NITRILE IMINES: VERSATILE INTERMEDIATES IN THE SYNTHESIS OF FIVE MEMBERED HETEROCYCLES

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ABSTRACT
Nitrile imines are considered as the versatile reactive intermediates and are recognized as a linear-type 1,3-dipoles extensively used in 1,3-dipolar cycloaddition reactions for constructing biologically potent five membered heterocycles. This review article comprises the brief history, up to date information about the various methods employed for the generation, stability, reactivity and synthetic applications of nitrile imines. The stereochemistry of the products formed with the use of nitrile imines and biological activity associated with the cycloadducts formed was also presented.

Keywords: Pyrolysis, photolysis, cycloaddition, pyrazoles, tetrazoles.

INTRODUCTION

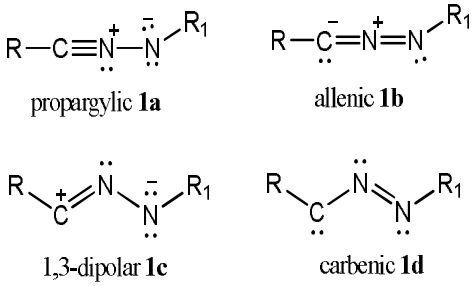
The concept of 1,3-dipolar cycloaddition was developed in the early 1950s Huisgen and co-workers; which has led to one of the most versatile methods for the construction of five-membered ring heterocycles. Most nitrile imines are highly reactive and in the absence of trapping agents they undergo rapid dipolar cycloaddition with themselves. Although first known only as transient intermediates, nitrile imines have been at the heart of mechanistic studies of 1,3-dipolar cycloaddition reactions.

Although hundreds of mechanistic papers on nitrile imines were appeared in 1970s; reliable spectroscopic observations were achieved in the early 1980s both at low temperatures and in the gas phase; the first crystalline nitrile imine was reported in 1988. The unusual structures found by X-ray analyses as well as the facile rearrangements observed experimentally have fostered a new interplay between experiment and theory. The story of nitrile imines, from matrix characterization to stable compounds, nicely illustrates the role that main group elements can play in organic chemistry[1]. Hans Bock et al[2] reported the photoelectron spectra of nitrile imines obtained by flash vaccum pyrolysis of tetrazoles; their study accounts the geometry and electronic structure of nitrile imines.

An isomer of diazomethane, the nitrile imine, HC≡N=NH is reported to be a stable molecule in the gas phase. Upon neutralizing the α-distonic $HCNNH^+$ cation in a beam experiment, this long-time predicted ylide can be generated. The experiments are supported by theoretical calculations (DFT/HF hybride method) on the neutral and cationic diazomethane, nitrile imine, and *N*-isocyano amine as well as the transition states for their interconversion[3].

Four alternative structures have been postulated for the non-stabilized nitrile imines: propargylic (1a), allenic (1b), 1,3-dipolar (1c), and carbonic (1d) structure.

These structures were depicted in (Scheme-1).

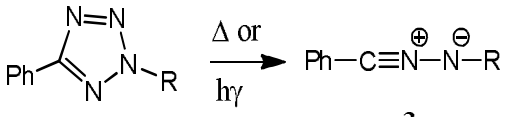


Scheme-1

The literature reveals that the theoretic calculations of the nitrile imine structures have generated the conflicting results. For instance, a high-level calculation study with the configuration interaction (QCISD) and a large basis-set concluded that the stable nitrile imine structure has a non-planar, allenic geometry and that the propargylic structure does not correspond to a local minimum on the potential energy surface. DFT calculations in combination with the natural resonance theory indicated that all four resonance structures are necessary for a full description and that the carbenic form dominates for F-CNN-F and H_2N-CNN-NH_2. In contrast, a spin-coupled valence bond calculation using the geometry from a CASSCF calculation suggested that the stable electronic structure of H-CNN-H is predominantly propargylic. To overcome this; Zheng et al[4] conducted photocrystallography experiments and reported the direct observation of a bent geometry for a nonstabilized nitrile imine in a metal-coordination crystal. The photoinduced tetrazole ring rupture to release N_2 appears to depend on the size of voids around the N(3)-N(4) bond in the crystal lattice. Accoridng to their studies, the bent nitrile imine geometry agrees with the 1,3-dipolar structure, a transient reactive species that mediates the photoinduced 1,3-dipolar cycloaddition in the aqueous medium.

