HL **ISSN: 2231 – 3087(print) / 2230 – 9632 (Online)**
http://heteroletters.org **Vol. 2: (4), 2012, 485-514**

1,3-DIPOLAR CYCLOADDITIONS APPROACH TO BIOACTIVE SPIROHETEROCYCLIC COMPOUNDS

Essam M. Hussein

Department of Chemistry, Faculty of Science, Assiut University, Assiut 71516, Egypt
e-mail: essam.hussein78@yahoo.com

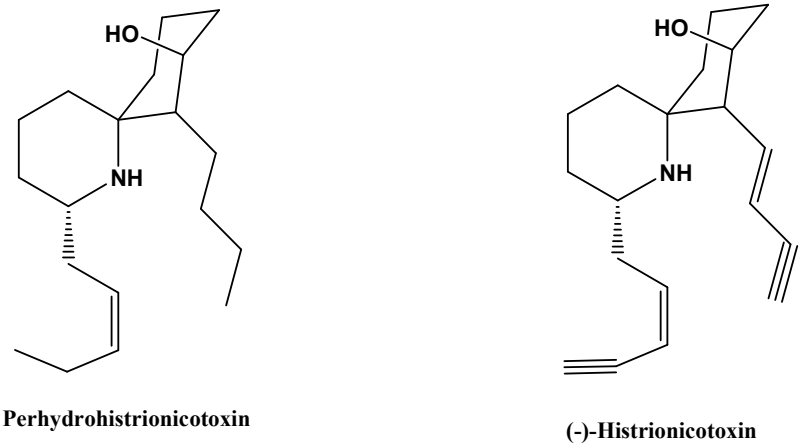
Abstract
Spiro compounds represent an important class of naturally occurring substances characterized by highly pronounced biological properties. The most developed avenue for the synthesis of these compounds depends on the cycloaddition to an exocyclic bond. 1,3-dipolar cycloaddition reactions are considered to be one of the most useful processes for the construction of five membered heterocyclic ring systems in highly regio- and stereoselective manner.
This review describes 1) general methods for generation and preparation of most important 1,3-dipoles such as nitrones, nitrile oxides and azomethine ylides; and 2) the most recent examples of synthetic applications of 1,3-dipolar cycloaddition reactions to bioactive spiroheterocyclic compounds.

Keywords: 1,3-dipolar cycloaddition, spiro, nitrone, nitrile oxide, azomethine ylide, bioactive.

INTRODUCTION

A "spirounion" is one formed by a single atom, which is the only common member of two rings. A "free spirounion" is one constituting the only union direct or indirect between two rings. The common atom is designated as the "spiro atom". According to the number of spiro atoms present, the compounds are distinguished as monospiro, dispiro, trispiro compounds, etc.
In 1900, Bayer created the first spiran described as a bicyclic hydrocarbon linked by a single carbon. Due to the tetrahedral nature of the spiro (linked) carbon, two ring planes are closely perpendicular to each other.
Spiro compounds having cyclic structures fused at a central carbon are of recent interest due to their interesting conformational features and their structural implications on biological systems. The asymmetric character of the molecule due to the chiral spiro carbon is one of the important criteria of the biological activities. The retention of neurotoxic properties of perhydrohistrionicotoxin, an analogue of a natural product (-)-histrionicotoxin, is clear evidence of the role of the spiro carbon in navigating the biological activity (**Figure1**).[1]
Spiroheterocyclic compounds are by far considered one of the most important and essential derivatives in the field of organic chemistry. Many outstanding chemists devoted a lot of efforts which paved the way for the synthesis of new spiroheterocyclic derivatives as well as for studying and understanding their valuable applications. The wide scope of the synthesis of spiroheterocyclic systems is due, in part to the liability

of a great number of the new synthesized derivatives to be used as drugs and dyes.



Perhydrohistrionicotoxin **(-)-Histrionicotoxin**

Figure 1: Structure of Perhydrohistrionicotoxin and (-)-Histrionicotoxin

Resent literature surveys revealed that the syntheses and applications of spiroheterocyclic compounds have gained importance. Spirooxindolyl nucleus represents an important part of many naturally occurring alkaloids,[2] such as strychnofoline,[3] alstonisine,[4] coerulescine,[5] pteropodine,[6] formosanine,[7] spirotryprostatine A, spirotryprostatine B, (+)-elacomine, (-)-horsfiline and rychnophyilline,[8] with highly pronounced pharmacological properties (**Figure 2**).

1. BIOACTIVE SPIROHETEROCYCLES

The spiro functionality has been known for a long time to be presented in phytochemical either in alkaloids, lactones or terpenoids. The spirocyclic alkaloid (-)-histrionicotoxin , isolated from skin extracts of the poison dart frog, *Dendrobats histrionius*, found in Columbia, is a very potent nicotinic receptor antagonist.[9] Spiroketals are reported to be the subunits of many naturally occurring substances of biological interest such as insect pheromones, anti-feedants and polyether antibiotics.[10] A series of spiroketals (**1-4**) have been isolated from *Chrysanthemum coronanium*, a common vegetable of South China.[11] Some of these compounds are found to have antifeeding activity towards silkworm[12] and spasmolytic and antiphlogistic activity (**Figure 3**).[13,14] Unsaturated spiroacetals such as 1,6-dioxaspiro[4.4]nona-3,8-diene[15] and 1,6-dioxaspiro[4.5]decane[16] have also been isolated from *Artemisia sp*.

The spiro[pyrrolidin-3,3'-indole] ring system is a recurring structural motif in a number of natural products such as vinblastine and vincristine, that function as cytostatics and are of prime importance in cancer chemotherapy.[17]

The derivatives of spiro-oxindole find very wide biological application as antimicrobial,[18] antitumor, and antibiotic agents, and inhibitors of human NK-1 receptor[19, 20] and potent non-peptide inhibition of the p53–MDM2 interaction (**Figure 4**).[21]

Horsfiline, an oxindole alkaloid containing a spiro-[indole-pyrrolidone] nucleus, has been isolated by Bodo and co-workers[22] from *Horsfieldia superba*, a tree from Malaysia, the extracts of which are commonly employed in local medicine. The saponaceolides (A–D), **5** are found to possess antitumor activity in 60 human cancer cell lines. [23] Each of these compounds contains a unit of tricyclic trioxaspiroketal (**Figure 5**).

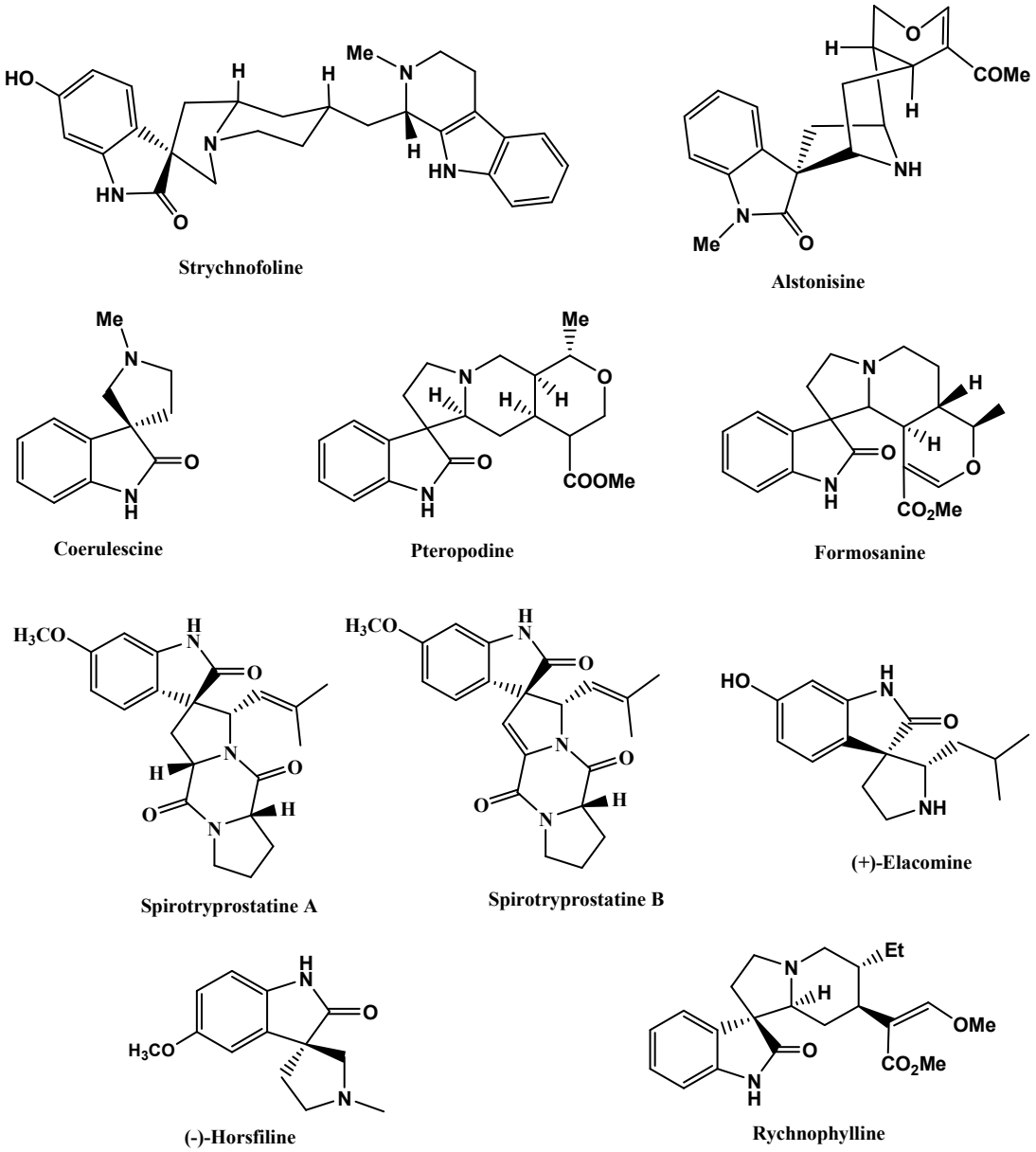


Figure 2: Representative naturally occurring spiropyrrolidinyl-oxoindole alkaloids

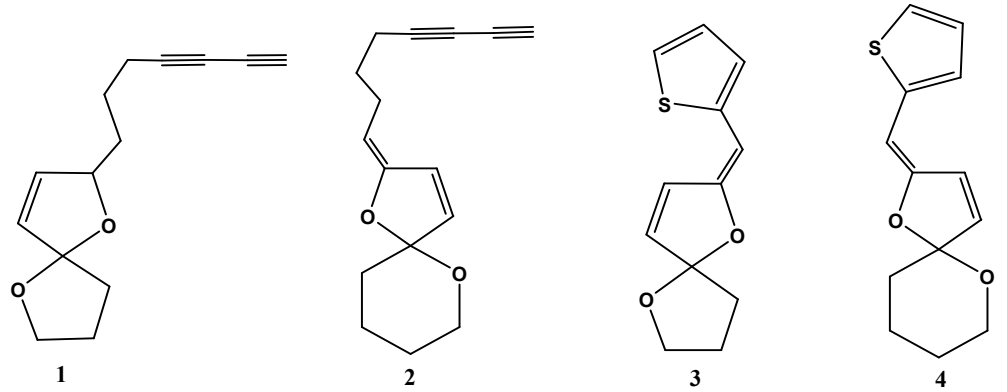


Figure 3: Structure of some naturally occurring spiroketals

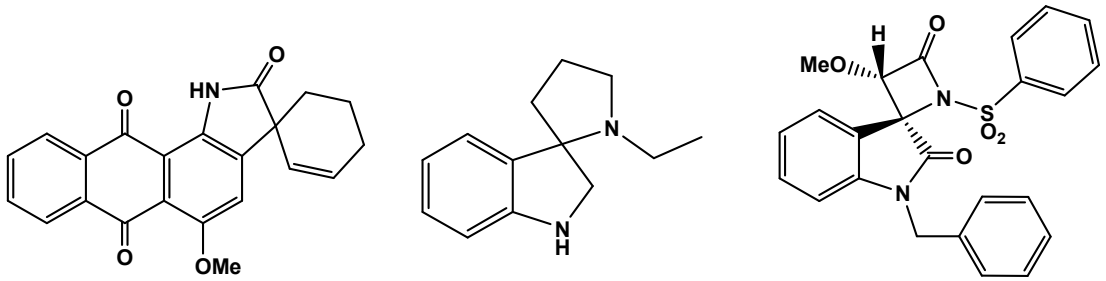
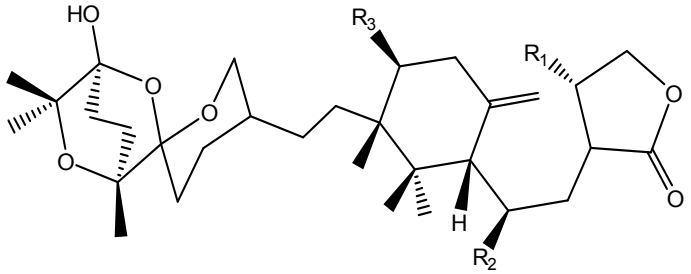


Fig. 4: Representative bioactive spiro-oxindoles

Wrobel *et al.* prepared spirosuccinimide incorporated with isoindolones (**6**) and benzisothiazole-1,1-dioxide moieties (**7**) as aldose reductase inhibitors and anti-hyperglycemic agents **(Figure 6)**.[24]



5: A: R_1= OH, R_2 = R_3 = H **C: R_1= R_2 = OH, R_3 = H**
B: R_1= R_2 = R_3 = H **D: R_1= R_3 = OH, R_2 = H**

Fig. 5: Structure of Saponaceolides

Zen *et al*. synthesized some spiro-isoxazolines (**8**) to be used as anticancer reagents (**Figure 7**).[25]

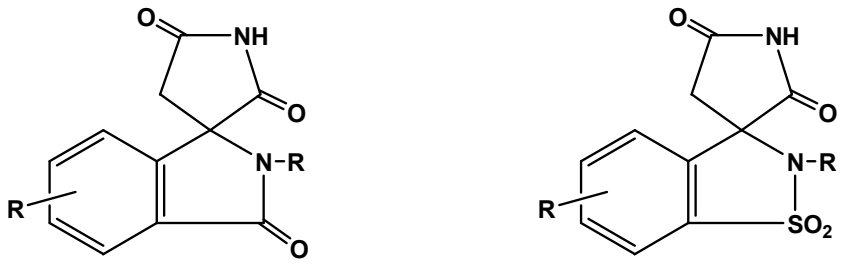


Figure 6: Structure of bioactive spirosuccinimide derivatives

2. 1,3-DIPLOAR CYCLOADDITION REACTIONS

The preparation of chiral compounds is an important and challenging area of contemporary synthetic organic chemistry. The 1,3-dipolar cycloaddition, also known as the "Huisgen cycloaddition" is a classic reaction in organic chemistry consisting of the reaction of a dipolarophile with a 1,3-dipolar compound that allows the production of various five-membered heterocycles.

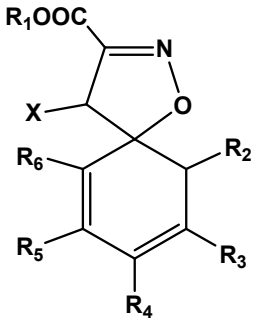
This reaction represents one of the most productive fields of modern synthetic organic chemistry. Most of dipolarophiles are alkenes, alkynes and molecules possessing related heteroatom functional groups (such as carbonyls and nitriles).

