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Recent advancement in the synthesis of diverse spiro-indeno[1,2-*b*]quinoxalines: a review

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The nitrogen-containing indeno[1,2-*b*]quinoxaline ring is a privileged structurally fused active system and has notable applications in various fields of chemistry. For the past several years, it has been recognized as an important building block in organic synthesis. This review summarizes the reactions of indeno[1,2-*b*]quinoxalinone as a key construction block for producing a variety of indeno[1,2-*b*]quinoxaline-based spiro-heterocyclic frameworks by means of a wide range of chemical reactions. Most of the reactions described here are multicomponent ones with readily available starting materials that produce complex molecular spiro architectures. Some of the synthesized spiro-indenoquinoxalines exhibit interesting biological activities and have promise for the generation of new drug candidates. Spiro compounds in which two cyclic rings are fused at a common carbon atom are promising interesting skeletal systems in drug discovery due to their unique conformational features, structural complexity and rigidity. The present review aims to highlight the reactions, synthetic strategies and pharmaceutical applications of diverse spiro-indeno[1,2-*b*]quinoxalines to date.

1. Introduction

Nitrogen-containing heterocyclic compounds occupy a prominent place among organic compounds due to their key role in drug discovery and significant impact on the pharmaceutical industry. The quinoxaline skeleton is a central structure of drugs including brimonidine (**I**), quinacillin (**II**), and varenicline (**III**), which are well known as therapeutic treatments for glaucoma and to aid in the cessation of smoking (Fig. 1).[1] The quinoxaline drugs CQS (chloroquinoxaline sulfonamide) (**IV**) and XK469 (**V**) have been observed to have anticancer activity against solid tumors. (2-Quinoxalinyloxy)phenoxypropanoic acid derivatives, such as Assure (**VI**), are well known to act as herbicides (Fig. 1).[2] The quinoxaline structural motif is also found in several natural products and antibiotics such as echinomycin, leromycin, and actinomycin,[3] which are known to inhibit the growth of Gram-positive bacteria. Compounds with a quinoxaline core are used as allosteric dual Akt1 and Akt2 inhibitors,[4] human cytomegalovirus polymerase inhibitors,[5] Src-family kinase p56Lck inhibitors,[6] SRPK-1 inhibitors,[7] and monoamine oxidase A inhibitors.[8]

Indeno[1,2-*b*]quinoxalinones derived by the reaction of ninhydrin and substituted 1,2-phenylenediamines have potential pharmaceutical applications with anti-cancer,[9] c-Jun N-terminal kinase inhibitory,[10] anti-inflammatory, anti-nociceptive,[11] antiproliferative,[12] *etc.*, activities. Additionally, indeno[1,2-*b*]quinoxalines show potential as acid corrosion inhibitors for mild steel surfaces.[13]

Spiro compounds have received special attention in medicinal chemistry because the presence of spiro carbon provides rigidity to the structure, and their ability to elaborate along well defined vectors.[14,15] Indeno[1,2-*b*]quinoxalinone is a heterocyclic ketone used as privileged scaffold in construction of various spiro polycyclic frameworks like spiro-pyran, spiro-pyrrolidine/pyrrolizidine, spiro-β-lactam, spiro-indolizine, and spiro-furan derivatives with pharmaceutical importance. A literature survey reveals no published review article on the synthesis of spiro-indenoquinoxalines and this review therefore gives an overview on the synthesis of spiro-indenoquinoxalines constructed to date.

2. Synthesis of indeno[1,2-*b*]quinoxalinone

The most widely used method for the synthesis of indeno[1,2-*b*]quinoxalinone **3** involves the condensation reaction of ninhydrin **1** with 1,2-phenylenediamines **2** in EtOH/MeOH at room temperature.[16] Under similar conditions, various substituted indeno[1,2-*b*]quinoxalinones **3** were prepared from the corresponding substituted 1,2-phenylenediamines in good yields (Scheme 1). This one-step route has emerged as a valuable method due to its mild reaction conditions, high atom economy, and non-toxicity as a convenient approach towards green chemistry.

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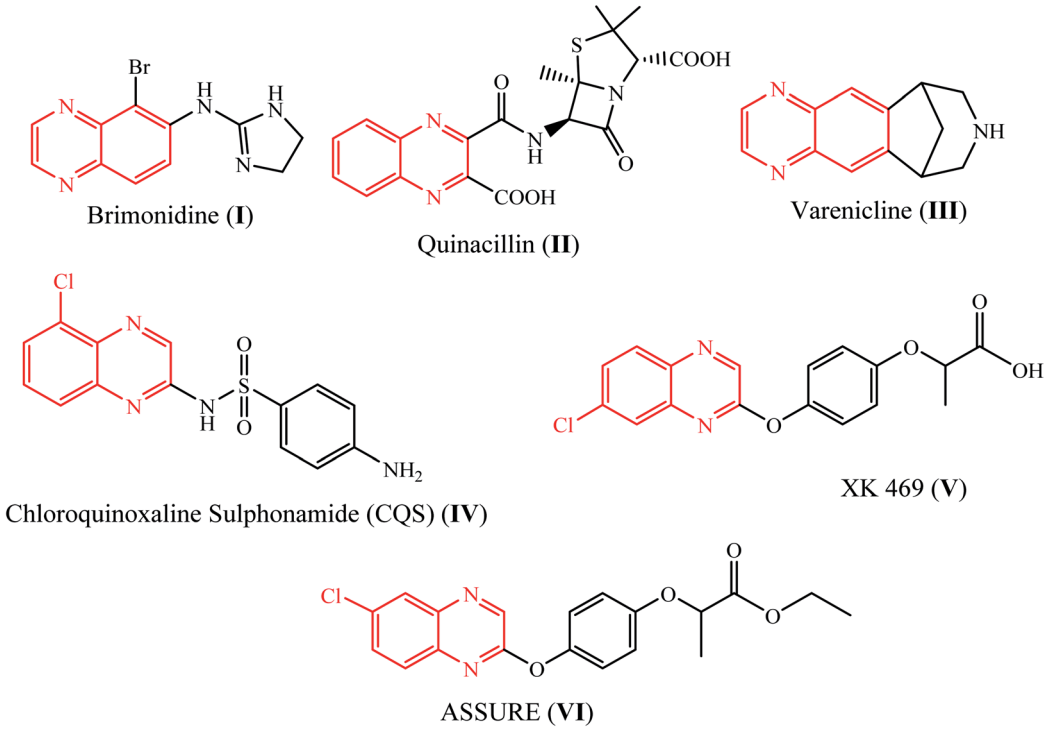


Fig. 1 Selection of quinoxaline moiety-containing drugs.

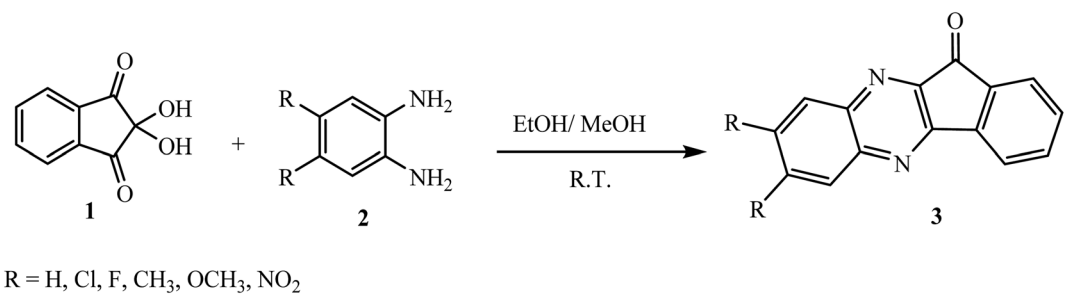
3. Generation of a three-membered ring on the indeno[1,2-*b*]quinoxaline moiety

3.1. Synthesis of [indeno[1,2-*b*]quinoxalin-11,1′-cyclopropane]

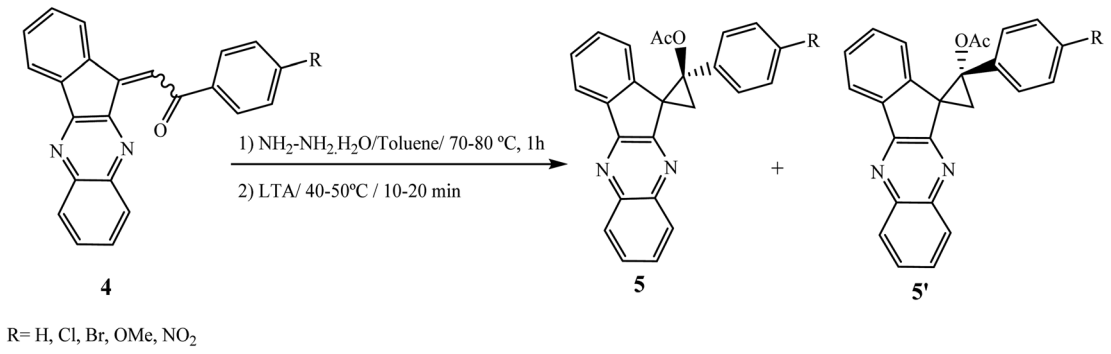
Cyclopropane ring-containing compounds are structural parts of various synthetic and naturally occurring compounds and exhibit anti-viral, anti-tumor, antibiotic and other potent activities.[17–20] Shaabanzadeh *et al.*[21] have reported the synthesis of two diastereoisomers of a new spiro-indenoquinoxaline system 2′-acetyloxy-2′-phenylspiro[indeno[1,2-*b*]quinoxalin-11,1′-cyclopropane] **5** and **5′** in a 3 : 1 ratio from the reaction of chalcones of indeno[1,2-*b*]quinoxaline **4** with hydrazine hydrate in the presence of solid lead(IV) tetraacetate (LTA) at 85 °C (Scheme 2). Chalcones have previously been prepared by the reaction of indenoquinoxalinone **3** with acetophenones in the presence of dimethylamine as a base catalyst in acetic acid and HCl.[22]

A plausible mechanism for the synthesis of the presented spiro system involves the intermediate spiro-indenoquinoxaline-pyrazoline **6** formed *in situ* by the reaction of **4** and hydrazine hydrate, which subsequently react with LTA to afford the desired product 2′-acetyloxy-2′-phenylspiro[indeno[1,2-*b*]quinoxalin-11,1′-cyclopropane] **5** and its diastereoisomer **5′** (Scheme 3).

Later on, authors also accomplished this reaction in another solvent, *ortho*-xylene, and observed the same diastereoselective ratio of **5** and **5′**.[23] Their chemical structures were fully optimized at the B3LYP/6-311+G(d,p) level of theory using the Gaussian 03W program package. Previously, the same research group also reported the synthesis of spiro-indenoquinoxaline-pyrazolines **6**, separately by the reaction of chalcones **4** and hydrazine hydrate.[24]



Scheme 1 Synthesis of indeno[1,2-*b*]quinoxalinones **3**.



Scheme 2 Diastereoselective synthesis of spiro-indenoquinoxaline-cyclopropanes **5** and **5′**.

4. Generation of a four-membered ring on indeno[1,2-*b*]quinoxaline

4.1. Synthesis of spiro[azetidine-2,11′-indeno[1,2-*b*]quinoxalin]-4-one

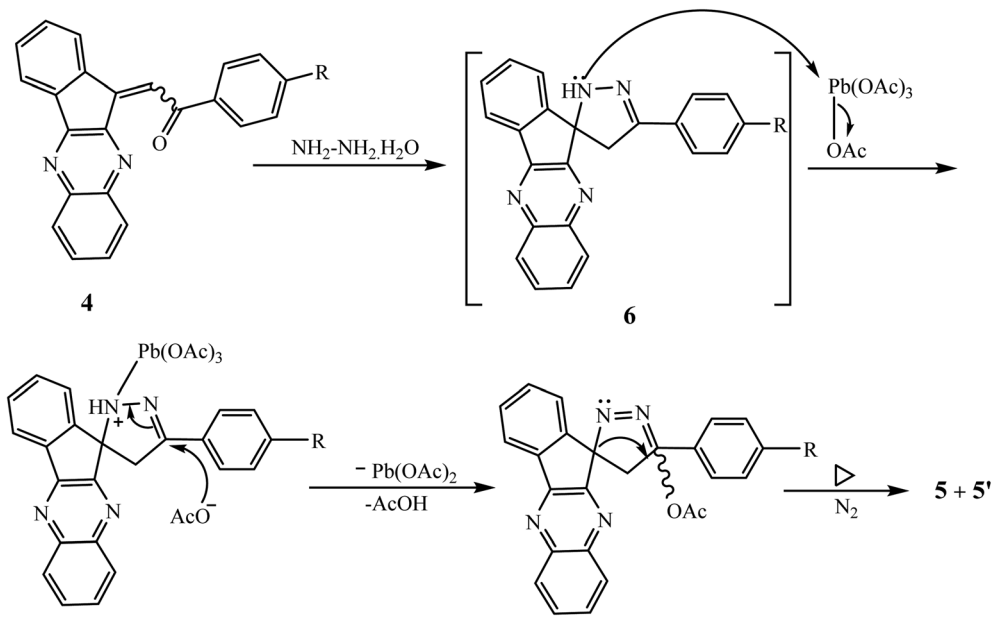
β-Lactam ring is a very important structural unit present in important antibiotics like penicillins, cephalosporins and carbapenems.[25] Jarrahpour and coworkers[26] have designed and finished the synthesis of novel spiro-β-lactams bearing indeno [1,2-*b*]quinoxaline hybrid system **8** *via* a modified Staudinger reaction in a short reaction time with high yields. The construction of spiro-β-lactam system **8** involves the [2 + 2] cycloaddition reaction between *N*-phenyl-11*H*-indeno[1,2-*b*] quinoxalin-11-imine derivatives **7** and various phenoxyacetic acid derivatives in the presence of triethylamine and *p*-toluenesulfonyl chloride (TsCl) at room temperature using CH_2Cl_2 as a solvent. The resultant spiro-β-lactams have been obtained in two diastereomeric forms **8** and **8′** in equal amount. Further enhancement of the diastereoselectivity of the reaction was studied, in anhydrous CH_2Cl_2 at low temperature, −10 or −83 °C, or in toluene at various temperatures but satisfactory results were not observed (Scheme 4).

5. Generation of a five-membered ring on indeno[1,2-*b*]quinoxaline

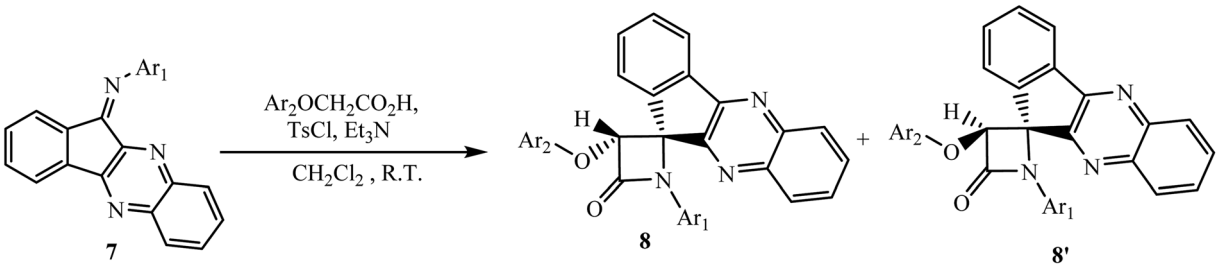
5.1. Synthesis of spiro-furan indenoquinoxaline derivatives

γ-Spirolactones are the subject of great attention because of their consequence as aldestrone inhibitors.[27] By considering this fact, various types of γ-spirolactones of pharmacological interest have been derived by researchers. Azizian and coworkers[28] have reported the synthesis of γ-spiroiminolactones **11** *via* a three-component condensation of indenoquinoxalin-11-ones **3**, dialkylacetylenedicarboxylates **9** and isocyanides **10** under microwave irradiation using montmorillonite KSF as a solid support in a shorter reaction time and in good yields in comparison to conventional synthesis (Scheme 5).

Later on, Mahdavinia and co-workers[29] modified the method by reducing the steps and they synthesized spirofuran-



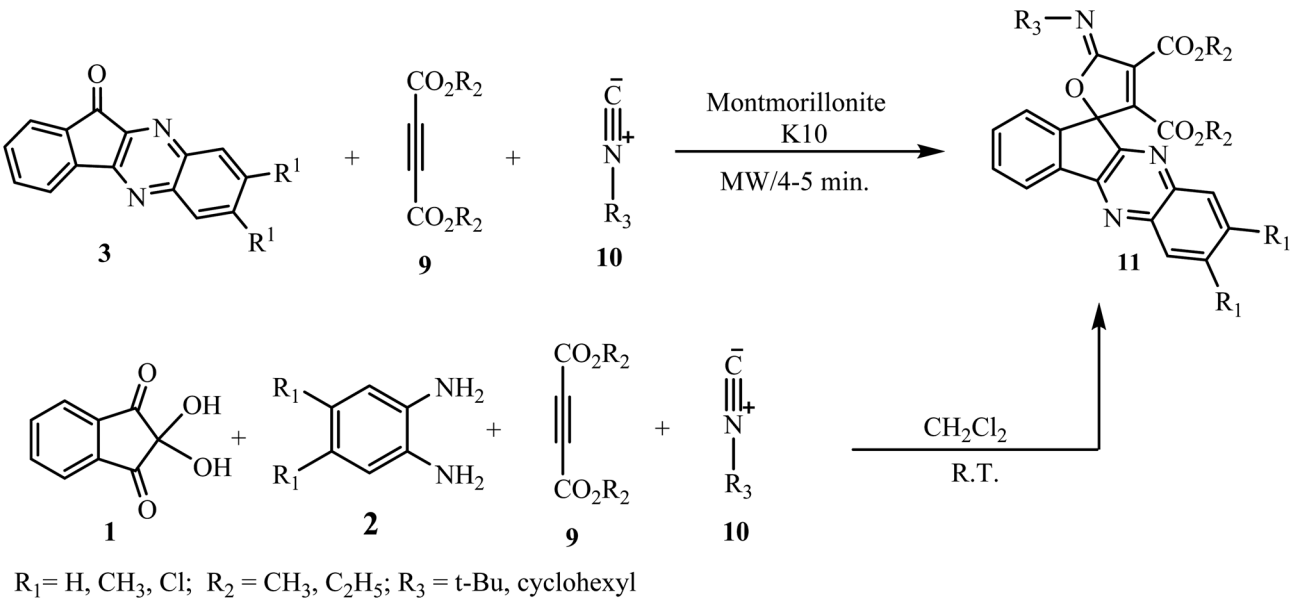
Scheme 3 Plausible mechanism for the synthesis of **5** and its diasteroisomer **5′**.



Ar_1: 4-MeO.C_6H_4, 4-Me.C_6H_4, 4-Isopropyl.C_6H_4, 3,4-diMeO.C_6H_3

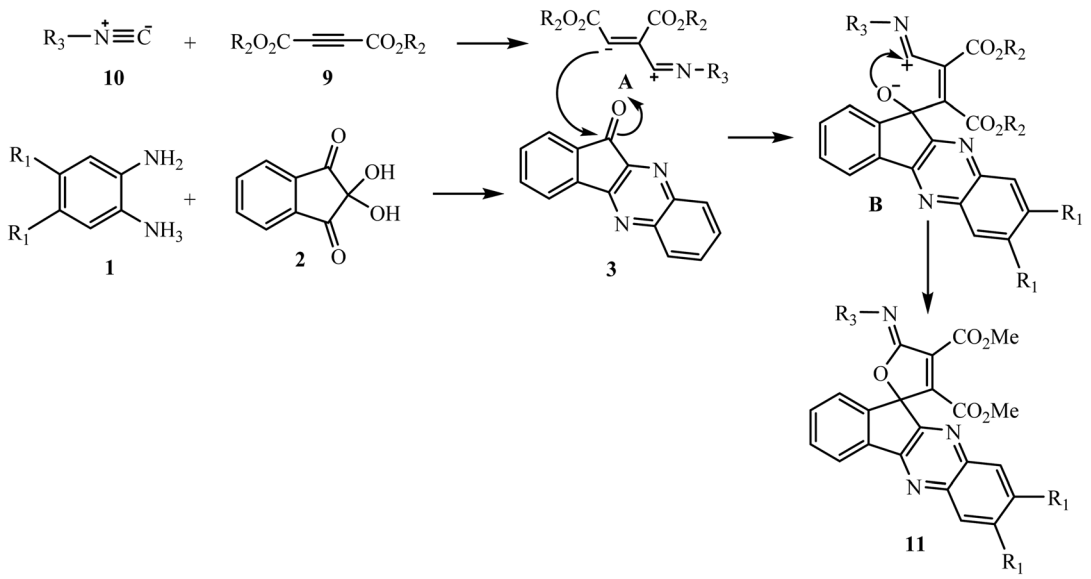
Ar_2: C_6H_5, 4-Cl.C_6H_4, 2,4-diCl.C_6H_3

Scheme 4 Diastereoselective synthesis of spiroazetidine-indenoquinoxalin-4-ones **8** and **8′**.

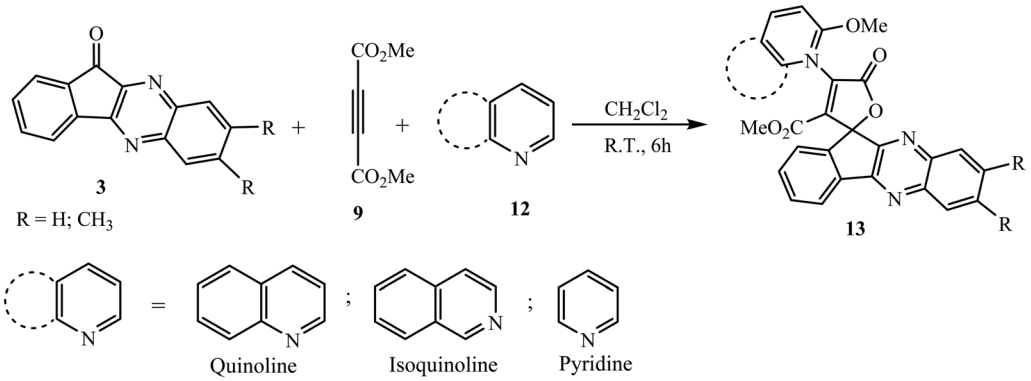


R_1= H, CH_3, Cl; R_2 = CH_3, C_2H_5; R_3 = t-Bu, cyclohexyl

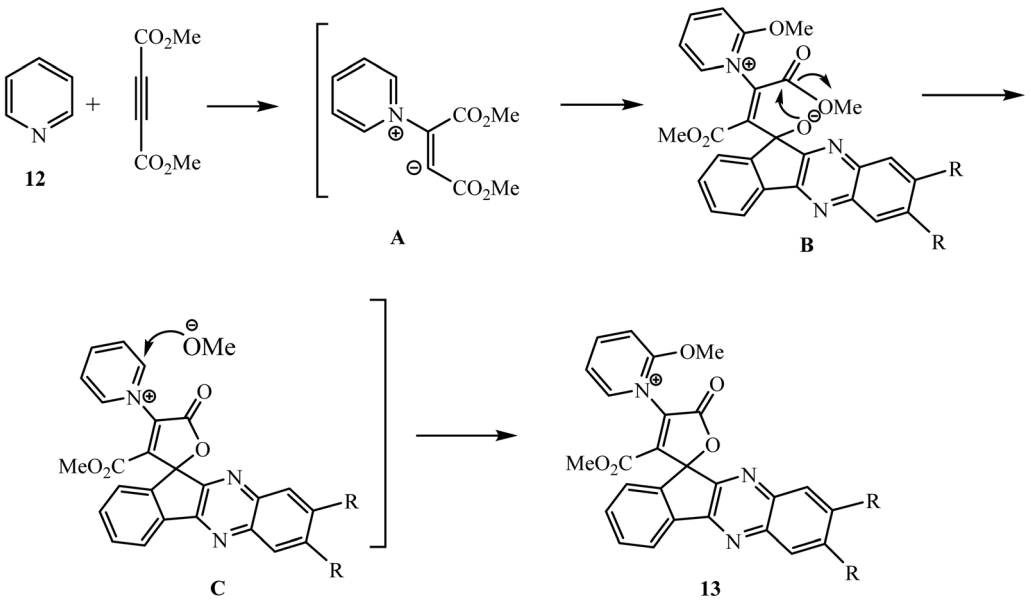
Scheme 5 Synthesis of imino-substituted γ-spiro-indenoquinoxaline-lactones **11**.



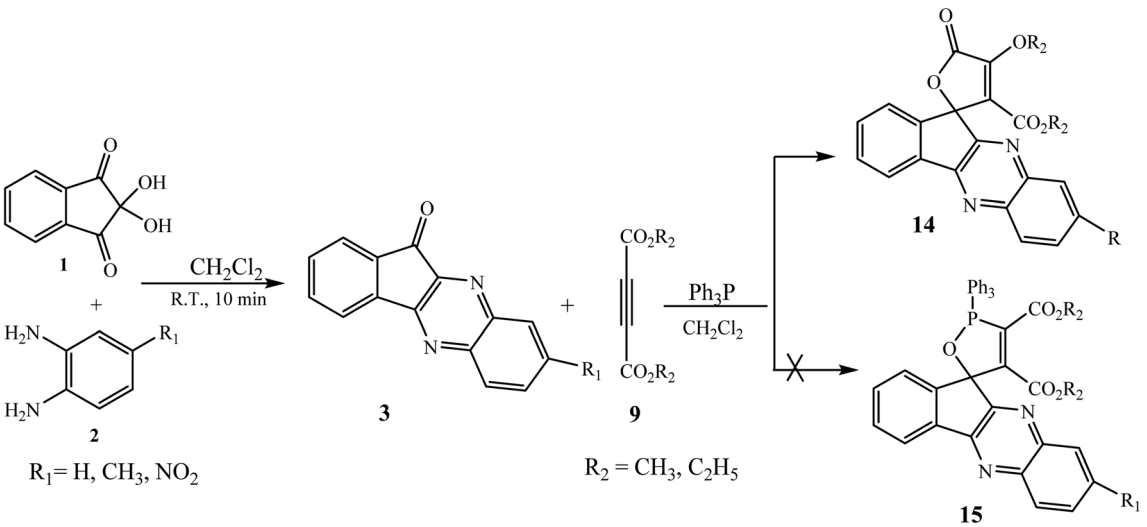
Scheme 6 Plausible reaction mechanism for the synthesis of spirofuran-indenoquinoxaline **11**.



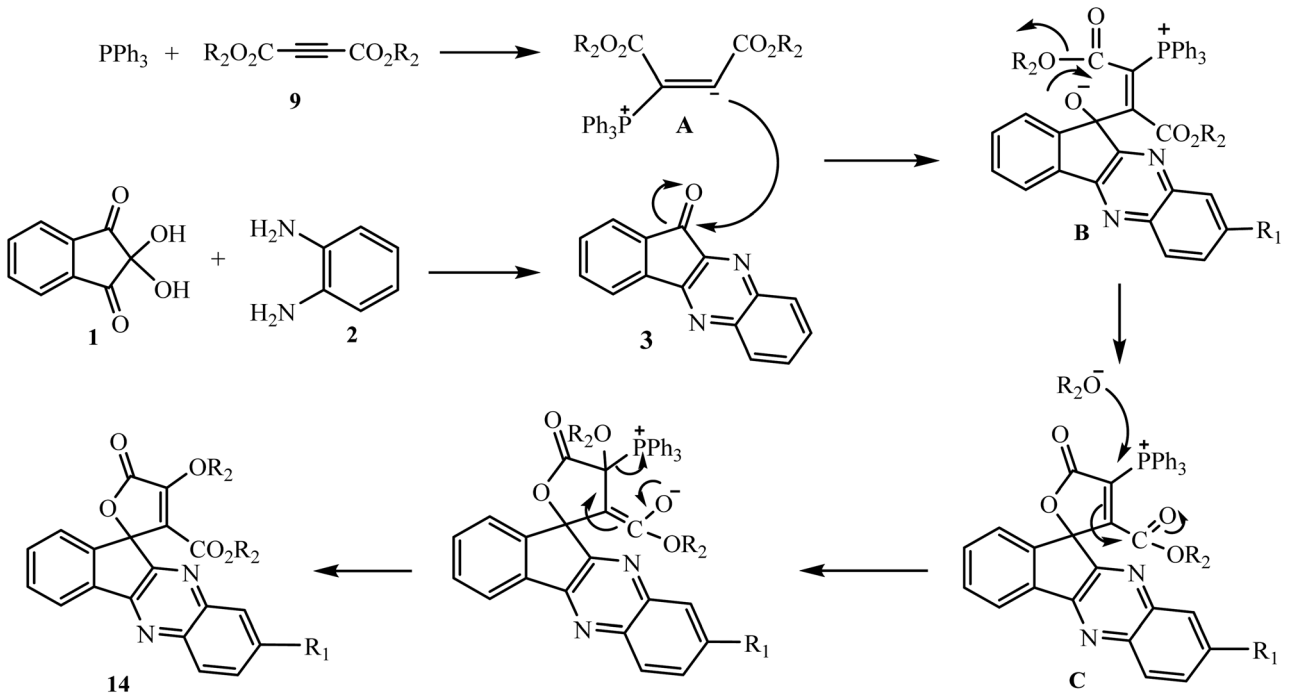
Scheme 7 Synthesis of N-heterocycle-substituted γ-spiroindenoquinoxaline-lactones **13**.



Scheme 8 Plausible reaction mechanism for the synthesis of γ-spirolactones **13**.



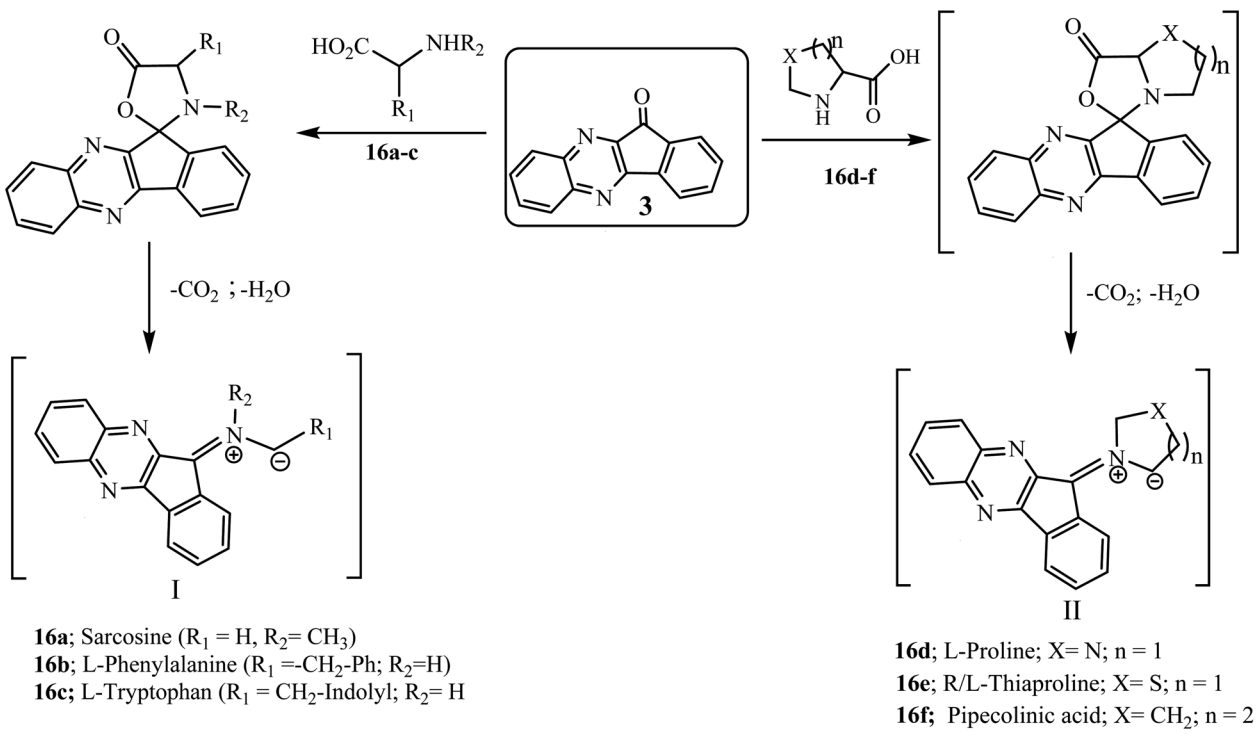
Scheme 9 Synthesis of spirofuran-indenoquinoxaline derivatives **14**.