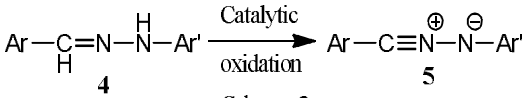
GENERATION OF NITRILE IMINES

The usual synthesis of nitrile imines (**3**) involves the thermolysis or photolysis of tetrazole (**2**)[5-6], flash vaccum pyrolysis of tetrazoles[2] (Scheme-2).



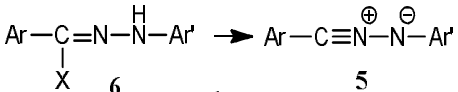
Scheme-2

Catalytic oxidation of aldehyde hydrazones (**4**) with lead tetraacetate[7], Chloramine-T[8], mercuric acetate[9], leads to the formation of nitrile imines (**5**) (Scheme-3); which can be trapped in situ by various dipolaphiles to produces five membered heterocycles such as pyrazolines, pyrazoles, triazoles, tetrazoles etc.



Scheme-3

Dehydrohalogenation of hydrazonoyl chlorides (**6**) by treating with a base triethylamine[5], or with silver carbonate in dioxane[10] also leads to the generation of nitrile imines (**5**) (Scheme-4). There were reports that nitrile imines are also generated by the photolysis of sydnones[11].



Scheme-4

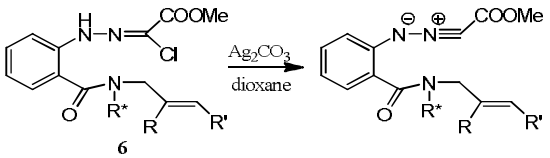
The spectral and kinetic behavior of nitrile imines photogenerated from sydnones and tetrazoles in fluid solutions has been studied by laser and lamp flash photolysis. The nitrile imines are characterized by lifetimes of milliseconds and are quenchable by the dipolarophile dimethyl acetylenedicarboxylate and by carboxylic acids. The

phototransformation of 3,4-diaryl-sydnones to the corresponding N,C-diarylnitrile imines occurs rapidly; this suggests that bicyclic diaziridine, diazirine or 1,2,3-oxadiazolin-5-one intermediates, postulated in the literature as precursors for nitrile imines, are either very short lived or not involved at all. The laser flash photolysis of the sydnones unsubstituted at the 4-position or bearing a methyl group at this position gives rise to additional, fast-decaying, transient species which become progressively longer lived upon interaction with hydroxylic reagents. Possible assignments of these transient species in terms of ylide structures are discussed in the light of the results of steady state photolysis at low temperatures[11].

APPLICATIONS OF NITRILE IMINES

Rai and co-workers[8] reported a new approach for the synthesis of pyrazoles via 1,3-diplar cycloaddition of acetyl acetone and *in situ* generated nitrile imines by the catalytic dehydrogenation of phenylhydrazones using chloramine-T as oxidant. The reaction afforded the regioselective cycloadducts in good yield. They developed and first reported the *in situ* generation of nitrile imines by the reaction of aldehyde hydrazones with mercuric acetate[9]. They carried out the reaction of aldehyde hydrazones with mercuric acetate in the presence of olefins and obtained the 1,3,5-trisubstituted 2-pyrazolines in good yield.

The reaction of homochiral hydrazonoyl chlorides (**6) with silver carbonate in dioxane produced corresponding nitrile imne; which undergo** intramolecular cycloaddition in the absence of trapping agents to give diastereoisomeric mixture of 3,3a-dihydro-pyrazolo[1,5-*a*][1,4]benzodiazepine-6(4*H*)-ones (**7)** and (**8)** in enantiopure form (Scheme-5)[10].