The 1,3-dipoles can be basically divided into two different types:

i. The allyl anion type such as nitrones, azomethine ylides, nitro compounds, bearing a nitrogen atom in the middle of the dipole, carbonyl ylides, or carbonyl imines, bearing an oxygen atom in the middle of the dipole.

ii. The linear propargyl/allenyl anion type such as nitrile oxides, nitrilimines, nitrile ylides, diazoalkanes, or azides.

Two π-electrons of the dipolarophile and four electrons of the dipolar compound contribute in a concerted pericyclic reaction pathway. The addition is stereo-conservative (*suprafacial*), and the reaction is therefore a [$\pi 4_S + \pi 2_S$] cycloaddition (**Figure 8**).



8

R_1 = H, lower cyclo alkyl, alkoxyalkyl, C_6H_5, arylalkyl; R_2 = halo, aryl X = halo

R_3-R_6 = H, lower alkyl; R_2,R_3,R_4,R_5 may from aromatic ring.

Figure 7: Structure of bioactive spiro-isoxazolines derivatives

However, the dipole might be stabilized by the adjacent central heteroatom Y (nitrogen, oxygen, or sulfur) through resonance, and a non-concerted reaction pathway might also occur.

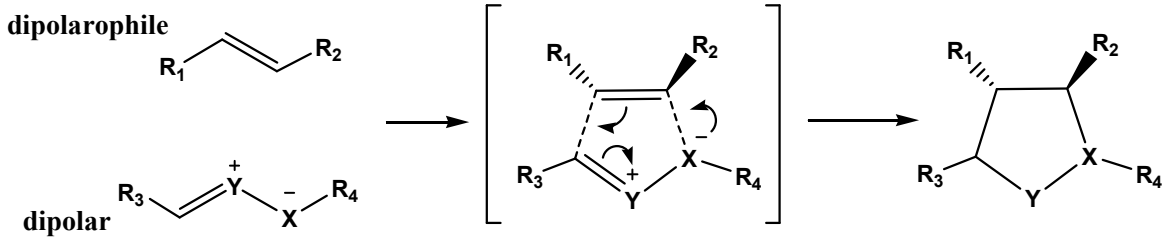


Figure 8: General concerted 1,3-dipolar cycloaddition

The transition state of the concerted 1,3-dipolar cycloaddition reaction is controlled by the frontier molecular orbitals of the substrates. Hence, the reaction of dipoles with dipolarophiles involves either a LUMO–dipole/HOMO–dipolarophile reaction or a HOMO–dipole/LUMO–dipolarophile interaction, depending on the nature of the dipole and the dipolarophile.

1,3-Dipolar cycloaddition reactions constitute a highly versatile and powerful tool for the construction of pharmacologically important five-membered heterocycles in highly regio- and

stereoselective manner through a 1,3-dipolar cycloaddition of nitrone, nitrile oxide, or azomethine ylides to exocyclic olefinic bond of heterocycles or carbocycles.[26]

3. NITRONES

For the last 60 years many scientists have drawn special attention to nitrones due to their successful application as building blocks in the synthesis of various natural and bioactive compounds. The reactions of nitrone dipoles play an important part in the history of cycloaddition reactions. The 1,3-dipolar cycloaddition of nitrones with olefinic dipolarophiles proceeds through a concerted mechanism yielding highly substituted isoxazolidines with generation of as many as three new adjacent chiral centers in a single step.

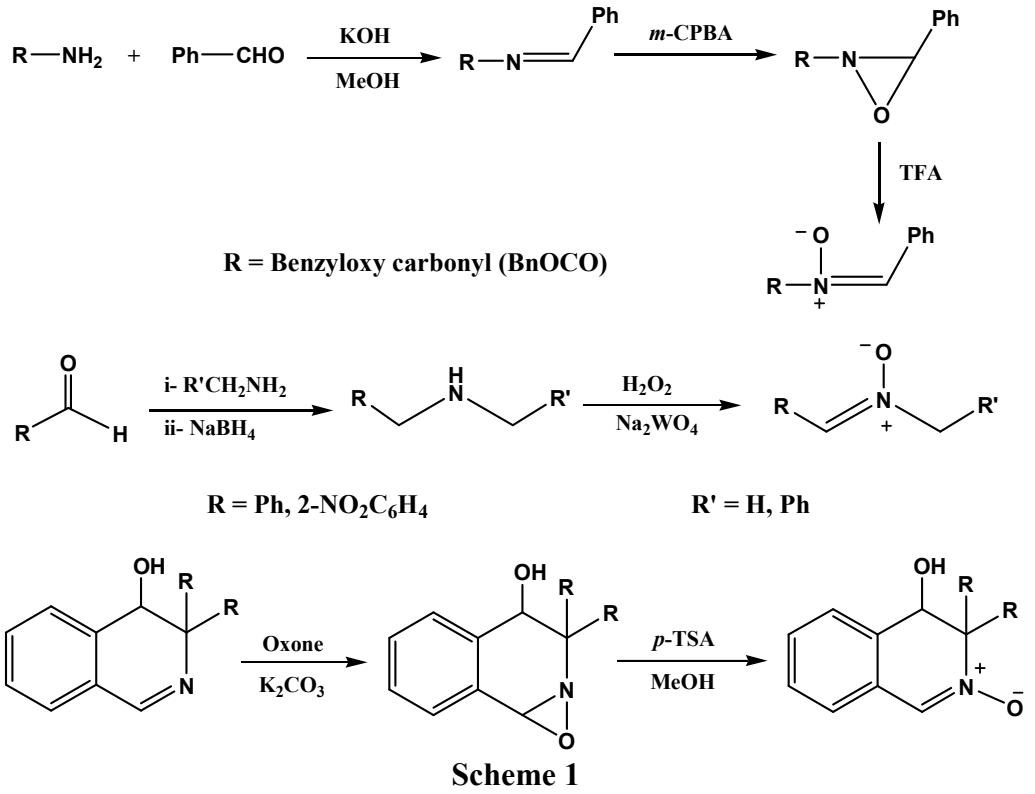
The 1,3-dipolar cycloaddition of exocyclic olefins with nitrones result in highly substituted spiro-isoxazolidines and they have also been transformed into complex heterocycles.

3.1. Synthesis of Nitrones

3.1.1. Oxidative Methods

3.1.1.1. Oxidation of Amines

Direct oxidation of primary amines usually leads to a mixture containing oximes, nitroso and nitro compounds. However, oxidation to nitrones can be accomplished after their conversion into secondary amines or imines. Occasionally, oxidation of secondary amines rather than direct imine oxidation seems to provide a more useful and convenient way of producing nitrones (**Scheme 1**).[27]

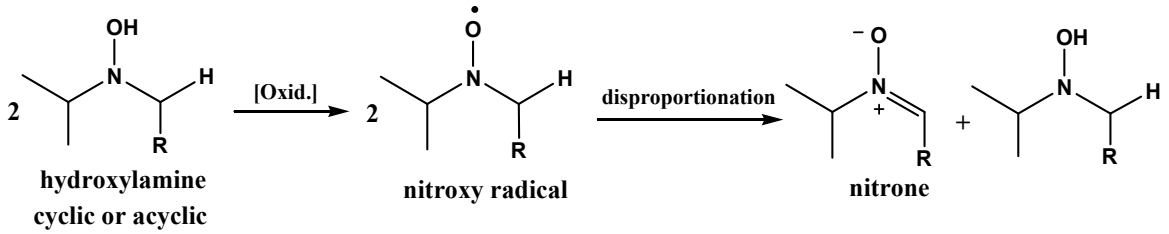


Scheme 1

3.1.1.2. Oxidation of Hydroxylamines

Mild oxidation of hydroxylamines containing one or more protons at α-C seems to be one of the most convenient methods of nitrone formation (**Scheme 2**). Air, H_2O_2, *m*- chloroperbenzoic acid

(*m*-CPBA), oxides of different metals (MnO_2, PbO_2, HgO, Ni_2O_3, etc.) can be used as oxidizing agents.[28]



Scheme 2

3.1.2. Nonoxidative Methods

3.1.2.1. Synthesis from Oximes

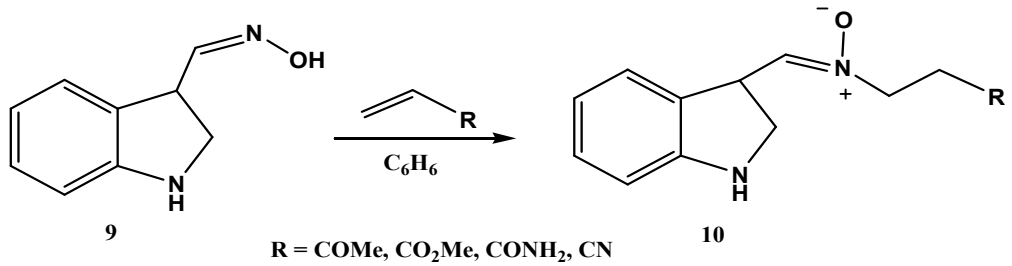
Alkylation of oximes at the nitrogen atom with various electron poor alkenes is one of the easiest and convenient methods for synthesizing nitrones.

The reaction known as Grigg's nitrone formation and the advantage of this method is that there is no need to use oxidants.[29-31] In most cases, the resulting nitrones quickly become involved in a specific 1,3-cycloaddition reaction. Thus, the reaction of indol-oxime (**9**) with methyl acrylate, methyl vinyl ketone, acrylonitrile, and acrylamide gives indol-nitrones (**10**) (**Scheme 3**).[32,33]

Bromo-intramolecular cyclization of *γ,δ*-unsaturated oximes (**11**) and (**12**) affords the corresponding bromomethylpyrroline-N-oxides (**13**) and (**14**) in 23% - 87% yield depending on the structure of the oxime (**Scheme 4**).[34]

3.2. Nitrone Cycloadditions Approach to Bioactive Spiroheterocycles

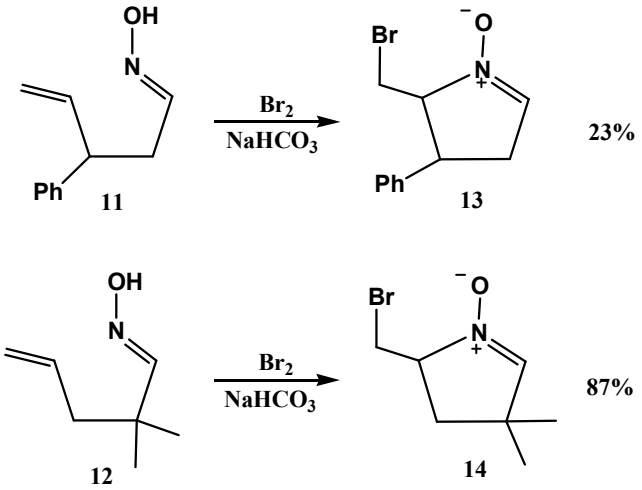
Isoxazolidines are potential precursors for biologically important compounds such as amino sugars,[35] alkaloids,[36,37] β-lactams[37] and amino acids,[38] and exhibit antibacterial and antifungal activities. Among the dipoles, nitrones have been extensively used as they readily undergo both interand intra-molecular 1,3-dipolar cycloaddition with olefins.[39]



Scheme 3

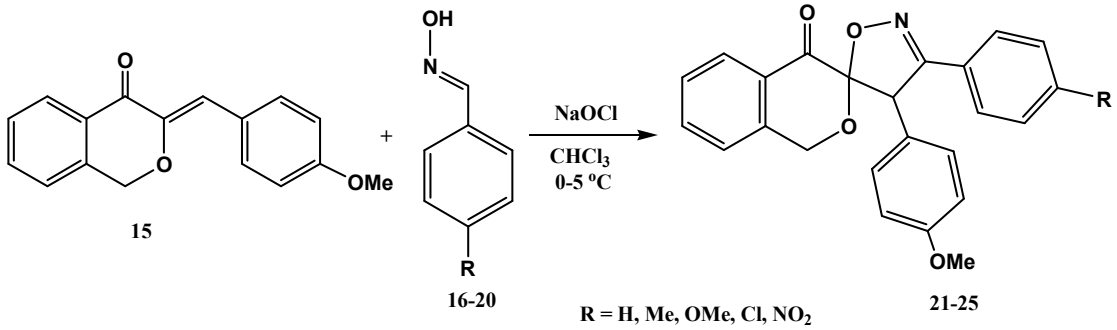
The 1,3-dipolar cycloaddition of exocyclic olefins with nitrones result in highly substituted spiro-isoxazolidines[40] and they have also been transformed into complex heterocycles.[41]

4-(4'-Methoxyphenyl)-3-aryl-4H-spiro[isochromene-3',5-isoxazol]-4(1H)-one (**21-25**) was synthesized by reaction of (R)-*p*-benzadoxime (**16-20**) and 3-β-methoxy-benzylidene-isochroman-4-one (**15**) in chloroform and aqueous solution of sodium hypochlorite.[42]



Scheme 4

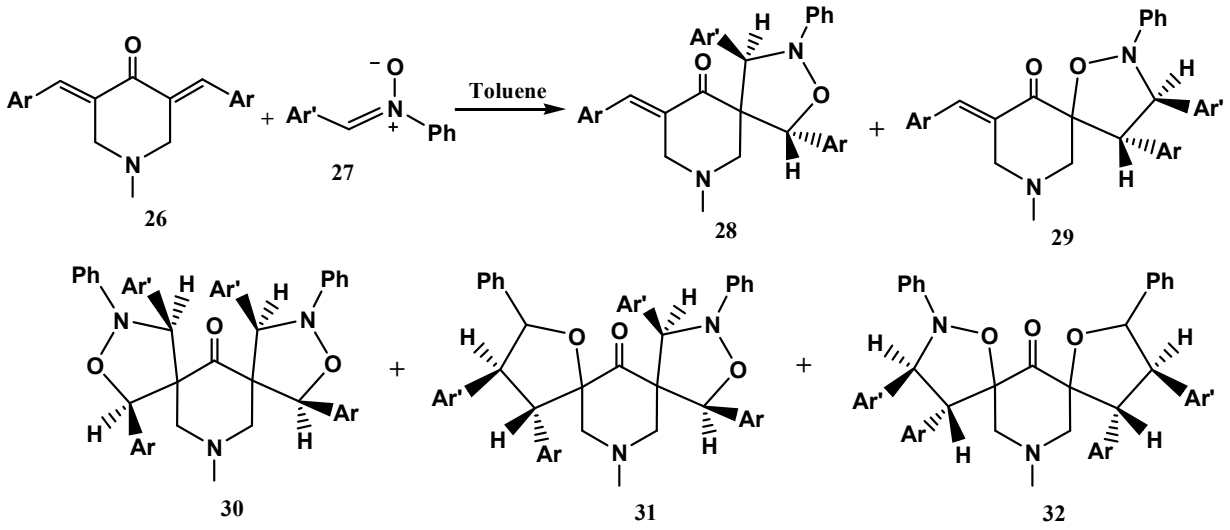
These compounds typically form the highly stable antitubercular pharmacophore site. Based on their pharmacological properties and thermal stability, these compounds may be useful as anti-tubercular agents (**Scheme 5**).



