene (BBDB; **257**) (Figure 15). They then synthesized novel coordination compounds with tricarbonylrhenium, polypyridylruthenium, and ammineruthenium moieties containing BBDB. These new complexes were characterized by spectroscopic, electrochemical, and computational techniques. Density Functional Theory (DFT) and Time-Dependent Density Functional Theory (TD-DFT) calculations were used to describe the optical properties and electronic structures of the complexes.[144]



257

Figure 15.

7. Conclusions

The present review describes a wide array of standard and modified methodologies toward azine synthesis. It also describes the chemical, physical, and biological significance of azines based on the literature. Recent progress in these important and convenient procedures provides a platform for future innovation because of their versatility, molecular economy, and strong potential in the synthesis of complex organic compounds. Recently, biological aspects of these molecules have been examined more intensively, and several new activities have been observed. In the near future, some molecules in this class may be in clinical use, leading to real commercial significance of these molecules. Further synthetic advancements in modification of this scaffold to tailor it to biological applications are being attempted. There is a large scope for exploration of the cycloaddition chemistry on these molecules using different substituents or their double bonds. We sincerely hope that this work would stimulate further serious research in this area.

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8. Notes and references
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