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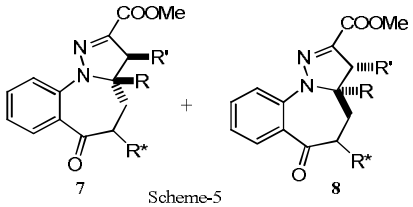
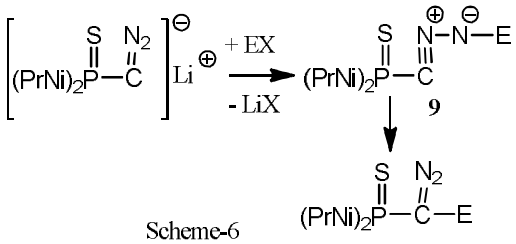


7 + 8

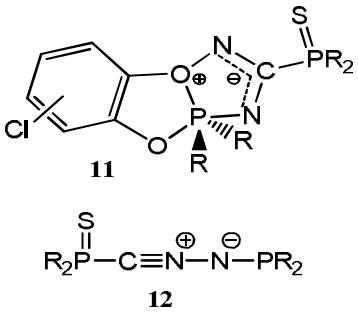
Scheme-5

The nitrile imines (**9)** undergo rearrangement reaction between -78 and +55°C, the rearrangement temperature depending on the substituents to produce rearranged products (**10)**. The nitrile imines can be characterized in solution by NMR and IR spectroscopy. Compounds (**9)**, E = $SiMe_3$ and $SiPh_3$, have also been trapped with methanol and with methyl acrylate (Scheme-6)[12].



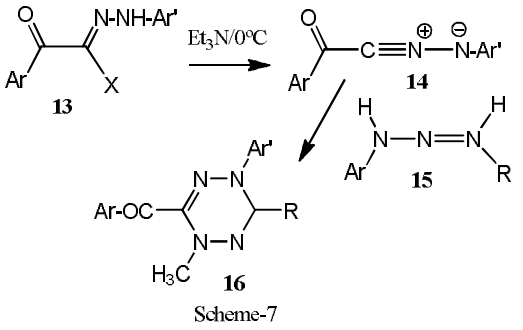
Scheme-6

Compound (**11)**, which first melts above 300°C without decomposition, is formed via nitrile imine–imidoylnitrene rearrangement upon reaction of the nitrile imine (**12)** with tetrachloro-*o*-benzoquinone. The surprising thermal stability of (**11)** could be due to the coordination of an oxygen atom to the nitrene nitrogen atom (R = N*i*Pr_2)[13].



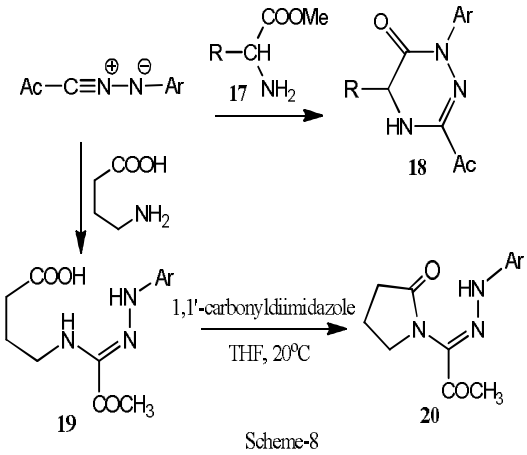
N-Aryl-*C*-ethoxycarbonylnitrile imines react with *meso*-tetrakis (pentafluorophenyl) porphyrin in 1,3-dipolar cycloadditions to yield novel pyrazolochlorins in moderate yields. The nitrile imines were generated *in situ* by base-induced dehydrobromination of ethyl hydrazono-α-bromoglyoxylates. A number of different experimental conditions were considered for these cycloadditions, namely different bases, solvents and temperature; the best results were obtained using potassium carbonate in refluxing toluene. The photophysical properties of the new chlorins were investigated and the results suggest that two of them have potential for use in photodynamic therapy[14].