Scheme 5

The 1,3-dipolar cycloaddition of 3,5-bis-(arylidene)-1-methylpiperidin-4-ones, **26a–o**, with C-aryl-N-phenylnitrones, **27a** and **27b** (4 molar equiv), proceeds chemo-, regio- and stereoselectively affording mono- and bis-spiroisoxazolidines, the former predominating, with the electron-rich oxygen of the nitrone attached to the more electron-deficient β-carbon of the benzylidene moiety, ascribable to the steric hindrance exerted by the mono spiro-isoxazolidine ring for the second cycloaddition leading to bis- isoxazolidines (**Scheme 6**).

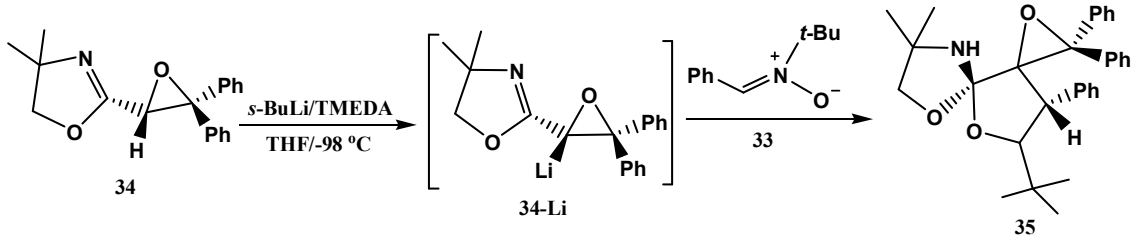
The sterically bulky groups such as 1-naphthyl and o-anisyl in **26** lead to the formation of only mono-spiroisoxazolidines. The cycloaddition of mono-spiroisoxazolidines to furnish bis-spiroisoxazolidines displays facial diastereoselectivity ascribable to steric control.[43]



Ar = C_6H_5, *p*-ClC_6H_4, *p*-MeC_6H_4, *p*-$MeOC_6H_4$, *p*-FC_6H_4, *o*-ClC_6H_4, *o*-MeC_6H_4, *o*-$MeOC_6H_4$, *2*-Thienyl, *m*-$O_2NC_6H_4$; Ar' = C_6H_5, *p*-MeC_6H_4

Scheme 6

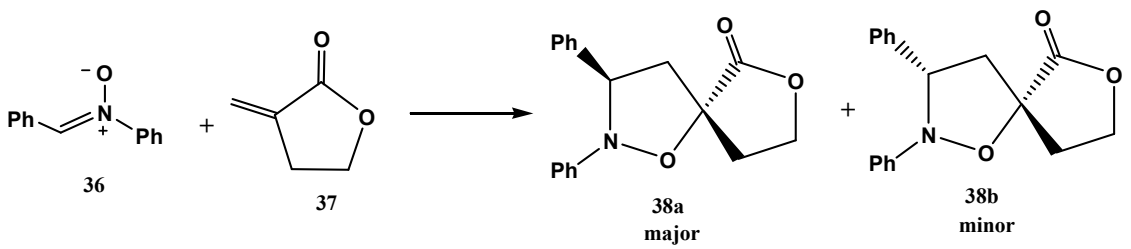
Reaction of (*Z*)-N-*tert*-butyl-α-phenylnitrone (**33**) with lithiated 3,3-diphenyl-2-oxazolinyloxirane (**34-Li**) affording diazadispiro[2.0.4.3]undecane derivative (**35**) in a good yield (**Scheme 7**).[44] Lithiation of 3,3-diphenyl-2-oxazolinyloxirane (**34**) was performed using *s*-BuLi/ tetramethylethylenediamine (TMEDA) in THF.[45]



Scheme 7

Cycloaddition of *C*,*N*-diphenylnitrone to α-methylene-γ-butyrolactone afforded two diastereomeric 5-spirosubstituted isoxazolidines with high selectivity.[46] The ratio of products formed in the cycloaddition depends on the reaction conditions, increasing on lowering the temperature (**Scheme 8**). However, for practical reasons, the boiling temperature of benzene represents a good compromise between selectivity and reactivity: a good 9:1 ratio of products was obtained after 5 h.

A comparison of the possible transition states leading to the two diastereoisomers shows unfavorable steric interactions between the hydrogen at C-4 of the lactone pointing towards the nitrone and the N-phenyl group of nitrone in the *exo*-C=O transition state (**Figure 9**). The attack to the opposite face of lactone places the C=O group in the *endo* position, removing the strongest steric repulsions. Moreover, in the *endo*-C=O transition state the carbonyl group, facing the *N*-phenyl, is established for a stabilizing secondary orbital interaction, which might work together steric effects in determining the high stereoselectivity.[47]



Benzene, 80 °C, 5h. 82% (90:10)
Toluene, 110 °C, 3h. 89% (80:20)

Scheme 8

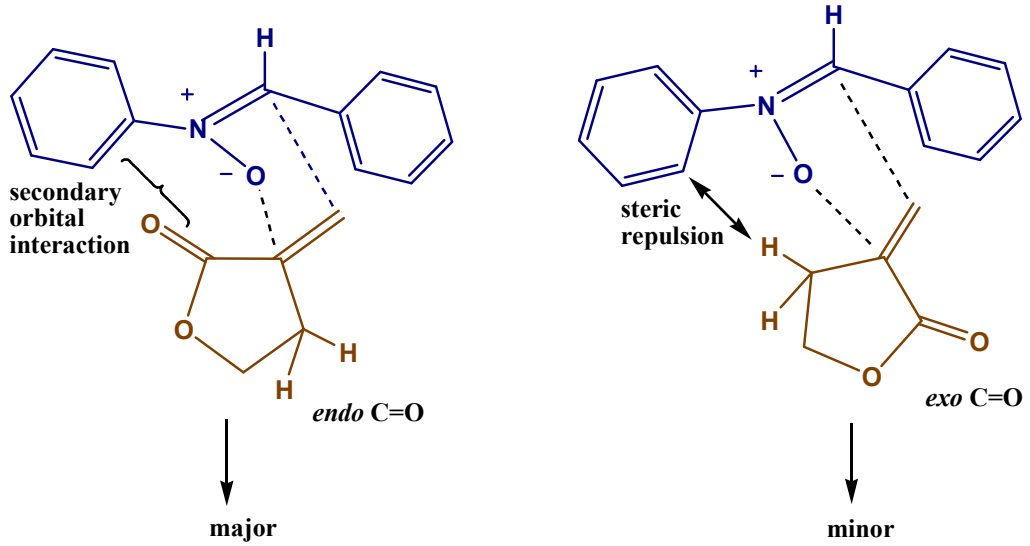
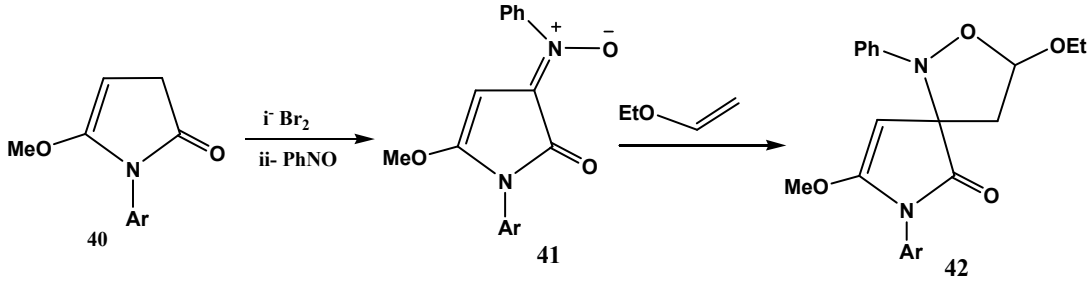


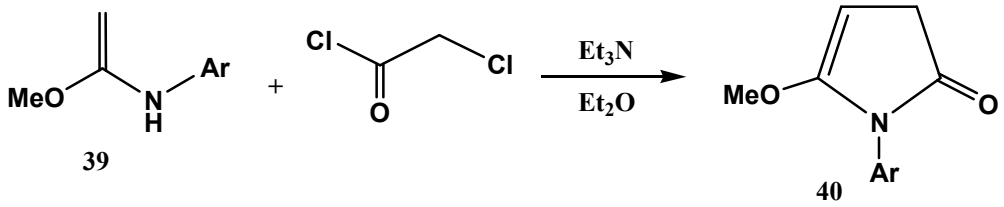
Figure 9: Transition state modes for formation of the two diastereoisomers **38a** and **38b**

Heterocyclic aryl nitrone (**41**) was synthesized in 62-73% yield by bromination of 1-aryl-5-methoxy-2,3-dihydro-1H-2-pyrrolone (**40**) followed by treatment with nitrosobenzene at room temperature. Reaction of arylnitrone (**41**) with ethylvinyl ether afforded spiroisoxazolidino-pyrrolidine derivative (**42**) (**Scheme 9**).[48]



Scheme 9

1-Aryl-5-methoxy-pyrrol-2-one (**40**) were easily synthesized, in 74-82% yield, from the reaction of N-aryl-acetimidic ester (**39**) with chloroacetyl chloride (**Scheme 10**).[49]



Scheme 10

4. NITRILE OXIDES

Nitrile oxides, RNCO, are derivatives of *fulminic acid* (R=H). They can be named as *fulmido*-substituted parent molecules, but usually their names are derived from corresponding nitriles, for example, benzonitrile oxide, toluonitrile oxide, pyridine-4-carbonitrile oxide, mesitonitrile oxide. Specific properties of nitrile oxides depend on the structure of the functional group, which have highly polarized C-N and N-O bonds (**Figure 10**).

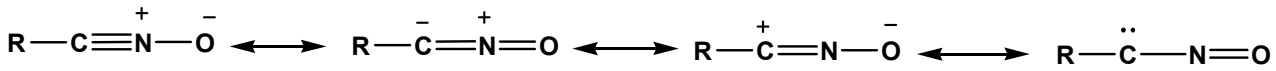
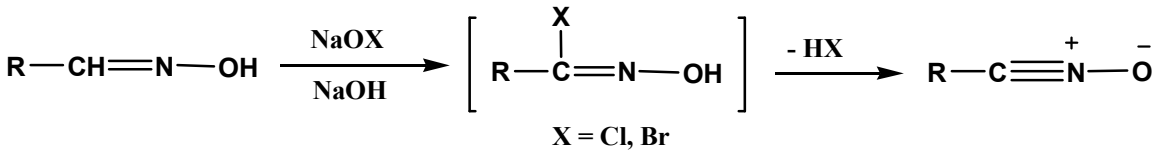


Figure 10: Electronic structure of nitrile oxides

4.1. Synthesis of Nitrile Oxides

4.1.1. From Aldoximes

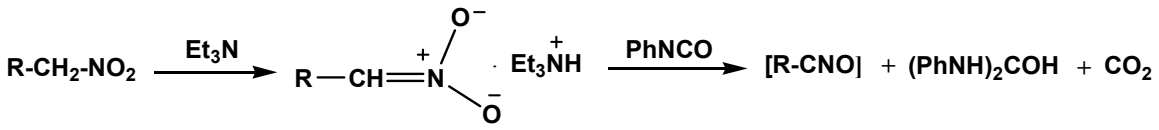
The conversion of aldoximes to nitrile oxides is principally a dehydrogenation process. It is only necessary to note here that the process is carried out mainly as halogenation-dehydrohalogenation. The reaction is convenient for both the generation of unstable nitrile oxides (in the presence of a dipolarophile) and the preparation of stable nitrile oxides. The intermediate hydroximoyl halide is frequently not isolated (**Scheme 11**). It is usually carried out in a two-phase water-organic solvent system with methylene chloride as the preferred solvent.[50, 51]



Scheme 11

4.1.2. From Aliphatic Nitro Compounds (Mukaiyama Procedure)

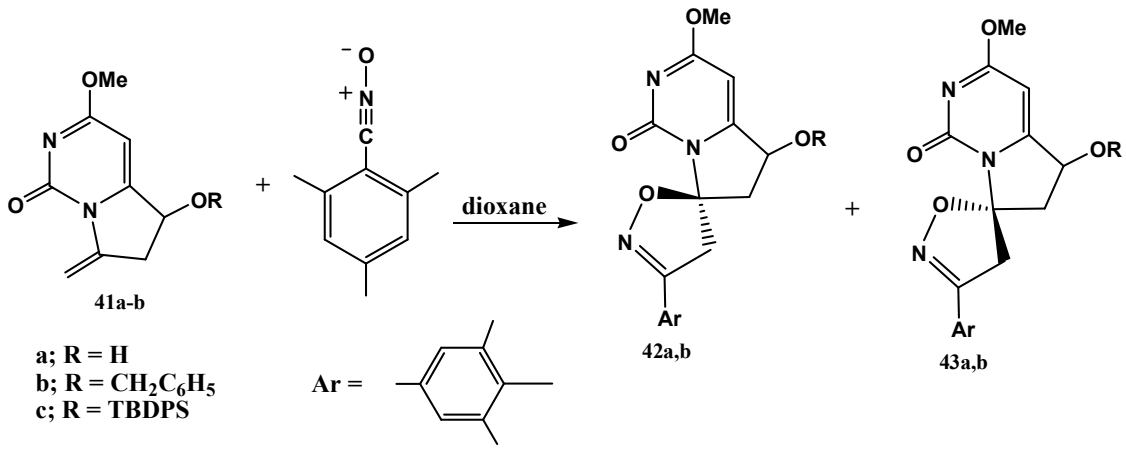
Generation of nitrile oxides via dehydration of primary nitroalkanes with an aryl isocyanate, usually in the presence of Et_3N as a base, is one of most importance methods in nitrile oxide synthesis (**Scheme 12**). Many reagents, other than arylisocyanates, have been tested for the dehydration of nitroalkanes, such as $POCl_3$, $(CH_3CO)_2O$, CH_3COCl, CH_3SO_2Cl, *p*-toluenesulfonyl chloride. Dehydration of primary nitroalkanes results in unstable nitrile oxides, and, therefore, is limited by *in situ* transformation of nitrile oxide.[52, 53]



Scheme 12

4.2. Nitrile Oxide Cycloadditions Approach to Bioactive Spiroheterocycles

1,3-Dipolar cycloadditions of mesitonitrile oxide to the exocyclic double bond of 7-methylenepyrrolo[1,2-*c*]pyrimidin-1(5H)-ones (**41a-c**) as dipolarophiles proceed with complete regioselectivity and lead to the spiroisoxazolinyl nucleosides (**42a,b**) and (**43a,b**) in good yields (**Scheme 13**).[54]



Hint: TBDPS = *tert*-Butyldiphenylsilyl

Scheme 13

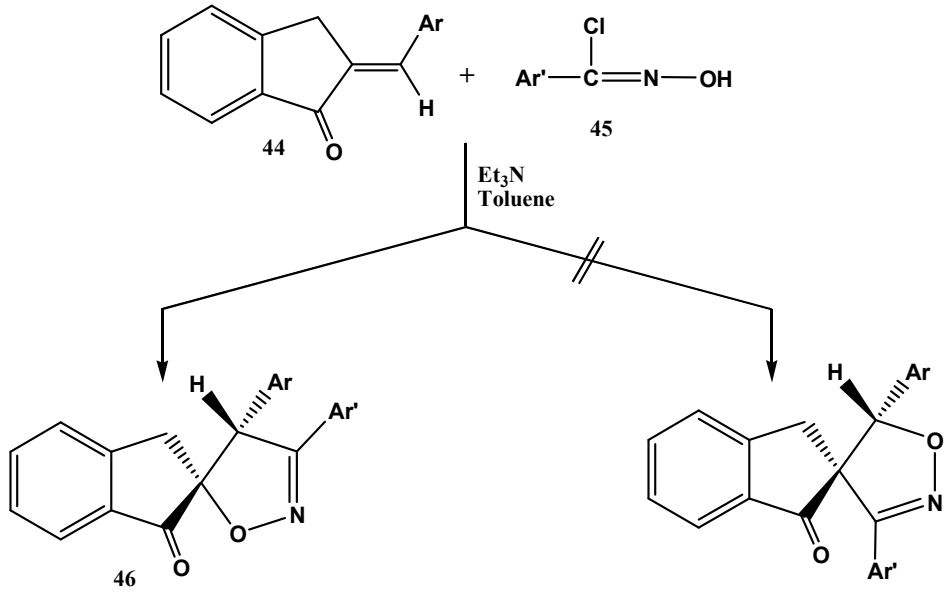
The approach of the dipole takes place predominantly from the less sterically hindered site of the dipolarophiles (R = H, CH_2Ph) providing a mixture of two 5,7-*cis* **42a**,**b** and 5,7-*trans* **43a**,**b** isomers.