Scheme 10 Plausible reaction mechanism for the synthesis of γ-spirolactones **14**.

indenoquinoxaline **11** *via* four-component reaction of ninhydrin **1**, benzene-1,2-diammine **2**, *tert*-butyl isocyanide **10**, and dialkylacetylenedicarboxylates **9** in dry CH_2Cl_2 at room temperature in 8 h. In this process the intermediate indenoquinoxalinones **3** were generated *in situ* from the reaction of ninhydrin **1** and benzene-1,2-diamines **2** (Scheme 5).

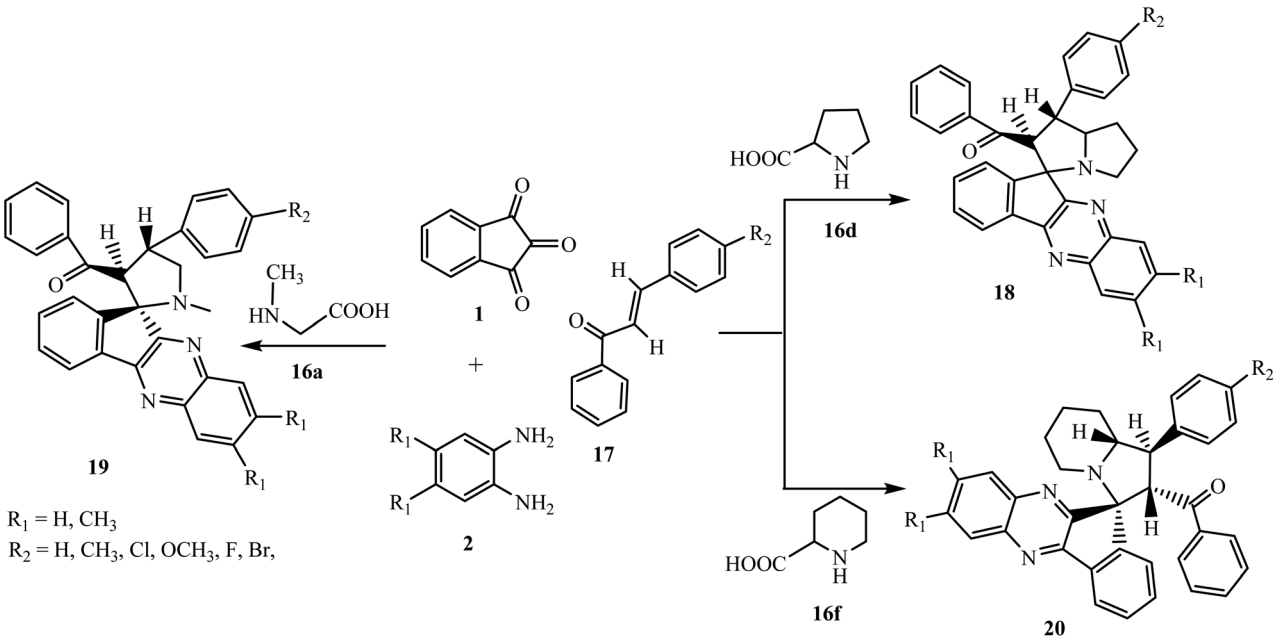
In the cited report the authors discussed the detailed mechanism for formation of adduct **11.** Initially, the formation of a zwitterionic intermediate **A** occurs by the reaction of isocyanide **10** and acetylenedicarboxylate **9**, which further attacks the carbonyl group of indenoquinoxalinone **3** (formed by interaction between ninhydrin **1** and benzene-1,2-diamine **2**) to



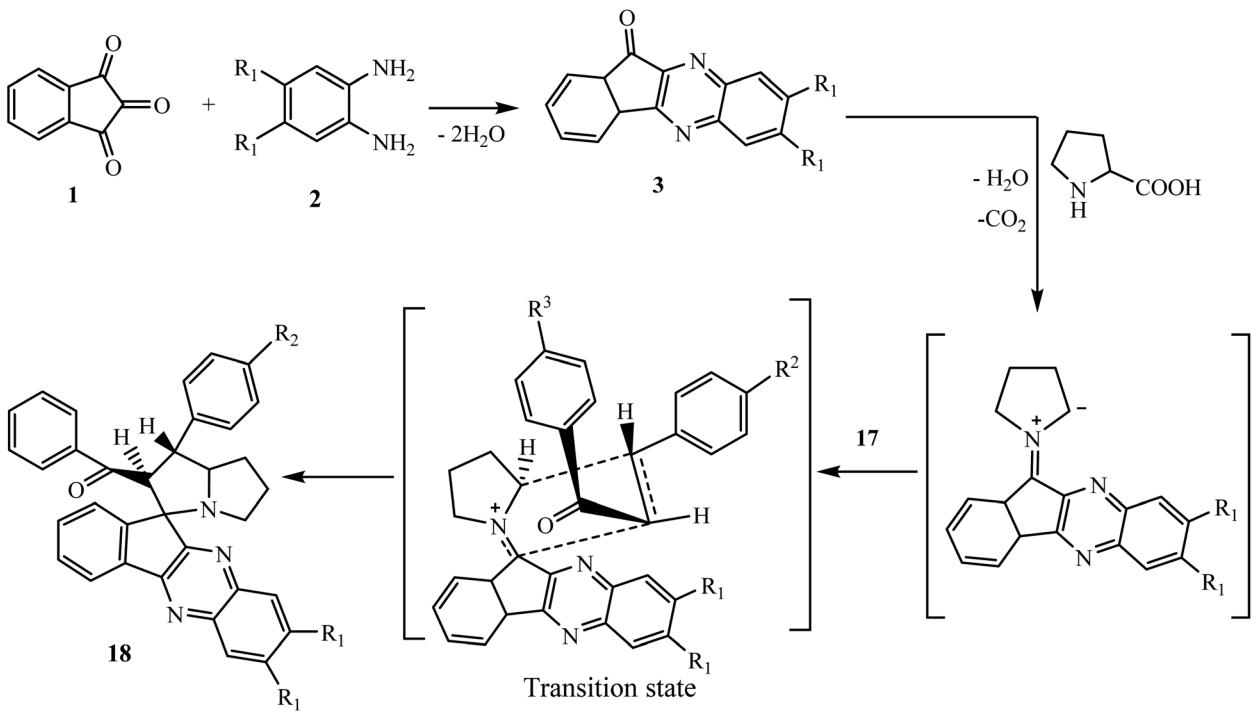
16a; Sarcosine (R_1 = H, R_2= CH_3)
16b; L-Phenylalanine (R_1 =-CH_2-Ph; R_2=H)
16c; L-Tryptophan (R_1 = CH_2-Indolyl; R_2= H

16d; L-Proline; X= N; n = 1
16e; R/L-Thiaproline; X= S; n = 1
16f; Pipecolinic acid; X= CH_2; n = 2

Scheme 11 Generation of various azomethine ylides I and II *via* decarboxylative condensation.



Scheme 12 Synthesis of spiroindenoquinoxalines **18–20** using simple chalcones **17**.

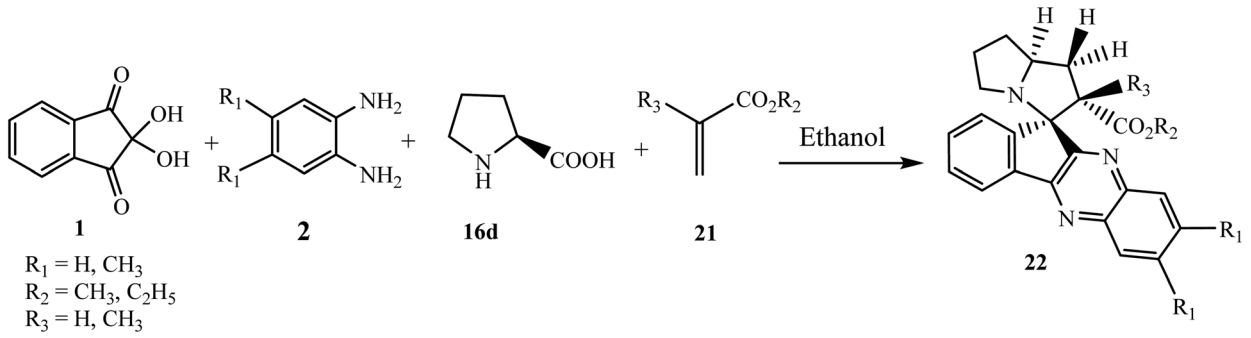


Scheme 13 Regio- and diastereoselective route for synthesis of spiro[indeno[1,2-*b*]quinoxaline-11,3′-pyrrolizine] **18**.

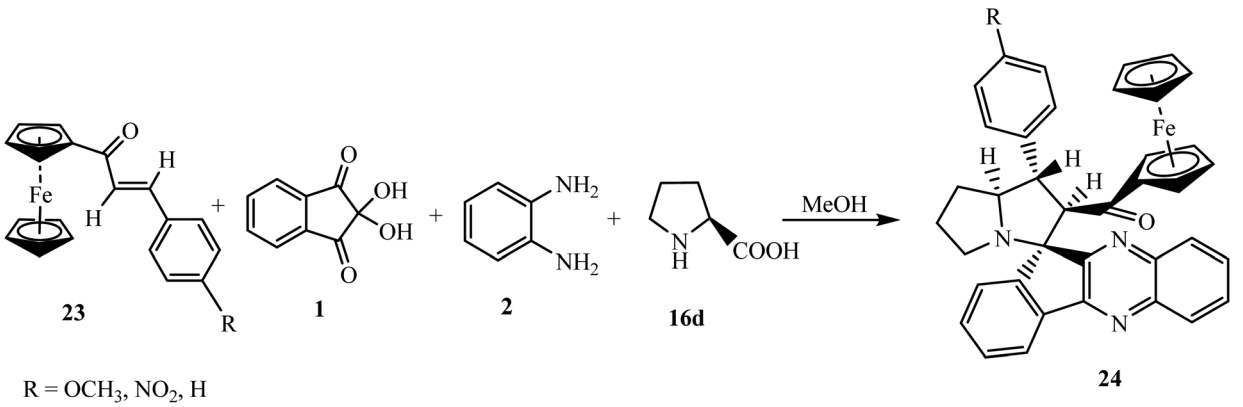
form a dipole intermediate **C**, and after that cyclization leads to spirocyclic adduct (Scheme 6).

The structure and arrangement of functional groups in spiro systems can be fully characterized by single-crystal X-ray analysis. Various isocyanides **10** and acetylenedicarboxylates **9** have been condensed with different substituted *o*-phenylenediamine **1** and ninhydrin **2** to afford the corresponding desired spirofuran-indenoquinoxaline derivatives **11** in excellent yields.

Mosslemin and co-workers have developed a new and efficient protocol for the present four-component reaction using imidazolium-based ionic liquid [bmin]BF_4 as a catalyst and solvent at ambient temperature.[30] Maghsoodlou *et al.*[31] demonstrated a convenient, efficient, one-pot approach for the



Scheme 14 Synthesis of spiro[indenoquinoxaline-11,3′-pyrrolizine]-2′-carboxylates **22**.



Scheme 15 Synthesis of ferrocene grafted spiroindenoquinoxaline-pyrrolizidines **24**.

synthesis of N-heterocycle-substituted spiroindenoquinoxaline-lactones **13** *via* the three-component reaction of 11*H*-indeno[1,2-*b*]quinoxalin-11-one **3**, DMAD **9** and N-heterocyclic compounds **12** such as pyridine, quinoline and isoquinoline using CH_2Cl_2 as a solvent (Scheme 7).

The mechanism involves the generation of 1,3-dipolar intermediate **A** *via* the reaction of DMAD and pyridine **12**, which further react with the carbonyl carbon of indeno[1,2-*b*]quinoxalin-11-one **3** by nucleophilic attack, and subsequent cyclization and attack of the methoxy anion generate the spirolactone **13** (Scheme 8).

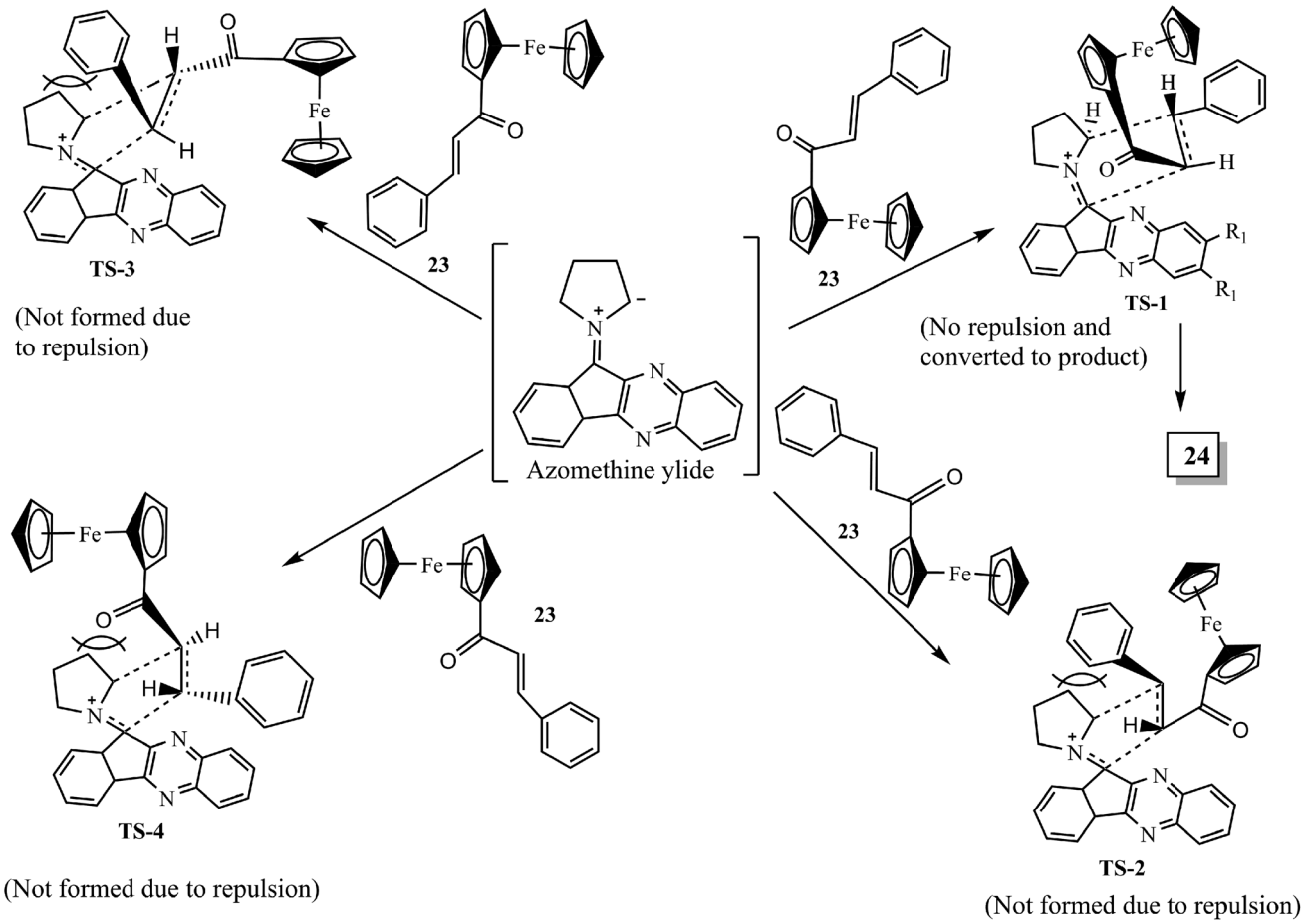
In ongoing research in this area, Maghsoodlou *et al.* have investigated a domino reaction between ninhydrin **1**, benzene-1,2-diammine **2**, dialkylethynedicarboxylates **9** and triphenylphosphine (Ph_3P) to synthesize the expected desired product spiro-1,2-oxaphosphorus **15**. However, the results showed the successful formation of unexpected product spirofuran-indenoquinoxaline derivatives **14** instead of the formation of **15** (Scheme 9).[32]

In this reaction Ph_3P acts as catalyst, and initially 1,3-dipolar intermediate **A** is formed by the interaction of dialkylethynedicarboxylates **9** with Ph_3P and subsequently **A** attacks the carbonyl carbon of **3** leading to the formation of zwitterionic intermediate **B**, which on further cyclization gives intermediate **C** and is then converted into desired spirocyclic products **14** in excellent yields (Scheme 10).

The one-pot domino strategy has several advantages, such as mild and neutral conditions, high atom economy with excellent yield, good functional group tolerance, and no need for chromatographic purification.

5.2. Synthesis of spiro-pyrrolidine/pyrrolizine/pyrrolothiazole-indenoquinoxalines

The 1,3-dipolar cycloaddition reaction has been described as the single most important method for the construction of heterocyclic five-member ring compounds in organic chemistry.[33,34] The reaction of azomethine ylides with dipolarophiles offers an effective approach for the construction of mono- and di-spiropyrrolidine, pyrrolizidine and pyrrolothiazole derivatives that are present in many biologically active compounds.[35–38] Azomethine ylides are an important and well documented class of 1,3-dipoles generated *in situ* from the decarboxylative condensation of carbonyl compounds with α-amino acids. The subsequent addition of azomethine ylides with appropriate dipolarophiles leads to the construction of these significant bioactive spiro compounds. Various azomethine ylide type I and II in a [3 + 2] cycloaddition reaction can be generated *in situ* from the decarboxylative condensation of carbonyl compounds, *i.e.*, indeno[1,2-*b*]quinoxalin-11-one **3**, with α-amino acids such as sarcosine **16a**, L-phenylalanine **16b**, L-tryptophan **16c**, L-proline **16d**, R/L-thiaproline **16e**, and pipecolinic acid **16f** (Scheme 11).

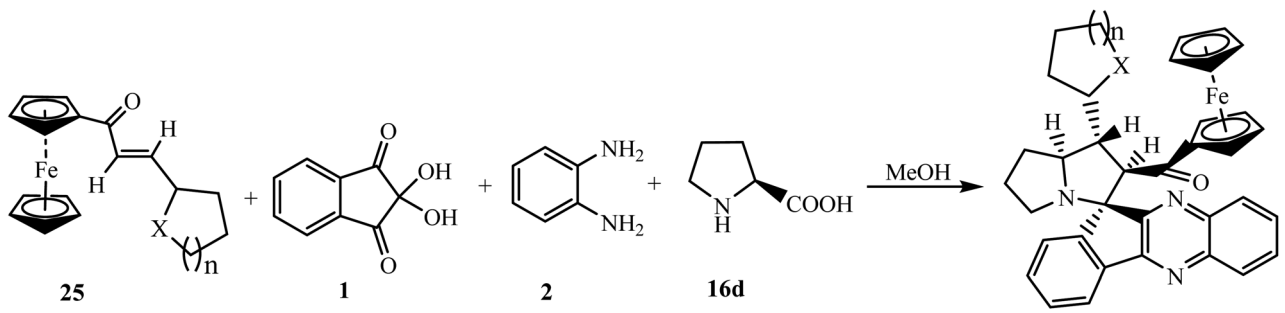


Scheme 16 Possible transitions states TS-1 to TS-4 formed during the synthesis of spiro adduct **24**.

5.2.1. Synthesis of mono-spiroindenoquinoxaline-pyrrolidine/pyrrolizidine/indolizidine derivatives *via* [3 + 2] cycloaddition

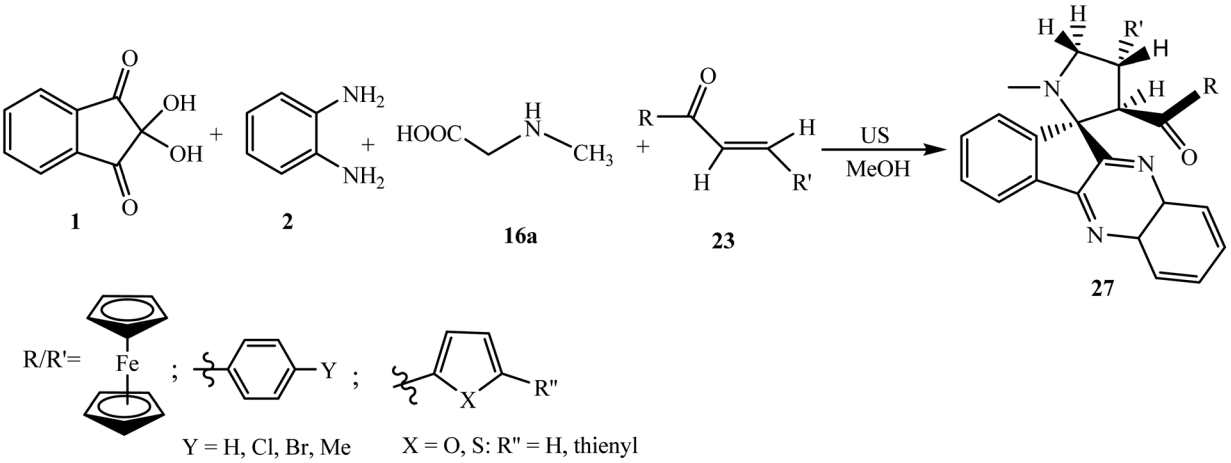
5.2.1.1. Using α,β-unsaturated carbonyl compounds as a dipolarophile. Mohammadizadeh and co-workers[39] investigated a four-component 1,3-dipolar reaction of ninhydrin **1**, 1,2-phenylenediamine **2**, substituted chalcones **17** and α-amino acid L-proline **16d** in ethanol to fabricate the novel spiro[indeno [1,2-*b*]quinoxaline-11,3′-pyrrolizine] scaffold **18** stereoselectively (Scheme 12). After that Jadidi and co-workers expanded the work and reported the synthesis of new cycloadducts spiro [indeno[1,2-*b*]quinoxaline-11,2′-pyrrolidines] **19** and spiroindenoquinoxaline-indolizidines **20** using α-amino acid sarcosine **16a**[40] and pipecolinic acid **16f**,[41] respectively, in place of L-proline **16d**.

A reasonable mechanism for the construction of spiro[indeno [1,2-*b*]quinoxaline-11,3′-pyrrolizine] **18** is shown in Scheme 13. The mechanism involves the *in situ* generation of intermediate



X = S, O, N; n = -CH_2-, -CH_2-CH_2-

Scheme 17 Synthesis of heterocyclic ring-containing ferrocene-grafted spiroindenoquinoxaline-pyrrolizidines **26**.



Scheme 18 Synthesis of ferrocene grafted spiro-indenoquinoxaline-pyrrolidines **27**.

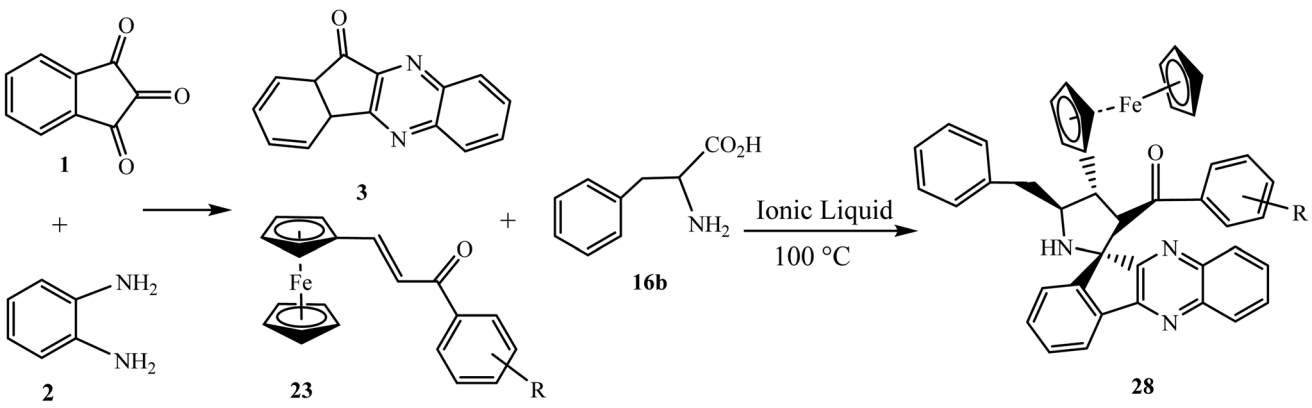
indenoquinoxalinone **3**, which subsequently reacts with L-proline **16d** to produce 1,3-dipolar azomethine ylide type II. Finally, azomethine ylide interacts with the most electrophilic β-carbon of C=C bond of dipolarophile chalcone **17** selectively from the less hindered side to afford *endo*-cycloadduct **18** in good yields with excellent regio- and diastereoselectivity without the formation of other possible diastereoisomers. Similarly, the azomethine ylide generated *in situ* from the reaction of sarcosine **16a** or pipecolinic acid **16f** with indenoquinoxalinone **3** reacts with chalcone **17** to afford single isomers of spiro[indeno[1,2-*b*]quinoxaline-11,2′-pyrrolidines] **19** and spiroindenoquinoxaline-indolizidine **20**, respectively.

Sosnovskikh and co-workers[42] have accomplished the synthesis of new derivatives of spiropyrrolizidines **18** and spiropyrrolidine-indenoquinoxalines **19** in an *endo*- and diastereoselective manner using arylideneacetones as a dipolarophile.

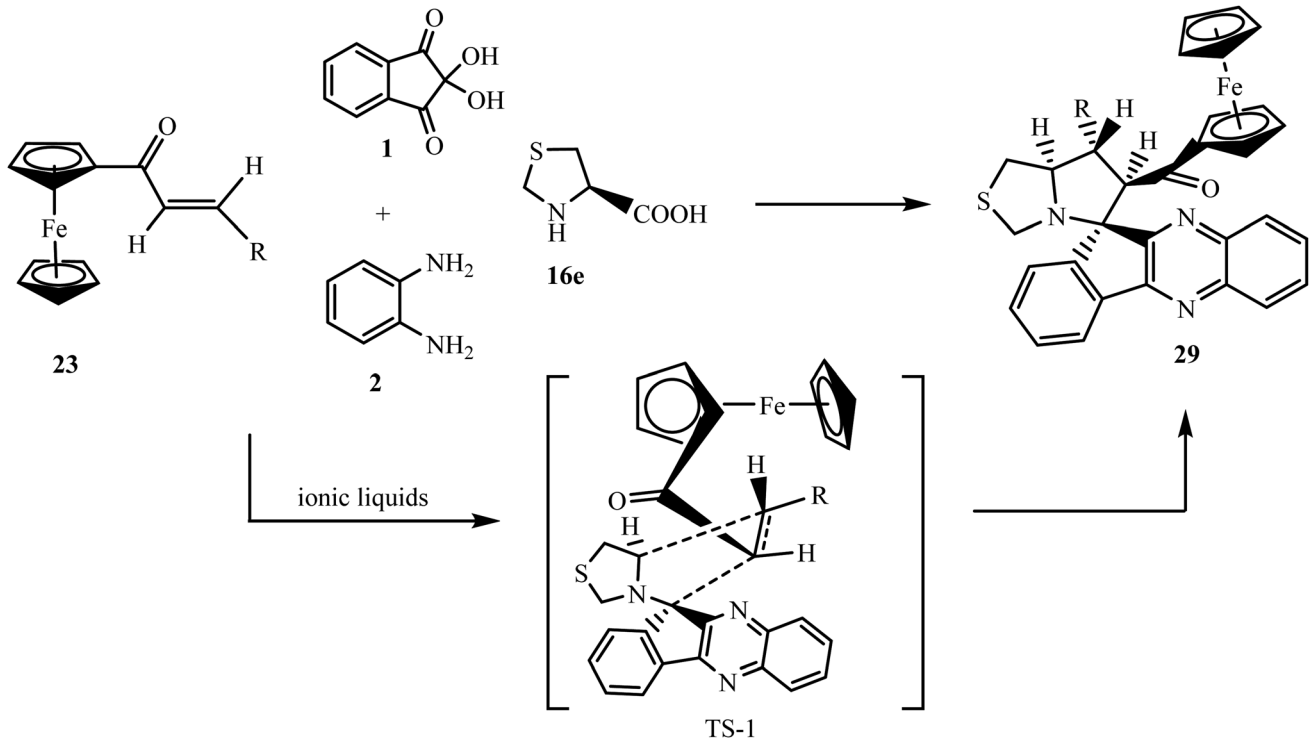
Mohammadizadeh *et al.*[43] reported the synthesis of novel alkylspiro[indeno[1,2-*b*]quinoxaline-11,3′-pyrrolizine]-2′-carboxylates **22** using acrylic acid **21** as a dipolarophile *via* the four-component reaction of ninhydrin **1**, *o*-phenylenediamine **2**, L-proline **16d** and acrylic acid **21** in ethanol at reflux temperature (Scheme 14). The stereochemistry of the product was confirmed by ^{1}H nuclear Overhauser effect spectroscopy (NOESY).

5.2.1.2. Using ferrocene grafted α,β-unsaturated carbonyls as a dipolarophile. Ferrocene derivatives have attracted worldwide attention over other organometallics due to their sandwich structure, synthetic versatility, thermal and photochemical stability, and biological activity.[44] Hence, there has been a renewed interest in the synthesis of ferrocene-based heterocyclic frameworks in organic chemistry. Raghunathan *et al.*[45] described the synthesis of highly functionalized and ferrocene grafted spiroindenoquinoxaline-pyrrolizidines **24** *via* the one-pot four-component reaction of ninhydrin **1**, 1,2-phenylenediamine **2**, and L-proline **16d** with various ferrocene-derived chalcone dipolarophiles **23** using methanol as a reaction medium (Scheme 15).

A plausible mechanism for the formation of ferrocene grafted spiroindenoquinoxaline-pyrrolizidines **24** is shown in Scheme 16. The mechanism involves the *in situ* formation of azomethine ylide, which subsequently interacts with ferrocene-derived chalcones **23** leading to the formation of product **24**.



Scheme 19 Synthesis of new spiropyrrolidine-engrafted ferrocene **28** using L-phenylalanine **16b**.



Scheme 20 Mechanism for the selective synthesis of spiro-indenoquinoxaline derivative **29**.

The authors demonstrated all of the possible transition states TS-1 to TS-4 that can be formed during the interaction of dipolarophile **23** and azomethine ylide II regio- and stereochemically. However, due to the lower steric hindrance in *exo*-TS-1, the reaction proceeds *via exo*-TS-1 leading to the formation of single isomer spirocycloadduct **24** with regio- and diastereoselectivity. The stereochemical assignments of cycloadducts have been confirmed by nuclear Overhauser effect (NOE) studies and single-crystal X-ray analysis.