Nitrilimines are found to be useful reactive intermediates in azaheterocyclic synthesis; They undergo two main cyclization reactions: 1,3-dipolar cycloaddition reactions with multiple bonds and cyclocondensation reactions with nucleophilic substrates containing suitably located electrophilic centers leading to various heterocyclic compounds. For instance; *C*-Aroyl-*N*-arylnitrilimines (14) generated by the reaction of hydrazonoyl halides (13) with triethylamine in tetrahydrofuran was trapped in situ by alkanal methylhydrazones (15) to afford 1,3,4,6-tetrasubstituted 1,2,4,5-tetrazines (16) in good yield (Scheme-7)[15].



Scheme-7

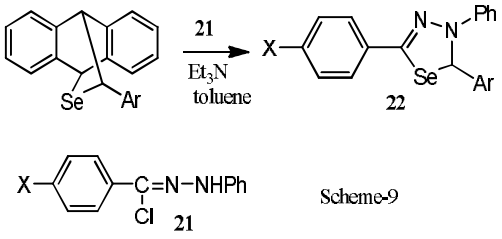
Nitrile imine generated *in situ* from *N*-arylhydrazonoyl chloride precursor reacts with methyl ester of α-amino carboxylic acid (**17**) to give condensed product; which undergo cyclisation under reaction conditions to form substituted triazine analogs (**18**). On the otherhands, it adds onto γ-Aminobutyric acid (GABA) to deliver the corresponding acyclic amidrazone adducts (**19**); which in the presence of 1,1'-carbonyldiimidazole undergo cyclocondensation involving the activated carboxyl and the amidrazone -CH_2NH groups to afford the respective *N*-[1-(arylhydrazono)-2-oxopropan-1-yl]pyrrolidin-2-ones (**20**) (Scheme-8)[16].



Scheme-8

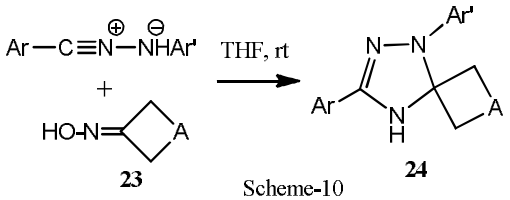
1,3-Dipolar cycloaddition between aromatic selenoaldehydes and aromatic *N*-phenyl nitrile imines generated in situ by the dehydrochlorination of hydrazonoyl chlorides (21) with triethylamine proceeded efficiently to give the corresponding [3+2]

cycloadducts as a single isomer 1,3,4-selenadiazoles (22) in good yields (Scheme-9)[17]. The study reports that these selenium containing five-membered heterocycles were stable at room temperature in the atmosphere.



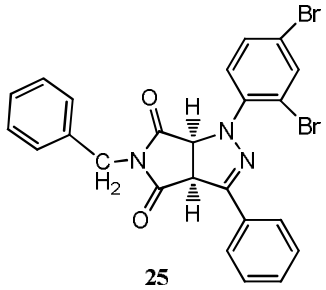
Scheme-9

The reaction of nitrile imines generated in situ by the dehydrochlorination of C-(2-furoyl)-, C-(2-thenoyl)- and C-(phenylaminocarbonyl) hydrazonoyl chlorides with triethylamine with cycloalkanone oximes (23) give unexpected 3-substituted 1-aryl-1,2,4-triazaspiroalk-2-enes (24) (Scheme-10)[18]. Although initially, the reaction was expected to produce cycloaddition products 1,2,4-triazoles or cyclocondensation products 1,2,4,5-oxatriazines, it produced (24); the formation of compounds (24) is assumed to involve cycloaddition adducts 1,2,4-triazoles which tautomerize to amine oxide-type intermediates that are deoxygenated by triethylamine.