The [3+2] cycloaddition reactions of (*E*)-2-arylidene-(2*H*)-indanones (**44**) and (*E*)-2-arylidene-(2*H*)-3-methylindanones (**47**) with the arylnitrile oxides generated in situ from arylhydroxyaminoyl chlorides (**45**) and triethylamine led to single adducts in each case (**Scheme 14** & **15**).

The reaction yielded regioselectively (100%) respectively a series of the spiro[3,4-diaryl-2-isoxazoline-5:2'-indanones] (**46**) and the spiro[3,4-diaryl-2-isoxazoline-5:2'-3'-methylindanones] (**48**).[55]

Face selectivity in the 1,3-dipolar cycloaddition reactions of benzonitrile oxide and its 4-substituted derivatives with 5-substituted adamantane-2-thiones (**49**) have been previously studied.[56, 57] In particular, X-ray single-crystal analysis confirmed the structure of the spiro-oxathiazoline derivative (**50**), resulting from the favored attack of nitrile oxide on the 5-fluoroadamantane-2-thione (**Scheme 16**).[58]

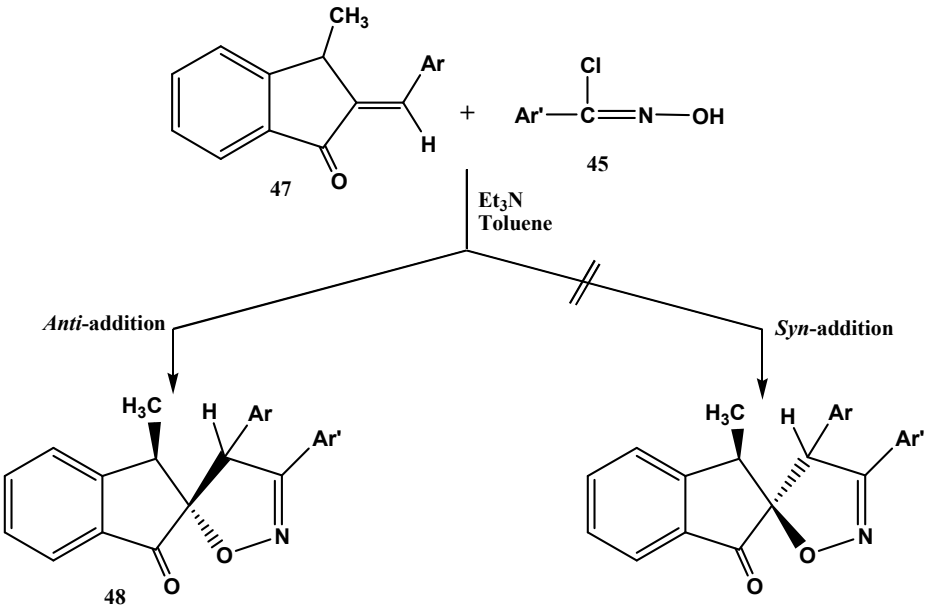
1,3-Dipolar cycloaddition of 3-cyano-4*H*-1-benzopyran-4-thione (**51**) with benzonitrile oxide proceeded regioselectively to give cycloadduct (**52**) (involving the thione group). The unstable cycloadduct fragmented to yield 3-cyanochromone (**53**) and phenyl isothiocyanate (**Scheme 17**).[59]



Ar = Ph, 4-H_3C-C_6H_4, 4-CH_3O-C_6H_4, 4-O_2N-C_6H_4; Ar' = Ph, 4-H_3C-C_6H_4, 4-CH_3O-C_6H_4

Scheme 14

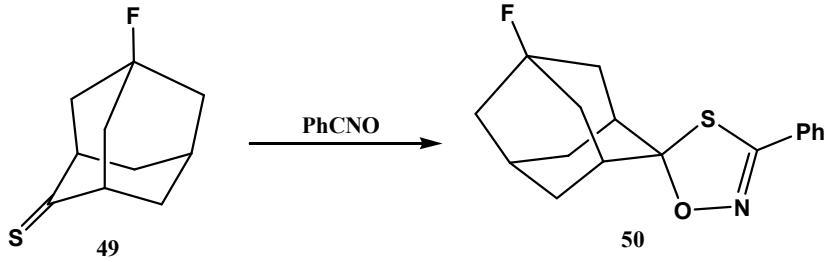
The 1,3-cycloaddition reaction of 2,6-dichlorobenzonitrile oxide (**55**) with 2,10-bis (arylmethylene)-5-phenyl-2,3,6,7,8,9-hexahydro-5*H*-cyclohepta[1,2-*d*]thiazolo-[3,2-*a*]pyrimidine-3-one (**54**) gave the corresponding isooxazoline derivative. The surprising cycloadducts of nitrile oxide to π-rich exocyclic double bond have been obtained as a couple of regioisomers (**56** & **57**) (**Scheme 18**).[60]



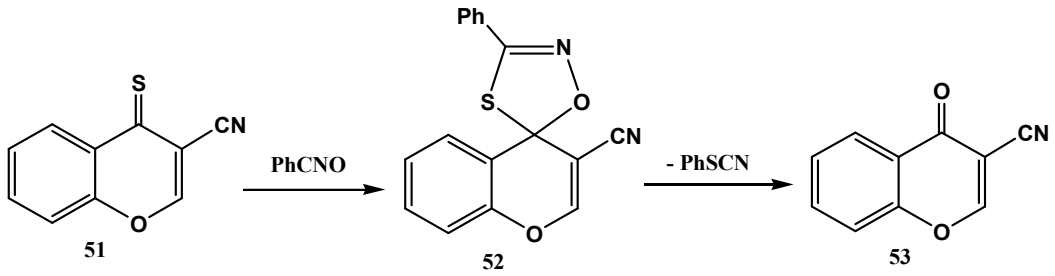
Ar = Ph, 4-H_3C-C_6H_4, 4-CH_3O-C_6H_4, 4-O_2N-C_6H_4; Ar' = Ph, 4-H_3C-C_6H_4, 4-CH_3O-C_6H_4

Scheme 15

The (*R*)-1-(1-phenylethyl)-3-[(*E*)-arylmethylidene]tetrahydro-4(1*H*)-pyridinones (**55**) were synthesized in moderate yields (58–72%) through a solvent-free reaction of pyridinone (**54**) with aromatic aldehydes in the presence of pyrrolidine as basic catalyst under microwave irradiation (**Scheme 19**).[61]



Scheme 16



Scheme 17

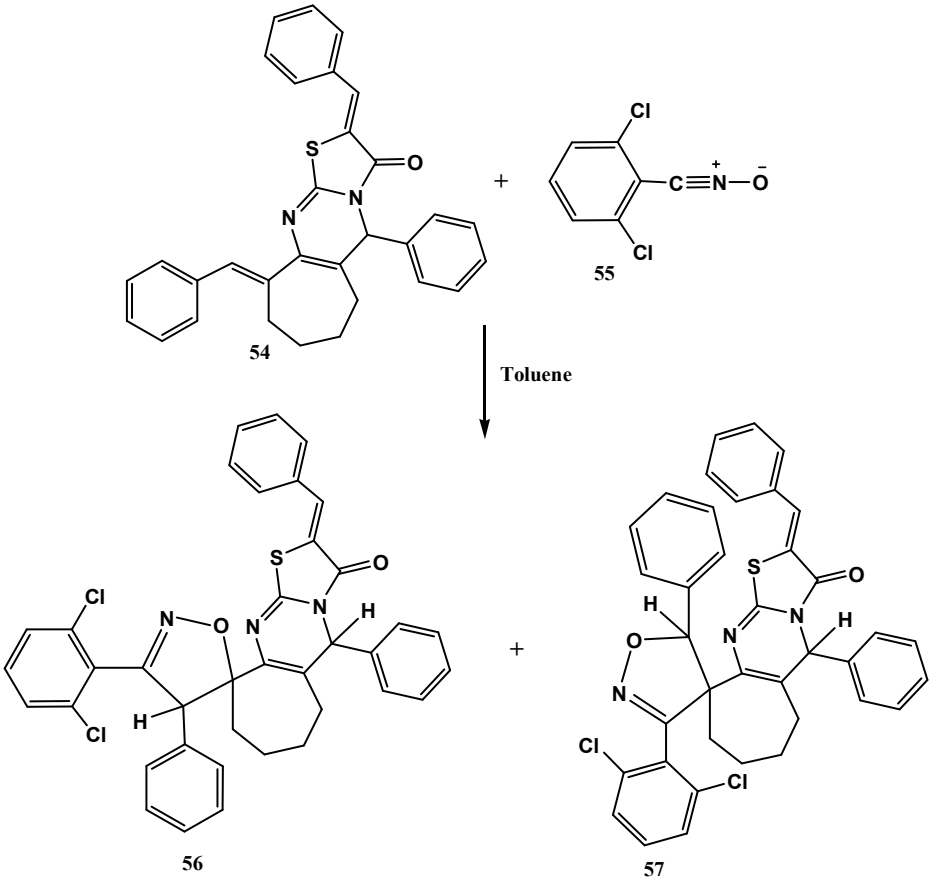
The 1,3-dipolar cycloaddition of nitrile oxide, generated *in situ* from 4-chlorobenzohydroximoyl chloride and triethylamine to (*R*)-1-(1-phenylethyl)-3-[(*E*)-arylmethylidene] tetrahydro-4(1*H*)-pyridinones (**55**) (**Scheme 20**), afforded two spiroisoxazolines, (**56**) and (**57**), in 52–56% and 8–10%, respectively. In the case of (**55**) with a 2-chlorophenyl ring, dispiro compound, (**58**), in 6-7% yields, was also obtained.[62]

The predominant formation of (**56**) in all the reactions shows that the cycloaddition proceeds as following:

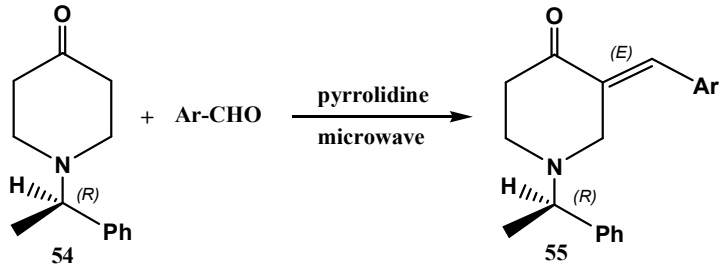
(i) chemoselectively, with the nitrile oxide preferring to react with the C=C and not with C=O bond of (**55**),

(ii) regioselectively, the oxygen of the nitrile oxide adding over the α-carbon of the C=C bond of (**55**), and

(iii) stereoselectively, affording only one of the stereoisomers of the isoxazoline (**56**) as the major product.



Scheme 18



Scheme 19

5. AZOMETHINE YLIDES

Azomethine ylides are planar 1,3-dipoles composed of one nitrogen and two terminal sp^2 carbon atoms (**Figure 11**). In recent years, azomethine ylides have become one of the most investigated classes of 1,3-dipoles and, based on their cycloaddition chemistry, various methods for the synthesis of pyrrolidine derivatives have been developed.[63]

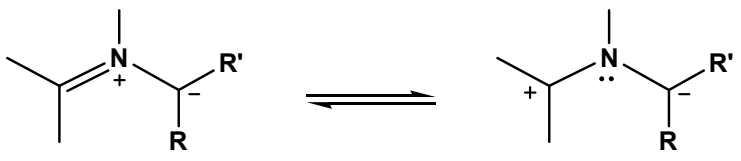
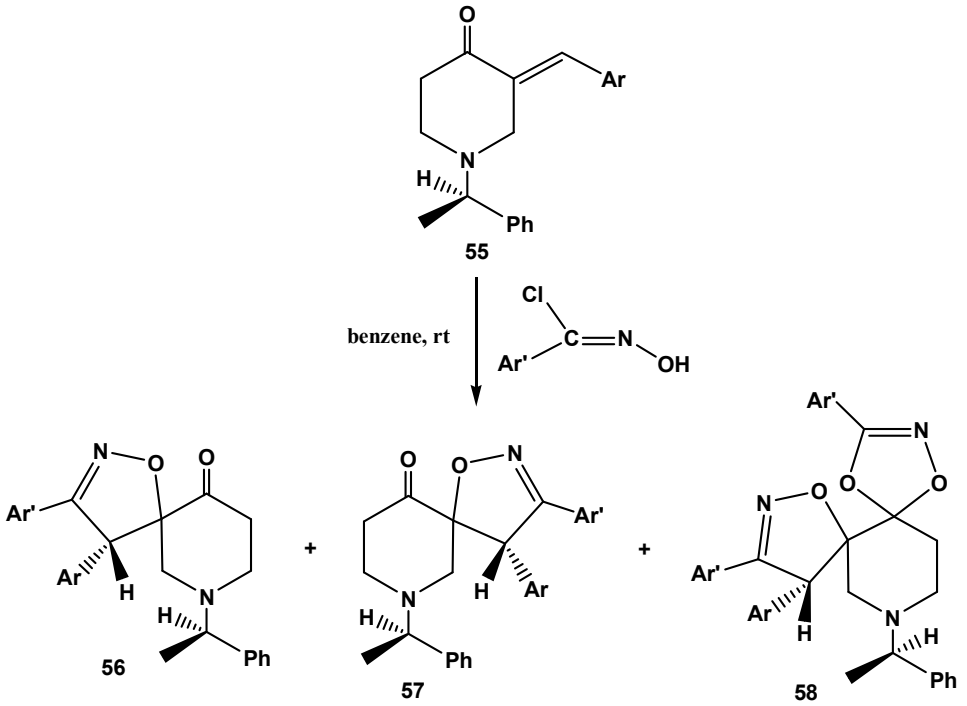


Figure 11: General structure of azomethine ylides

Their cycloadditions to olefinic dipolarophiles provide a direct and general method for the synthesis of pyrrolidine derivatives. There are both stabilized and unstabilized azomethine ylides, depending on R and R` groups, although there are examples of stable, isolable azomethine ylides, they are normally generated in situ and trapped by almost any multiple C–C or C–X (X = N, O, or S) bond.