To further expand the work, 1-ferrocenyl-3-furylprop-2-ene-1-one/1-ferrocenyl-3-thienylprop-2-ene-1-one/1-ferrocenyl-3-pyridylprop-2-ene-1-one and 1,3-diferrocenylprop-2-ene-1-one **25** as dipolarophiles have also been used to synthesize the corresponding spiroindenoquinoxaline-pyrrolizidines **26** (Scheme 17).

Later on in 2013, Raghunathan *et al.*[46] expanded the scope of the reaction by employing sarcosine **16a** in place of L-proline **16d** to build highly substituted novel ferrocene grafted

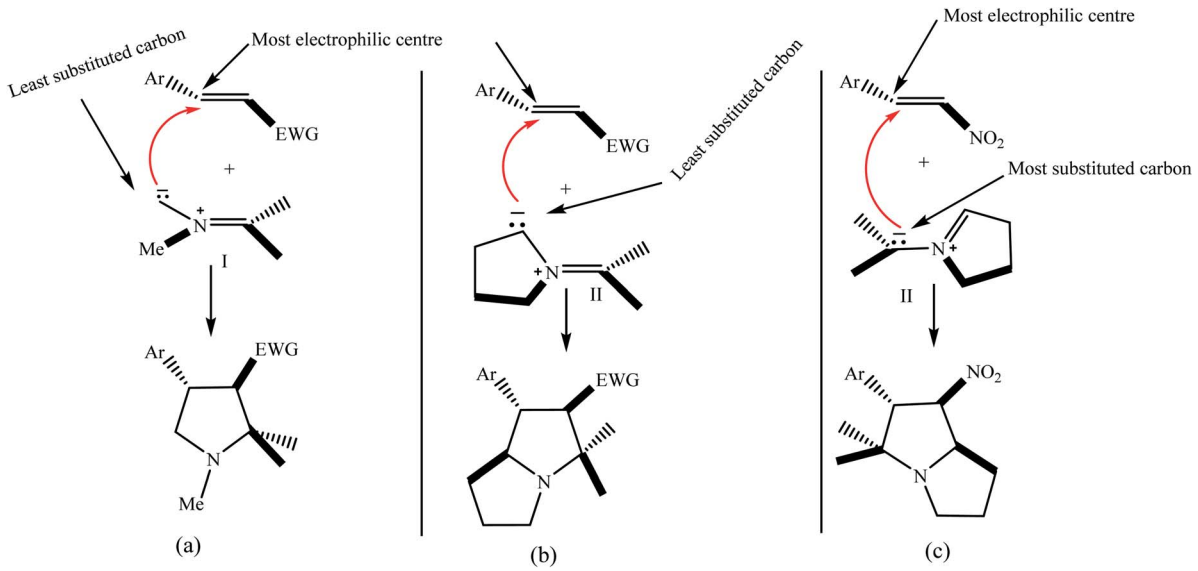
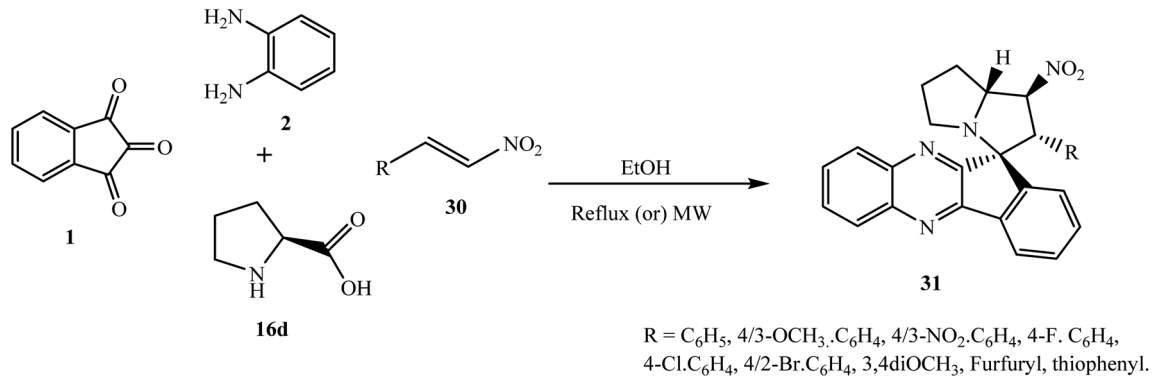


Fig. 2 (a–c) Representations of the regioselective attack of azomethine ylide types I and II with dipolarophiles.



Scheme 21 Synthesis of spiro-indenoquinoxalines using β-nitrostyrenes **30**.

spiroindenoquinoxaline-pyrrolidines **27** of biological significance under ultrasound irradiation in shorter time and with better yield compared to the conventional method (Scheme 18). Two sets of single-crystal X-ray data of spiroindenoquinoxaline-pyrrolidines **27** have also been reported.[47,48] The observed regio- and diastereoselectivity was found to be similar to that of the spiro adduct **24**.

Recently, Arumugam *et al.*[49] fabricated a new spiropyrrolidine grafted ferrocene heterocycle **28** by the four-component reaction of ninhydrin **1**, *o*-phenylenediamine **2**, L-phenylalanine **16b** and ferrocenyl chalcones **23** utilizing an ionic liquid, 1-butyl-3-methylimidazoliumbromide, affording excellent yields.

The *in situ* generated azomethine ylide type I derived from a combination of ninhydrin **1** and *o*-phenylenediamine **2** along with L-phenylalanine **16b** reacts efficiently with ferrocenyl chalcone **23** in [bmim]Br affording spiro cycloadduct **28**, regioselectively. The ionic liquid [bmim]Br plays an important role in accelerating this cycloaddition reaction sequence in a sustainable fashion (Scheme 19).

Raghunathan and coworkers[50] have introduced a new amino acid, (*R*)-thiazolidine-4-carboxylic acid **16e**, to accomplish new ferrocene grafted spiro-indenoquinoxaline-pyrrolo[1,2-*c*]thiazole **29** using a new ionic liquid, *N*-(1-acroloyl)-*N*-(4-cyclopentyl) piperazinium dihydrogen phosphate, as a reaction medium and accelerator. Azomethine ylide type II generated *in situ* from the condensation of indenoquinoxline-11-one **3** and (*R*)-thiazolidine-4-carboxylic acid **16e** interacts with ferrocene derived dipolarophile **23** *via* *endo*-transition state TS-1 to exclusively form spiro adduct **29**. The *endo*-transition state TS-1 minimizes the steric interaction between the phenyl ring of dipolarophile **23** and CH_2 of the thiazolidine ring proximate to the quinoxaline ring of azomethine ylide (Scheme 20).

5.2.1.3. Using nitrostyrenes as a dipolarophile. A literature survey reveals that azomethine ylides type I derived from open-ring α-amino acids like sarcosine **16a** and cyclic carbonyl compounds usually react with their least substituted terminal atom interacting with the most electrophilic carbon of electron-deficient alkenes regioselectively (Fig. 2a). In the case of cyclic azomethine ylides type II, where the nitrogen atom is a part of pyrrolidine/thiazolidene or piperidine ring, related regioselectivity of the reaction was observed for dipolarophiles such as acrylates, chalcones, and CX_3-nitroalkenes (Fig. 2b).

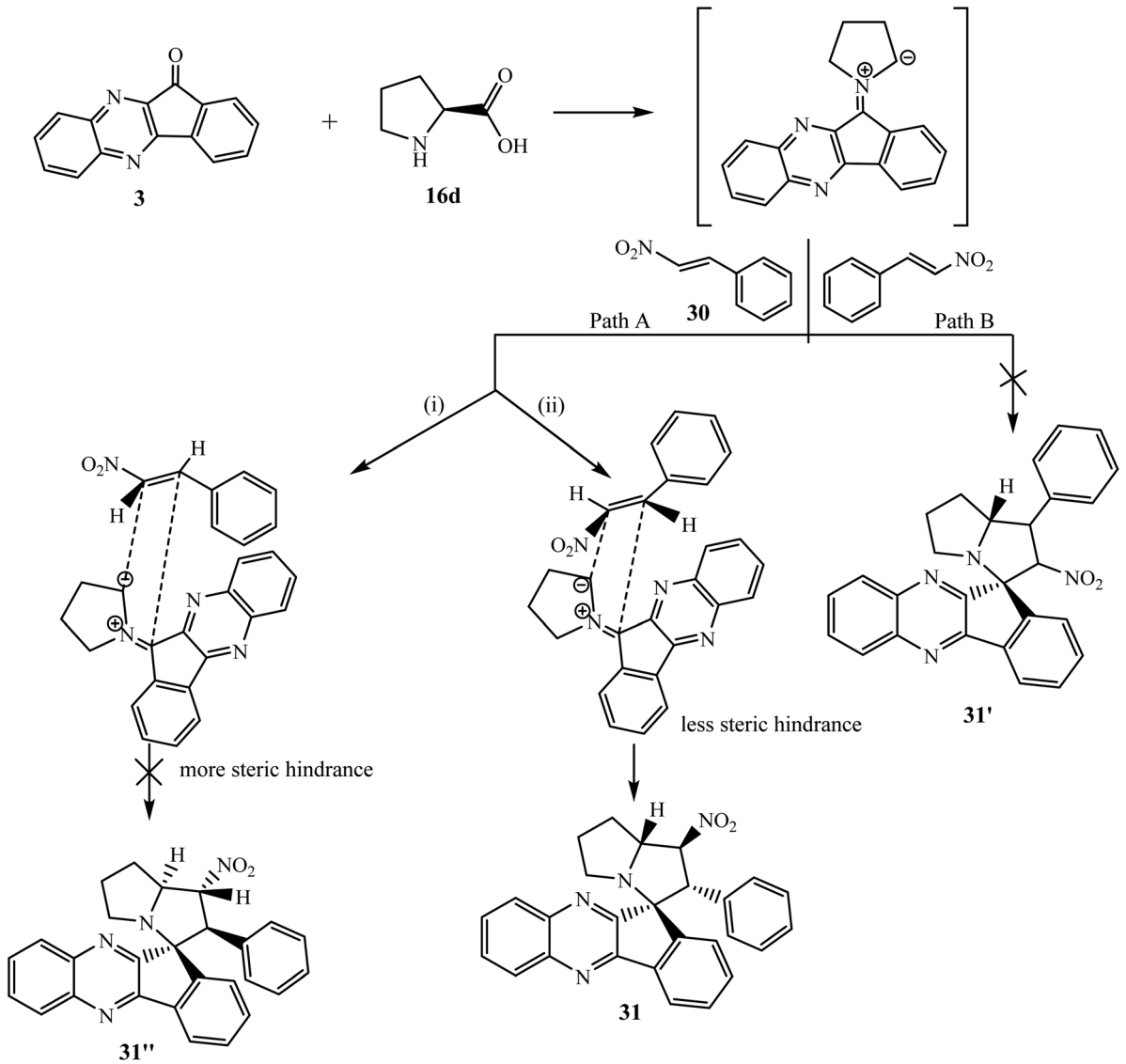
However, in the case of dipolarophiles *trans*-β-nitrostyrenes, the practical regioselectivity was dissimilar and the most electrophilic carbon of C=C bond of the dipolarophile attached to the more substituted end of the 1,3-dipole (Fig. 2c).

Due to the unique and unpredictable reactivity of β-nitrostyrenes, Trivedi *et al.*[51] have investigated a four-component [3 + 2] cycloaddition reaction of ninhydrin **1**, *o*-phenylenediamine **2**, L-proline **16d** and *trans*-β-nitrostyrenes **30** under microwave irradiation and classical conditions to synthesize densely functionalized heterocyclic scaffold spiro[indeno[1,2-*b*]quinoxaline-11,3′-pyrrolizine] **31** regio- and diastereoselectively (Scheme 21).

Mechanistically, reaction of 1,3-dipolar azomethine ylide generated from indenoquinoxalinone **3** and L-proline **16d** with dipolarophiles β-nitrostyrenes **30** can proceed *via* two paths A and B regioselectively, to afford two regioisomers **31** and **31′**. In the present case, the reaction proceeded *via* an unusual path and the more substituted electron-rich carbon of azomethine ylide type II attacks exclusively the most electrophilic center of the dipolarophile leading to the formation of only single regioisomer **31** through path A. Furthermore, this reaction is also diastereoselective, and in path A the addition of azomethine ylide with β-nitrostyrene **30** can proceed in two ways (i) *exo* and (ii) *endo* with respect to NO_2 group, but due to less hindrance and thermodynamic stability, only single *endo* product **31** was formed and no trace of *exo*-isomer **31″** was detected (Scheme 22).

The regio- and stereochemistry of the product was determined based on single-crystal X-ray analysis. β-Nitrostyrenes with methyl, methoxy, nitro and halogen functions were reacted smoothly in the presented cycloaddition reaction affording corresponding spiro adducts **31**. Additionally, all the synthesized spiro[indeno[1,2-*b*]quinoxaline-11,3′-pyrrolizine] **31** were screened for AChE inhibitory activity and 6 out of 21 compounds exhibited significant activity in the low micromolar IC_{50} range.

Earlier reports mentioned that the presence of an OH group in the reacting alkenes influences the regioselectivity of the reaction, due to the possibility of intermolecular hydrogen bond



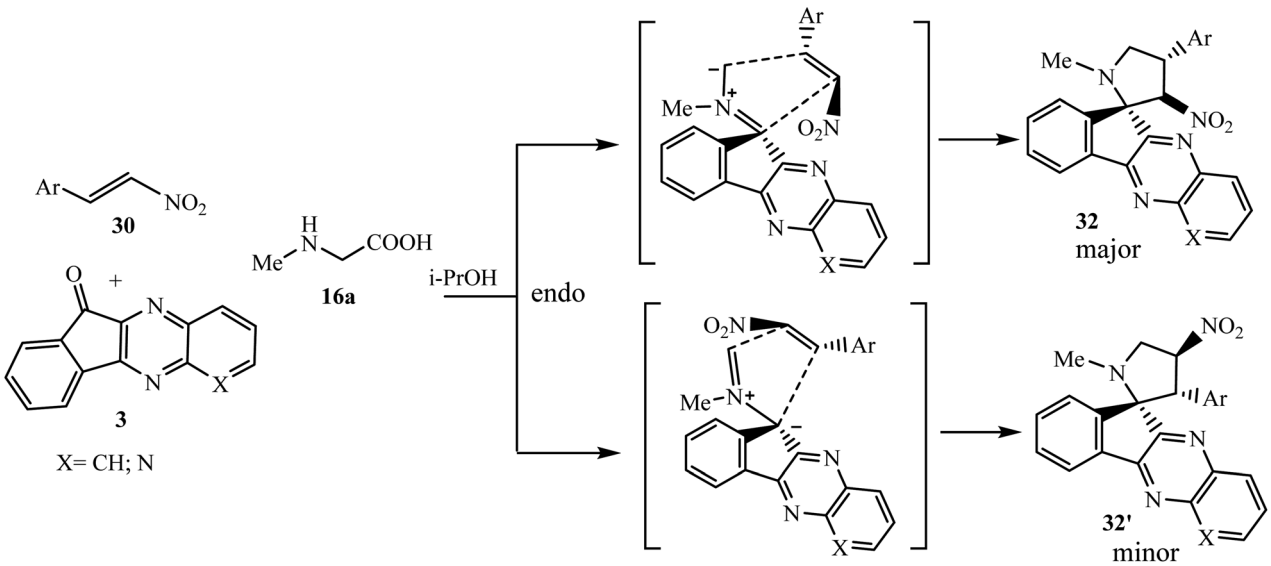
Scheme 22 Mechanism for the synthesis of spiroindenoquinoxalines **31** regio- and diastereoselectively.

formation, which tends to stabilize the transition state leading to a selective regioisomer.[52] Considering this, Sosnovskikh *et al.*[53] investigated the [3 + 2] cycloaddition reaction with hydroxyl-substituted β-nitrostyrenes **30** along with other substituents using 2-propanol as a solvent medium. In the majority of cases, spiro-nitropyrrolizidines **31** were formed as a single isomer. The single-crystal X-ray structure analysis of **31** justified the formation of *endo* cycloadduct with a *trans* relationship of the quinoxaline moiety and nitro group, as reported by Trivedi and co-workers.[51] The presence of a phenolic hydroxyl group in β-nitrostyrene did not interfere in this reaction and the interaction of β-nitrostyrene with azomethine ylide generated from indenoquinoxalinone **3** and L-proline **16d** proceeded *via* the attack of the more electrophilic center of the alkene with the less available atom of the dipole.

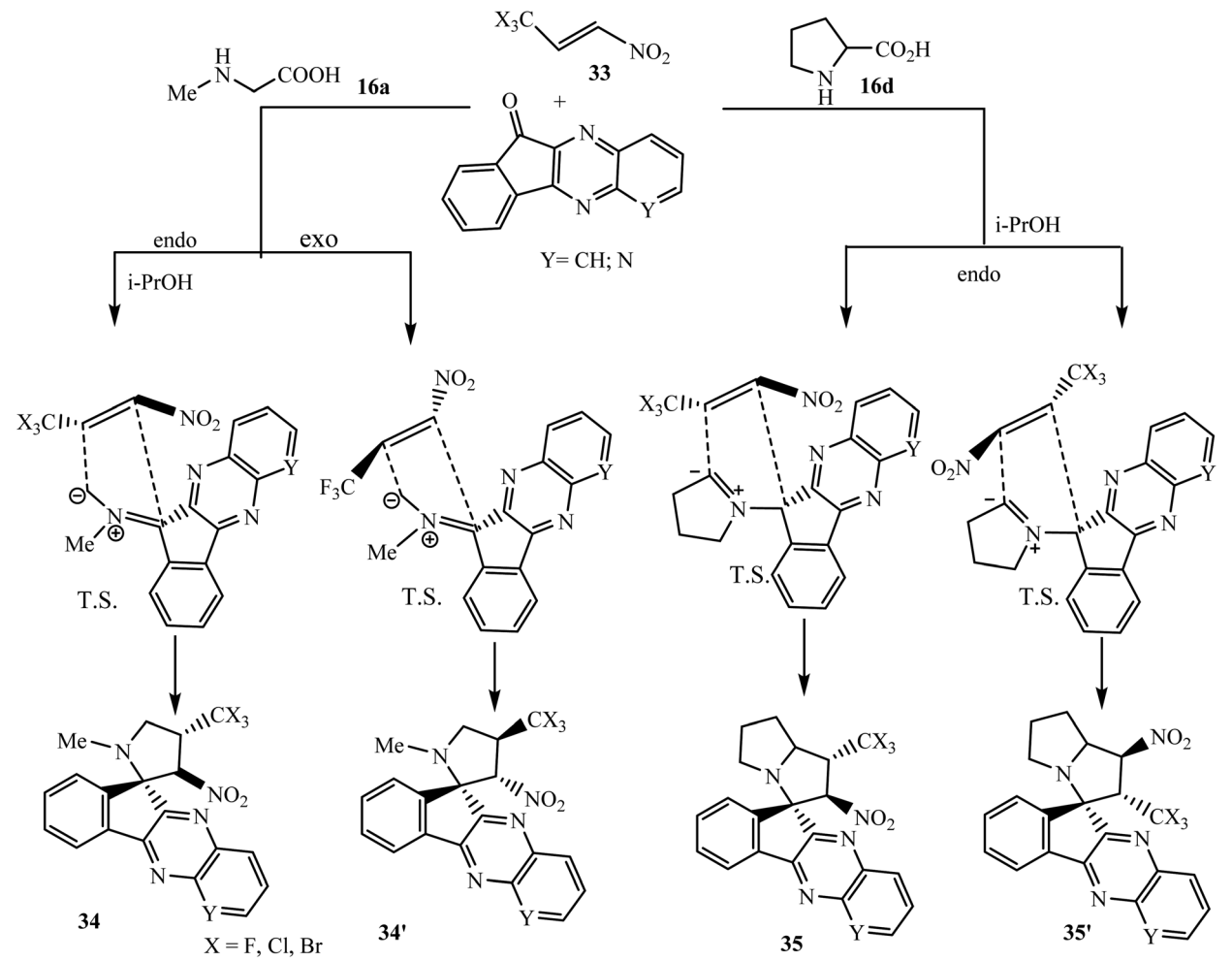
In further elaboration of this work, a three-component reaction was investigated with sarcosine **16a** in place of L-proline **16d** under similar conditions, and two regioisomers of spiro-indenoquinoxaline-nitropyrrolidines **32** as the main isomer and **32′** as the minor isomer were obtained with decreased regioselectivity. The reaction proceeded successfully with β-nitrostyrenes with phenyl and methoxy and chlorine substituents on the aryl ring, but failed to occur with OH-substituted β-nitrostyrenes.

The single-crystal X-ray characterization of **32** clearly indicates a different regiomeric nature from spiro-nitropyrrolizine **31** due to the faster attack of the more electrophilic α-carbon atom of β-nitrostyrenes **30** with the more readily available less substituted terminal atom of the ylide through an *endo*-transition state. Similarly to spiro-nitropyrrolizidines **31**, the *trans* configuration of the starting β-nitrostyrene was also conserved in spiro-nitropyrrolidines **32** (Scheme 23).

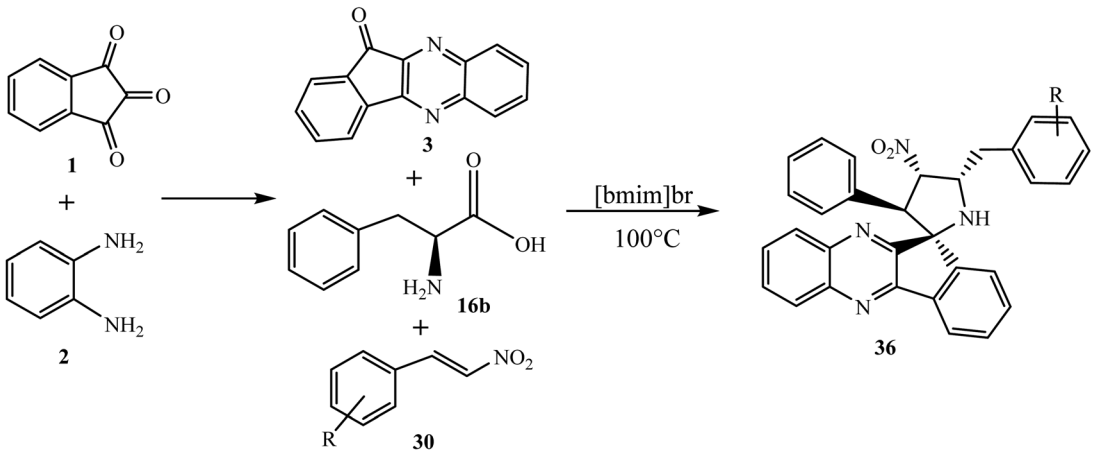
The introduction of trihalomethyl groups, particularly CF_3 groups, in organic molecules not only enhances their



Scheme 23 Regioselective synthesis of spiro-indenoquinoxaline-pyrrolidines 32 and 32′.



Scheme 24 Selective synthesis of trihalomethylated spiroindenoquinoxalines 34 and 35.

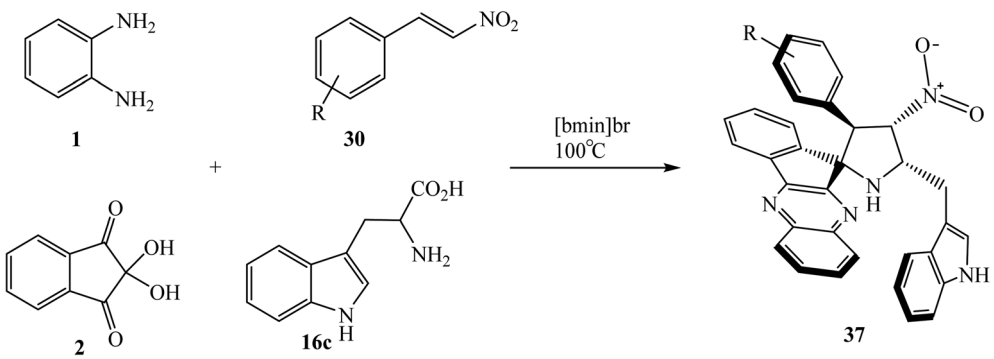


Scheme 25 Synthesis of benzyl-substituted spiroindenoquinoxaline-pyrrolidines **36**.

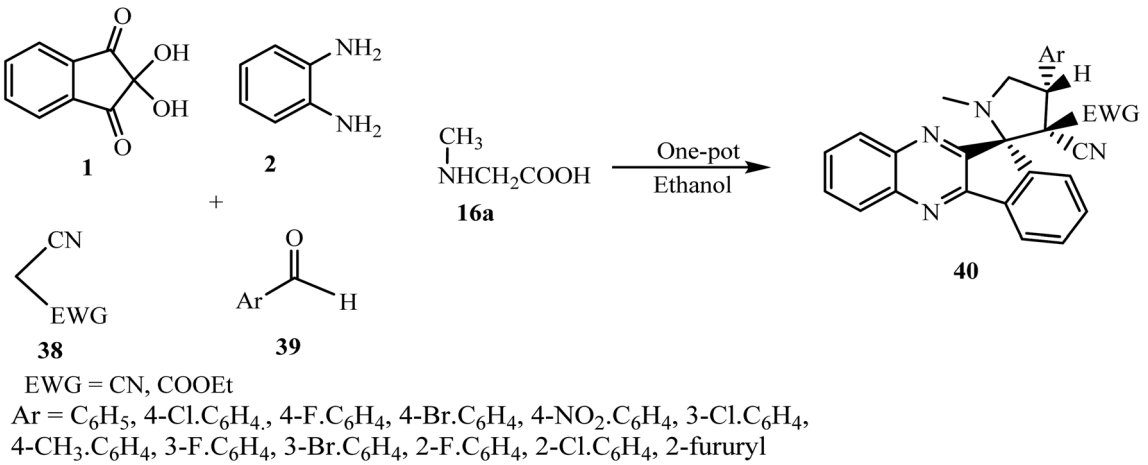
therapeutic index, but sometimes influences the regio- and stereochemistry of compounds.[54] In this connection, Sosnovskikh *et al.*[55] have described the [3 + 2] cycloaddition reaction of (*E*)-3,3,3-trihalogeno-1-nitropropenes **33** with azomethine ylides type I and II to synthesize a number of trihalomethylated spiroindenoquinoxaline-pyrrolidines **34** and spiroindenoquinoxaline-pyrrolizidines **35** regio- and diastereoselectively in isopropanol solvent. Azomethine ylides derived from indenoquinoxalinones **3** and sarcosine **16a** react with 3,3,3-trichloro-1-nitropropene **33** giving only the *endo* regioisomer **34** with the NO_2 group at C-3′ and the CX_3 group at C-4′ exclusively according to a general mechanism and interaction occurs between the more electrophilic alkene atom and the more nucleophilic and accessible terminal ylide atom. The alternative *exo* regioisomer does not form due to the steric repulsion of the bulky CCl_3 group with the π-system of the quinoxaline ring. However, in the case of 3,3,3-trifluoro-1-nitropropene **33**, a small quantity of *exo* isomer **34′** was detected with major *endo* isomer **34**. Hence, the selectivity of CCl_3-alkene is better than CF_3-alkene, and CBr_3-alkene is found not to be suitable due to the formation of unidentifiable mixture of products.

Similarly, dipolarophile nitroalkenes **33** having CF_3 and CCl_3 groups react with azomethine ylides type II generated from indenoquinoxalinones (Y = CH, N) and L-proline **16d** to produce *endo*-adducts spiroindenoquinoxaline-pyrrolizidines **35** with similar regio- and diastereoselectivity as observed in product **34.** However, in the case of the ylide derived from indenoquinoxalinone **3** (X = CH), the appearance of a small amount of regioisomers **35′** (4–6% according to the ^{1}H NMR data) was observed in the crude product. Regio- and stereochemistry of spiropyrrolidines **34** and spiropyrrolizidines **35** were clearly confirmed by single-crystal X-ray analysis of the representative compounds (Scheme 24).

Recently, Arumugam and co-workers[56] constructed a novel series of structurally interesting spiropyrrolidine grafted quinoxaline heterocyclic hybrids **36** in ionic liquid using β-nitrostyrenes **30** as dipolarophiles, and a new 1,3-dipole component azomethine ylide, generated *in situ* from indenoquinoxalinone **3** and L-phenylalanine **16b** in good yield (Scheme 25).



Scheme 26 Synthesis of spiroindenoquinoxaline-pyrrolidine hybrids **37** using L-tryptophan **16c**.

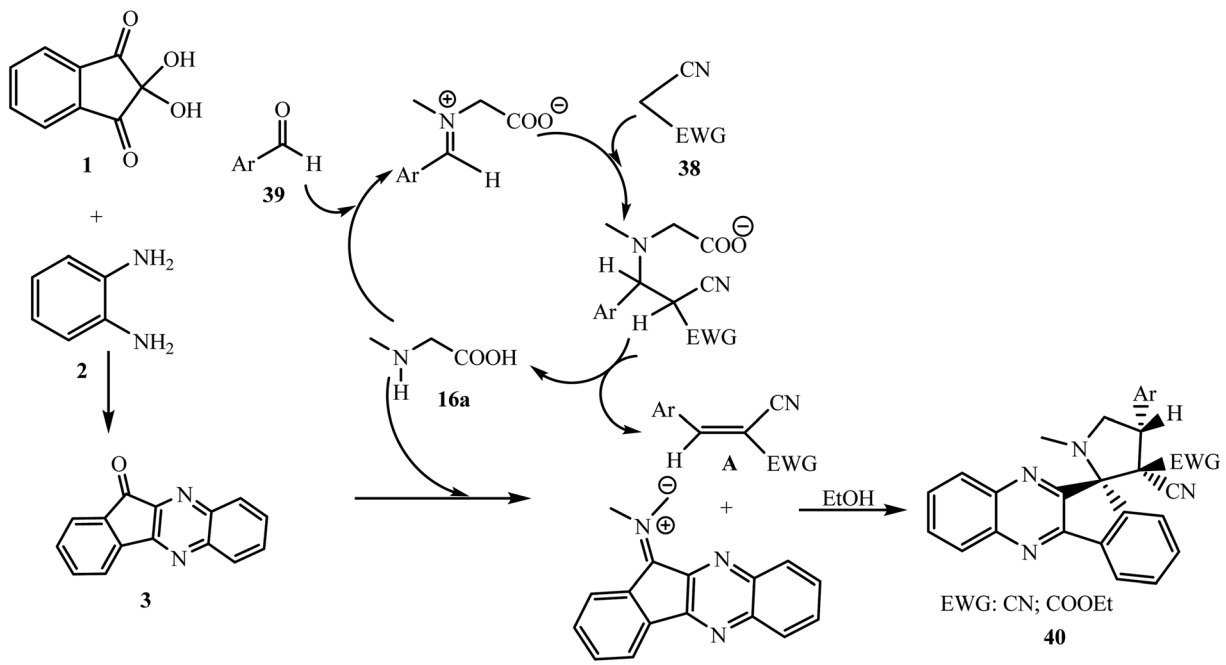


Scheme 27 Five-component synthesis of nitrile-substituted spiro indenoquinoxaline-pyrrolidine derivatives **40**.