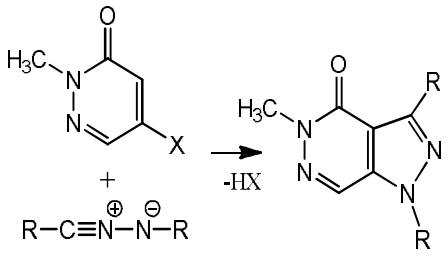


Scheme-10

The 1,3-dipolar cycloaddition reaction between nitrile imines and resin-bound enamines gives resin-bound pyrazoline intermediates. The piperazine resin functions as a traceless linker and allows these intermediates to be cleaved directly from the resin under mild acid conditions to afford 1,4-diarylpyrazoles. Alternatively they may be chemically modified on the resin prior to elimination from the polymer. The cycloaddition-elimination sequence is regiospecific for the 3,4-disubstituted pyrazole isomer and the products are obtained in good to high yield and in high purity[19]. Huisgen reaction of nitrile imines generated in situ in the presence of N-benzylmaleimide afforded regiospecifically the corresponding cycloadducts (25)[20] in good yield.

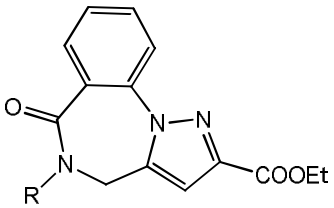


The 1,3-cycloaddition of the nitrile imines to the carbon-carbon double bond in benzalacetophenone leads to the formation of 4-phenyl-5-benzoylpyrazolines; which were converted into 4-phenyl-5-benzoylpyrazoles upon treatment with chloranil in xylene. However, the cycloaddition of nitrile imines to the carbon-carbon double bond in the enol tautomer of dibenzoylmethane gives the regioisomers 5-phenyl-5-hydroxy-4-benzoylpyrazolines which loose elements of water to yield 4-benzoyl-5-phenylpyrazoles[21]. Reaction of 5-substituted-2-methyl-3(2*H*)-pyridazinones with diarylnitrile imines generated in situ with chloramine-T has been shown to afford diarylpyrazolo[3,4-*d*]pyridazin-4(5*H*)-ones (Scheme-11)[22]. Reactivity and regiochemistry were analyzed by FMO theory.



Scheme-11

Reactions of nitrile imines with 2-methoxyvinyl phenyl ketone are less regioselective yielding both 4-benzoylpyrazoles and 5-benzoytpyrazoles, whereas no bis-cycloadducts were isolated[23]. A synthetic route to the pyrazolo[1,5-a][1,4]benzodiazepines (26) system is described, which starts from isatoic anhydride and allylamines, and involves as the key step an intramolecular nitrile imine cycloaddition. The title ring system has been prepared through a synthetic sequence involving a intramolecular nitrile imine cycloaddition as the key step[24].



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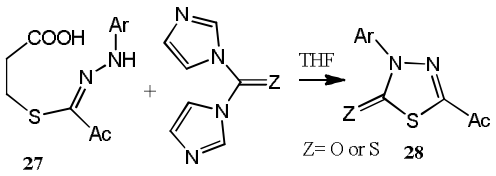
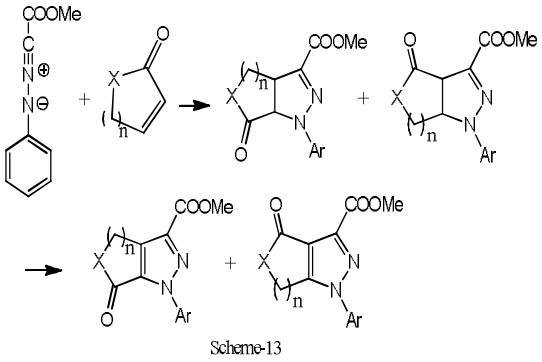
3-Mercaptopropionic acid-nitrile imine acyclic adducts (27) undergo cyclocondensation with 1,1′-carbonyldiimidazole to afford the respective 1,3,4-thiadiazol-2-(3*H*)-ones or 1,3,4-thiadiazol-2(3*H*)-thiones (28) with consequent elimination of the propionate moiety (Scheme-12)[25]. The constitution of these heterocyclic products follows from analytical and spectral data and is confirmed by single crystal X-ray structure determination.