Ar = C_6H_5, 4-ClC_6H_4, 4-MeC_6H_4, 2-ClC_6H_4, 2-naphthyl; Ar' = C_6H_5, 4-ClC_6H_4

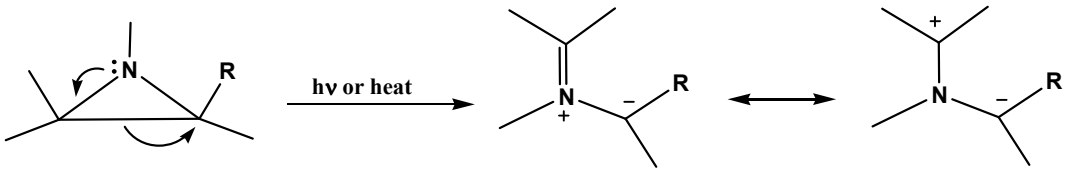
Scheme 20

5.1. Generation Routes of Azomethine Ylides

A number of methods have been developed for their generation, including the ring opening of aziridines, the imine-tautomerization, and the decarboxylative condensation of amino acids.

5.1.1. Aziridine Route

The first example of the ring opening of an aziridine generating an azomethine ylide 1,3-dipole was reported earlier by Heine and peavy (**Scheme 21**).[64]



Scheme 21

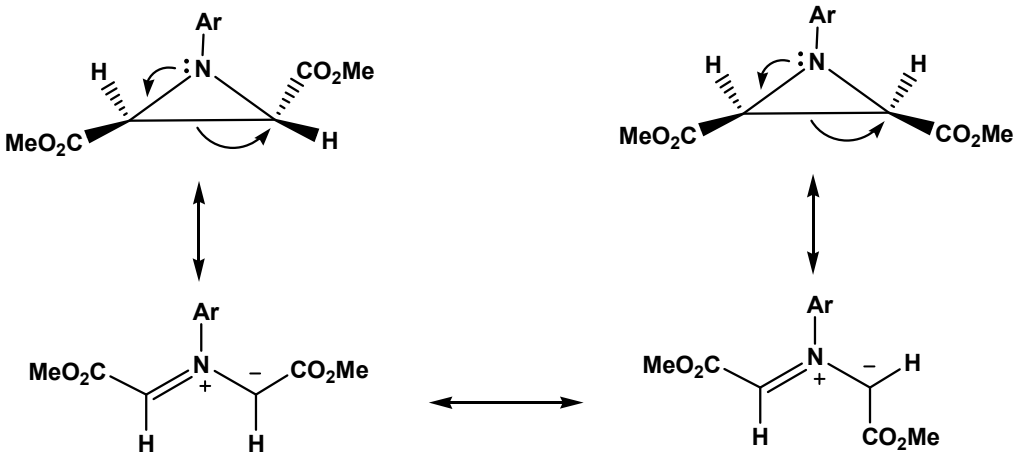
Aziridine rings open quite readily if the carbon atoms are substituted by electron-withdrawing groups. Ring-opening is stereospecific; however ylides can interconvert and must be trapped by reactive dipolarophiles (**Scheme 22**).

5.1.2. Carbene-Imine Route

Unstable azomethine ylides was obtained from imine and carbene (especially dihallocarbene) (**Scheme 23**).[65]

5.1.3. Tautomerization Route

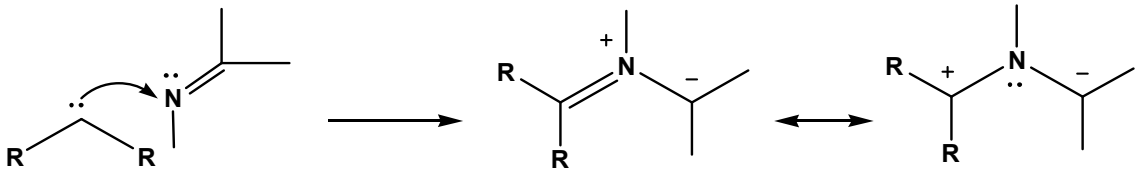
The imine toutomerization method discovered by Grigg,[66, 67] Joucla,[68] and Tsuge[69] is one of the most commonly used methods for generation of azomethine ylides stabilized by hydrogen bond. One general approach to create azomethine ylides is the condensation of glycine derivative with an aldehyde (especially the aromatic ones), which gives stable imines. Tautomerization of imines results in the formation of intermediate azomethine ylides that can be trapped with dipolarophiles (**Scheme 24**).[70]



Scheme 22

5.1.4. Decarboxylative Condensation Route

This method is one of the most important methods for preparing unstable azomethine ylides. Formation of this type of azomethine ylides almost generated in situ through condensation reaction of aldehydes or ketones with α-amino acids followed by losing of carbon dioxide (**Scheme 25**).[71, 72]



Scheme 23

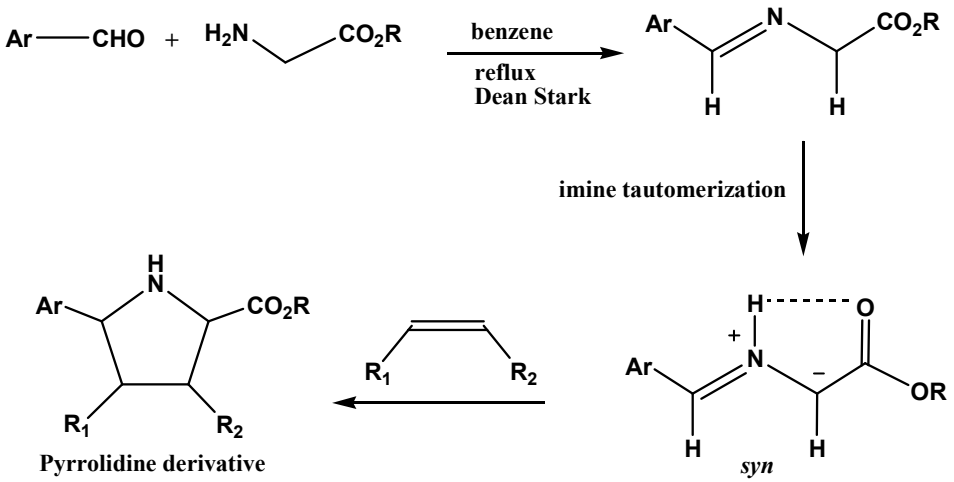
5.1.5. N-Metalation Route

The most recent advance in the chemistry of azomethine ylides is the use of chiral catalysts in the stereoselective synthesis of pyrrolidine derivatives via metallo-azomethine ylides,[73] which was reviewed by Savic and Husinec, covering the literature until the beginning of 2005.[74] Although a variety of Lewis acids have provided excellent results in the stereoselective metal-catalysed dipolar cycloaddition of azomethine ylides, arguably Ag^{+} salts (e.g. $AgOCOCH_3$, AgF) are the most effective Lewis acids in the cycloaddition reactions of metallo-azomethine ylides.

The reaction times in these cases are generally short, requiring no more than a few hours, and the products are normally isolated in excellent yields (**Scheme 26**).

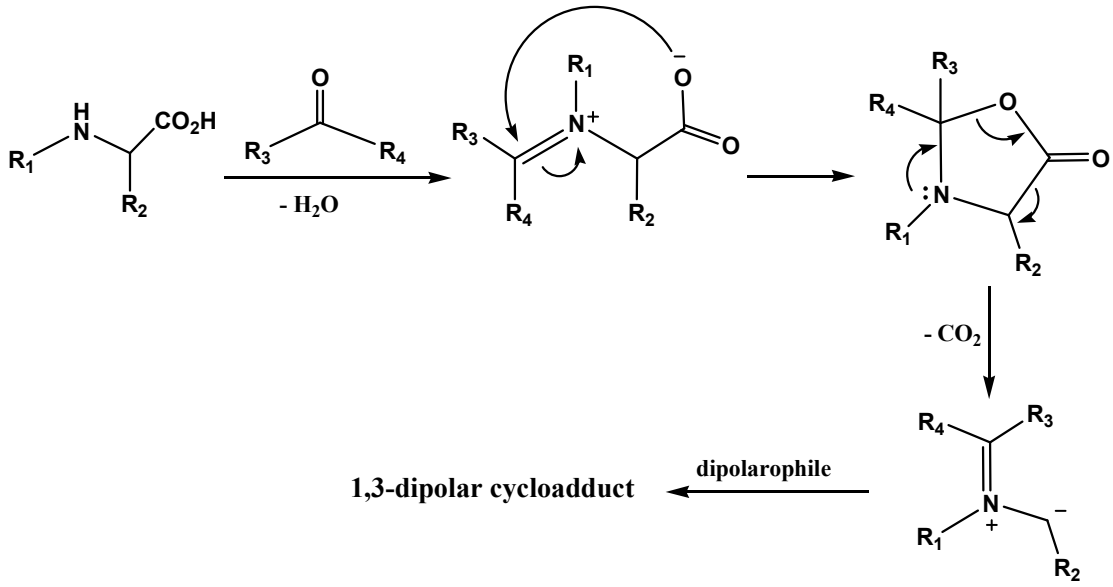
5.2. Azomethine Ylides Cycloadditions Approach to Bioactive Spiroheterocycles

Advances in this area, over the last few decades, have made cycloaddition reactions of azomethine ylides a potent synthetic tool, extensively used in the synthesis of natural products as well as other biologically interesting compounds.



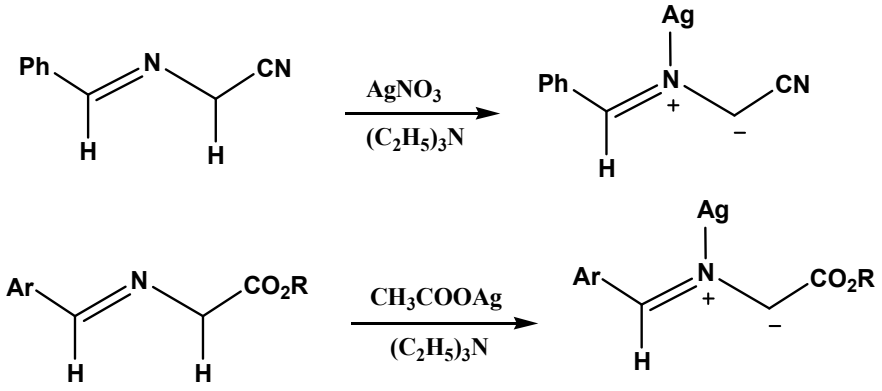
Scheme 24

The azomethine ylide represents one of the most reactive and versatile classes of 1,3-dipoles and is trapped readily by a range of dipolarophiles, either inter or intramolecularly, forming substituted pyrrolidines.[75]



Scheme 25

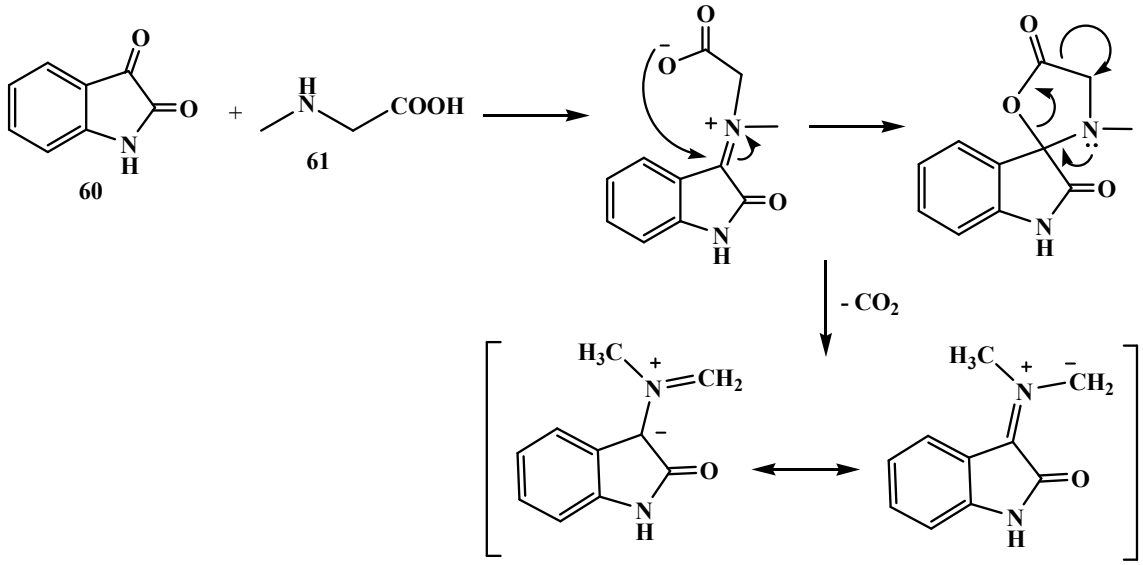
Pyrrolidine, pyrrolizidine and oxindole alkaloids constitute classes of compounds with significant biological activity and the spiro[pyrrolidine/oxindole] ring system is common to most oxindole alkaloids.



Scheme 26

Dispiro[indane-2,3'-pyrrolidine-2',3''-indoline]-1,2'',3-triones (**62a-j**) which reveal promising anti-inflammatory activities obtained by the reaction of 2-arylidene-indan-1,3-diones (**59a-j**) with non-stabilized azomethine ylides, generated in situ via decarboxylative condensation of sarcosine (**61**) and isatin (**60)** (**Scheme 27**)[76] in refluxing methanol afforded only one product in a highly regio- and stereoselective manner (**Scheme 28**).[77]

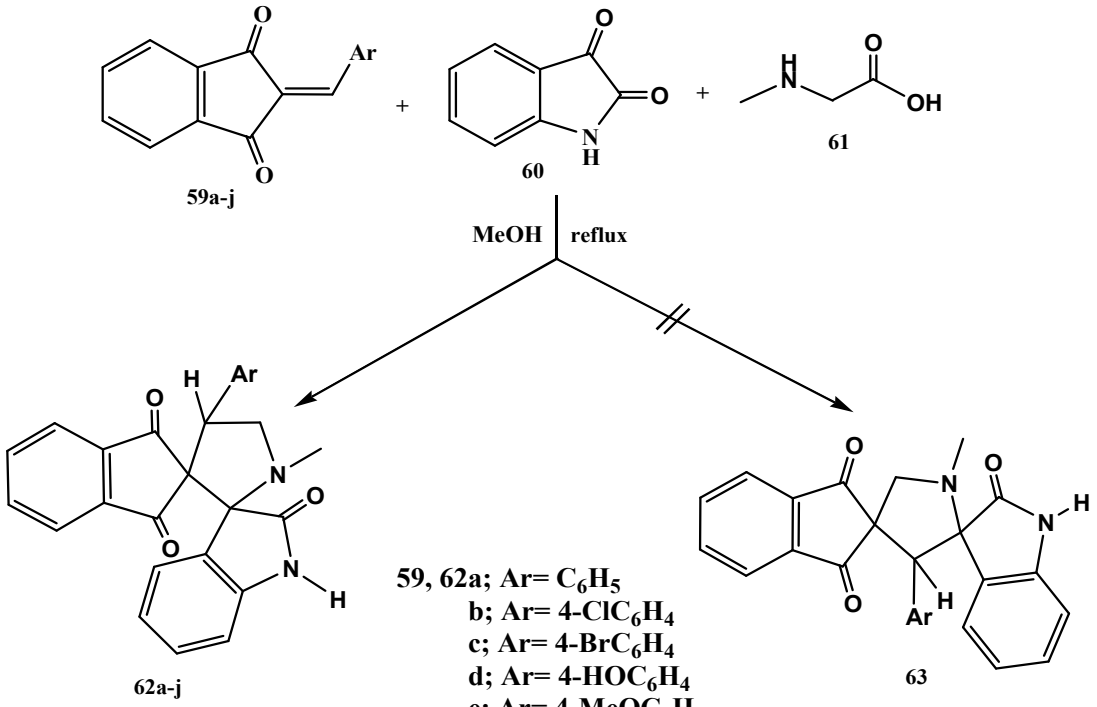
This cycloaddition is regioselective with the electron rich carbon of the dipole adding to the β-carbon of the α,β-unsaturated moiety of (**59**) and stereoselective affording only one diastereomer exclusively, despite the presence of three stereocentres in the product as found in many similar cycloaddition studies.[78, 79]



Scheme 27

The regioselectivity in the product formation can be explained by considering secondary interaction of the orbitals of carbonyl group of dipolarophile (**59**) with those of the azomethine

ylide as shown in (**Figure 12**).[80] Accordingly, the observed regioisomer (**62**) via path **A** is more favorable than (**63**) due to the secondary orbital interaction (**SOI**) which is not possible in path **B**. Hence, only one regioisomer (**62**) was formed.