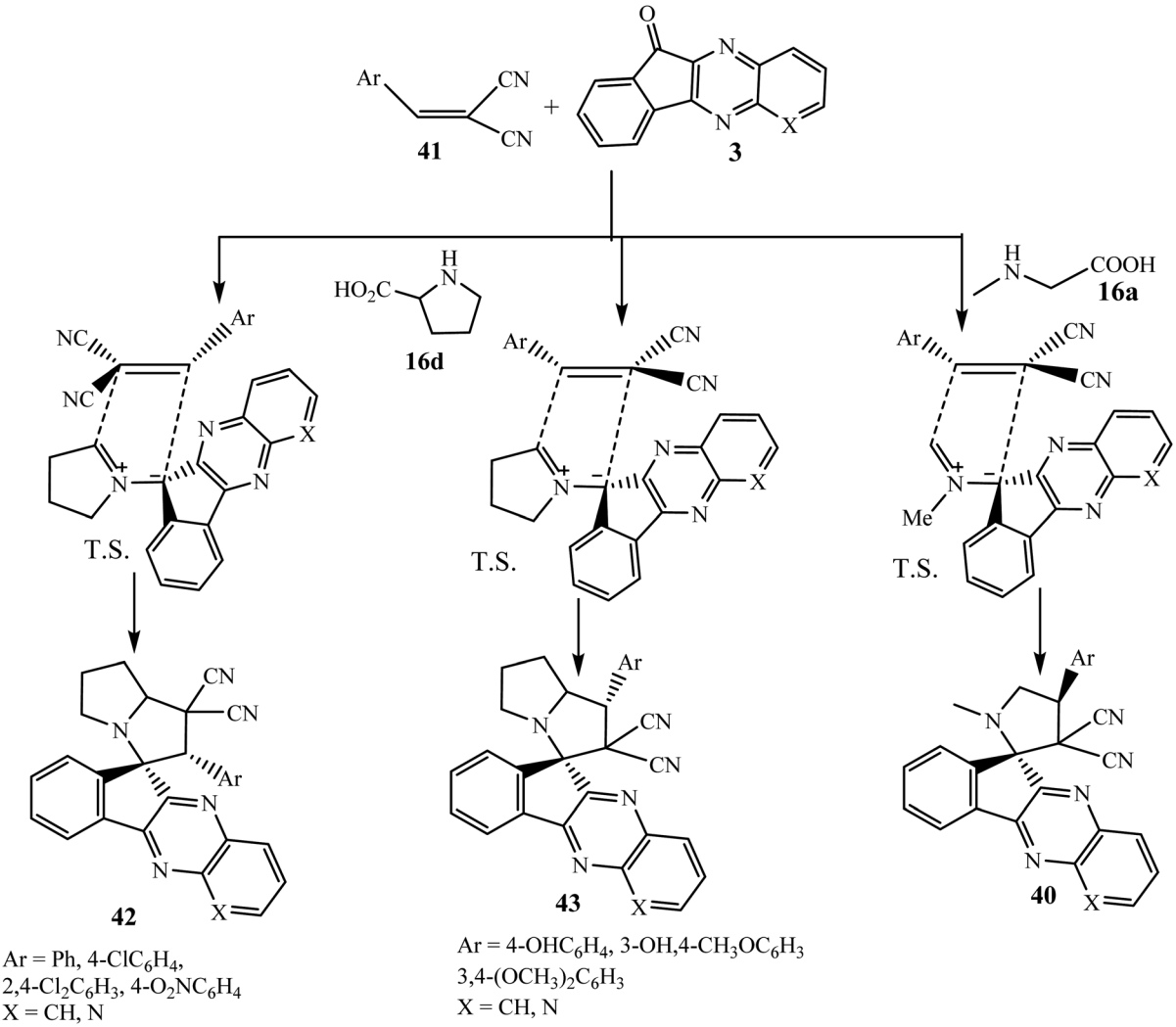
The observed regio- and diastereoselectivity of synthesized spiro hybrid **36** is comparable to that of spiro compound **31** (Scheme 22), where the more substituted electron-rich carbon of the azomethine ylide exclusively attacks the most electrophilic center of dipolarophile **30** leading to the formation of only single regioisomer **36** to minimize the repulsion and stabilize the transition state.

The reaction provided three new bonds and four contiguous stereocenters with full diastereomeric control. The synthesized spiro heterocyclic hybrids **36** have been evaluated for their *in vitro* anti-bacterial activity against *Mycobacterium tuberculosis* H37Rv by microplate alamar blue assay (MABA). *In vitro* activity of these spiro heterocyclic hybrids revealed that the compounds with *m*-nitro, *p*-bromo and *o*-chloro substituents on the aryl ring displayed potent activity against Mtb and exhibited MIC values, but a nitro group on the phenyl ring was found to give the most active candidate among the other analogues of the series and leads to an activity similar to that of the standard drug ethambutol.

Recently, Arumugam *et al.*[57] successfully synthesized novel spiro[indeno[1,2-*b*]quinoxaline-pyrrolidine] hybrids **37** regio- and stereoselectively, comprising spiropyrrolidine, indenoquinoxaline and indole structural units, in excellent yields. In this 1,3-dipolar cycloaddition reaction, a new class of azomethine ylide is generated *in situ* from indenoquinoxalinone **3** and L-tryptophan **16c** and reacts with various substituted β-nitrostyrenes **30** affording the spiro heterocyclic hybrids **37** with similar regio- and stereoselectivity as observed in the case of



Scheme 28 Plausible mechanism of the synthesis of spiro-pyrrolidines **40** *via* a five-component reaction.



Scheme 29 Synthesis of spiro[indeno[1,2-*b*]quinoxaline-11,3′-pyrrolizine]-dicarbonitriles **42**.

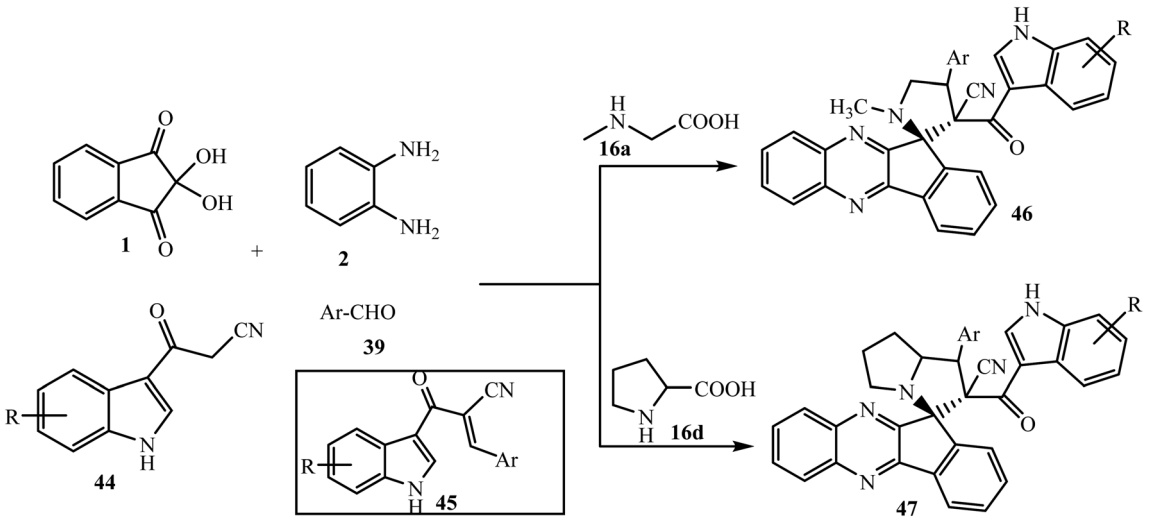
spiro adduct **36** (Scheme 26). The ring system thus creates two C–C and three C–N bonds and four adjacent stereogenic carbons, one of which is quaternary, and the reaction proceeds with full diastereomeric control. All of the synthesized compounds were evaluated for their *in vitro* activity against *Mycobacterium tuberculosis* H37Rv using MABA. Interestingly, the compound bearing a 2-fluoro substituent on the aryl ring displayed an equipotent activity (MIC of 1.56 mg mL^{-1}) to that of ethambutol against *Mycobacterium tuberculosis* H37Rv.

5.2.1.4. Using nitrile-substituted Knoevenagel adducts as a dipolarophile. Li *et al.* in 2011[58] successfully accomplished the synthesis of new spiro indenoquinoxaline-pyrrolidine derivatives **40** *via* the five-component tandem reaction of ninhydrin **1**, 1,2-phenylenediamine **2**, sarcosine **16a**, malononitrile or cyanoacetic ester **38** and aldehydes **39** in a one-pot operation for the first time. This was a great achievement in a Huisgen reaction, in which the dipole azomethine ylide and dipolarophile were both evaluated *in situ* and converted into spiro cycloadduct **40** with high regio- and diastereoselectivity. The optimized reaction conditions for this cycloaddition reaction were using ethanol as a solvent and a temperature of 100 °C to obtain a maximum yield of the product (Scheme 27).

Mechanistically, in this reaction sarcosine pays a dual role as a catalyst as well as a substrate. The dipolarophile Knoevenagel adducts **A** are formed by the Knoevenagel condensation of malononitrile or cyanoacetic ester **38** and aldehydes **39** in the presence of sarcosine **16a**, showing catalytic behavior (Scheme 28). The Knoevenagel adducts **A** then react with azomethine ylide formed by indenoquinoxalinone **3** and **16a** regioselectively, as well as diastereoselectively, leading to the formation of only single product **40** without any trace of other possible regio- and diastereoisomers.

The addition of dipolarophile Knoevenagel adducts **A** to azomethine ylide proceeds in the usual way where the less substituted end of the ylide and β-carbon of alkene-nitrile (Knoevenagel adducts) **A** interact with each other in an *exo* manner and the aryl ring of alkene-nitrile **A** and indenoquinoxaline rings are present in a *trans* orientation.

Later on, this reaction was studied by Velikorodov *et al.*[59] to synthesize highly functionalized spiro[indeno[1,2-*b*]

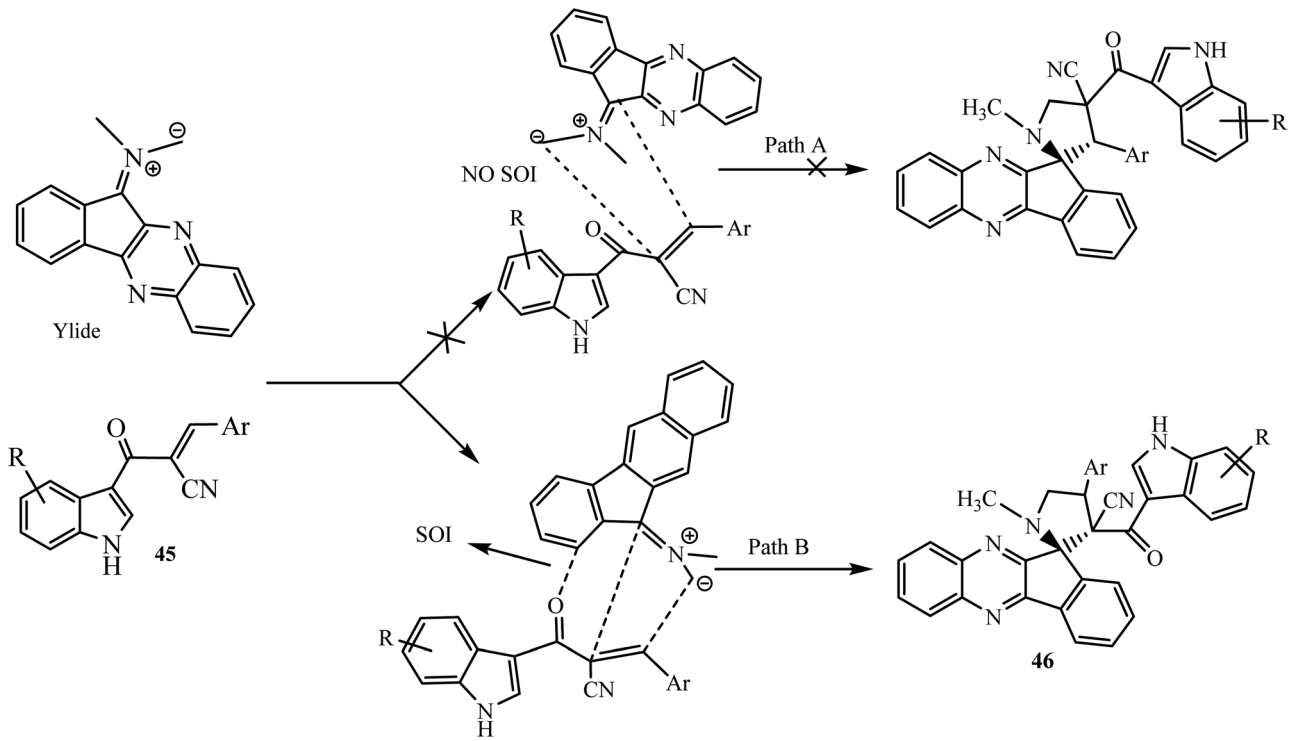


Scheme 30 Five-component synthesis of indole-substituted spiroindenoquinoxaline-pyrrolidines/pyrrolizidines **46**/**47**.

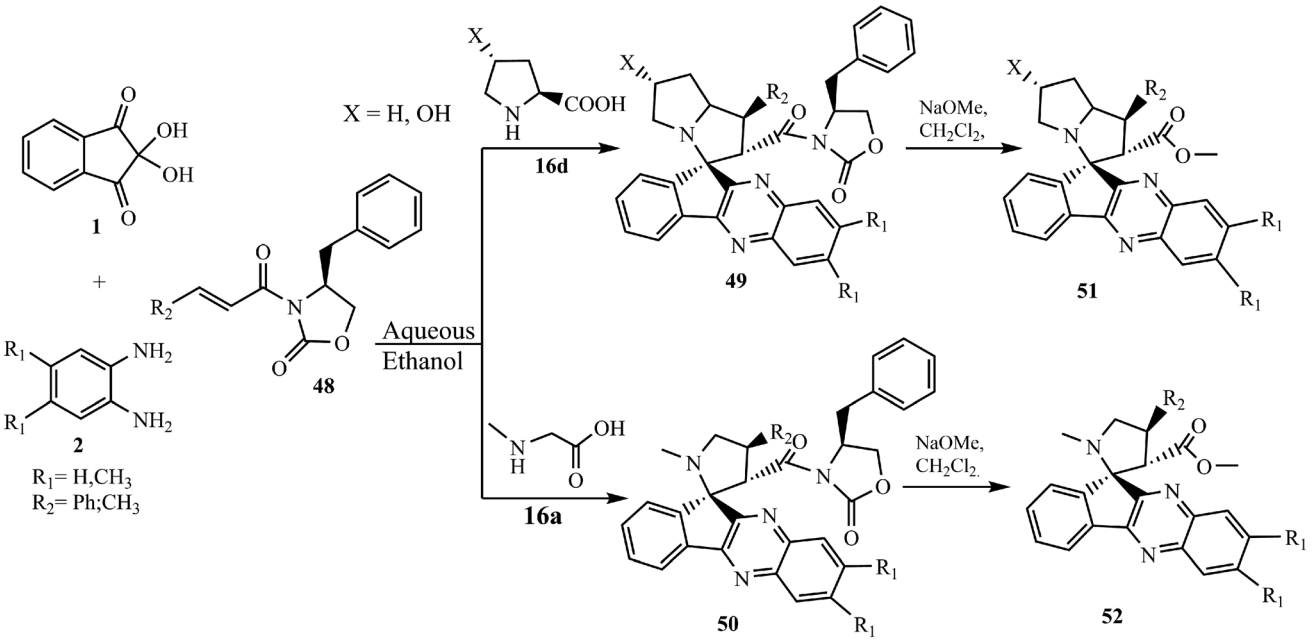
quinoxaline-11,2′-pyrrolidine] derivative **40** *via* the five-component condensation of ninhydrin **1**, *o*-phenylenediamine **2**, sarcosine **16a**, malononitrile/ethylcyanoacetate **38** and 4-formylphenyl *N*-phenylcarbamate in refluxing EtOH conditions with [bmin]Br.

After that, Korotaev *et al.*[60] investigated the 1,3-dipolar cycloaddition of azomethine ylides generated *in situ* from L-proline **16d** and indenoquinoxalinones **3** with previously synthesized dipolarophile arylidene malononitriles **41** using isopropanol as a solvent, to generate new hybrid spiro[indeno[1,2-*b*]quinoxaline-11,3′-pyrrolizine]-1,1′(2′*H*)-dicarbonitriles **42**/**43** (Scheme 29).

The regioselectivity of the process is very interesting and depends upon the nature of substituents present on the



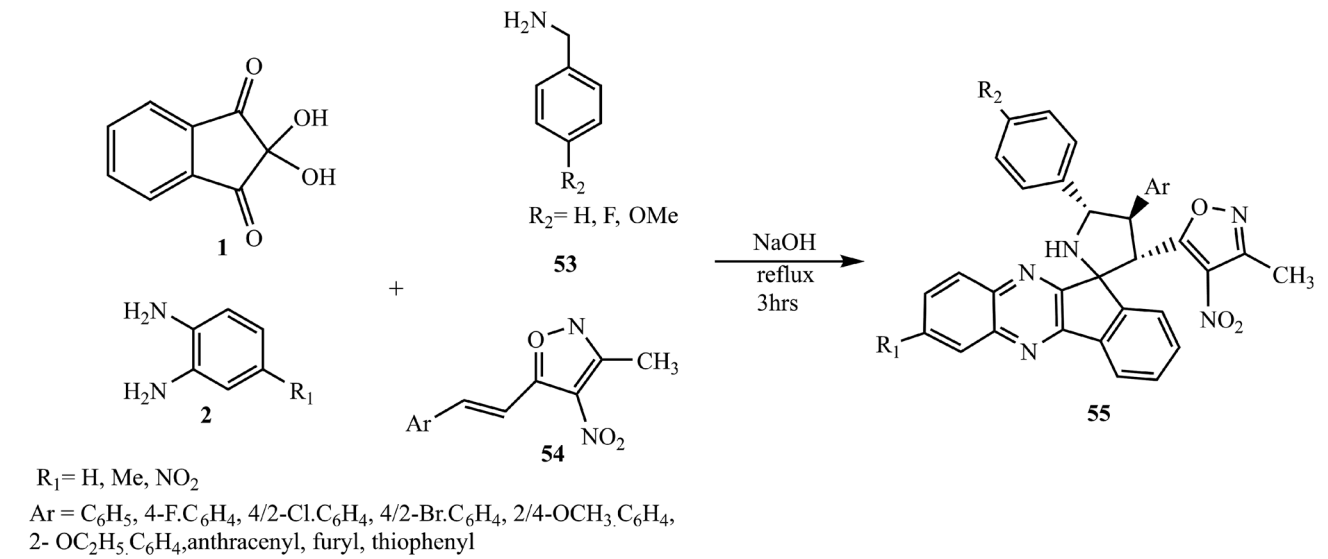
Scheme 31 Proposed mechanisms for the selective synthesis of spiroindenoquinoxaline-pyrrolidines **46**.



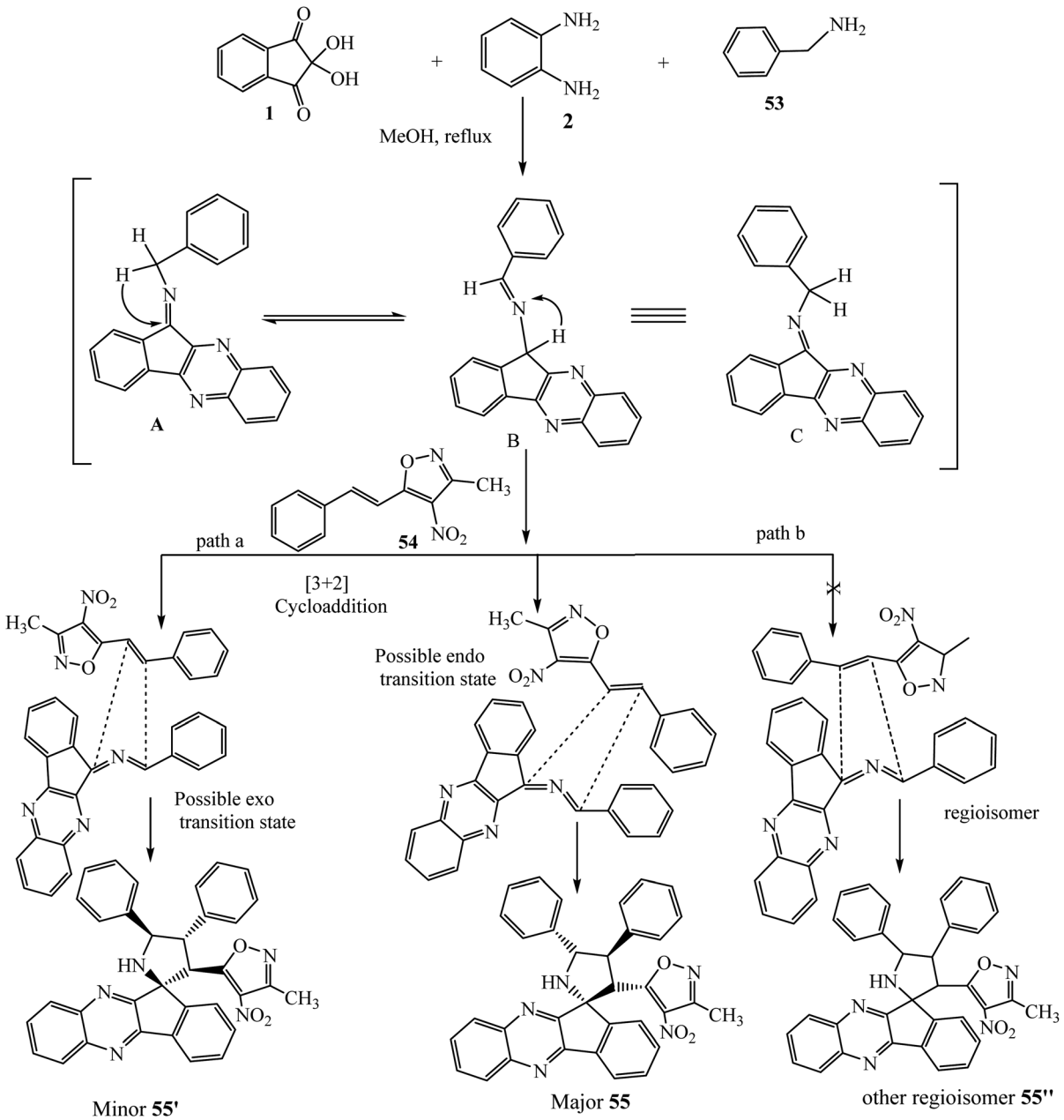
Scheme 32 Synthesis of oxazolidine-containing spiroindenoquinoxalines 49/50.

aromatic ring of dipolarophile molecule **41**. The three-component reaction of dinitriles **41** with an unsubstituted benzene ring or electron-withdrawing substituents (Cl, NO_2), L-proline **16d** and quinoxalinones **3** (X = CH, N) produced spiropyrrolizidines **42** (56–86% yields) with unexpected regioselectivity. Here, the electrophilic β-C atom of dipolarophile **41** attacks at the more substituted terminus of the ylide, an unusual direction that was previously observed only in β-nitrostyrenes **30**. However, when the benzene ring of dinitriles **41** is substituted with one or two electron-donating substituents (OH, OCH_3), the standard direction was observed where the interaction of the less substituted terminal atom of the ylide and the β-C atom of the alkene was observed to produce regioisomer **43** in 60–88% yields. However, in a few cases different results were obtained.

To further elaborate, the present three-component reaction has also been studied with azomethine ylide derived from indenoquinoxalinone **3** and sarcosine **16a**. This reaction was found to fail with dinitriles **41** substituted with electron-donating groups and only succeeded with dinitriles **41** containing electron-withdrawing substituents to produce spiroindenoquinoxaline-pyrrolidines **40** through interaction of the electrophilic site (the β-C atom) with the less substituted terminus of the dipole to produce regioisomer **40** exclusively



Scheme 33 Synthesis of isoxazole ring-substituted spiroindenoquinoxalines 55.



Scheme 34 Plausible mechanism for the *in situ* generation of imines and their conversion to spiroindenoquinoxalines **55** and other possible isomers.

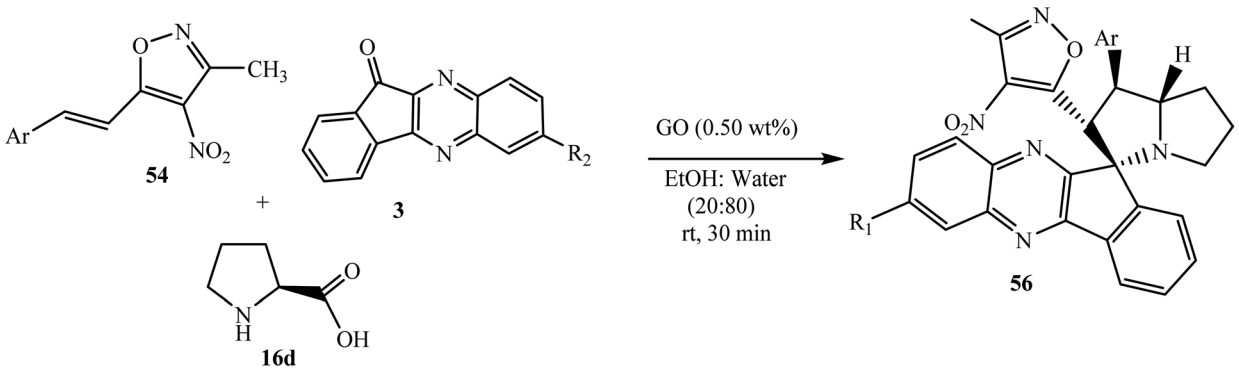
with a *trans* configuration of the bulkiest substituents, as observed by Li *et al.*[58] (Scheme 29).

Novel indole-appended spiroindenoquinoxaline-pyrrolidines/pyrrolizidines **46**/**47** were derived by Zhu *et al.*[61] through the five-component reaction of ninhydrin **1**, *o*-phenylenediamine **2**, amino acids **16a**/**16d**, 3-cyanoacetyl indoles **44** and aryl aldehydes **39** in EtOH. The Knoevenagel product **45** generated from 3-cyanoacetyl indoles **44** and aryl aldehydes **39** acts as a dipolarophile (Scheme 30). Notably, the utilization of primary amino acids such as glycine or phenylalanine in this reaction did not afford the target product.

A reasonable mechanism of the reaction is shown in Scheme 31. The formation of the regio- and diastereoisomer **46** *via* path B is more favorable due to the presence of a secondary orbital interaction (SOI) that takes place between the carbonyl group of dipolarophile **45** and the azomethine ylide.

This type of SOI is not possible in path A. Hence, the reaction proceeds *via* path B to lead to the exclusive formation of regio- and diastereoselective spiropyrrolidines as products. The selective formation of spiropyrrolidines **46** and spiropyrrolizidines **47** in this reaction is also confirmed by single-crystal X-ray studies of representative compounds.

5.2.1.5. Using heterocyclic ring-containing dipolarophiles. Jadidi *et al.*[62] described an efficient, four-component process for the construction of novel oxazolidinone-containing spiroindenoquinoxaline-pyrrolidines **49** and



54 + 3 + 16d → 56

R_2 = H, Me, NO_2

Ar = C_6H_5, 4-F. C_6H_4, 4-Cl.C_6H_4, 4-Br.C_6H_4, 4-NO_2.C_6H_4, 2-Cl.C_6H_4, 2-Br.C_6H_4, 3-NO_2.C_6H_4, 4-CH_3.C_6H_4, 4-OCH_3.C_6H_4, 2-OC_2H_5.C_6H_4, furyl.

Scheme 35 Graphene oxide-catalyzed synthesis of isoxazole-substituted spiroindenoquinoxaline-pyrrolizidines **56**.

spiroindenoquinoxaline-pyrrolizidines **50** with high regio-, diastereo- (up to 96 dr), and enantioselectivity (up to 99% ee), using optically active cinnamoyl-crotonoyl oxazolidinone **48** as dipolarophile. Revealing the mechanism was based on the assignment of the absolute configuration of the cycloadducts and using quantum mechanical calculations. The regio- and stereoselectivity of spiroindenoquinoxaline-pyrrolidines **49** and spiroindenoquinoxaline-pyrrolizidines **50** was explained in terms of transition state stabilities and global and local reactivity indices of the substrates. The chiral auxiliary was removed easily from spiro compounds **49** and **50** in the presence of sodium methoxide in CH_2Cl_2 to afford the corresponding carboxylate derivatives **51** and **52**, respectively (Scheme 32).

Recently, Chowhan *et al.*[63] expanded the scope of the reaction and introduced a new dipole moiety using benzylamines **53** in place of α-amino acids and described an expedient synthesis of novel polyheterocyclic spiropyrrolidinylquinoxaline derivative **55** *via* the four-component [3 + 2] cycloaddition reaction of dipolarophile 3-methyl-4-nitro-5-alkenylisoxazoles **54**, ninhydrin **1**, *o*-phenylenediamine **2** and benzylamines **53** under convenient reaction conditions (Scheme 33). The striking feature of this work is the variability in the yield and diastereoselectivity of products **55**, depending upon the nature and position of substitutions present on all partners of this reaction. In the case of 4-methyl-substituted *o*-phenylenediamine **2**, an excellent yield of products was obtained, while no reaction occurred using 4-nitro-substituted *o*-phenylenediamine **2**. The reactivity of halosubstituted styrenes (3-methyl-4-nitro-5-alkenylisoxazoles) **54** was found to be better than that of simple and alkoxy-substituted styrenes. Naphthalene-substituted dipolarophile afforded excellent yields, and in the case of heteroaromatic styrenes poor yield of product was obtained.