Scheme-12

1,3-Dipolar cycloaddition of nitrile imines with α,β-unsaturated five- and six-membered lactones, thiolactones and lactams gave ring-fused pyrazoles. Regioisomeric mixtures have been obtained with the 5-substituted pyrazole as the major cycloadducts (Scheme-13). Only with the five-membered lactone the major product was the 4-acyl derivative. Computational studies, the use of the topological analysis of the Fukui functions and the potential energy surfaces (PES) theory allowed a theoretical description of the local reactivity in agreement with the observed high regiochemistry and with the role of the heteroatom adjacent to the carbonyl group[26].

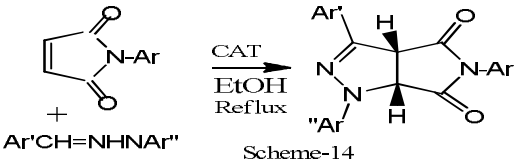


Scheme-13

Extremely fast fluorescence labeling (<1 min) of a recombinant alkene-encoded protein in living Escherichia coli cells was observed with tetrazole. The electron-donating methoxy substituent raises the energy of the highest occupied molecular orbital of the nitrile-imine intermediate derived from tetrazole. This strategy greatly accelerates the functionalization of alkenes by 1,3-dipolar cycloaddition in living systems[27]. 6-Aryl-2-ethoxycarbonyl

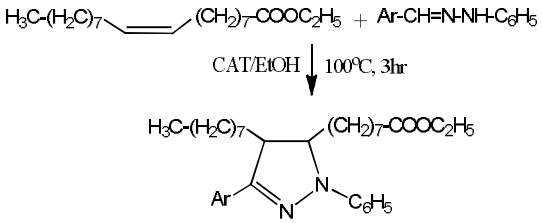
pyridazin-3(2*H*)-ones[28] have been synthesized as useful synthetic intermediates; they allow formation of a new hydrazides, hydrazidoyl chlorides and the highly reactive nitrile imine species. Dimerization and reaction of the latter species with benzonitrile, benzaldehyde and their *p*-methoxy and *p*-nitro derivatives provides a convenient method for the synthesis of substituted 1,2,4,5-tetrazines, 1,2,4-triazoles and 1,3,4-oxadiazoles respectively, with pyridazin-3(2*H*)-one moiety.

Huisgen reaction of nitrile imines generated in situ in the presence of *N*-benzylmaleimide afforded region-specifically the cis-3-aryl-5-benzyl-1-(2',4'-dibromophenyl)-3a, 4,6,6a-tetrahydro-1*H*,5*H*-pyrrolo[3,4-*c*]pyrazole-4,6-diones in good yield[29]. Nitrile imines react with 1-phenylsulphonyl-2-benzoyl (or methoxycarbonyl)alkenes to give 4-phenylsulphonyl-5-benzoyl (or methoxycarbonyl) substituted pyrazolines[30]. The cycloaddition regioselectivity is discussed in terms of Frontier Orbital energies and coefficients. Recently Ajay Kumar and co-workers[31] reported the use of in situ generated nitrile imines in the synthesis of 1,3,5-triaryl-4,6-dioxo-pyrrolo[3,4-*d*]-7,8-dihydropyrazoles. They carried out a reaction of a mixture of *N*-aryl maleimide, aldehyde hydrazone and chloramine-T in ethyl alcohol and obtained the cycloadducts in moderate to good yield (Scheme-14). The synthesized 1,3,5-triaryl-4,6-dioxo-pyrrolo[3,4-*d*]-7,8-dihydropyrazoles have been evaluated in vitro for their antibacterial, antifungal and antioxidant activities. The results of the study indicated that some of the compounds posses promising activity[32].