59, 62a; Ar= C_6H_5
b; Ar= 4-ClC_6H_4
c; Ar= 4-BrC_6H_4
d; Ar= 4-HOC_6H_4
e; Ar= 4-$MeOC_6H_4$
f; Ar= 4-$Me_2NC_6H_4$
g; Ar= 3,4-$(OH)_2C_6H_3$
h; Ar= 3-(MeO)-4-$(HO)C_6H_3$
i; Ar= 3-pyridyl
j; Ar= 2-thienyl

Scheme 28

Novel dispiro[pyrazolidine-4,3'-pyrrolidine-2',3"-indoline]-2",3,5-triones (**65**) which reveal remarkable in vivo anti-inflammatory activities were obtained regioselectively by 1,3-dipolar cycloaddition reaction of 4-arylidene-1-phenylpyrazolidine-3,5-diones (**64**) as dipolarophiles with non-stabilized azomethine ylides, generated in situ via decarboxylative condensation of isatins **60a,b** and sarcosine (**61**) in dry ethanol (**Scheme 29**).[81]

Tuberculosis (TB) caused by *Mycobacterium tuberculosis* bacteria (MTB) is one of the most prevalent diseases, responsible for the death of about one billion people during the last two centuries. A facile 1,3-dipolar cycloaddition of azomethine ylide generated *in situ* from the reaction of 1,3-thiazolane-4-carboxylic acid (**67**) and isatins (**66**) to 2-arylidene-1,3-indanediones (**59**) (**Scheme 30**) furnished novel dispiro- oxindolylpyrrolothiazoles (**68**) regio- and stereoselectively in moderate to good yields (60-92%). These dispiroheterocycles exhibited good *in vitro* antimycobacterial activity against *Mycobacterium tuberculosis* H37Rv (MTB).[82]

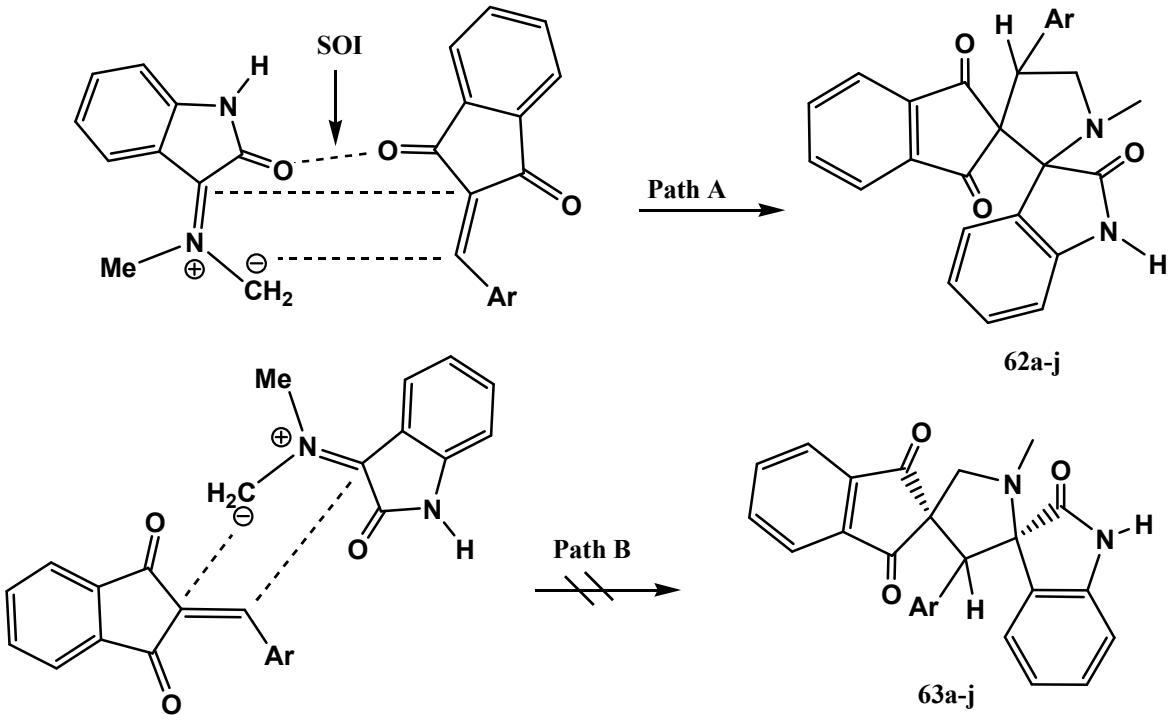
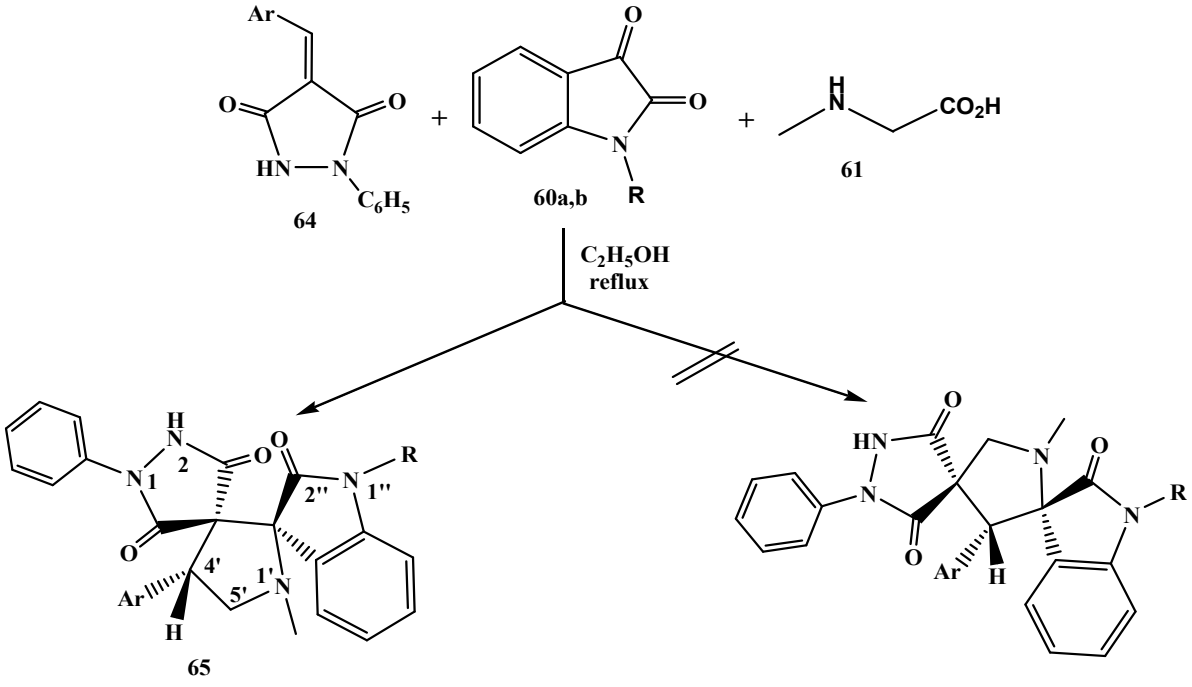
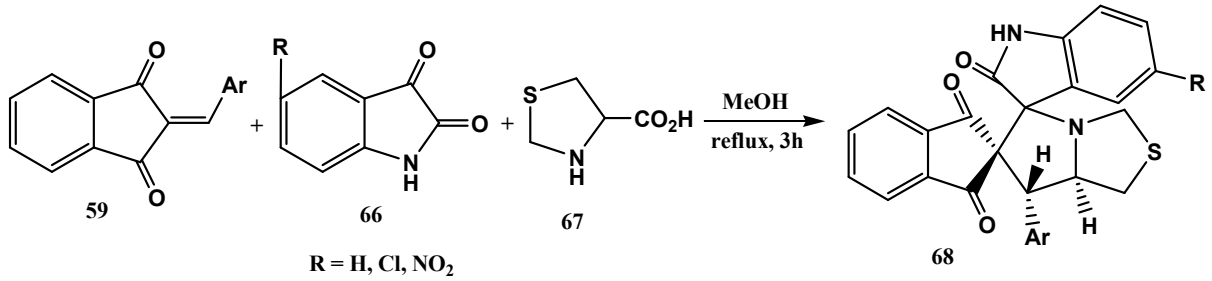


Figure 12



R = H, CH_3; Ar = Ph, 4-ClC_6H_4, 4-BrC_6H_4,4-HOC_6H_4,4-$CH_3OC_6H_4$

Scheme 29



R = H, Cl, NO_2

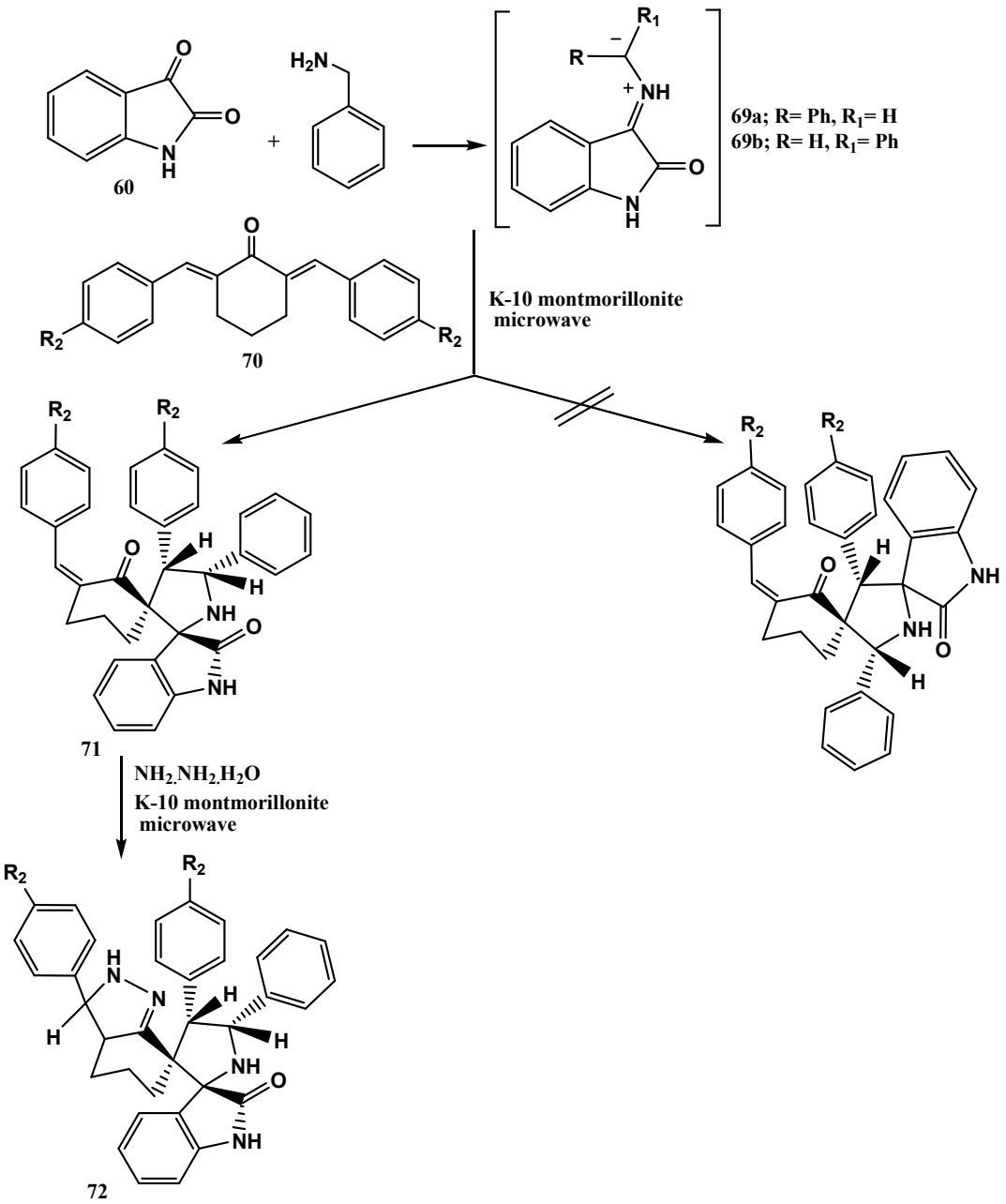
Ar = C_6H_5, 4-ClC_6H_4, 4-$Pr^iC_6H_4$, 4-$MeOC_6H_4$, 2-MeC_6H_4, 2-ClC_6H_4, 2-BrC_6H_4, 3-$O_2NC_6H_4$, 3,4-$(MeO)_2C_6H_3$, 3,4,5-$(MeO)_3C_6H_2$

Scheme 30

Condensation of benzylamine with isatin could give rise to two configurationally distinct azomethine ylides, **69a** and **69b**. The transition state leading to the azomethine ylide **69a** is favored over **69b** due to the developing steric interaction between the carbonyl moiety and the phenyl group.[83] Thus, **69a** preferentially interacts with bis-arylmethylidenecyclohexanones (**70**) through 1,5-prototropic shift under solvent-free conditions, by grinding together the reactants with K-10 montmorillonite under microwave irradiation (600 W), to give a series of novel dispirooxindole derivatives (**71**) in a regioselective manner. The reaction had occurred at one of the exocyclic double bonds of (**70**), steric hindrance of the spiropyrrolidinyloxindole moiety prevents the attack of the 1,3-dipole on the other exocyclic double bond. The dispiro[oxindole/cyclohexanone]pyrrolidines were further annulated by grinding the mono-adduct and hydrazine hydrate with K-10 montmorillonite thoroughly and irradiating under microwave conditions to afford a series of novel 4-aryl-5-phenyl(spiro[2.3"]oxindole)-3`-aryl-3',3a',4',5',6',7'-hexahydro-2*H*-indazolospiro[7`.3]pyrrolidines (**72**) (**Scheme 31**).[84]