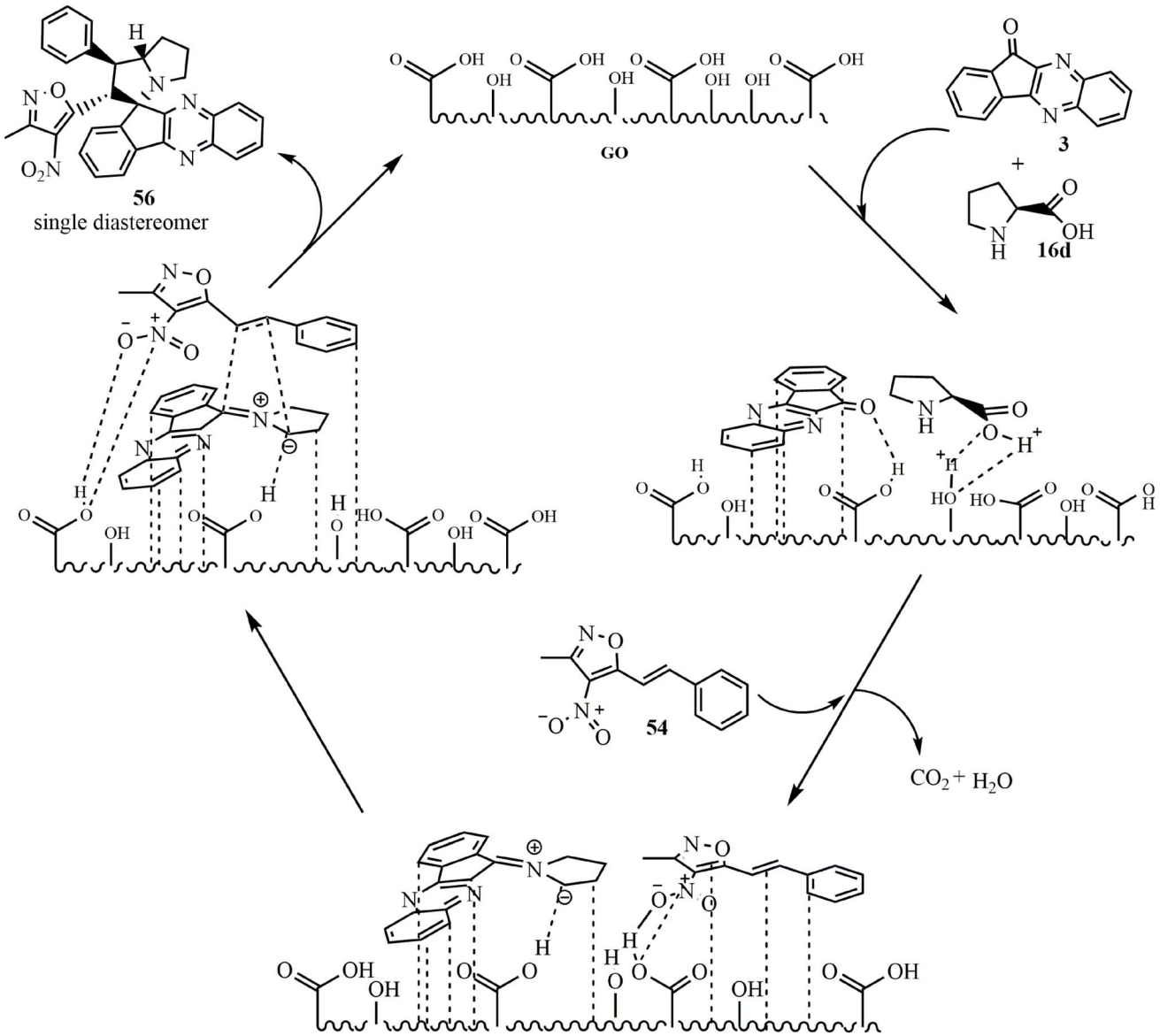
During the reaction, indeno[1,2-*b*]quinoxalinone **3** reacts with benzylamines **53** to form a dynamic isomeric intermediate ketimine (**A**) and aldimine (**B**) after 1,3-hydride shift and its equilibrium structure (**C**). This intermediate (**C**) acts like azomethine ylides generated by α-amino acids and undergoes [3 + 2] cycloaddition with dipolarophile 3-methyl-4-nitro-5-alkenylisoxazoles **54** through two plausible paths (path a and path b). The formation of major *endo* isomer **55** over *exo* isomer **55′** is due to less steric hindrance and proximity of the **54** core with the dipolar region. However, in path b, the formation of possible regioisomer **55″** was not detected (Scheme 34).

Reddy and Chowhan for the first time[64] established a graphene oxide (GO)-catalyzed 1,3-dipolar cycloaddition reaction to achieve polyheterocyclic spiroindenoquinoxaline-pyrrolizidines **56** in good to excellent yields along with excellent regio- and diastereoselectivity. An ultra-low catalyst loading of 0.50 wt% was found to be efficient to catalyze the reaction in aqueous ethanolic solution. In this work, 3-methyl-4-nitro-5-alkenylisoxazoles **54** were used as a dipolarophile and azomethine ylides were derived from indenoquinoxalinone **3** and L-proline **16d** (Scheme 35).

GO has an acidic nature and catalyzed imine formation and decarboxylation to generate the corresponding azomethine ylide. The reactants are localized onto the surface of the catalyst due π-stacking and hydrogen bonding capability of GO and dipolarophile and ylide exclusively react only on one side to yield single diastereomer **56** as the product. The regioselectivity can be reasonably assumed to be due to possible additional interactions that arise between heteroatoms in the isoxazole motif (Scheme 36).

Recently, Khurana *et al.*[65] extended this reaction and synthesized spiroindeno[1,2-*b*]quinoxaline-11,3′-pyrrolizines **56**/thia-pyrrolizines **57** *via* the four-component domino reaction of reactants **1**, **2**, dipolarophile **54** and L-proline **16d**/L-thioproline **16e** with regio- and diastereoselectively (Scheme 37).

Azizian *et al.*[66] studied the diastereoselective synthesis of novel spiropyrrolo fused pyrrolizidines **59** *via* a four-component 1,3-dipolar cycloaddition of azomethine ylide generated *in situ* from L-proline **16d** and indenoquinoxalone **3** with dipolarophile *N*-arylmaleimides **58**. The reaction was carried out under microwave irradiation using DMSO as a solvent to afford the corresponding spiroindenoquinoxaline-pyrrolizidines **59** with high diastereomeric excess (Scheme 38).



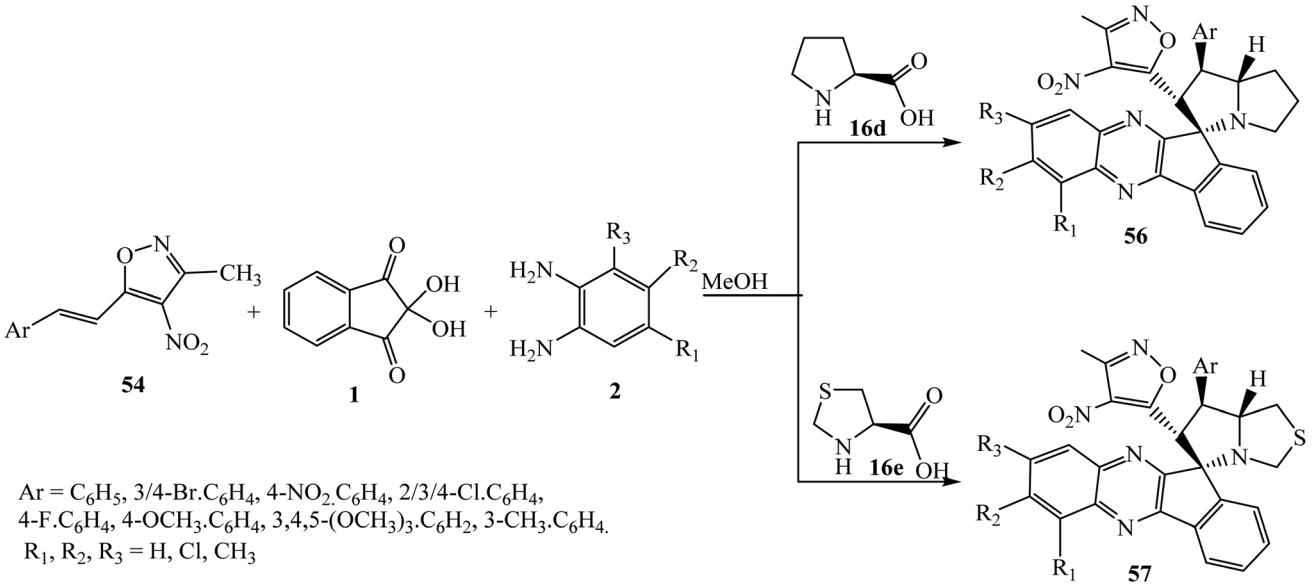
Scheme 36 Plausible mechanism for GO catalysed spiro pyrrolizidines **56**.

Nayak *et al.*[67] reported the efficient and selective one-pot synthesis of highly substituted novel functionalized indenoquinoxalinone grafted spiropyrrolizine/spiropyrrolidine connected chromene-3-carbonitrile conjugates **61** and **62** *via* the 1,3-dipolar cycloaddition reaction of indenoquinoxalone **3**, L-proline **16d**/benzylamine **53** and dipolarophile chromene-3-carbonitrile **60** in ethanol under microwave irradiation and conventional conditions (Scheme 39).

To test the generality of the reaction, a number of chromene-3-carbonitrile derivatives **60** with substituents such as methoxy, ethoxy, naphthyl, and halogen groups at different positions were used. In all cases, the reaction proceeded smoothly and only single diasteroisomers of spiroindenoquinoxaline-pyrrolizines **61**/pyrrolidines **62** were obtained in good to excellent yields. Yields of products were variable with respect to the substituent and their positions on the aromatic ring of the 3-cyano-chromene **60**. The reaction failed to occur with pipecolic acid **16f** and L-phenylalanine **16b**.

The dipolarophile chromene-3-carbonitriles **60** have been synthesized *via* the treatment of acrylonitrile with salicylaldehydes in the presence of DABCO under solvent-free conditions *via* an oxa-Michael–aldol reaction. The more substituted electron-rich side of the azomethine ylide reacts with the β-carbon of the dipolarophile at the *endo* side leading to the formation of highly functionalized regio- and diastereoselective molecular hybrids.

Recently, Nayak *et al.*[68] have extended this work and reported the synthesis of spiroindenoquinoxaline-pyrrolizidines **64** and spiroindenoquinoxaline-pyrrolidines **65** *via* the 1,3-dipolar cycloaddition reaction of aryl-substituted 3-nitrochromens **63** as dipolarophile and L-proline **16d** and L-phenylalanine **16b** as α-amino acids to generate the corresponding azomethine ylide



Scheme 37 Synthesis of isoxazole-substituted spiroindenoquinoxaline-pyrrolizidines **56**/thia-pyrrolizidines **57**.

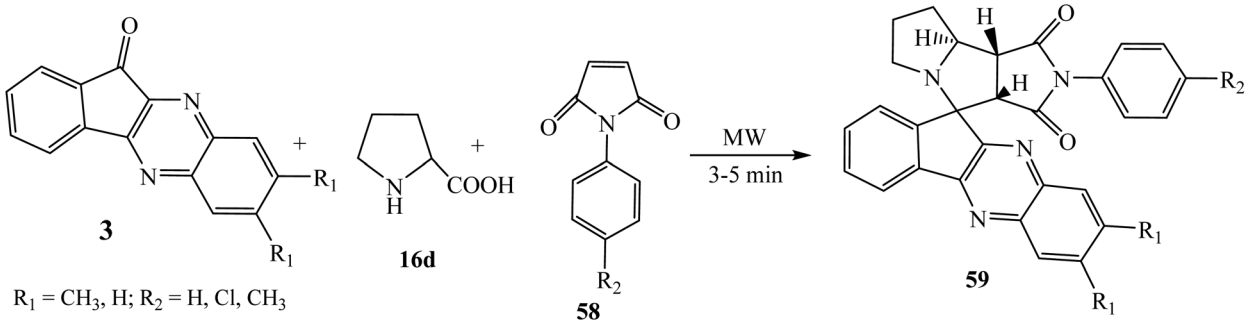
with indenoquinoxalinone **3** under microwave heating (Scheme 40).

Nowadays, synthetic chemists are engaged in the synthesis of novel bioactive molecules for cancer treatment with low side effects. In this direction Rajendran *et al.*[69] described a facile synthesis of new bioactive quinoline ring-containing spiroindenoquinoxaline-pyrrolizine hybrids **67** *via* four-component 1,3-dipolar cycloaddition reaction of ninhydrin **1**, 1,2-phenylenediamine **2**, L-proline **16d** and quinolone-bearing chalcones **66**. Parallel to this work, Rajendran *et al.*[70] also synthesized spiroindenoquinoxaline-pyrrolothiazoles **68** through the 1,3-dipolar cycloaddition reaction of azomethine ylides generated *in situ* from indenoquinoxalinone **3** and thiazolidin-2-carboxylic acid **16e** and quinolone-bearing dipolarophiles **66** (Scheme 41).

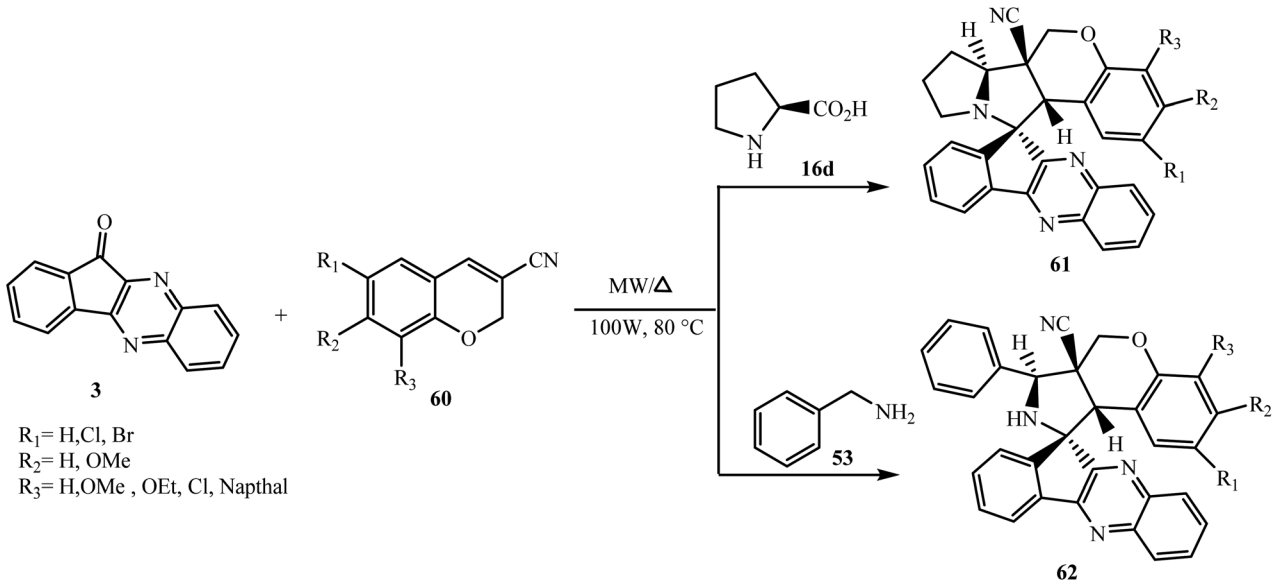
The formation of both spiro compounds **67** and **68** proceeds *via* the initial generation of the corresponding azomethine ylides followed by the interaction with dipolarophiles **66** leading to the formation of single final products regio- and diastereoselectively. In the presented study, the authors reported the different regioselectivity of both spiro compounds **67** and **68** due to the different modes of interaction of azomethine ylides with dipolarophile **66.** During the formation of spiro compound **67** the electrophilic β-C atom of dipolarophile quinoline attacks at the more substituted terminus of the ylide generated from L-proline **16d** and indenoquinoxalinone **3** by means of an unusual direction. While, in the case of spiro compound **68** the β-C atom of the dipolarophile interacts with the less substituted terminus of the azomethine ylide generated from thiazolidin-2-carboxylic acid **16e** and indenoquinoxalinone **3** *via* the usual pattern (Scheme 42).

5.2.1.6. Using carbohydrate-based dipolarophile. Carbohydrate-derived heterocycles have attracted special attention in medicinal chemistry due to their promising bioactivities.[71,72] Chromenes are important classes of heterocycles because of their core being incorporated in a large variety of natural products and biologically active compounds.[73,74]

Raghunathan *et al.*[75] have introduced a structurally unique sugar and chromene based dipolarophile hybrid, namely (4-oxo-2-glyco-4*H*-chromene-3-carboxylate) **71**, and accomplished a 3 + 2 cycloaddition reaction with dipoles generated *in situ* by the reaction of indenoquinoxalinone **3** and α-amino acids such as



Scheme 38 Synthesis of novel pyrrolo fused spiroindenoquinoxaline-pyrrolizidines **59**.

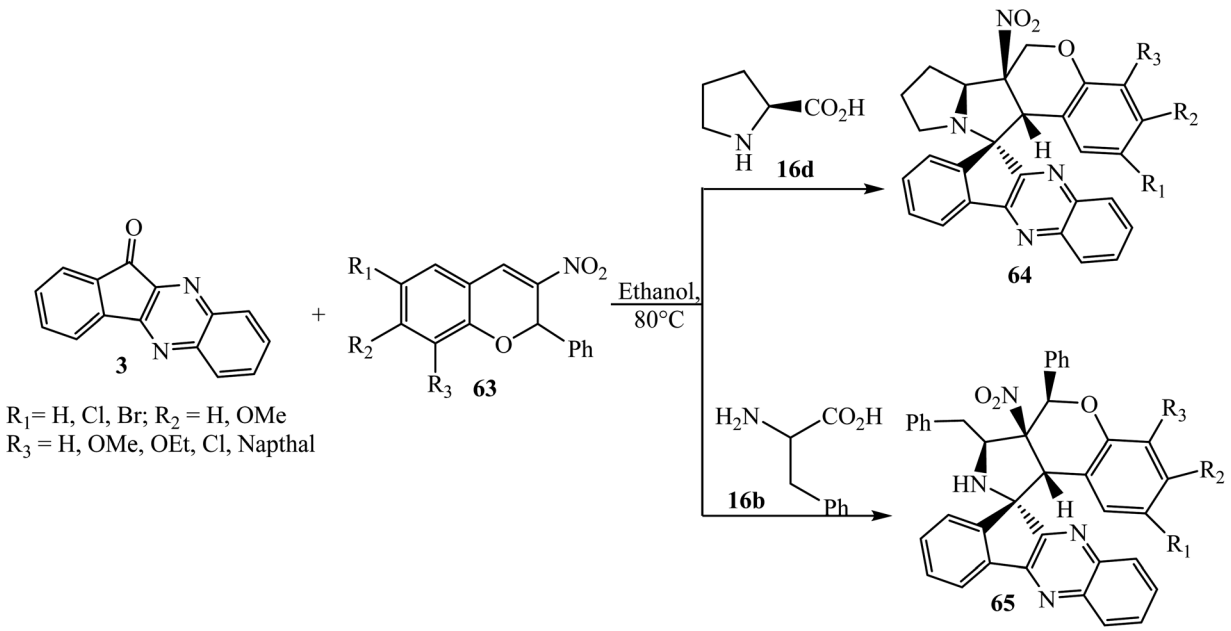


Scheme 39 Synthesis of spiroindenoquinoxaline-pyrrolizidine/pyrrolidine fused chromene-3-carbonitriles **61**/**62**.

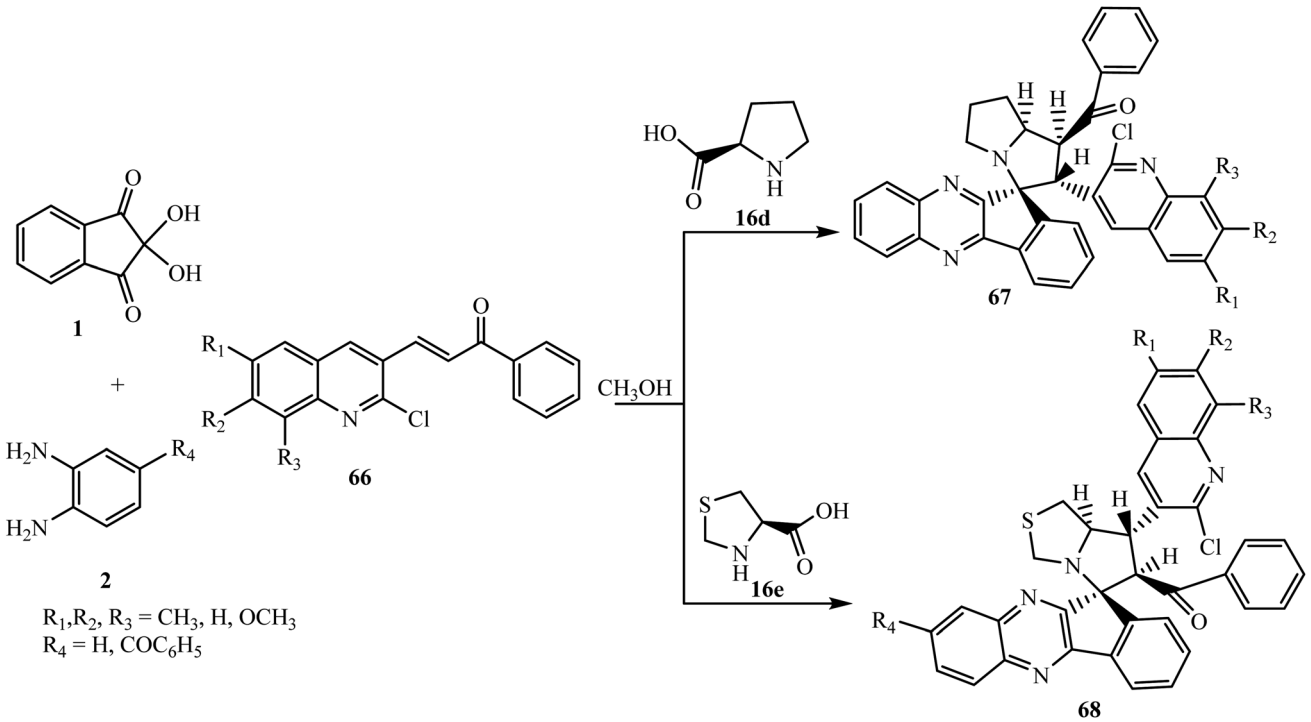
sarcosine **16a**, L-proline **16d**, and pipecolinic acid **16f** in the presence of base NaOMe to produce the corresponding glyco polycyclic spiroindenoquinoxalines **72–74**, respectively. The dipolarophile was synthesized by the reaction of glyco-nitroalkene **69** with 4-hydroxycoumarin **70** in the presence of Et_3N and methanol (Scheme 43).

The important feature of this reaction is that, in the absence of NaOMe, the [3 + 2] cycloaddition does not proceed due to steric hindrance around the double bond of the chromene moiety; but in the presence of base NaOMe, dehydrobenzyloxylation of dipolarophile **71′** occurs and 1,3-dipolar cycloaddition is completed across the sterically less hindered double bond of the diene with regio- and diastereoselectivity.

Raghunathan *et al.*[76] also synthesized the glyco 3-nitrochromane hybrid spiroindenoquinoxaline-pyrrolidines/pyrrolizines **78**/**79** *via* a [3 + 2] cycloaddition reaction using glycol-3-nitrochromenes **77** as dipolarophiles, which were synthesized from glyco-β-nitroalkenes **75** with salicylaldehyde **76** in the presence of DABCO. In this reaction, the dipole attacks from the face opposite to the carbohydrate moiety in glyco-3-nitrochromenes **77** to avoid high steric crowding. This leads to the projection of a NO_2 group and Ha proton towards the β-



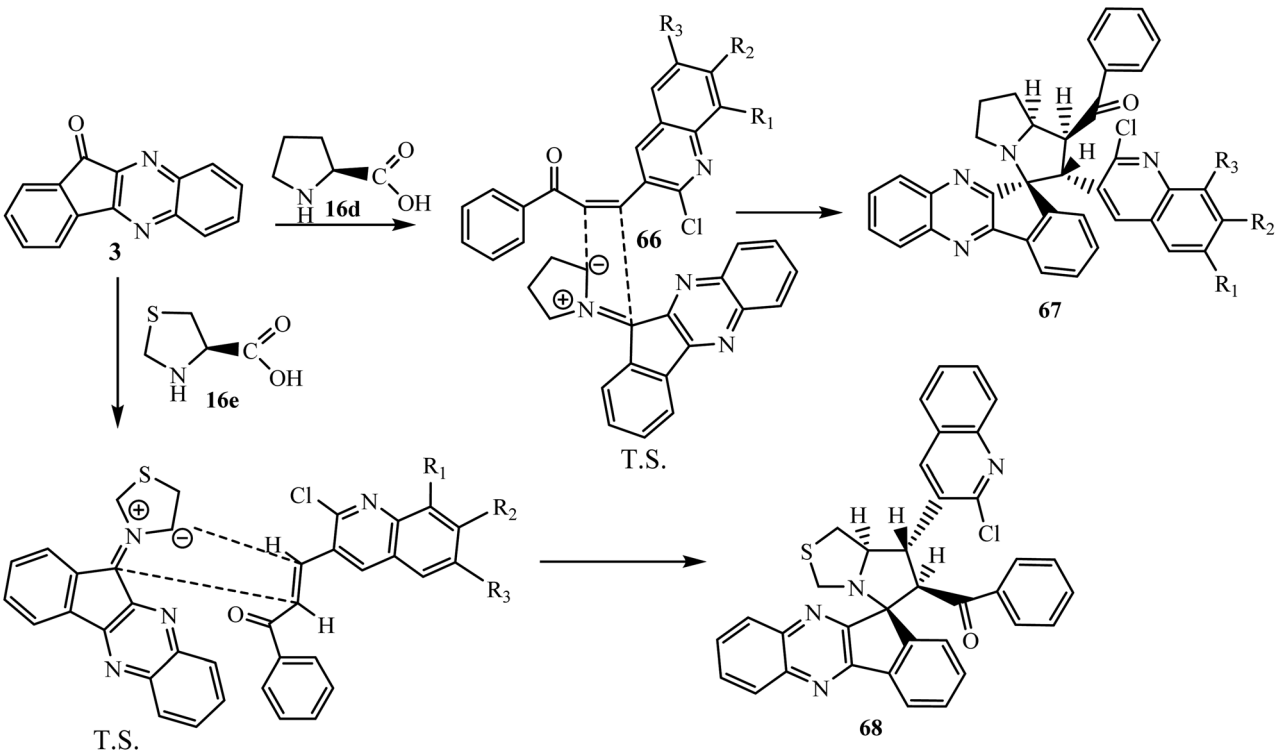
Scheme 40 Synthesis of spiroindenoquinoxaline-pyrrolizidine/pyrrolidine fused 3-nitro-2*H*-chromenes **64**/**65**.



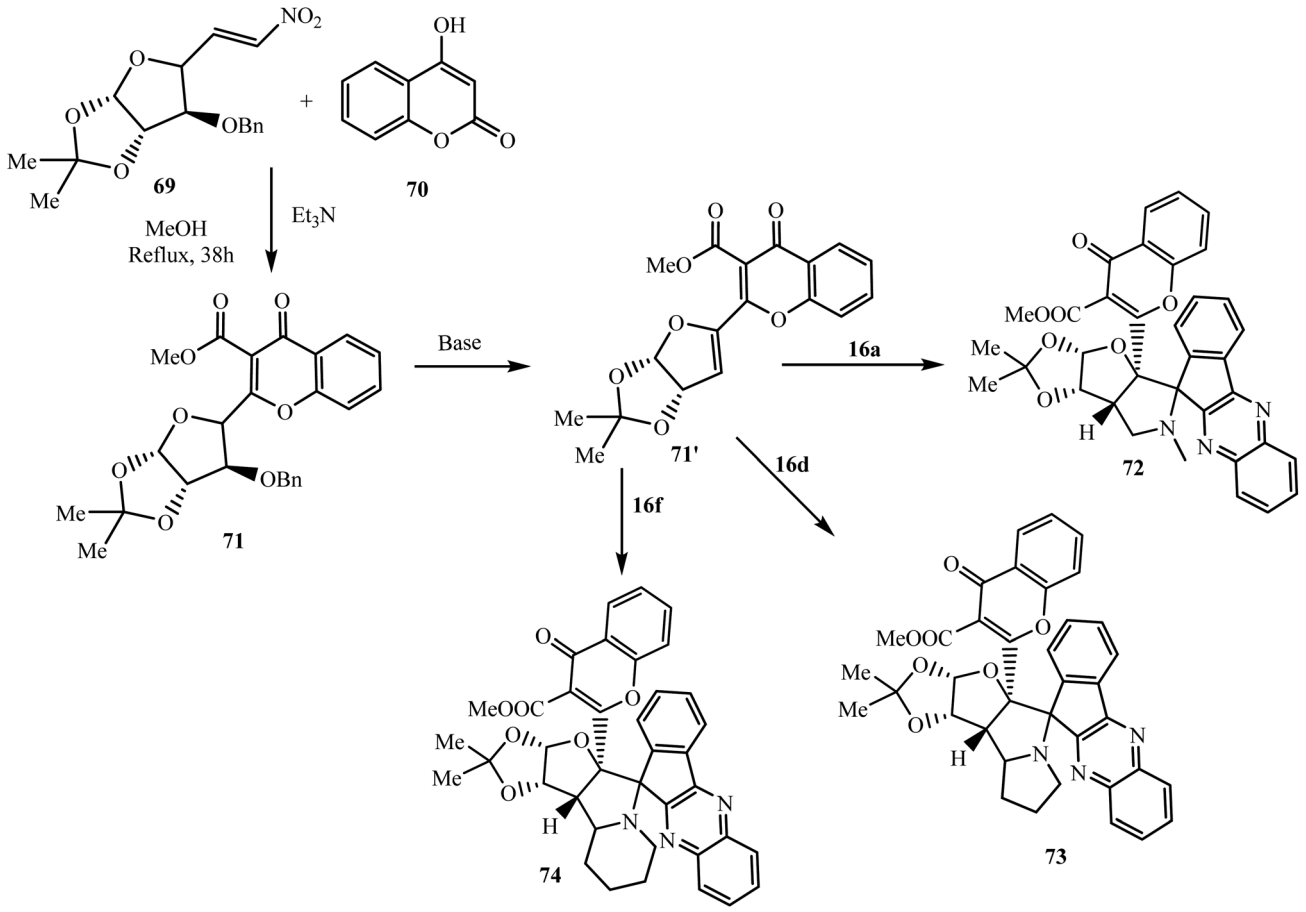
Scheme 41 Synthesis of benzoyl-substituted spiroindenoquinoxaline-pyrrolizines **67**/pyrrolothiazoles **68**.

face. The regio- and stereochemical results of the cycloaddition reaction were confirmed by X-ray crystallographic analysis (Scheme 44).