Scheme-14

Aldehyde phenyl hydrazones undergo oxidative dehydrogenation with Chloramine-T to give nitrile imines, which are trapped in situ by ethyl oleate to afford 8-(5-Aryl-4-octyl-2-phenyl-3,4-dihydro-2H-pyrazol-3-yl)-octanoic acid ethyl esters in good yield (Scheme-15)[33]. The pyrazole derivatives have shown moderate antimicrobial and antioxidant activities[34].

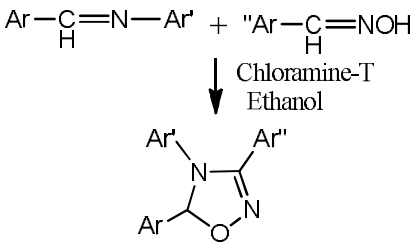


Scheme-15

1,3-Dipolar cycloaddition of *C*-aryl-*N*-aryl- and *C*-carboxymethyl-*N*-aryl-nitrile imines with functionalized acetylenes produces regioisomeric mixtures of 5-substituted pyrazoles as the major cycloadduct. Under scandium triflate catalysis a reversal in the regiochemistry was observed, especially in the case of *C*-carboxymethyl-*N*-aryl-nitrile imines[35]. *tert*-Butyl isocyanide reacts with acceptor-substituted nitrile imines to give derivatives of tetrahydro-1,2,5,6-tetrazocines along with substituted 5-hydrazonoyl-1,2,4-triazoles. Replacement of *tert*-Butyl isocyanide with aryl or *sec*-alkyl isocyanides leads to substituted α-hydrazonoamides) rather than to analogues of tetrahydro-1,2,5,6-tetrazocines[36].

Rai and co-worker[37] reported the synthesis of series of trisubstituted 1,2,4-oxadiazoles via 1,3-dipolar cycloaddition reactions. They carried out a cycloaddition reaction of imines and nitrile oxides generated *in situ* by the catalytic dehydrogenation of aromatic aldoximes using chloramine-T reagent

and obtained the cycloadducts in good yield. The cycloadducts have been tested for their antifungal and antibacterial activity, results of their study revealed that all the cycloadducts exhibited a promising activity (Scheme-16).



Scheme-16

o-Alkenylthio and *o*-alkynylthio substituted arylhydrazonyl chlorides react with triethylamine in acetonitrile at room temperature to give 3*H*-4,1,2-benzothiadiazines as a result of intramolecular attack of the sulphur on the intermediate nitrite imines followed by a 2,3-sigmatropic shift in the resulting ylides. The reaction leading from the nitrile imine intermediates to benzothiadiazines is reversed on heating, allowing formation of intramolecular 1,3-dipolar cycloadducts as the thermodynamic products[38]. Nitrile imines react with cyclooctatetraene and its diene adduct with dimethyl acetylene-dicarboxylate to yield cyclobutane-condensed pyrazoline systems. The different reactivity of cyclobutene and cyclohexadiene double bonds in the same molecule has been evaluated and compared with the reactivity toward other 1,3-dipoles[39]. The intramolecular cycloaddition of nitrile imines generated in situ from the aryl hydrazones in the presence of chloramine-T with α,β-unsaturated ketones results in the formation of tetrasubstituted pyrazolines in moderate yield[40].

A series of nitrile imines bearing alkenyl substituents on the nitrogen atom of 1,3-dipole were generated in situ by the photolysis of 2-alkenyl-5-phenyl substituted tetrazoles or by the base treatment of 1-chlorohydrazones. When the nitrile imine was generated in the presence of active dipolarophile, bimolecular 1,3-dipolar cycloaddition occurred. Under these conditions; the intramolecular 1,3-dipolar cycloaddition is completely suppressed[41]. Reaction of *N*-(2,4-dinitrophenyl)-*C*-alkyl hydrazonyl chlorides with diverse dipolarophiles gave a variety of novel heterocyclics, which are expected to possess biological activities. The ring closure is brought about by a concerted process involving nitrile imine as an intermediate[42].