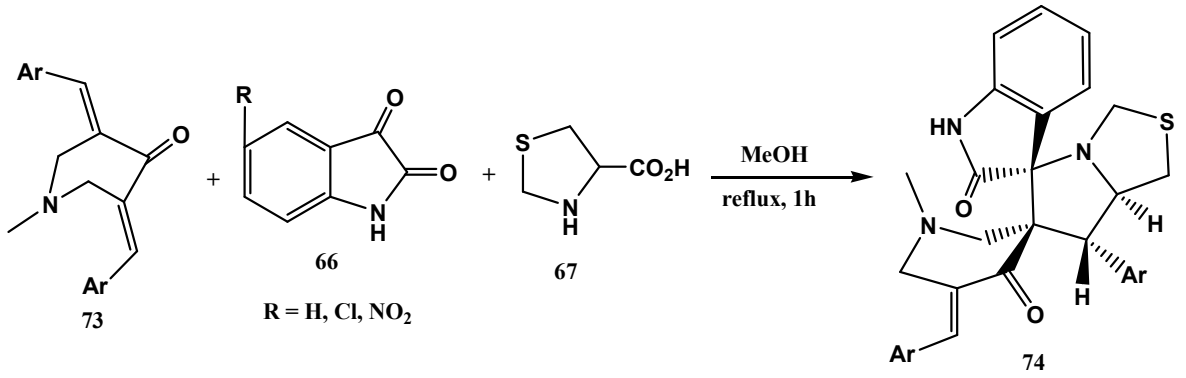
Spiro-pyrrolothiazoles (**74**) obtained by 1,3-dipolar cycloaddition of azomethine ylide generated in situ from substituted isatin (66) and 1,3-thiazolane-4-carboxylic acid (**67**) to 1-methyl-3,5-bis[(*E*)-arylmethyli-dene]- tetrahydro-4(1*H*)-pyridinones (**73**) in quantitative yields. These spiroheterocycles displayed good *in vitro* antimycobacterial activity against *Mycobacterium tuberculosis* H37Rv (MTB) and multi-drug resistant *M. tuberculosis* (MDR-TB). The antimycobacterial potency of these spiro heterocycles renders them valid leads for synthesizing new heterocycles endowed with enhanced activity (**Scheme 32**).[85]

Novel anti-microbial dispiro-oxindolopyrrolizidines (**76**) obtained in good yield under microwave irradiation *via* regioselective multicomponent 1,3-dipolar cycloaddition reaction of 2-arylidene-1,3-indanediones with the azomethine ylide derived from isatin and proline (**75**) (**Scheme 33**).[86]



Scheme 31

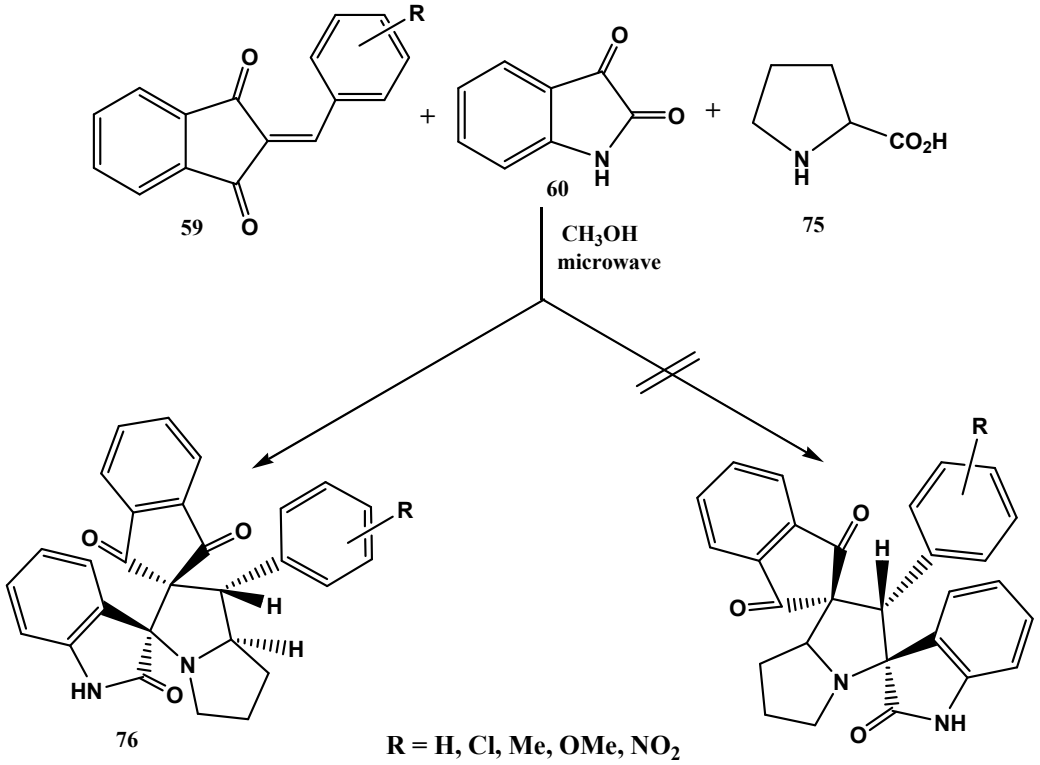
A series of novel dispirooxindolopyrrolizidine (**80**) derivatives have been synthesized by Periyasami *et al*. through 1,3- dipolar cycloaddition reaction of azomethine ylide generated from proline (**75**) and isatin (**60**) with the dipolarophile (*E*)-2-arylidine-1-keto carbazoles (**79**). The synthesized cycloadducts were evaluated for antimicrobial activities that showed relatively good antibacterial and antifungal activities (**Scheme 34**).[87] The required dipolarophiles (*E*)-2-arylidine-1-keto carbazoles (**77**) prepared by the reaction of 1-keto carbazole[88] with substituted benzaldehydes (**78**) in the presence of alcoholic potassium hydroxide as basic catalyst.



Ar = C_6H_5, 4-ClC_6H_4, 4-$Pr^iC_6H_4$, 4-$MeOC_6H_4$, 2-MeC_6H_4, 2-ClC_6H_4, 2-BrC_6H_4, 3-$O_2NC_6H_4$, 3,4-$(MeO)_2C_6H_3$, 3,4,5-$(MeO)_3C_6H_2$, 2-thienyl

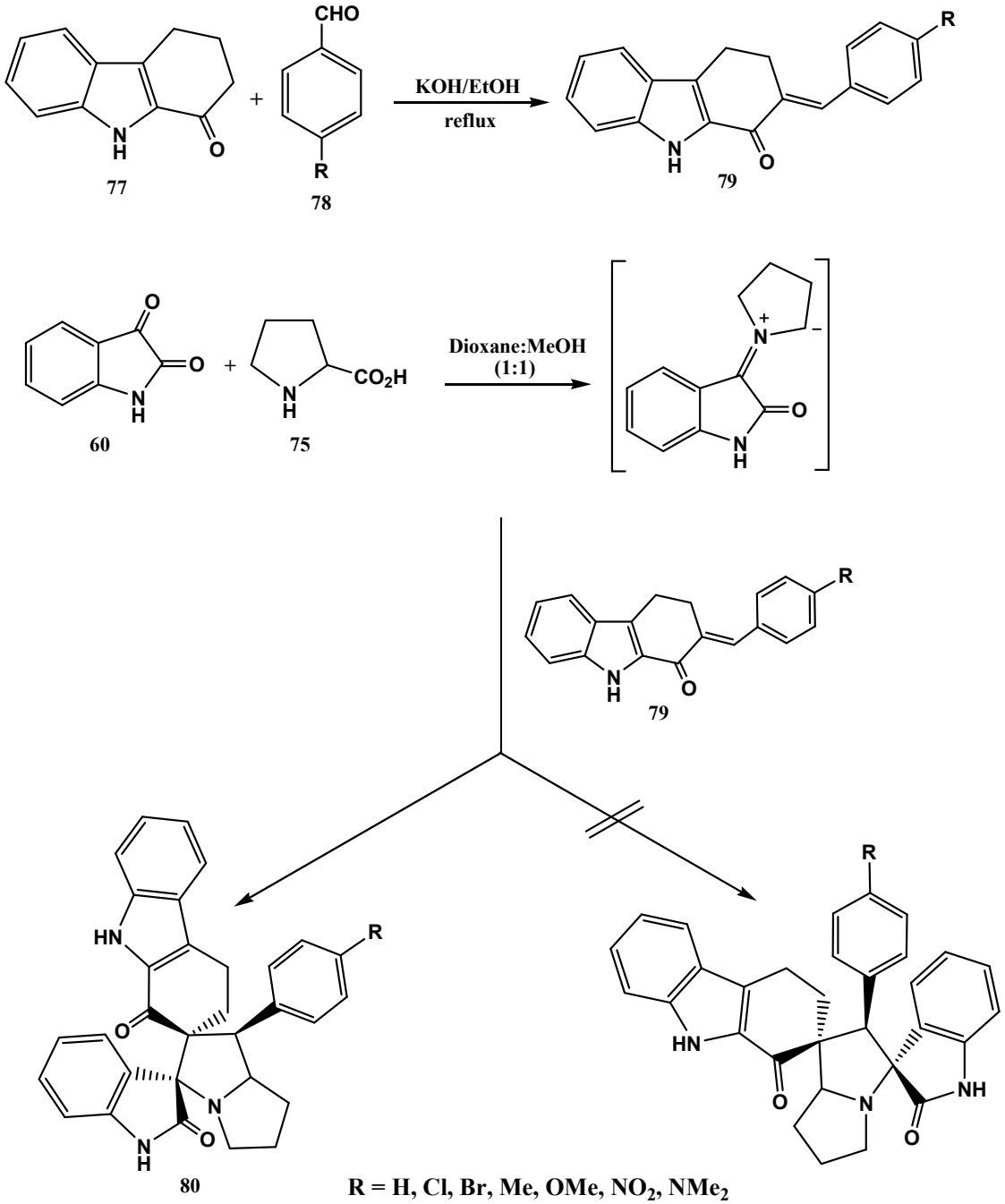
Scheme 32

For a quarter of a century, the pathogenesis of Alzheimer's disease has been linked to a deficiency in the brain neurotransmitter acetylcholine. Novel *N*-methyl-spiro[2.3`]oxindolespiro[3.2``]-5,6-dimethoxy-1``-indanone-4-(arylsubstituted)pyrrolidine (**83**) and spiro[2.3']oxindolespiro[3.2"]-5,6-dimethoxy-1`-indanone-4-(arylsubstituted)-5-phenyl pyrrolidine (**84**) obtained by 1,3-dipolar cycloaddition of azomethine ylides, generated *in situ* via decarboxylative condensation of substituted isatins (**66**) and sarcosine (**61**) or phenylglycine (**82**) respectively to 2- (arylmethylene)-5,6-dimethoxy-2,3-dihydro-1H-inden-1-ones (**81**) (**Scheme 35**). The spiropyrolidine derivatives (**83** & **84**) exhibited potent activity as acetylcholinesterase (AChE) inhibitors.[89]



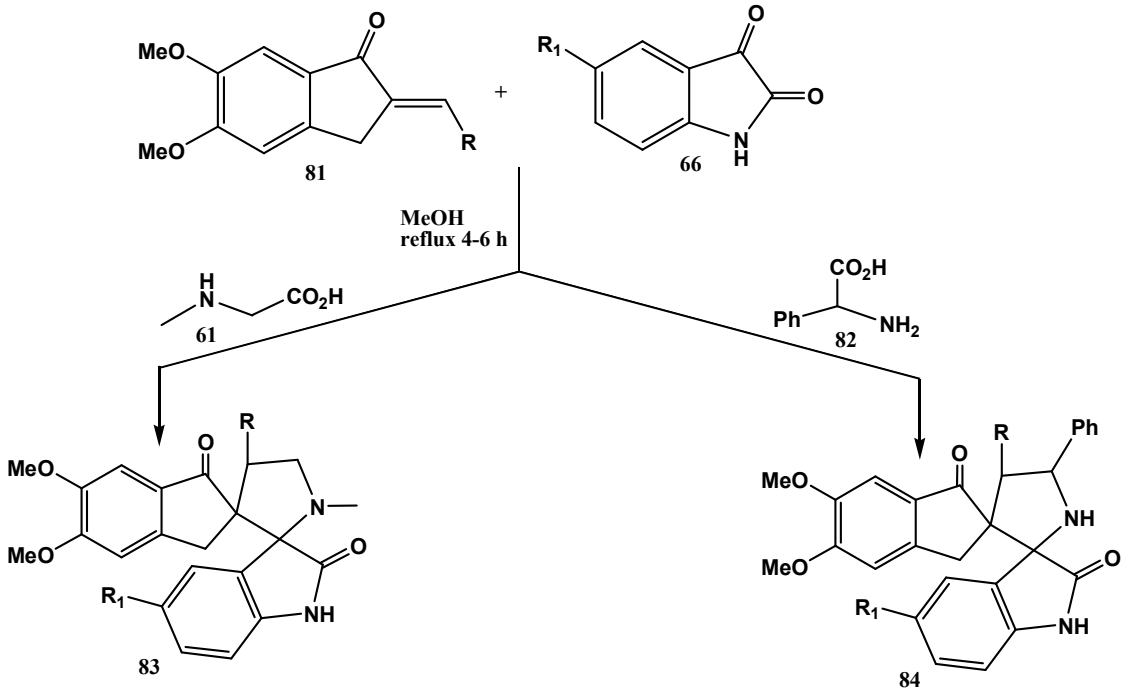
R = H, Cl, Me, OMe, NO_2

Scheme 33



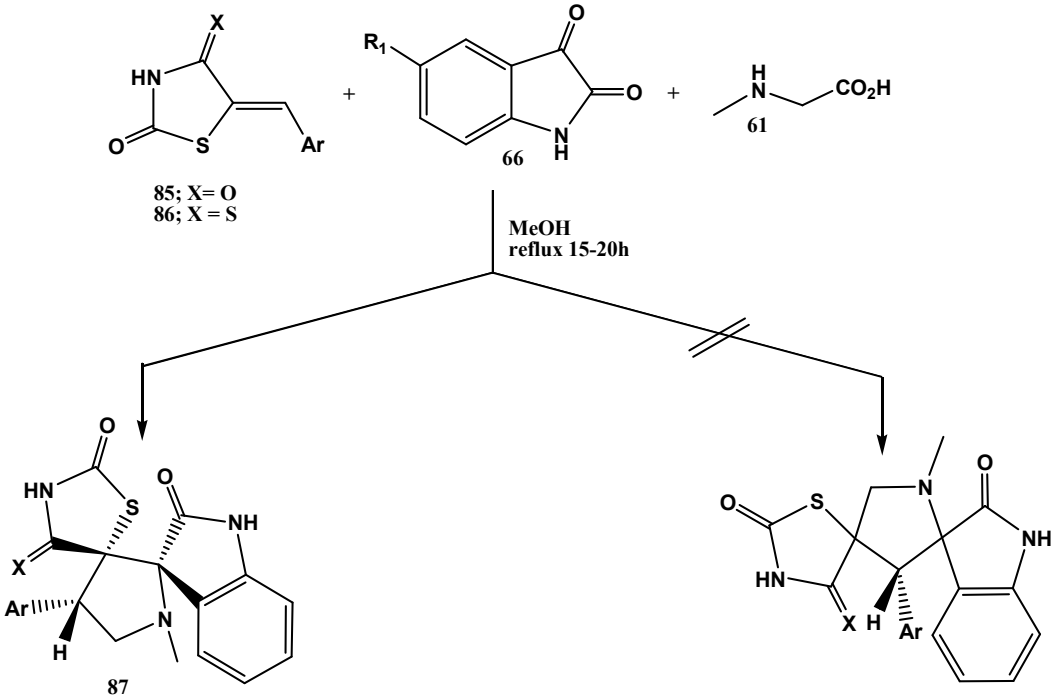
R = H, Cl, Br, Me, OMe, NO_2, NMe_2

Scheme 34



Scheme 35

Murugan et al. reported simple and efficient synthesis of regio- and stereocontrolled novel dispiropyrrolidine (**87**) derivatives which are found to exhibit attractive anti-diabetic properties, by 1,3-dipolar cycloaddition reaction with 5-arylidene-1,3-thiazolidine-2,4-dione and 5-arylidene-4-thioxo-1,3-thiazolidine-2-one derivatives (**85** & **86**) as dipolarophiles (**Scheme 36**).[90]