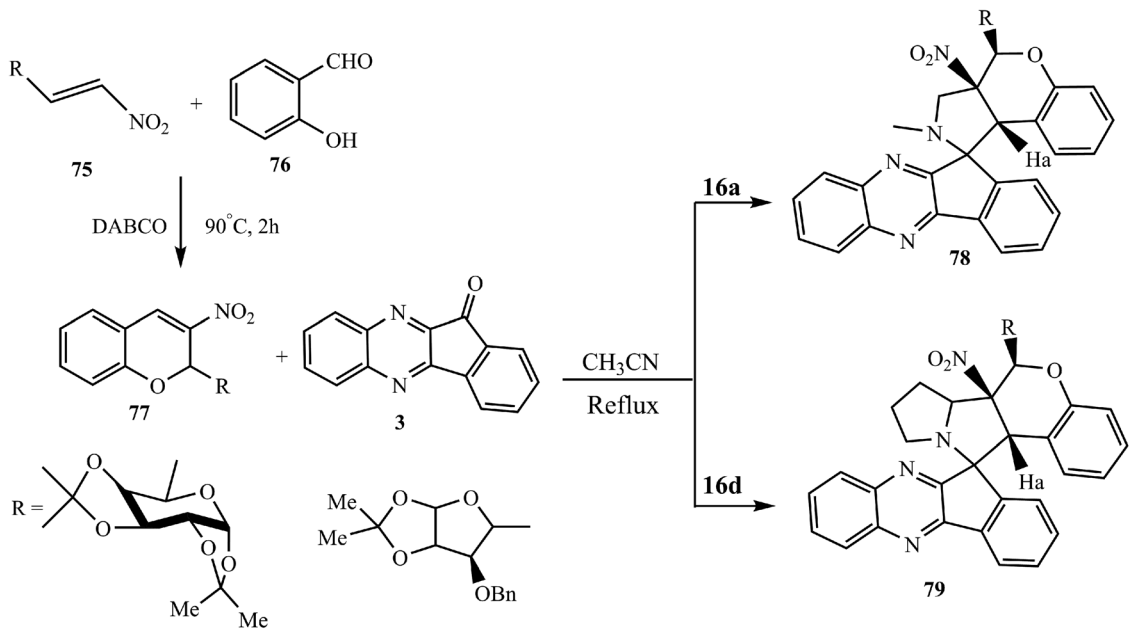
5.2.1.7. Using cyclopropenes as a dipolarophile. Boitsov *et al.*[77] reported the efficient synthesis of complex spiro systems **81–83** by combining 11*H*-indeno[1,2-*b*]quinoxaline and



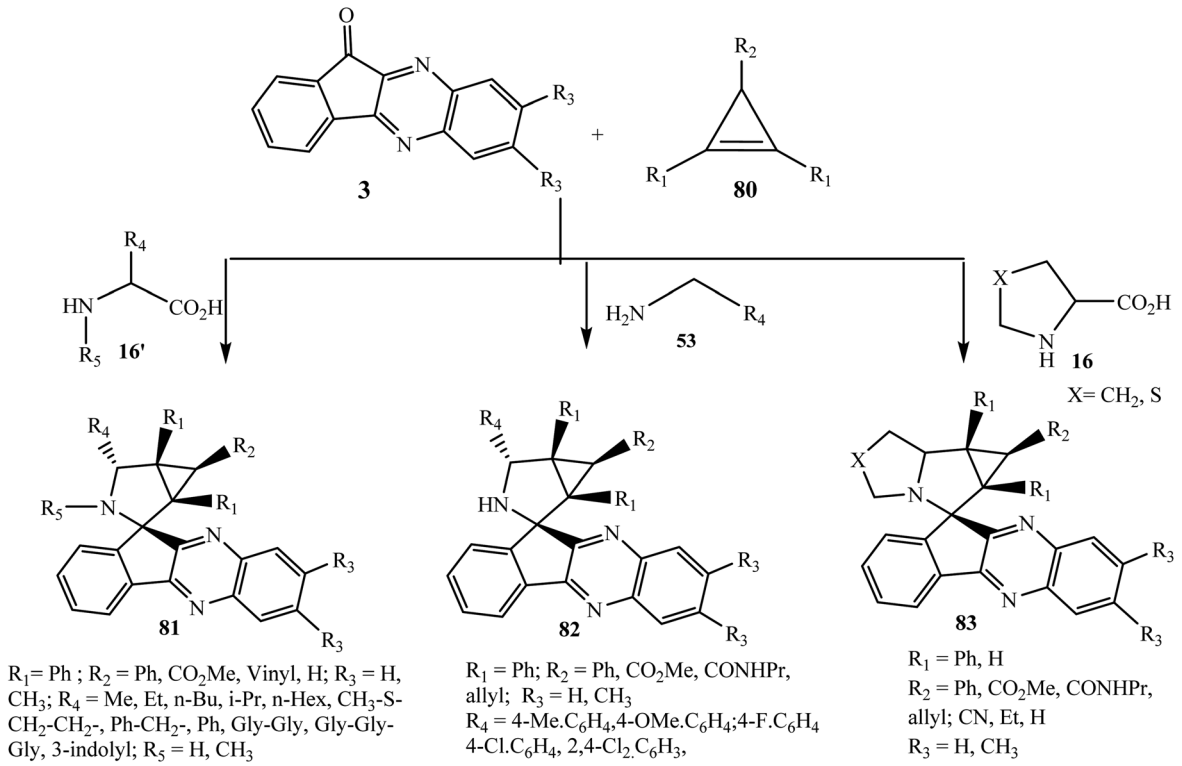
Scheme 42 Mechanism for the synthesis of spiroindenoquinoxalines **67** and **68**.



Scheme 43 Synthesis of glycol fused spiroindenoquinoxalines 72–74.



Scheme 44 Synthesis of glyco-3-nitrochromane hybrid pyrrolidinyl spiro indenoquinoxalines 78 and 79.



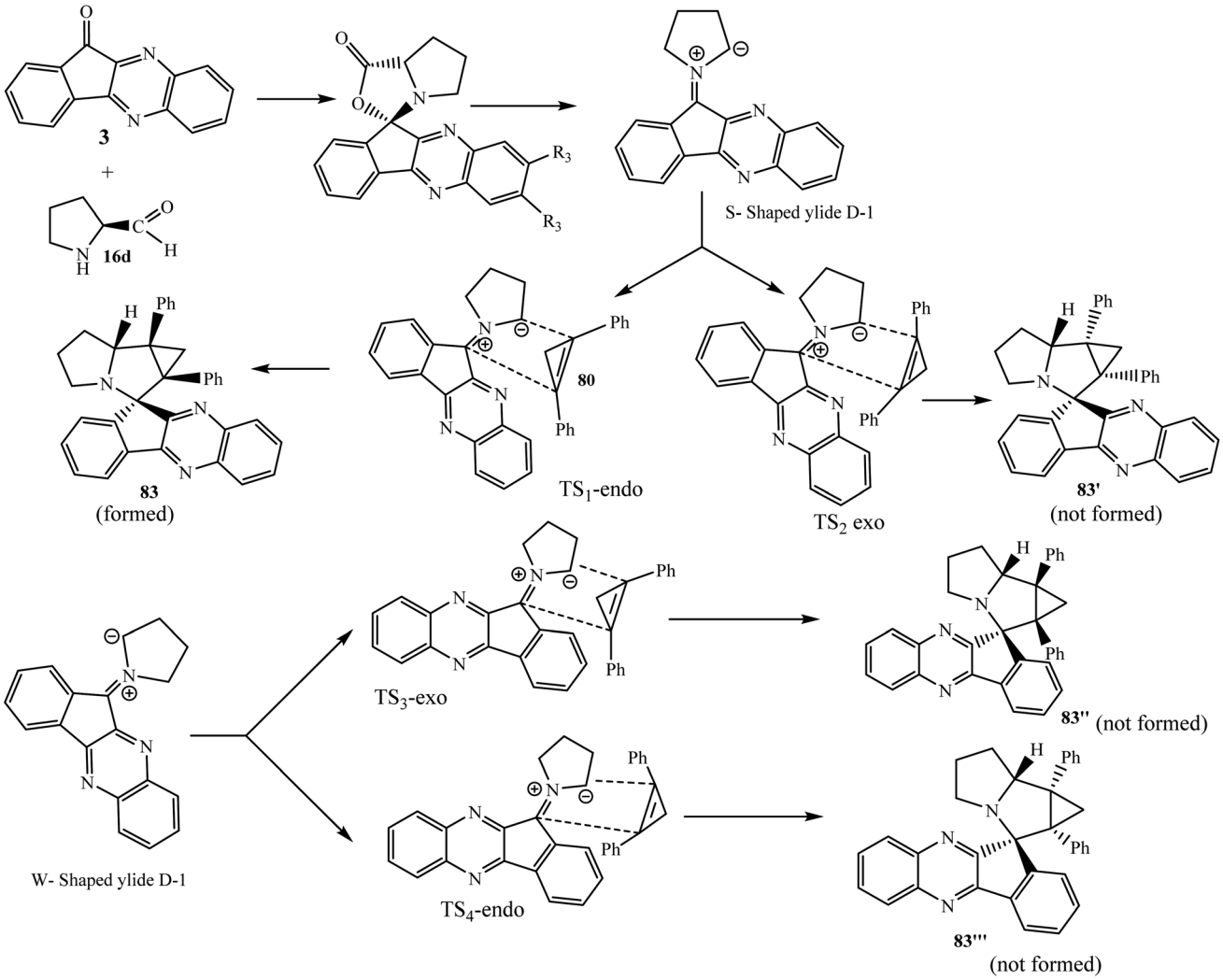
Scheme 45 Synthesis of 3-azaspirobicyclohexane-indenoquinoxalines **81–83**.

cyclopropa[*a*]pyrrolizines or azabicyclo[3.1.0]hexane moieties *via* the one-pot three-component 1,3-dipolar cycloaddition reaction of azomethine ylides with substituted dipolarophile cyclopropenes **80** in MeOH (Scheme 45). The reaction is variously oriented and dipolarophile cyclopropane smoothly reacted with various azomethine ylides generated *in situ* from 11*H*-indeno[1,2-*b*]quinoxalin-11-ones **3** and amines, such as *N*-substituted and *N*-unsubstituted α-amino acids **16** and **16′**, benzylamines **53**, and also peptides (dipeptide Gly–Gly and tripeptide Gly–Gly–Gly) **16′**. The desired cycloadducts were obtained in high yields with excellent diastereoselectivity. Some of the spiro compounds showed anticancer activity against the human leukemia K562 cell line *via* flow cytometry *in vitro*. The oxidation of their Ar–CH–NH bond with DDQ in toluene at 110 °C for 1 h.

The accepted mechanism of the reaction of 1,2-diphenylcyclo-propene **80** with the *in situ* generated azomethine ylide from 11*H*-indeno[1,2-*b*]quinoxalin-11-one **3** and L-proline **16d** is presented in Scheme 46. The formation of only one diastereomer from four possible enantiomer pairs is explained on the basis of quantum chemistry investigations and calculated Gibbs free energies for the reagents, intermediates, transition states, and possible products. The formation of only single spiro compound **83** proceeds through energetically favorable S-shaped ylide D-1 not through the other possible W-shaped ylide D-2. Further, the interaction of S-shaped ylide D-1 and dipolarophile 1,2-diphenylcyclopropene **80** occurs *via* the less sterically hindered transition state TS1-*endo*, leading to product **83** selectively out of the other possible transition states TS-2 to TS-4.

5.2.2. Synthesis of dispiroindenoquinoxaline-pyrrolidine/pyrrolizidine/indolizidine derivatives. 1,3-Dipolar reactions are well documented for the synthesis of mono- as well as dispiropyrrolidine/pyrrolizidine/thiapyrrolizidine derivatives. 1,3-Dipolar cycloaddition reactions of dipolarophiles with an exocyclic olefinic bond leads to the formation of dispiro derivatives with dipoles generated from α-amino acids and cyclic ketones. Due to the existence of two spiro centers in one molecule, there is more possibility of the inclusion of different bioactive moieties and an enhancement in the biological activity.

5.2.2.1. Cycloaddition reaction at the exocyclic double bond of piperidinone-based dipolarophiles. The piperidinone heterocyclic moiety is an important class of pharmacophore as its derivatives possess interesting biological profiles, as potential antitumor[78] and antimicrobial agents.[79] Structurally diverse heterocyclic hybrids comprising spiropyrrolidine and piperidone units have been reported as anti-cancer,[80] anti-mycobacterial,[81] anti-Alzheimer[82] and anti-microbial leads.[83] These considerations prompted researchers to explore the synthesis of novel heterocyclic hybrids containing dispiropyrrolidine, piperidinone, and indeno[1,2-*b*]quinoxaline in a single frame to further enhance the biological profile. Perumal *et al.*[84] synthesized a library of novel dispiro system 1-methyl-4-arylpyrrolo-(spiro[2.11′]-11*H*-indeno[1,2-*b*]quinoxaline)-spiro[3.3″]-1″-methyl/benzyl-5″-(arylmethylidene)piperidin-4″-ones **85** *via* the four-component 1,3-dipolar cycloaddition reaction of piperidinone-based dipolarophile 3,5-bis(4-chlorobenzylidene)-1-methylpiperidin-4-one **84**, ninhydrin **1**, *o*-phenylenediamine **2**



Scheme 46 Plausible reaction mechanism of the reaction of 1,2-diphenylcyclopropene **80**, 11*H*-indeno[1,2-*b*]quinoxalin-11-one **3**, and L-proline **16d**.

and sarcosine **16a** using [BMIm]Br ionic liquid as a reaction medium and reaction accelerator (Scheme 47).

This is an efficient and eco-compatible approach and spiro hybrid is formed by the simple attachment of the β-carbon of the dipolarophile to the less substituted side of the dipole through transition state A regio- and stereoselectively. The ionic liquid [BMIm]Br was also recyclable up to four times.

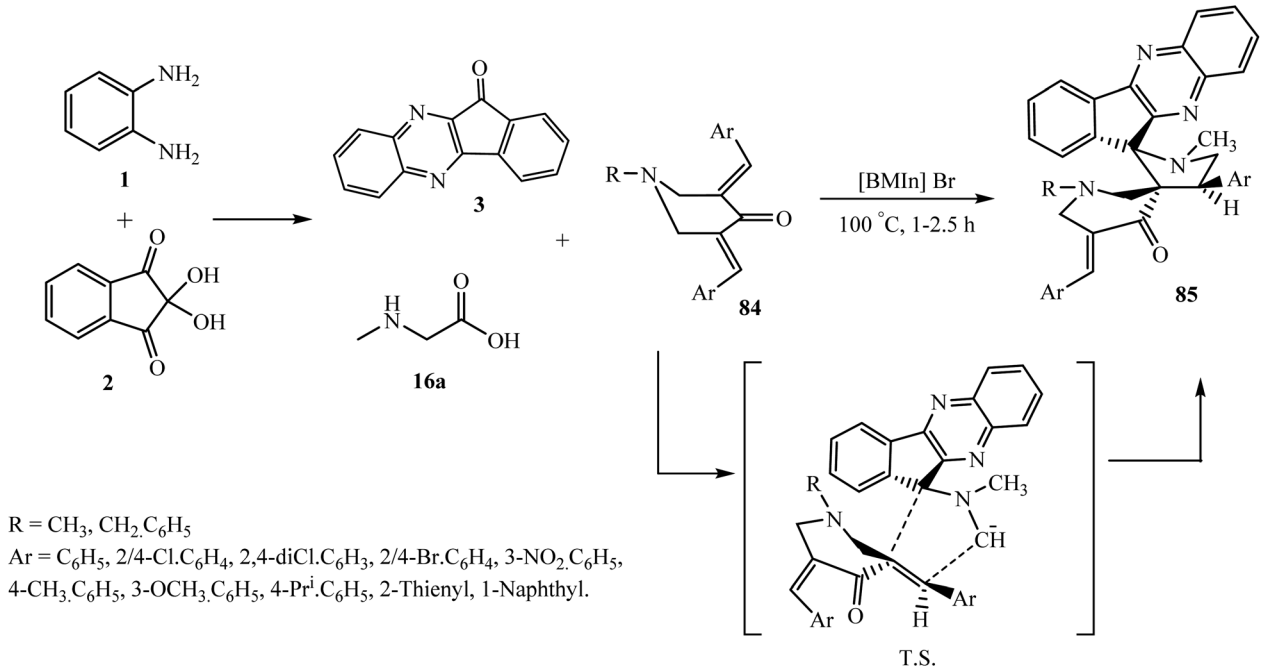
After that, Kumar *et al.*[85] explored this work with dipolarophile mono-3-arylidene-1-methylpiperidin-4-ones **86** and reported the synthesis of novel polycyclic dispiro systems *N*-methyl-4-piperidinone-indenoquinoxaline-pyrrolothiazole **87**/pyrrolidine hybrid heterocycles **88** using α-amino acid sarcosine **16a** and L-thiaproline **16e**, respectively. They also tried this reaction with amino acid L-proline **16d** in place of **16a** and **16e** but the reaction failed to occur (Scheme 48).

In 2019 Arumugam *et al.*[86] reported the expedient synthesis of novel dispiropyrrolidinyl-*N*-styrylpiperidone-indeno[1,2-*b*]quinoxaline heterocyclic hybrid **90** *via* a domino multicomponent strategy employing *N*-unsubstituted 3,5-dibenzylidenepiperidin-4-ones **84** as a dipolarophile, L-phenylalanine **16b** and indeno[1,2-*b*]quinoxalinone **3** in an ionic liquid, 1-butyl-3-methylimidazolium bromide (Scheme 49).

Mechanistically, this reaction is very interesting. The azomethine ylide **A** formed '*in situ*' from the reaction of L-phenylalanine **16b** and indeno[1,2-*b*]quinoxalinone **3** attacks regioselectively the β-carbon of C=C bond of the dipolarophile to form spiro compound **89.**

Simultaneously, ylide **A** is attacked by a water molecule to furnish 2-phenylacetaldehyde **91** *via* intermediate **B.** Subsequently, the secondary amine of the piperidone ring of spirocycloadduct **89** reacts with **91** through an enamine reaction to afford spiro adduct **90** (Scheme 50).

Synthesized compounds were tested for their antimicrobial activity against bacterial and fungal pathogens and compounds bearing chloro and methyl groups displayed significant activity against tested microbial pathogens. The synergistic effect revealed that the combination of a compound with a methyl group with streptomycin and vancomycin exhibited potent

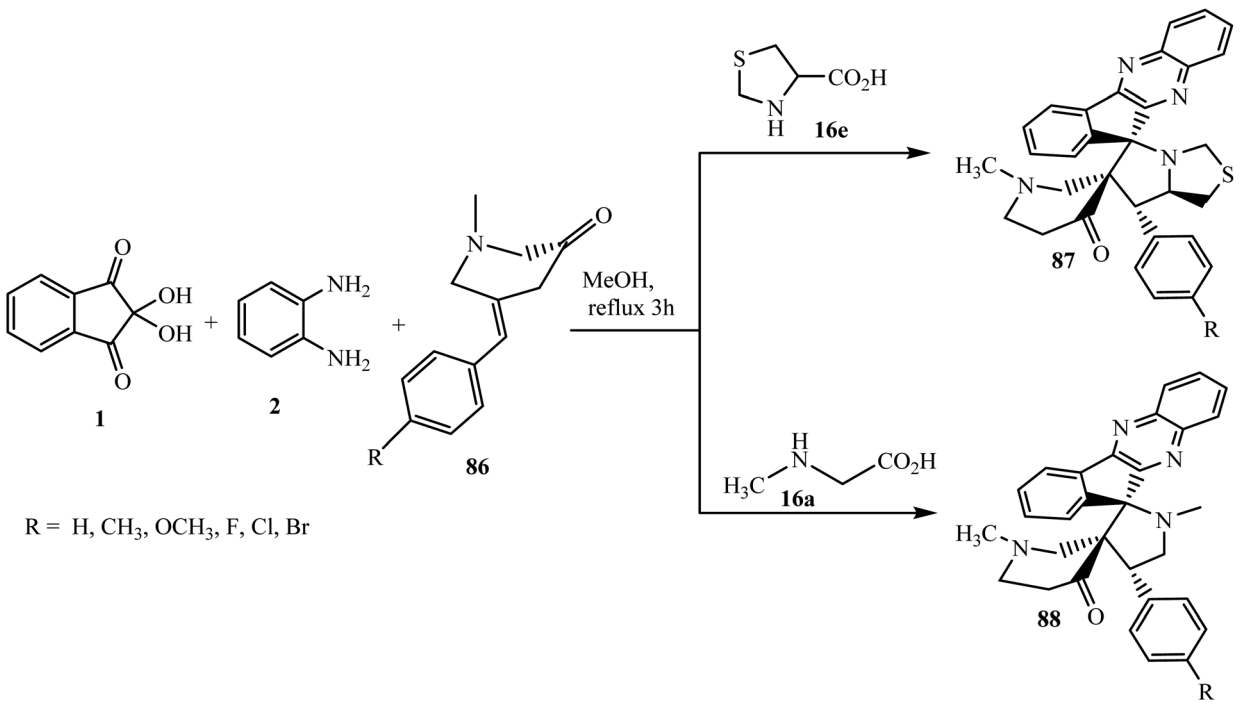


Scheme 47 Synthesis of arylidene-substituted dispiropyrrolidinyl-indenoquinoxaline-piperidinones **85**.

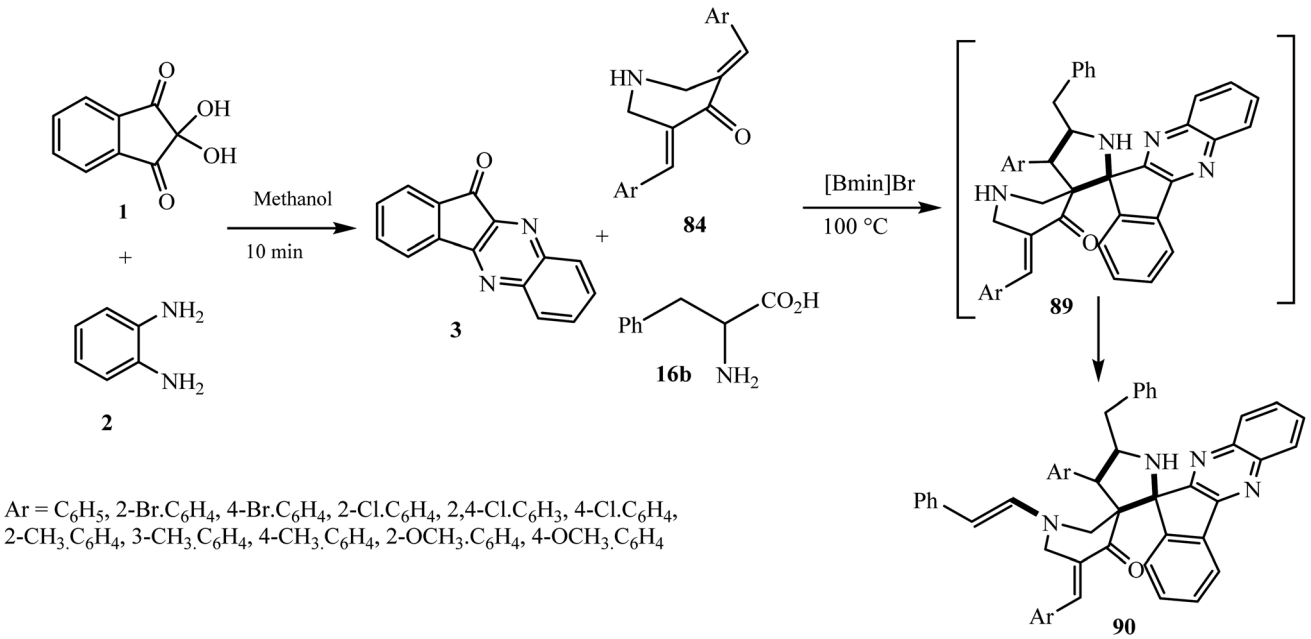
synergistic activity against *E. coli* ATCC 25922. In addition, molecular docking simulations were also studied for the most active compound.

Simultaneously, Arumugam *et al.*[87] accomplished the synthesis of a new class of dispiropyrrolidinyl-piperidone attached indeno[1,2-*b*]quinoxaline heterocyclic hybrids **92** by employing a new kind of azomethine ylide generated *in situ* from indenoquinoxalinone **3** and L-tryptophan **16c** for the first time (Scheme 51).

The synthesized heterocyclic hybrids **92** were evaluated for their *in vitro* acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) inhibitory activities. Compounds bearing nitro and methyl substituents on the piperidinone ring displayed more potent AChE and BChE enzyme inhibition than



Scheme 48 Synthesis of dispiropiperidinone-indenoquinoxaline-pyrrolothiazoles/pyrrolidine **87**/**88**.

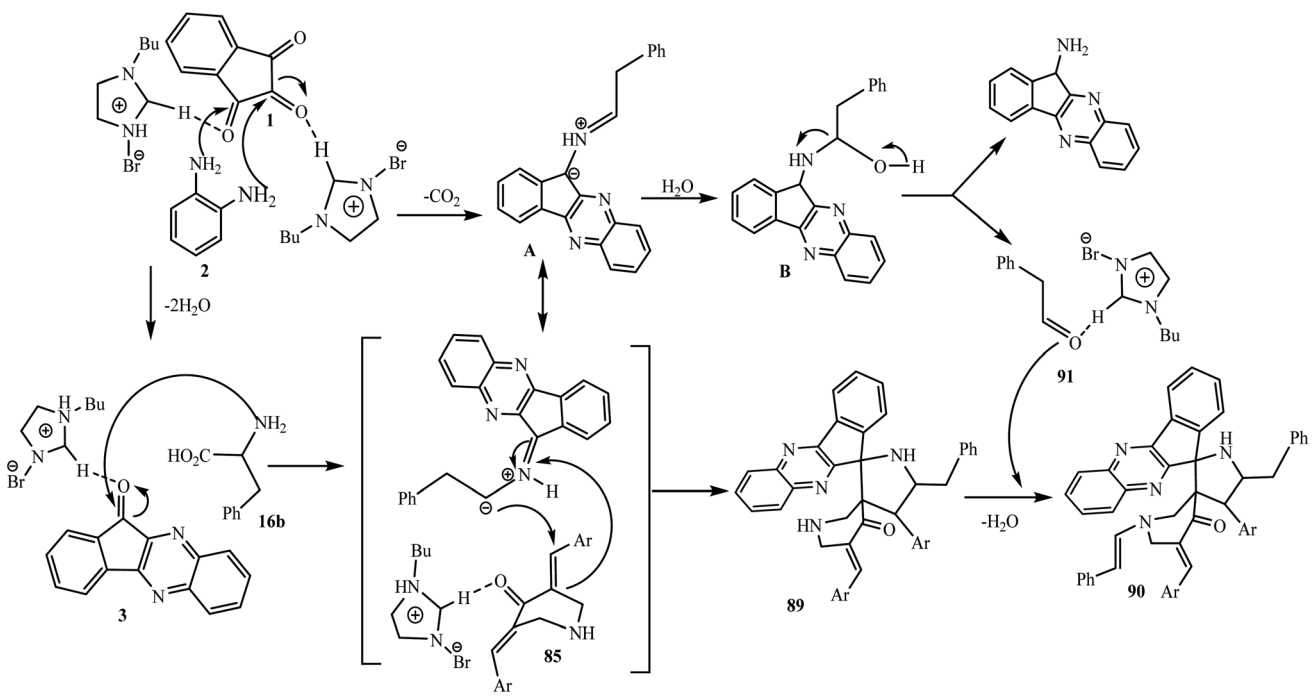


Scheme 49 Synthesis of novel dispiropyrrolidinyl-*N*-styrylpiperidone-indenoquinoxaline **90**.

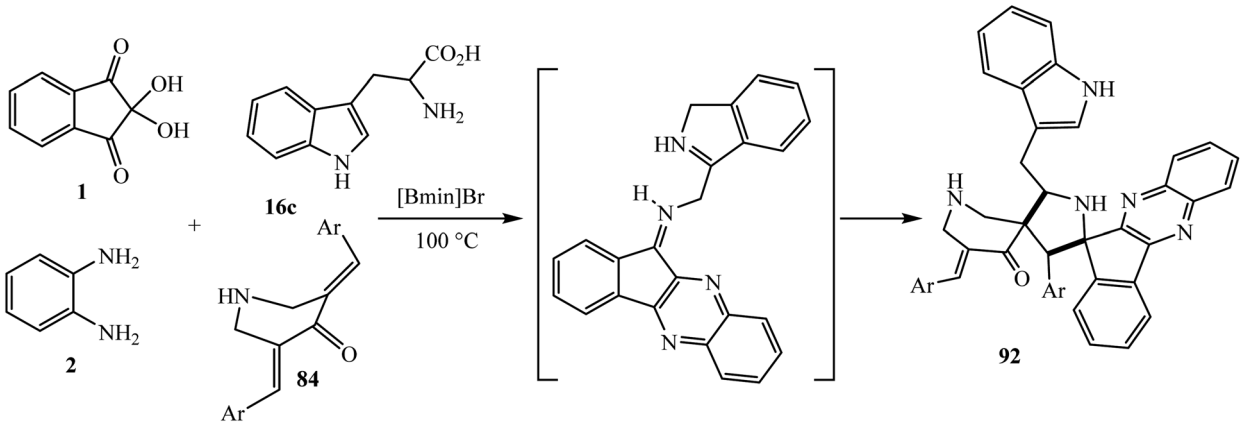
the standard drug with IC_{50} values of 3.22, 2.01, 12.40 and 10.45 mM, respectively. Molecular docking studies have also been conducted for the most active compounds that showed interesting binding templates to the active site channel of the cholinesterase enzyme.

The mechanistic pathway is similar to those previously described. In all ionic liquid-mediated reactions the ionic liquids play a twin role as a solvent and catalyst, and accelerate the reaction by increasing the electrophilicity of the carbonyl carbons.

5.2.2.2. Cycloaddition reaction at the exocyclic double bond of indole-based dipolarophiles. The spiro-pyrrolidine and oxindole ring systems have acquired importance because of their specific structural motifs in many pharmacologically relevant alkaloids, as typified by rhyncophylline, coryn-oxeine, mitraphylline, horsifiline, and spirotryprostatins.[88,89]



Scheme 50 Mechanism for the synthesis of dispiropyrrolidinyl-*N*-styrylpiperidone-indenoquinoxaline **90**.

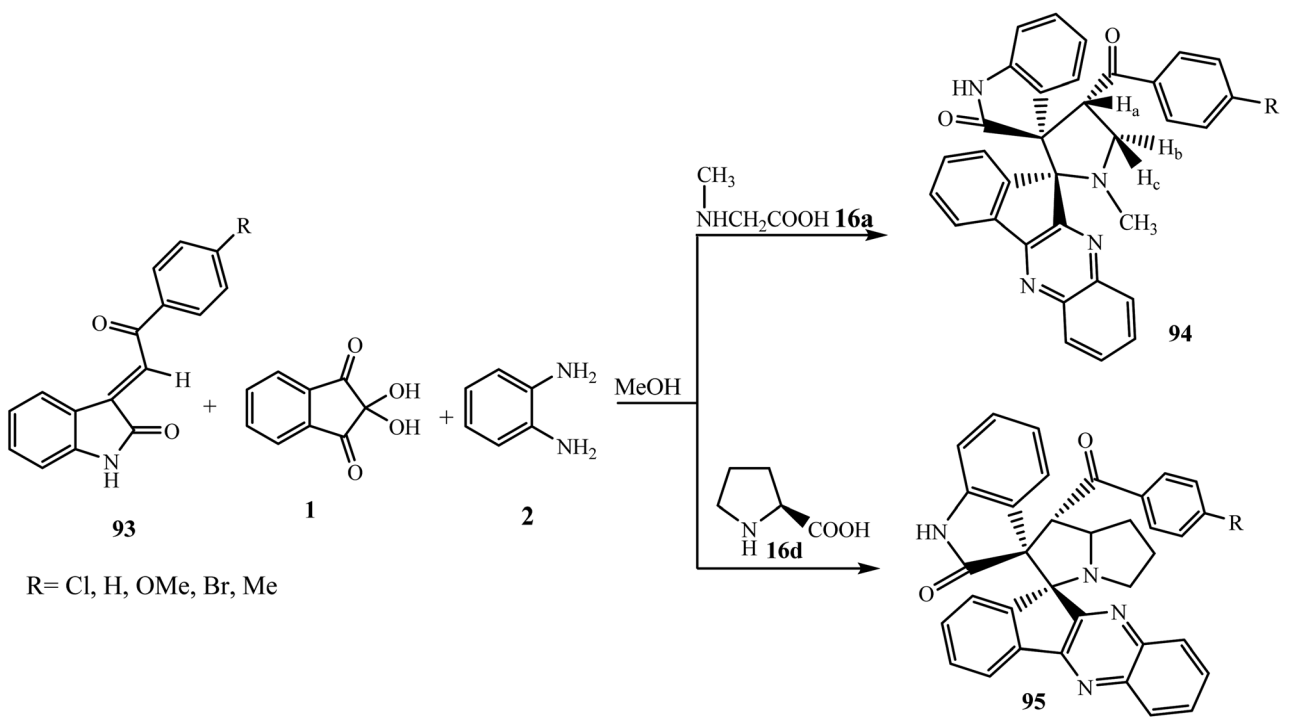


Scheme 51 Synthesis of indole-substituted dispiropyrrolidinyl-piperidone-indenoquinoxaline **92**.