Nitrile imines are added to the C=C bond of 4-arylidene-2-phenyl-5(4*H*)-thiazolones to afford spiro-pyrazolines. The cycloaddition reactions are regioselective and only one of the two possible regioisomers is isolated. Reactions of the cycloadducts with nucleophiles lead to pyrazole derivatives by opening of the thiazolone ring[43]. The readily available alkyl dicyanoacetates reacted with the 1,3-dipolar reagents arenecarbonitrile imines to afford 1,2,4-triazol derivatives. Arylnitrile imines reacted with to offer both bis- and mono-addition products; the bis-adducts possess an ester structure, whereas the mono-adducts present a ketene-hemiacetal structure[44].

1,3-Dipolar cycloadditions of *C*-carboxymethyl-*N*-arylnitrile imines with cyclic α,β-unsaturated ketones; after cycloaddition, oxidative aromatization gives the ring-fused pyrazoles. Computational studies and the use of topological analyses of the Fukui functions allows a theoretical description of the local reactivity was in agreement with the experimentally observed regiochemistry[45]. A synthesis of 1-substituted-1*H*-indazoles via 1,3-dipolar cycloaddition of nitrile imines to benzyne

was reported to be completed within 5 min, affording the corresponding N(1)-C(3) disubstituted indazoles in moderate to excellent yields[46].

Dihydropyrazoles bearing a chiral quaternary center at the 5-position have been prepared by enantioselective 1,3-dipolar cycloaddition of nitrile imines to α-substituted- and α,β-disubstituted-α,β-unsaturated carbonyl substrates. Use of α,β-unsaturated carbonyl substrates with a 1-benzyl-5,5-dimethylpyrazolidin-3-one auxiliary in conjunction with MgI_2 and a bisoxazoline ligand derived from (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol was proved optimal to obtain chiral dihydropyrazoles with high enantioselectivity[47].

The [3+2] dipolar cycloaddition reaction of nitrile imines with 3-alkylidene oxindoles produces the pyrazoline spiroadducts in high yields and with excellent regio- and diastereoselectivities. These spirocyclic intermediates have been elaborated to synthetically versatile 3-amino oxindole building blocks such as β-amino nitrile, 1,3-diamine, and pyrrolo[2,3-b]indoline derivatives[48].

The 1,3-cycloaddition of the nitrile imines to the carbon-carbon double bond in benzalacetophenone leads to the formation of 4-phenyl-5-benzoylpyrazolines; which were converted into 4-phenyl-5-benzoylpyrazoles upon treatment with chloranil in xylene. However, the cycloaddition of nitrile imines to the carbon-carbon double bond in the enol tautomer of dibenzoylmethane gives the regioisomers 5-phenyl-5-hydroxy-4-benzoylpyrazolines which loose elements of water to yield 4-benzoyl-5-phenylpyrazoles. The orientations in these reactions are interpretted in terms of the FMO theory[49].

6-Aryl-2-ethoxycarbonyl pyridazin-3(2H)-ones have been synthesized as useful synthetic intermediates because they allow formation of new hydrazides, hydrazidoyl chlorides and the highly reactive nitrile imine species. Dimerization and reaction of the latter species with benzonitrile, benzaldehyde and their p-methoxy and p-nitro derivatives provides a convenient method for the synthesis of substituted 1, 2, 4, 5-tetrazines, 1, 2, 4-triazoles and 1, 3, 4-oxadiazoles, respectively, with pyridazin-3(2H)-one moiety[50].

CONCLUSIONS

Although enormous amount of research was undertaken and research papers were published; the scanty of review papers were appeared which provoked us to take this project. This article may become an useful tool for the researchers who are working in the area of 1,3-dipolar cycloaddition reaction for devising new methodologies for the generation of nitrile imines and better use of them organic synthesis.

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