Scheme 36

References

1. Takahashi, K.; Witkop, B.; Brossi, A.; Maleque, M. A.; Albuquerque, E. X. *Helv. Chim. Acta,* **1982**, *65*, 252-261.
2. Trost, B. M.; Brennan, M. K. *Synthesis* **2009**, 3003-3025.
3. Bassleer, R.; Depauw-Gillet, M. C.; Massart, B.; Marnette, J-M.; Wiliquet, P.; Caprasse, M.; Angenot, L. *Planta Med.* **1982**, *45*, 123-126.
4. Garnick, R. L.; Le Quesne, P. W. *J. Am. Chem. Soc.* **1978**, *100*, 4213-4219.
5. Anderton, N.; Cockrum, P. A.; Colegate, S. M.; Edgar, J. A.; Flower, K.; Vit, I.; Willing, R. I. *Phytochemistry* **1998**, *48*, 437-439.
6. Kang, T. H.; Matsumoto, K.; Murakami, Y.; Takayama, H.; Kitajima, M.; Aimi, N.; Watanabe, H. Eur. J. Pharmacol. **2002**, *444*, 39-45.
7. Marti, C.; Carreira, E. M. Eur. J. Org. Chem. **2003**, 2209-2219.
8. Hilton, S. T.; Ho, T. C.; Pljevalijcic, G.; Jones, K. Org. Lett. **2000**, *17*, 2639-2641.
9. Daly, J. W.; Kale, I. L.; Myers, C. W.; Tokueyama, T.; Waters, J. A.; Witkop, B. *Proc. Natl. Acad. Sci. U.S.A*., **1971**, *68*, 1870-1875.
10. Perron, F.; Albizati, K. F. *Chem. Rev.,* 1989, **89**, 1617-1661.
11. Hegnauer, R. In Chemotaxonomie der Pflanzen, Vol. 3; Birkhauser: Basel, **1964**; 447-544.
12. Tada, M.; Chiba, K. *Agric. Biol. Chem.,* **1984**, *48*, 1367-1369.
13. Martinez, V.; Barbera, O.; Sanchez-Parareda, J.; Marco, J. A. *Phytochemistry,* **1987**, *26*, 2619-2624.
14. Breinclich, J.; Scharnagel, K. *Arznei,-Forsch.,* **1968**, *18*, 429-431.
15. Weyerstahl, P.; Wahlburg, H.; Kaut, V. K.; Lochynski, S. *Liebigs Ann. Chem.,* **1992**, *3*, 279-281.
16. Tan, R. X.; Jia, Z. J.; Zhao, Y.; Feng, S. L. *Phytochemistry,* **1992**, *31*, 3405-3408.
17. Cordell, G. A. *The Alkaloids: Chemistry and Biology; Academic: San Diego,* **1998**; Vol. 5, 259-311.
18. Okita, T.; Isobe, M. *Tetrahedron* **1994**, *50*, 11143-11152.
19. Rosemmond, P.; Hossemi, M. M.; Bub, C. *Liebigs Ann. Chem.,* **1994**, *2*, 151-158.
20. Kornet, M. J.; Thio, A. P. *J. Med. Chem*. **1976**, *19*, 892-898.
21. Skiles, J. W.; Mc Neil, D. *Tetrahedron Lett.* **1990**, *31*, 7277-7280.
22. Jossang, A.; Jossang, P.; Hadi, H. A.; Sevenet, T.; Bodo, B. *J. Org. Chem.,* **1991**, *56*, 6527-6530.
23. Vidari, G.; Larfranchi, G.; Santori, P.; Serra, S. *Tetrahedron: Asymmetry,* **1995**, *6*, 2977-2990.
24. Wrobel, J.; Dietrich, A.; Woolson, S. A.; Millen, J.; McCaleb, M.; Harrison, M. C.; Mohman, T. C.; Sredy, J.; Sullivan, D. *J. Med. Chem.,* **1992**, *35*(24), 4613-4627.
25. Zen, A.; Hiroya, K.; Iinuma, K. Jpn. Kokai Tokkyo Koho (Jp 05, 247, 006 [93, 247, 006] (Cl. CO7D261/20), 24 Sep. 1993, Appl. 92/44, 702, 2 Mar. 1992; p 7); *Chem. Abstr.,* 1994, *120*, 164156c.
26. Huisgen, R. *Angew. Chem.*, Int. Ed. Engl. **1963**, *10*, 565–598.
27. Katritzky, A. R.; Cui, X.; Long, Q.; Yang, B.; Wilcox, A. L.; Zhang, Y. -K. *Org. Prep. Proced. Int* . **2000**; *35*: 175–183.
28. Bowman, D. F.; Gillan, T.; Ingold, K. *J. Am. Chem. Soc.* **1971***; 93:* 6555–6561.
29. Coutouli-Argyropoulou, E.; Sabbas, I.; Konarski, S. *J. Heterocycl. Chem.* ***2000****; 37*: 1055-1060.

30. Grigg, R.; Dorrity, M. J.; Heaney, F.; Malone, J.F.; Rajviroongit, S.; Sridharan, V.; Surendrakumar, S. *Tetrahedron* **1991**; *47*: 8297-8322.
31. Grigg, R.; Hadjisoteriou, M.; Kennewell, P.; Markandu, J.; Thornton-Pett, M. *J. Chem. Soc., Chem. Commun*. **1992**: 1388-1389.
32. Ishikawa, T.; Tajima, Y.; Fukui, M.; Saito, S. *Angew. Chem., Int. Ed., Engl.* **1996***; 35:* 1863-1864.
33. Malamidou-Xenikaki, E.; Stampelos, X. N.; Charambilis, T. A.; Karapostolou, C. C. *Tetrahedron* **1997***; 53:* 747-758.
34. Grigg, R.; Hadjisoteriou, M.; Kennewell, P.; Markandu, J.; Thornton-Pett, M. *J. Chem. Soc., Chem. Commun.* **1993***:* 1340-1342.
35. Frederickson, M. *Tetrahedron* **1997**, 53, 403-425.
36. Goti, A.; Fedi, V.; Nanneli, L.; De Sarlo, F.; Brandi, A. *Synlett*. **1997**, 577-579.
37. Hall, A.; Meldrum, K. P.; Therond, P. R.; Wightman, R. H. *Synlett* **1997**, 123-125.
38. Annuziata, R.; Chinquini, M.; Cozzi, F.; Raimondi, L. *Tetrahedron* **1987**, 43, 4051-4056.
39. Kumar, K. R. R.; Mallesha, H.; Rangappa, K. S. *Synth. Commun*. **2003**, 33, 1545-1555.
40. Hossain, N.; Papchikhin, A.; Plavec, J.; Chattopadhyaya, J. *Tetrahedron* **1993**, 49, 10133-10156.
41. Colombi, S.; Vecchio, G.; Gottarelli, G.; Samori, B.; Lanfredi, A. M. M.; Tiripicchio, A. *Tetrahedron* **1978**, 34, 2967-2976.
42. Al Houari, G.; Kerbal, A.; Bennani, B.; Baba, M. F.; Daoudi, M.; Ben Hadda, T. *Arkivoc* **2008** (xii), 42-50.
43. Kumar, R. R.; Perumal, S.; Kaganb, H. B.; Guillot, R. *Tetrahedron* **2006**, *62,* 12380–12391.
44. Luisi, R.; Capriati, V.; Degennaro, L.; Florio, S. *Tetrahedron* **2003**, **59**, 9713–9718.
45. Abbotto, A.; Capriati, V.; Degennaro, L.; Florio, S.; Luisi, R.; Pierrot, M.; Salomone, A. *J. Org. Chem***. 2001**, *66*, 3049–3058.
46. Cacciarini, M.; Cordero, F. M.; Faggi, C.; Goti. A. *Molecules* **2000**, *5*, 637-647.
47. Tufariello, J. J. *In 1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley & Sons: New York, **1984**, pp. 83-168.
48. Abd El-Nabi, H. A. Tetrahedron **2000**, *56*, 3013-3020.
49. DeWolfe, R. H. *J. Org. Chem*. **1962**, 27, 490-493.
50. DeSarlo, F.; Brandi, A.; Guarna, A.; Goti, A.; Corezzi, S. *Tetrahedron Lett*. **1983**; *24*, 1815-1816.
51. DeSarlo, F.; Guarna, A.; Brandi, A.; Goti, A. *Tetrahedron* **1985**; *41*, 5181-5185.
52. Adams, J. P.; Paterson, J. R. *J. Chem. Soc., Perkin Trans. 1,* **2000**, 3695-3705.
53. Adams, J. P. *J. Chem. Soc., Perkin Trans. 1,* **2002**, 2586-2597.
54. Fischer, R.; Hýrosová, E.; Drucková, A.; Fisera, L.; Hametner, C.; Cyrański, M. K. *Synlett.* **2003**, *15*, 2364.2368.
55. Boudriga, S.; Wannassi, N.; Askri, M.; El Baker Rammah, M.; Strohman, C. *J. Soci. Chim. Tun.*, **2009**, *11*, 29-36.
56. Chung W-Sh.; Tsai T-L.; Ho Ch-Ch.; Chiang, M. Y. N.; le Noble, W. J. *J. Org. Chem*. **1997**, *62*, 4672-4676.
57. Tsai T-L.; Chen, W-Ch.; Yu Ch-H.; le Noble, W. J.; Chung, W-Sh. *J. Org. Chem*. **1999**, 64, 1099-1107.
58. Bonini, B. F.; Maccagnani, G.; Mazzanti, G.; Abdel-Lateef, G, Atwa A, Zani P, Barbaro G. *Heterocycles* **1990**, 31, 47-57.

59. Sain, B.; Prajapati, D.; Mahajan, A. R.; Sandhu, J. S. *Bull. Soc. Chim. Fr*. **1994**, 131, 313-316.
60. Hu, X.; Feng, Y.; Su, Q. A Study of the 1,3-Dipolar Cycloaddition Reactions of Nitrile Oxide with Unusual Dipolarphiles, **2005**, *The Proceedings of the 3rd International Conference on Functional Molecules.*
61. Kuehne, M. E.; Matson, P. A.; Bornmann, W. G. *J. Org. Chem*. **1991**, *56*, 513–528.
62. Kumar, R. S.; Perumal, S.; Kaganb, H. B.; Guillot, R. *Tetrahedron: Asymmetry* **2007**, *18,* 170-180.
63. Najera, C.; Sansano, J. M. *Curr. Org. Chem*. **2003**, *7*, 1105–1150.
64. Heine, H. W.; Peavy, R. Tetrahedrone Lett. **1965**, 6, 3123-3126.
65. Padwa, A.; Dean, D. C.; Hertzog, D. L.; Nadler, W. R.; Zhi, L. *Tetrahderon,* **1992**, *48*, 7565-7580.
66. Grigg, R.; Kemp, J. *J. Chem. Soc., Chem. Commun*. **1977**, 125-131.
67. Grigg, R.; Kemp, J. *J. Chem. Soc., Chem. Commun.* **1978**, 109-111.
68. Joucla, M.; Hamelin, J. *Tetrahedron Lett*. **1978**, *19*, 2885-2888.
69. Tsuge, O.; Ueno, K. O. *Chem. Lett.* **1979**, 1407-1410.
70. Dogan, O.; Koyuncu, H.; Kaniskan, U. *Turk. J. Chem*. **2001**, *25*, 365-371.
71. Amal Raj, A.; Raghunathan, R. *Tetrahedron* **2001**, 57, 10293-10298.
72. Grigg, R.; Aly, M. F.; Sridharan, V.; Thianpatanagul, S. *J. Chem. Soc., Chem. Commun*. **1984**, 182-183.
73. Najera, C.; Sansano, J. M. *Angew. Chem., Int. Ed*. **2005**, *44*, 6272–6276.
74. Husinec, S.; Savic, V. *Tetrahedron: Asymmetry* **2005**, *16*, 2047–2061.
75. Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765-2810.
76. Suresh Babu, A. R.; Raghunathan, R.; Gayatri, G.; Narahari Sastry, G. *J. Heterocycl. Chem.* **2006**, *43*, 1467-1472.
77. Hussein, E. M.; Abdel-Monem, M. I. *Int. Res. J. Pharm. Pharmacol.* **2012**, *2*(3), 45-51.
78. Karthikeyan, S. V.; Devi Bala, B.; Alex Raja, V. P.; Perumal, S.; Yogeeswari, P.; Sriram, D. *Bioorg. Med. Chem. Lett. **2010**, 20,* 350-353.
79. Ranjith Kumar, R.; Perumal, S.; Manju, S. C.; Bhatt, P.; Yogeeswari, P.; Sriram, D. Bioorg. *Med. Chem. Lett*. **2009**, *19*, 3461-3465.
80. Pardasani, R. T.; Pardasani, P.; Chaturvedi, V.; Yadav, S. K.; Saxena, A.; Sharma, I. *Heteroat. Chem*. **2003**, *14*, 36-41.
81. Hussein, E. M.; Abdel-Monem, M. I. *Arkivoc* **2011**, *x*, 85-98.
82. Maheswari, S. U.; Balamurugan, K.; Perumal, S.; Yogeeswari, P.; Sriram, D. *Bioorg Med Chem Lett*. **2010**, *20*, 7278-7282.
83. Ardill, H.; Dorrity, M. J. R.; Grigg, R.; Leon-Ling, M. S.; Malone, J. F.; Sridharan, V.; Thianpatanagul, S. *Tetrahedron* **1990**, *46*, 6433-6448.
84. Jayashankaran, J.; Manian, R. R. S.; Venkatesan, R.; Raghunathan, R. *Tetrahedron* **2005**, *61,* 5595–5598.
85. Karthikeyan, S. V.; Bala, B. D.; Raja, V. P. A.; Perumal, S.; Yogeeswari, P.; Sriram, D. *Bioorg Med Chem Lett*. **2010**, *20,* 350–353.
86. A. R. Suresh Babua, R. Raghunathan, K. Kumaresanb, N. Raaman. *Current Chemical Biology* **2009, *3,*** 432-443.
87. Periyasami, G.; Raghunathan, R.; Surendiranb, G.; Mathivanan, N. *Bioorg Med Chem Lett*. **2008**, *18,* 2342–2345.
88. Andreeva, N. I.; Farmak, T. *Chem. Abstr*. **1957**, 36, 713.

89. Ali M. A.; Ismail, R.; Choon, T. S.; Yoon, Y. K.; Wei, A. C.; Pandian, S.; Kumar, R. S.; Osman, H.; Manogaran, E. *Bioorg Med Chem Lett*. **2010**, *20,* 7064-7066.
90. Murugan, R.; Anbazhagan, S.; Narayanan, S. S. *Eur. J. Med. Chem*. **2009**, *44*, 3272–3279

Received on July 19,2012.