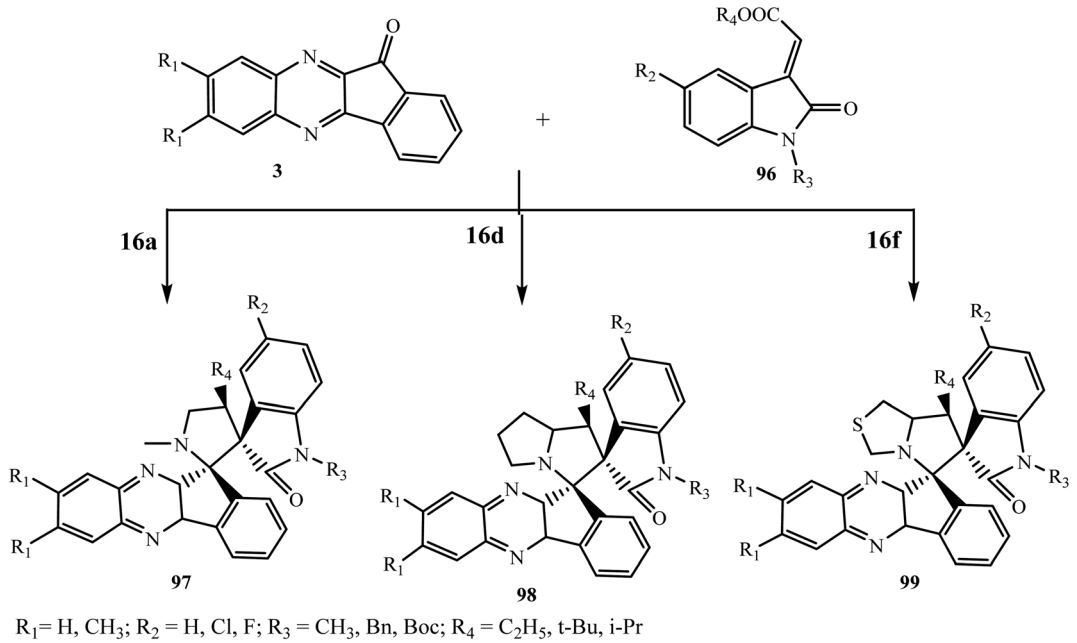
Raghunathan *et al.*[90] described the synthesis of novel spiro product 1-*N*-methyl-spiro[2.11′]indeno[1,2-*b*]quinoxaline-spiro[3.3″]oxindole-4-benzoyl-pyrrolidines **94** by combining an indole and an indeno[1,2-*b*]quinoxaline moiety together in a single frame through the four-component 1,3-cycloaddition reaction of dipolarophile (*E*)-2-oxoindolino-3-ylidene acetophenones **93** with the azomethine ylide generated from ninhydrin **1**, 1,2-phenylenediamine **2**, and sarcosine **16a** (Scheme 52).

Previously, Raghunathan *et al.*[91] described an efficient heteropolyacid $H_4[Si(W_3O_{10})_3]$–silica catalyzed synthesis of dispiroindenoquinoxaline-pyrrolizidine derivatives **95** *via* a four-component 1,3-dipolar cycloaddition reaction using dipolarophile **93** with an azomethine ylide generated from ninhydrin **1**, 1,2-phenylenediamine **2**, and L-proline **16d** with high regioselectivity (Scheme 52).

Recently Gu and coworkers[92] designed and synthesized novel spirooxindole-indenoquinoxaline derivatives **97–99** through the 3 + 2 cycloaddition reaction of new indole-based dipolarophile 3-ylideneoxindole **96**, α-amino acids (sarcocine **16a**, L-proline **16d** and L-thiaproline **16e**) and *in situ* generated indeno[1,2-*b*]quinoxalinone **3** in acetonitrile (Scheme 53). These compounds were assayed by biochemical TrpRS inhibition, using *in vitro* experiments to test against various Gram-positive and Gram-negative strains, and using diffuse large B cell lymphoma cell



Scheme 52 Synthesis of spiroindeno[1,2-*b*]quinoxaline-spiro[3.3″]oxindole-4-benzoyl-pyrrolidines **94** and **95**.



Scheme 53 Synthesis of dispirooxindole-indenoquinoxaline-pyrrolidenes/pyrrolizidenes **97–99**.

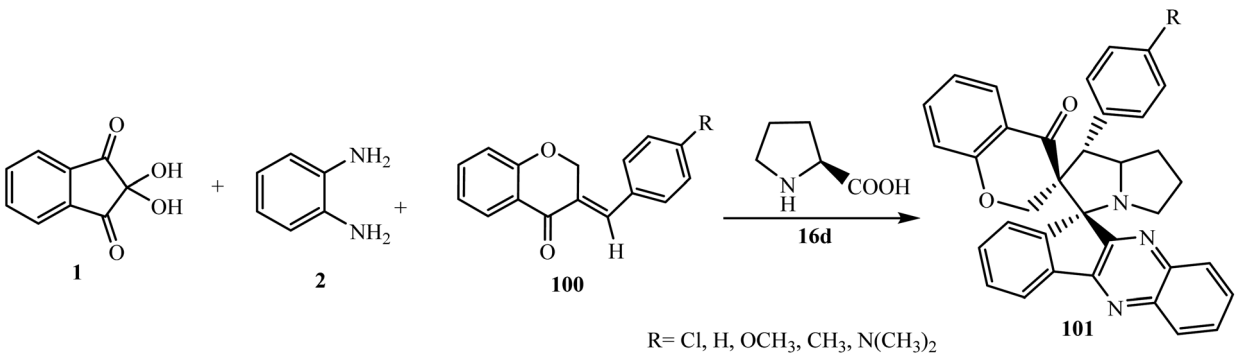
lines. The results showed that these compounds can act as novel TrpRS inhibitors as potential lead compounds for antibiotics and as novel anticancer agents.

5.2.2.3. Cycloaddition reaction at the exocyclic double bond of chromanone-based dipolarophiles. Due to the remarkable catalytic properties of heteropolyacid $H_4[Si(W_3O_{10})_3]$–silica in 1,3-dipolar cycloaddition reactions, Raghunathan *et al.*[91] constructed chromanone-grafted novel dispiroindenoquinoxaline-pyrrolizidine derivatives **101** *via* a four-component reaction using dipolarophile (*E*)-3-arylidene-4-chromanones **100** with an azomethine ylide generated from ninhydrin **1**, 1,2-phenylenediamine **3**, and L-proline **16d** selectively using heteropolyacid $H_4[Si(W_3O_{10})_3]$–silica (Scheme 54).

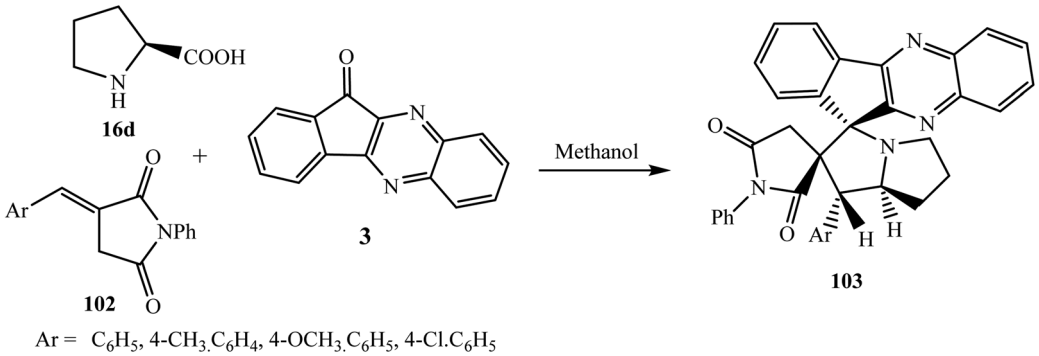
5.2.2.4. Cycloaddition reaction at the exocyclic double bond of pyrrolidine-based dipolarophiles. Askri *et al.*[93] reported the synthesis of a series of spiro[2,11″]indeno[1,2-*b*]quinoxaline-spiro[3,3′]-*N*-phenylsuccinimide-pyrrolizines **103** *via* the one-pot three-component [3 + 2] cycloaddition reaction of dipolarophiles (*E*)-3-arylidene-1-phenylpyrrolidine-2,5-diones **102**, L-proline **16d** and indenoquinoxalinone **3**. The observed regio- and stereoselectivity was calculated using DFT at the B3LYP/6-31G(d,p) level and found to be under kinetic control (Scheme 55).

5.2.2.5. Cycloaddition reaction at the exocyclic double bond of sulfur-based dipolarophiles. Li *et al.*[94] reported the synthesis of the novel dispiro system indeno[1,2-*b*]quinoxaline-11,3′-pyrrolizine-2′,2″-[1,3]thiazolo[3,2*a*]pyrimidine-1′,6″-dicarboxylates **105** *via* 3 + 2 cycloaddition reaction of a new dipolarophile, namely ethyl-5-aryl-2-(2-methoxy-2-oxoethylidene)-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylate **104**, and azomethine ylide generated '*in situ*' by the reaction of 11*H*-indeno[1,2-*b*]quinoxaline-11-one **3** and L-proline **16d** (Scheme 56).

Kumar *et al.*[95] reported a combinatorial four-component synthesis of novel dispiro-dihydrothiophenone-indenoquinoxaline-pyrrolidines **107** or pyrrolothiazole hybrids **108** heterocyclic systems utilizing bis(arylidine)



Scheme 54 Synthesis of chromanone-grafted novel dispiroindenoquinoxaline-pyrrolizidine derivatives **101**.



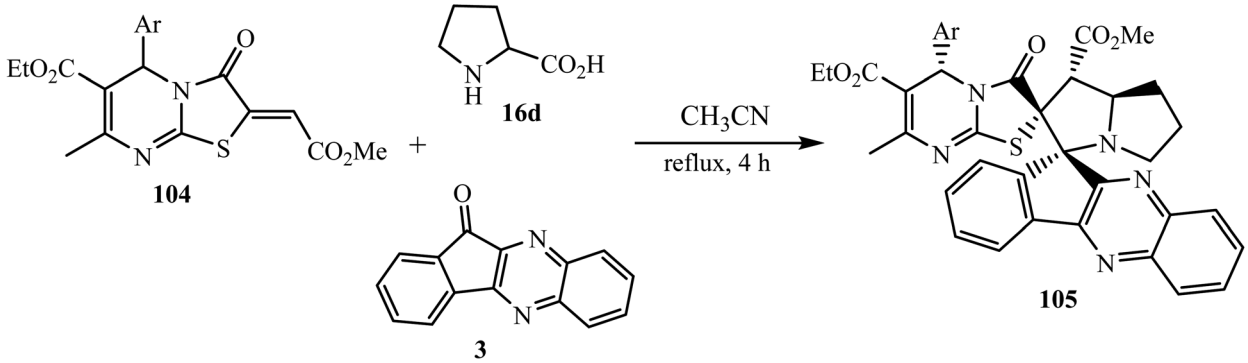
Scheme 55 Synthesis of dispiroindenoquinoxaline-succinimide-pyrrolizines **103**.

dihydrothiophen-3(2*H*)-ones **106** as dipolarophile and azomethine ylide generated *in situ* from indenoquinoxalinone **3** and α-amino acids, *i.e.*, sarcosine **16a**/thioproline **16e**, with high chemo-, regio- and stereoselectivity (Scheme 57).

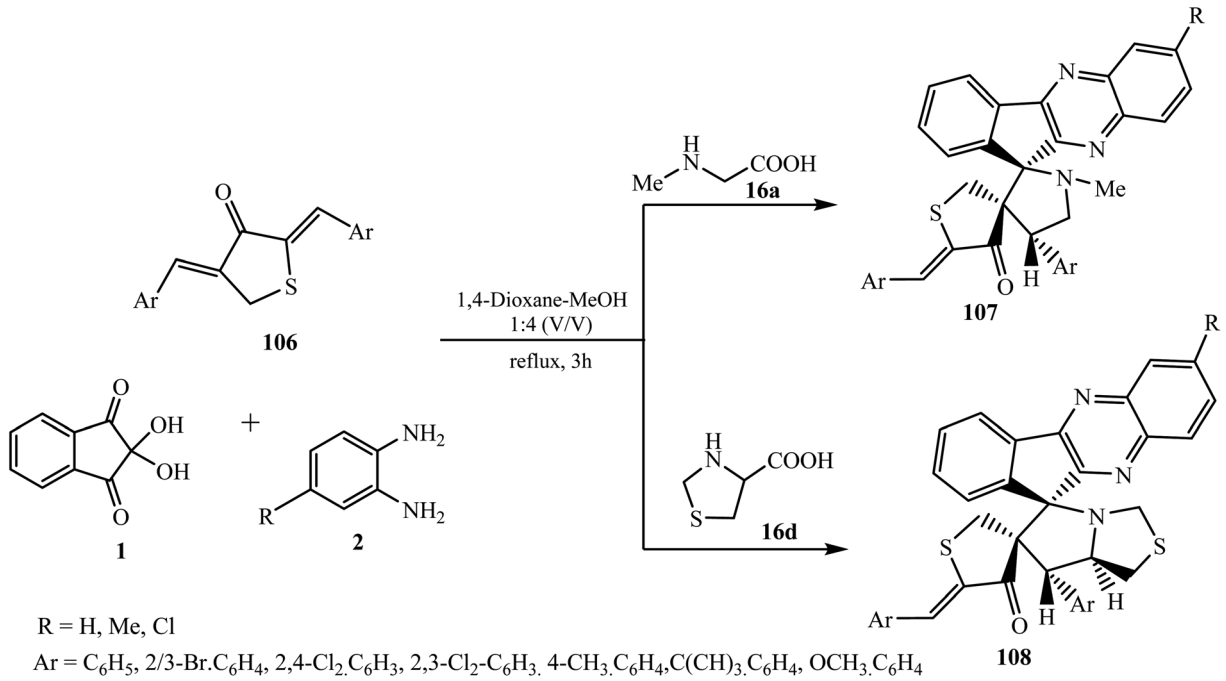
5.2.2.6. Cycloaddition reaction at the exocyclic double bond of simple cycloalkane-based dipolarophiles. In 2014, Raghunathan *et al.*[96] reported an efficient synthesis of highly substituted spiro-indenoquinoxaline-pyrrolidine heterocycles **110** *via* the [3 + 2] cycloaddition reaction of simple cycloalkane-based dipolarophiles 2,6-bis-arylmethylidenecyclohexanone and 2,5-bis-arylmethylidenecyclopentanones **109** regioselectively. The synthesized spiro adduct **110** further undergoes ring annulation using hydrazine hydrate to give a new pyrazolo-cyclohexane grafted spiro-indenoquinoxaline-pyrrolidine derivative **111** (Scheme 58). This facile, one-pot, sequential multicomponent reaction offers several advantages. It involves mild reaction conditions, straightforward easy workup, readily available and low-cost starting materials, excellent yield with high regioselectivity, without a catalyst and the use of green solvent and afforded a series of hitherto novel pyrazolo-cycloalkane grafted spiroindenoquinoxaline-pyrrolidine derivatives of biological significance.

Liu *et al.*[97] demonstrated an efficient and simple five-component cascade protocol to synthesize highly substituted dispiroindenoquinoxaline-indane-pyrrolidine derivatives **114** from ninhydrin **1**, 1,2-phenylenediamine **2**, sarcosine **16a**, 1,3-indanedione **112**, and aldehydes **39** *via* cascade reactions under mild conditions. In this five-component reaction the most electrophilic β-carbon of dipolarophile arylidene-1,3-indanedione **113** (formed *in situ* from 1,3-indanedione **112** and aldehyde **39**) is attacked by the electron-rich carbon of the azomethine ylide in a thermodynamically more stable *exo* manner to construct a single regioisomer and diasteroisomer without any trace of another isomer. It is of significance to mention that the dispiroindenoquinoxaline derivatives **114** that have aromatic aldehydes with substituents at the *ortho* position lead to the formation of rotamers in ratios of around 0.76 : 0.24 and 0.74 : 0.26, as determined by ^{1}H-NMR spectroscopy. Raghunathan *et al.* investigated the three-component 1,3-dipolar cycloaddition reaction of dipolarophile **113** with an azomethine ylide generated by the reaction of **3** and L-proline **16d** in the presence of heteropolyacid $H_4[Si(W_3O_{10})_3]$–silica to synthesize spiroindeno-pyrazolidines **115** (ref. 91) (Scheme 59).

5.2.2.7. Cycloaddition reaction of a steroidal grafted exocyclic double bond. Raghunathan *et al.*[98] investigated an expedient ionic liquid-assisted approach for the synthesis of a series of unknown novel steroidal grafted dispiroindenoquinoxaline-pyrrolidines **117** *via* a one-pot four-component [3 + 2]



Scheme 56 Synthesis of dispiroindenoquinoxaline-pyrrolizine-thiazolopyrimidines **105**.



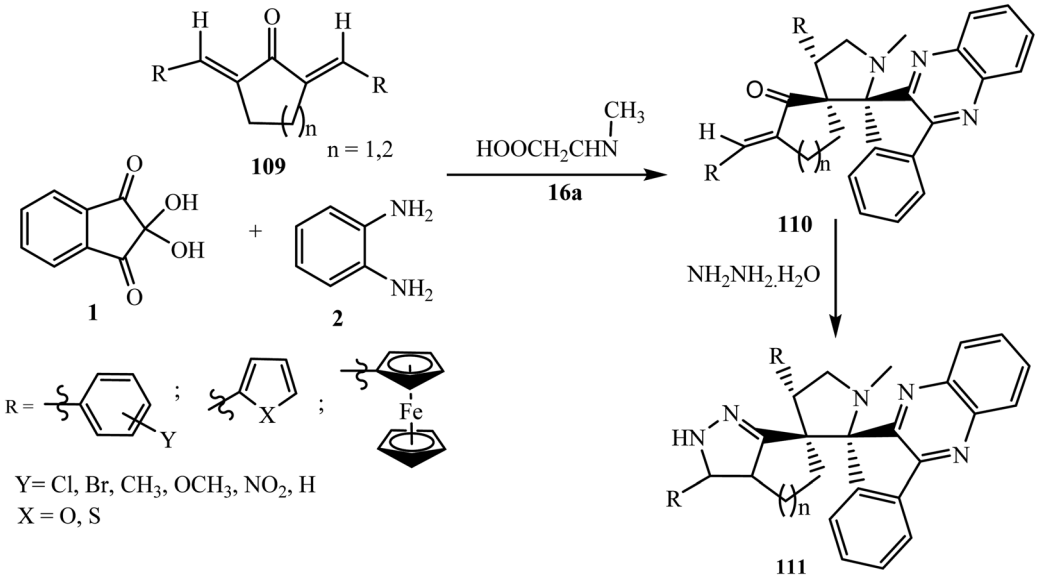
Scheme 57 Synthesis of thiophene-grafted dispiroindenoquinoxaline-pyrrolidine/pyrrolothiazoles 107/108.

cycloaddition reaction. Concomitant cycloaddition of the azomethine ylide to various unusual estrone-derived dipolarophiles **116** affords a series of hitherto novel steroid grafted cyclo adducts **117** with excellent yield and high regioselective purity. In this sequential method, the ionic liquid *N*-(1-acroloyl)-*N*-(4-cyclopentyl)piperazinium phosphate plays a dual role, firstly as a recyclable green solvent in which the reactants have better solubility, especially the amino acids, and secondly because of its catalytic effect, which makes this approach more convenient and environmentally benign (Scheme 60).

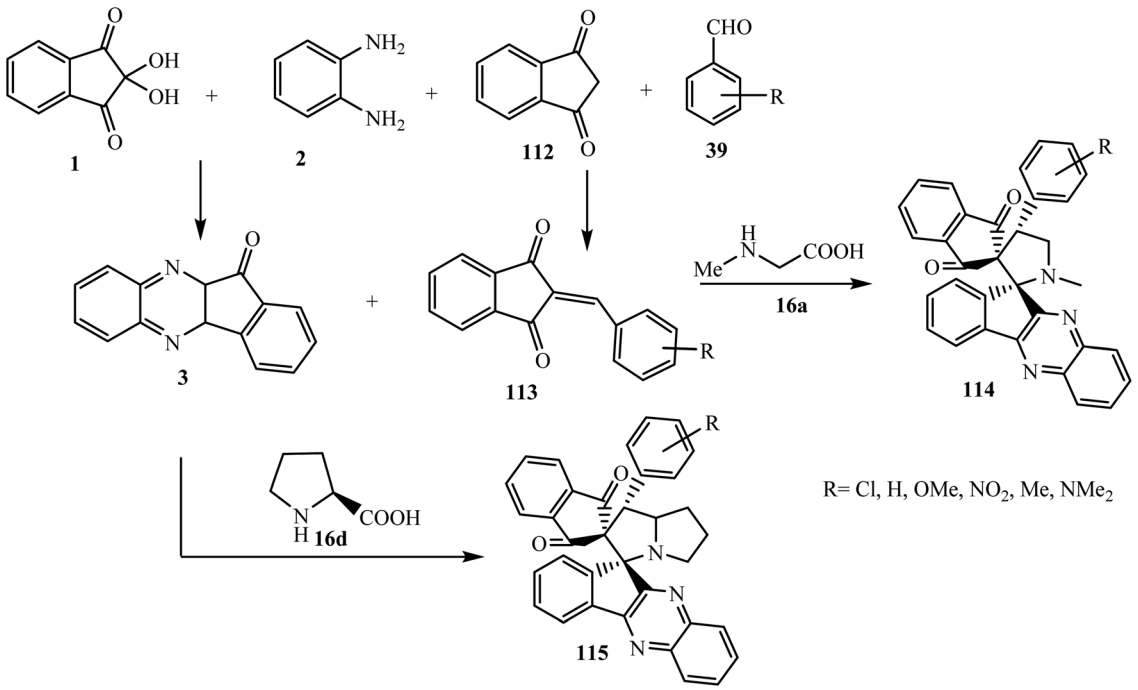
5.3. Synthesis of spiro[indeno[1,2-*b*]quinoxaline[1,3,4] oxadiazole]

Alizadeh and Moafi[99] accomplished the regio- and stereoselective synthesis of the novel spiro framework spiro[indeno[1,2-*b*]quinoxaline-11,2′-[1,3,4]oxadiazoles] **119** *via* the three-component reaction of ninhydrin **1**, *o*-phenylenediamines **2** and hydrazonoyl chlorides **118** in the presence of Et_3N in EtOH at room temperature.

Mechanistically, quinoxalinone **3** formed by the reaction of ninhydrin **1** and *o*-phenylenediamine **2** reacted with



Scheme 58 Synthesis of cycloalkane-grafted dispiroindenoquinoxaline-pyrrolidines 110 and their conversion to pyrazolo derivatives 111.



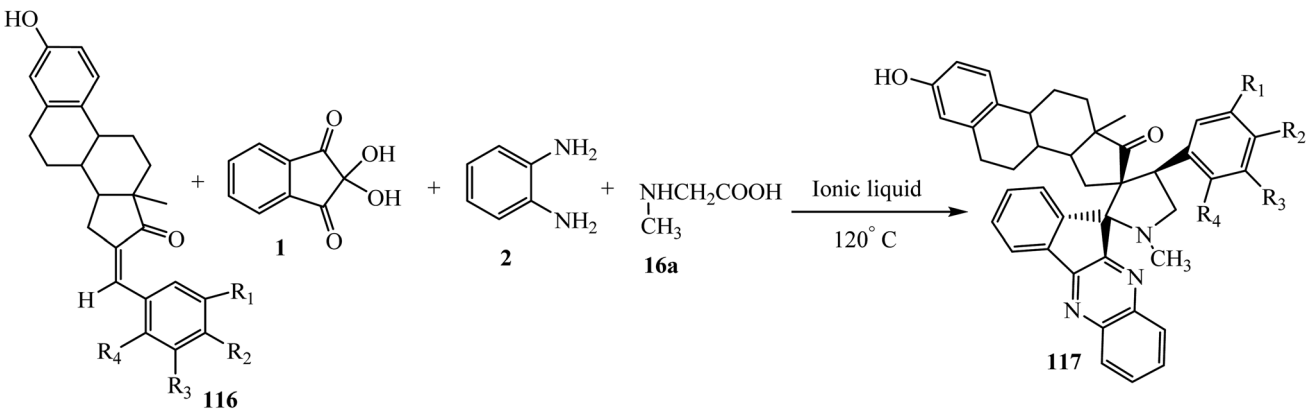
Scheme 59 Synthesis of dispiroindenoquinoxaline-indane-pyrrolidines **114**/pyrazolidines**115**.

intermediate nitrileimine **A** generated *in situ* from hydrazonoyl chloride **118** leading to the formation of the final product **119.** This reaction is interesting as only one isomer of spiro adduct **119** is formed in the case of unsubstituted *o*-phenylenediamine **2**; however, in the case of substituted *o*-phenylenediamines **2** two isomers **119** and **119′** were detected due to the presence of two nonequivalent amino groups (Scheme 61).

5.4. Synthesis of spiro[indeno[1,2-*b*]quinoxaline[11,2′] thiazolidine]-4′-ones

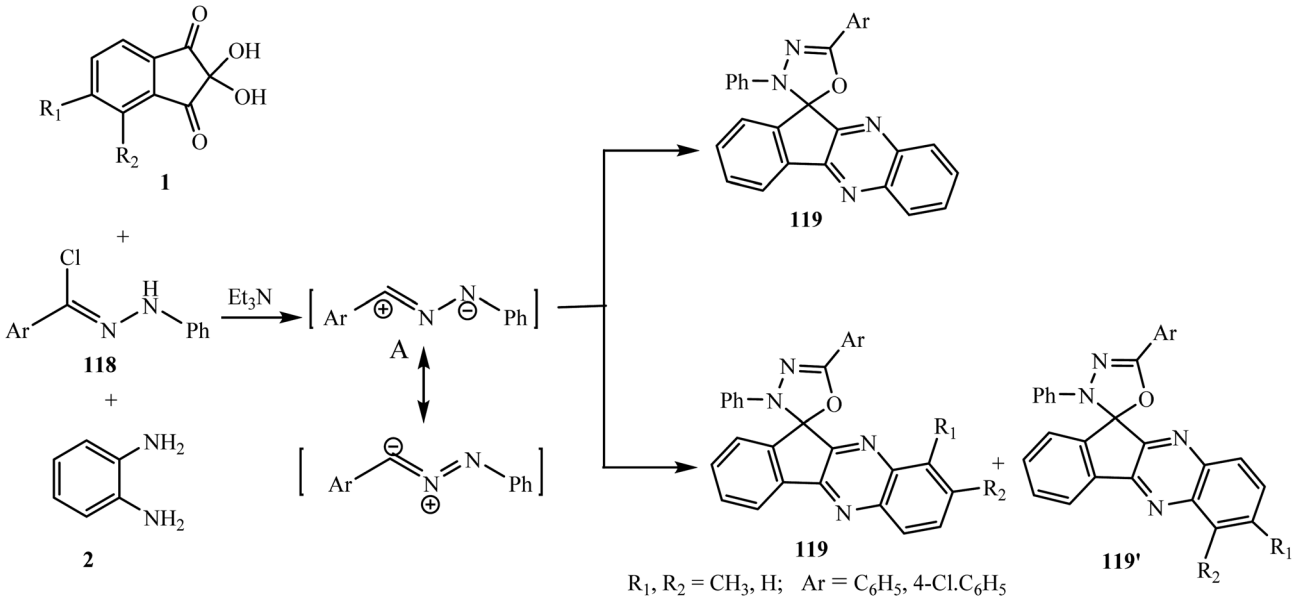
The 4-thiazolidinone moiety is also a very common and privileged heterocyclic target for building many pharmacologically important synthetic and naturally occurring compounds.[100] Recently, our group[101] developed a convenient and eco-compatible approach for the synthesis of medicinally important novel hybrid spiro[indeno[1,2-*b*]quinoxaline[11,2′]thiazolidine]-4′-ones **122** *via* the one-pot multicomponent reaction of indeno[1,2-*b*]quinoxalinone **3** with various types of amines **120** and α-mercaptocarboxylic acid **121** in the presence of carbon–SO_3H as a solid acid catalyst using the green reaction medium urea–choline chloride as a deep eutectic solvent at 80 °C (Scheme 62).

The proposed mechanistic pathway for the synthesis of spiro [indeno[1,2-*b*]quinoxaline[11,2′]thiazolidine]-4′-one **122** is shown in Scheme 63. Firstly, the reaction of indeno[1,2-*b*]quinoxalinone **3** with aromatic amines **120** affords the



R_1 = H, OCH_3, F ; R_2 = H, OCH_3, Cl; R_3 = H, OCH_3; R_4 = H, Cl

Scheme 60 Synthesis of steroidal spiroindenoquinoxaline-pyrrolidines **117**.



Scheme 61 Synthesis of spiro[indeno[1,2-*b*]quinoxaline-11,2′-[1,3,4]oxadiazoles] **119** and **119′**.

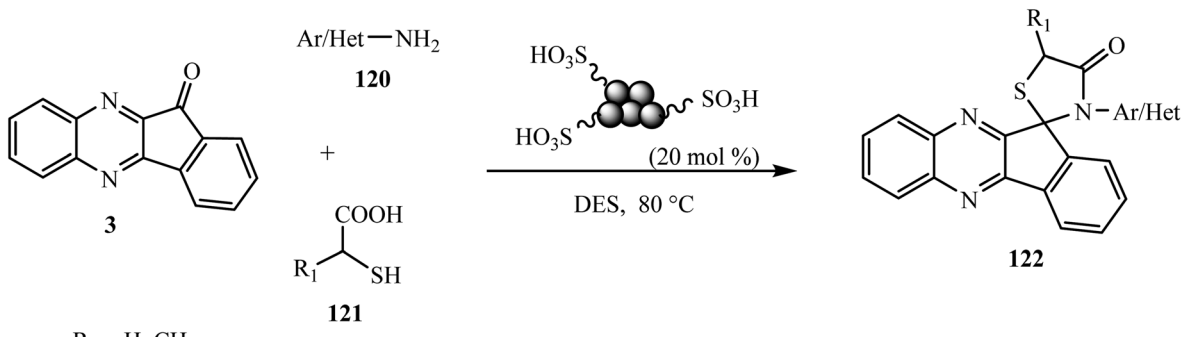
corresponding imine derivative **A**, and then in next step reacts with thioglycolic acid **121** to produce spirothiazolidinone **122**.

5.5. Synthesis of spiroindenoquinoxaline-pyran derivatives

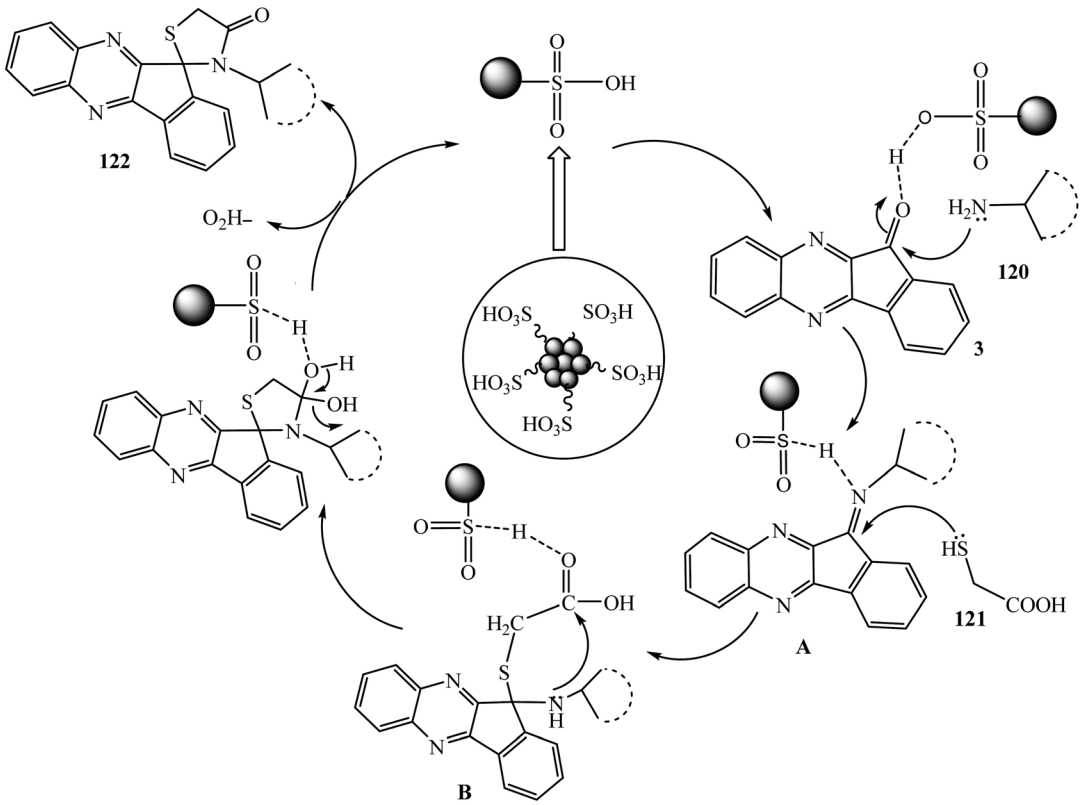
The spiropyrans have been reported for their good activities as hypertensive agents[102] and attracted significant interest as potential novel analgesic agents.[103] In this connection, Hasaninejad *et al.*[104] in 2011 synthesized 2′-aminospiro[11*H*-indeno[1,2-*b*]quinoxaline-11,4′-[4*H*]pyran] derivatives **124** *via* the four-component reaction of ninhydrin **1**, benzene-1,2-diamine **2**, malononitrile and its derivatives **38**, and α-methylene carbonyl compounds **123** in the presence of ammonium acetate as a neutral, inexpensive, and dual-activating catalyst. A variety of new spiro-indenoquinoxalines **124** were synthesized using various malononitrile derivatives **38** and α-methylene carbonyl compounds **123a–e** (Scheme 64).

The mechanism for the synthesis of spiro derivatives **124** involves firstly Knoevenagel condensation between indenoquinoxalinones **3** and malononitrile **38** in the presence of ammonium acetate to afford intermediate **A.** Thereafter the enol form of the α-methylene carbonyl compound undergoes Michael addition with intermediate **A** to give intermediate **B.** The carbonyl group of **123** further attacks the CN group followed by subsequent H-atom shift furnishing 2′-aminospiro[4*H*-indeno[1,2-*b*]quinoxaline-11,4′-[4*H*]pyran]-3′-carbonitriles **124** with 91% yield. In this transformation, $AcONH_4$ plays a dual role as it activates the C=O group of **3** *via* H-bond formation between one H-atom of NH_4 and the O-atom of the C=O group and the malononitriles **38** are activated through deprotonation by the acetate ion derived from $AcONH_4$ (Scheme 65).

After that, the synthesis of substituted 2′-aminospiro[4*H*-indeno[1,2-*b*]quinoxaline-11,4′-[4*H*]pyran]-3′-carbonitrile derivatives **124** was investigated by various researchers *via* three- and four-component reactions under different reaction conditions (Scheme 66). Hasaninejad *et al.*[105] described the four-component reaction in the presence of the inorganic catalyst indium(III) chloride in acetonitrile under reflux conditions. Previously, in 2007, Perumal *et al.* used silica gel impregnated



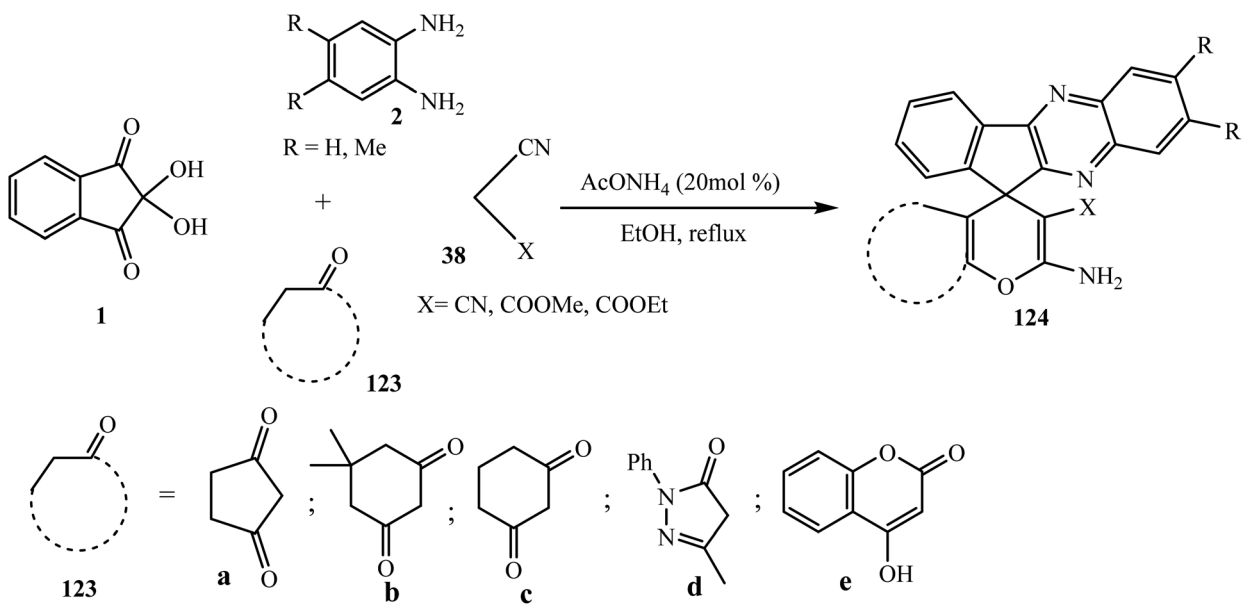
Scheme 62 Synthesis of spiro[indeno[1,2-*b*]quinoxaline[11,2′]thiazolidine]-4′-ones **122**.



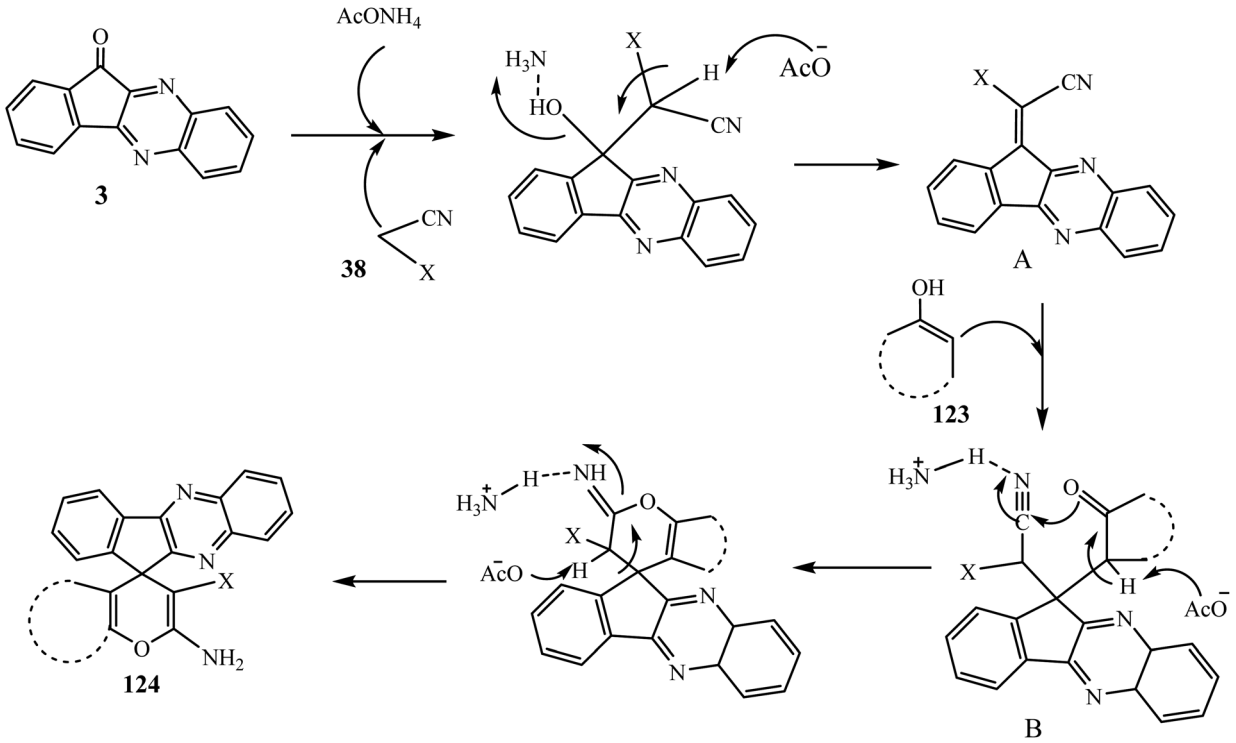
Scheme 63 C–SO_3H catalyzed synthesis of spiro[indeno[1,2-*b*]quinoxaline[11,2′]thiazolidine]-4′-ones **122**.

with indium(III) chloride for the synthesis of **124** under microwave irradiation and solvent-free conditions *via* three-component reaction using indenoquinoxalinones **3** as a starting substrate.[106]

In an another report, Hasaninejad[107] introduced a novel heterogeneous silica-supported ionic liquid catalyst, silica-bonded 5-*n*-propyloctahydropyrimido[1,2-*a*]azepinium chloride, (SB-DBU)Cl, for the synthesis of spiroindeno[1,2-*b*]quinoxaline-11′,4-pyrano derivatives **124** in EtOH/H_2O (1 : 1)



Scheme 64 Synthesis of 2′-aminospiro[11*H*-indeno[1,2-*b*]quinoxaline-11,4′-[4*H*]pyran] derivatives **124**.

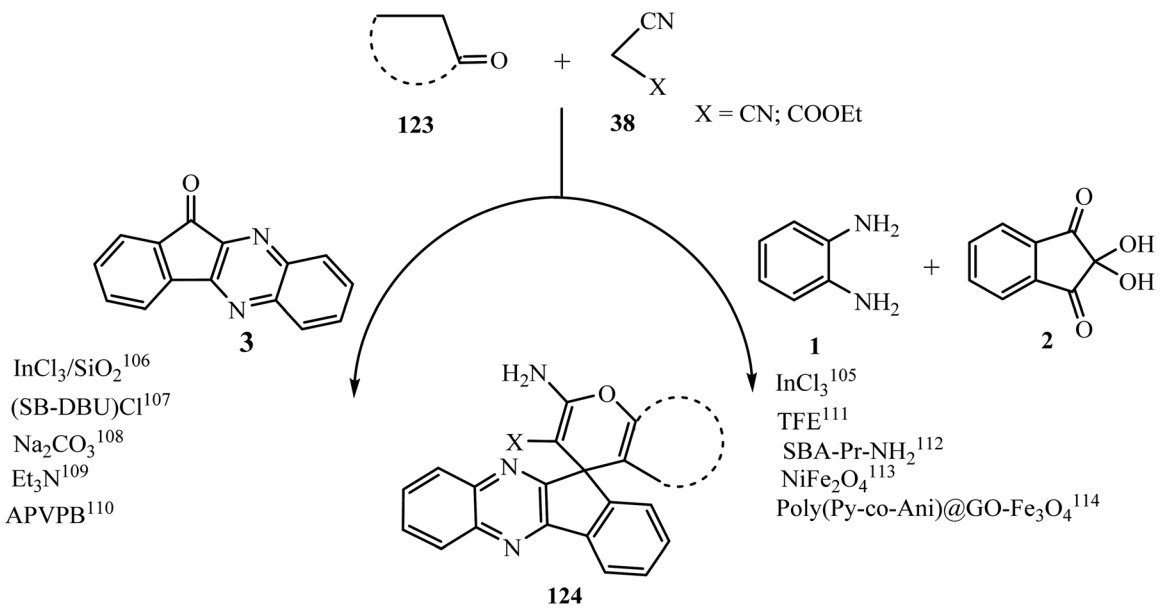


Scheme 65 Synthesis of 2′-aminospiro[4*H*-indeno[1,2-*b*]quinoxaline-11,4′-[4*H*]pyran]-3′-carbonitriles **124** catalyzed by ammonium acetate.

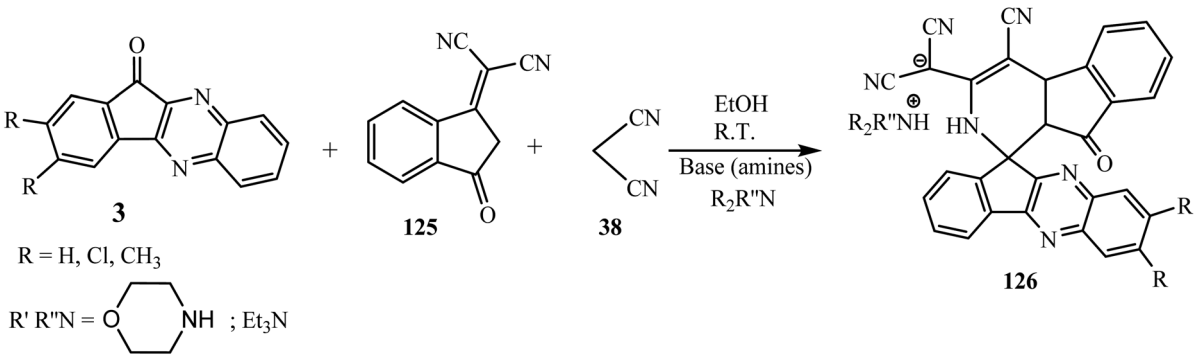
solvent. The used catalyst was recycled and reused fifteen times with unchanged yield.

Soleimani *et al.*[108] reported the synthesis of spiro[indeno[1,2-*b*]quinoxaline-11′,4-pyrano[2,3-*c*]pyrazole] carbonitrile derivative **124** *via* the one-pot three-component reaction of 11*H*-indeno[1,2-*b*]quinoxalinone **3** with malononitrile and pyrazolone. In addition, various basic catalysts such as Na_2CO_3, K_2CO_3, Et_3N, and NaOH were examined in this reaction with different organic solvents such as ethanol, methanol, ethyl acetate, acetonitrile, toluene, and dichloromethane. However, the best results were obtained when the reaction was carried out using Na_2CO_3 in ethanol.

In 2014, Chen *et al.*[109] introduced a three-component one-pot reaction between indenoquinoxalinone **3**, various α-methylene



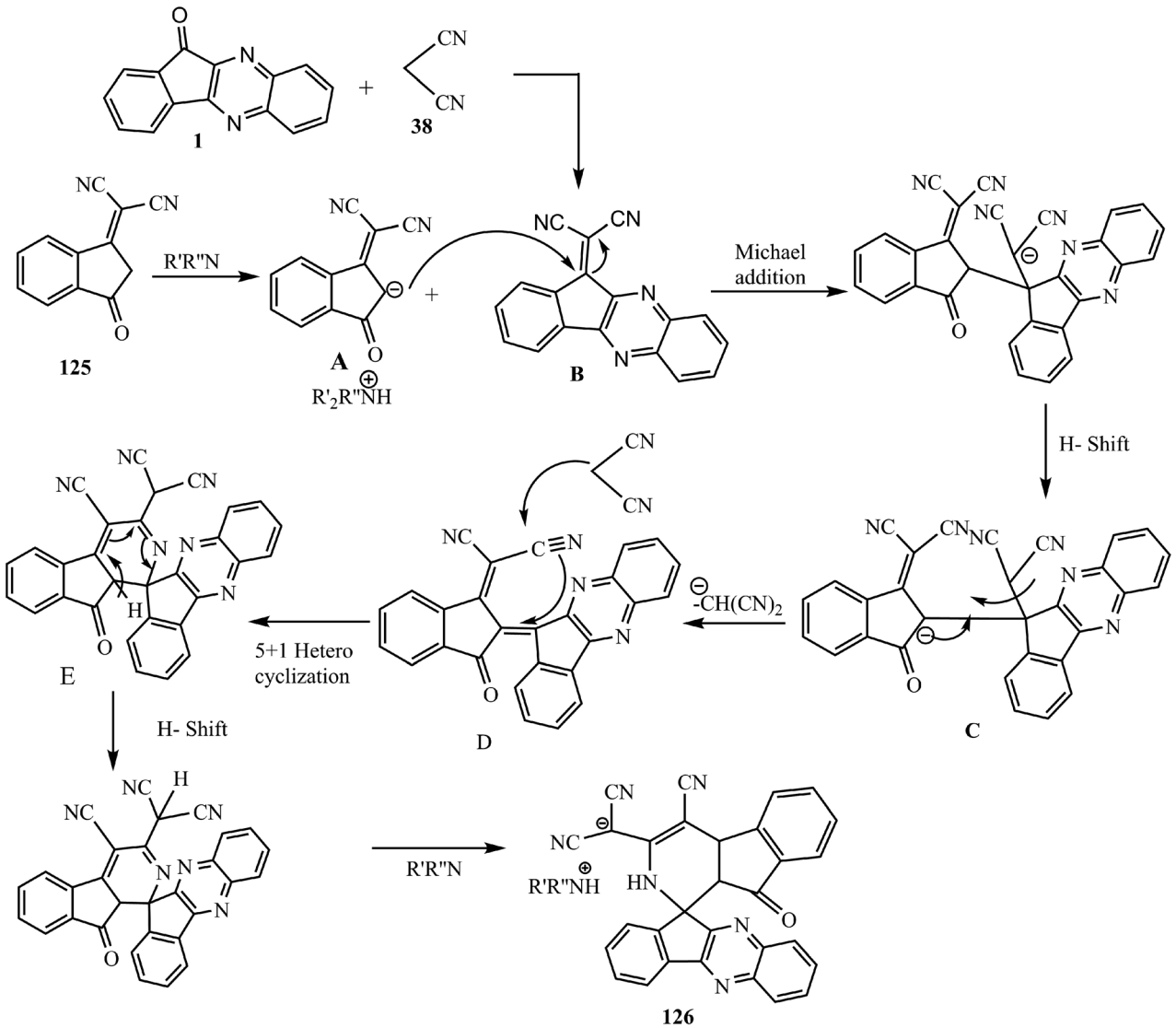
Scheme 66 Synthesis of diverse spiroindenoquinoxaline-pyrans **124** catalyzed by different catalysts.



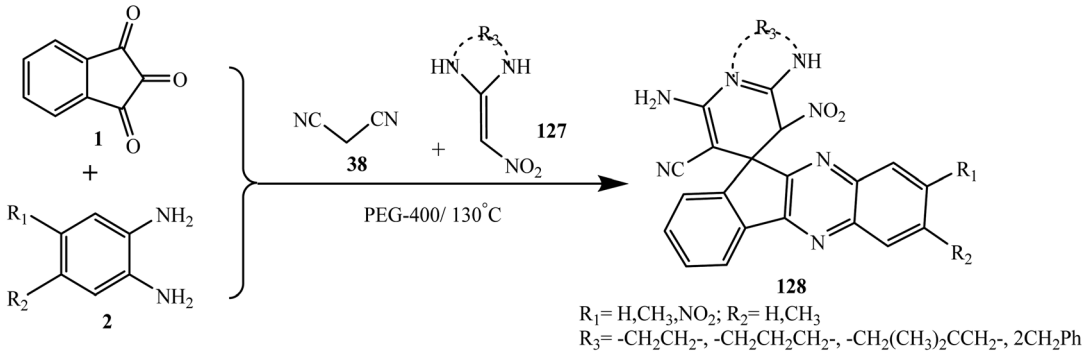
Scheme 67 Synthesis of spiroindeno[1,2-*b*]quinoxaline-11,1′-indeno[2,1-*c*]pyridine salts **126**.

carbonyl compounds (β-diketones, pyrazolones) and malononitrile **38** to give spiroindenoquinoxaline derivative **124** using Et_3N as a basic catalyst in EtOH.

In 2016, Zare *et al.*[110] introduced a novel heterogeneous catalyst, acetic acid-functionalized poly(4-vinylpyridinium) bromide, for the synthesis of spiro[indeno[1,2-*b*]quinoxaline-11′,4-pyrano] derivatives **124** under solvent-free and mild reaction conditions. The prepared spiropyrans were subjected to antioxidant activity screening by DPPH free radical scavenging assay and antifungal activity screening against *Fusarium*



Scheme 68 Proposed mechanism for the synthesis of spiroindenoquinoxaline-pyridine **126**.



Scheme 69 Synthesis of spiroindenoquinoxaline-pyridine/pyridopyrimidine derivatives **128**.

oxysporum. The synthesized spiropyrans showed strong antioxidant activity and also good inhibition activity against *Fusarium oxysporum*.

Heravi *et al.* in 2017[111] described the synthesis of spiro[indeno[1,2-*b*]quinoxaline-11′,4-pyrano] derivatives **124** under catalyst-free conditions from the condensation of malononitrile or ethyl 2-cyanoacetate **38**, ninhydrin **1**, 1,2-phenylenediamine **2**, and 1,3-dicarbonyl compounds **123** using trifluoroethanol as an efficient and recyclable medium under ultrasound irradiation at room temperature.

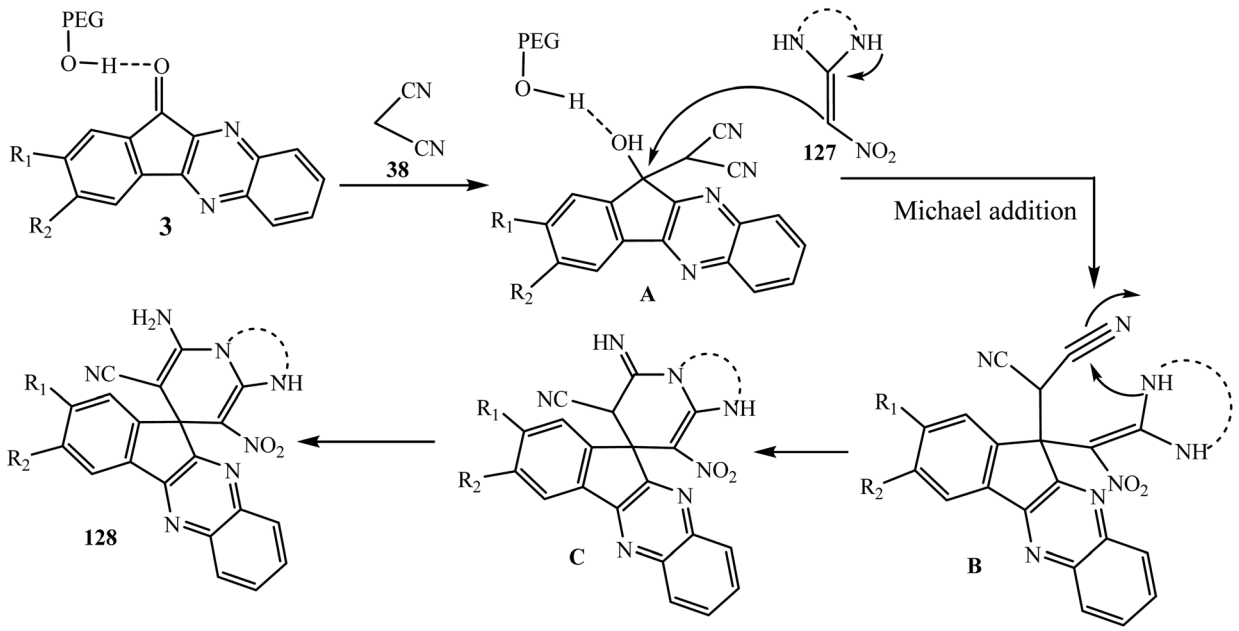
In 2016 Ahmadi *et al.*[112] amino-functionalized SBA-15 (SBA-Pr-NH_2) with a pore size of 6 nm. The organocatalyst was used as reusable catalyst for the synthesis of spiro compounds **124** in high yields and in short reaction times.

Safari *et al.* in 2019[113] demonstrated a four-component reaction using $NiFe_2O_4/Ag_3PO_4$ as a novel magnetically reusable nanocatalyst and reported the synthesis of spiro[indeno[1,2-*b*]quinoxaline-11,4-pyran]-2′-amines **124** in good yield in short reaction time with environmentally friendly conditions. Hojati and coworkers[114] demonstrated the synthesis of spiro[indeno[1,2-*b*]quinoxaline-11′,4-pyrano] derivatives **124** *via* four-component reaction using magnetically separable heterogeneous nanocatalyst poly(Py-*co*-Ani)@GO–Fe_3O_4 in mild reaction conditions.

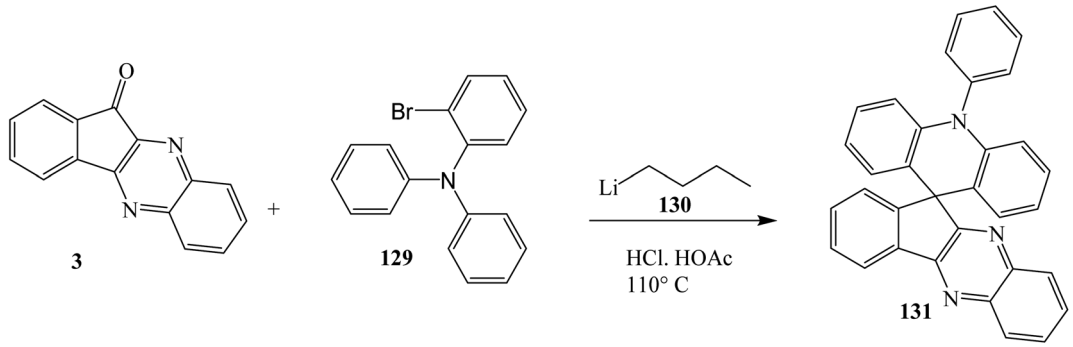
The mechanistic path for the synthesis of diverse spiroindenoquinoxalines-pyrans **124** involves an initial Knoevenagel condensation between indenoquinoxalinone **3** (derived from the reaction of ninhydrin **1** and benzene-1,2-diamine **2**) with the active methylene substrate (malononitrile/ethylcyanoacetate) **38** and after that Michael addition with 1,3-dicarbonyl **123** and then cyclization.

5.6. Spiroindenoquinoxaline-pyridine derivatives

The indenopyridine framework is a privileged heterocyclic scaffold since it appears in the 4-azafluorenone group of alkaloids and is also well known due to biological applications since



Scheme 70 Plausible mechanism for the synthesis of spiroindenoquinoxaline-pyridine/pyridopyrimidines **128**.



Scheme 71 Synthesis of spiro[acridine-9,110-indeno[1,2-*b*]quinoxaline] (SAIQ) **131**.

it has insecticidal, phosphodiesterase inhibiting, antifungal, anti-spermatogenic, antifertility, antagonistic, antidepressant and antiarrhythmic activities.[115] As a result, the synthesis of new heterocycles containing both spiroindeno[1,2-*b*]quinoxalines and indenopyridine moieties may result in the discovery of new drug candidates.

In 2016 Bazgir *et al.*[116] designed and synthesized highly functionalized complex products dicyano(4′-cyano-9′-oxo-2′,9′-dihydrospiro[indeno[1,2-*b*]quinoxaline-11,1′-indeno[2,1-*c*]pyridine]-3′-yl)methanide salts **126** regioselectively in good yields *via* multicomponent reaction of 1,1-dicyanomethylene-3-indanone **125**, indeno[1,2-*b*]quinoxalin-11-ones **3** and malononitrile **38** in the presence of amines as a base in ethanol (Scheme 67). The salt was successfully neutralized using dilute hydrochloric acid.

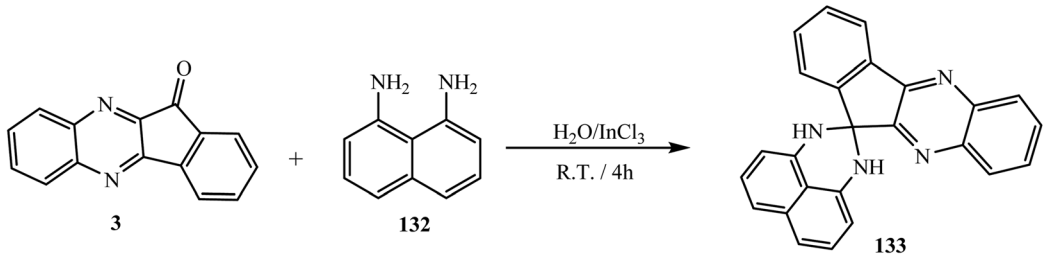
A feasible reaction mechanism for this one-pot process probably occurs *via* a domino reaction through a Knoevenagel/Michael/elimination/[5 + 1] cyclization series, as outlined in Scheme 68.

Initially, anion intermediate **A** is formed by the deprotonation of **125** in the presence of amine. Then, Michael-type addition reaction of **A** to intermediate **B** (formed *in situ* by the reaction of **3** and **38**) followed by H-shift, produces a new intermediate **C**, which further converts to intermediate **D** after the loss of dicyanomethanide from **C**. Next, the [5 + 1] heterocyclization of this intermediate with malononitrile leads to **E**. Finally, the H-shift and deprotonation by the amine afford spiro product **126.**

Hasaninejad *et al.*[117] discovered a convenient synthesis of hitherto unknown spiroindenoquinoxaline-pyridine/pyridopyrimidine derivatives **128** *via* the one-pot multicomponent reaction of ninhydrin **1**, substituted *o*-phenylenediamine **2**, malononitrile **38** and *N*,*N*′-substituted 2-nitroethene-1,1-diamines **127** under catalyst-free green conditions using PEG-300 (Scheme 69). Synthesized spiro compounds were evaluated both *in silico* and *in vitro* for their ability to inhibit AChE and BChE and the results were similar to those of galantamine as a positive control standard.

A tentative mechanism for this transformation is proposed in Scheme 70. It is conceivable that the reaction involves the formation of Knoevenagel adduct 11-(propane-2-ylidene)-11*H*-indeno[1,2-*b*]quinoxaline **A** *via* the condensation reaction of malononitrile **38** with indenoquinoxalinone **3** (generated *in situ* from the condensation reaction of *o*-phenylenediamine **2** with ninhydrin **1**) followed by the Michael addition of various 2-nitroethene-1,1-diamines **127**. Subsequently, the cycloaddition of an amine group to the cyano moiety occurs with successive rearrangements to afford the desired corresponding spiroindenoquinoxaline derivatives **128** in good yields.

In 2018, Fan *et al.*[118] reported the novel spirocyclic compound 10*H*-spiro[acridine-9,110-indeno[1,2-*b*]quinoxaline] (SAIQ) **131** containing an electron-donating acridine unit and an electron-withdrawing pyrazine segment by the reaction of indeno[1,2-*b*]quinoxalinone **3**, 2-bromo-*N*,*N*-diphenylaniline **129** and *n*-butyl lithium **130** using THF at −78 °C (Scheme 71). In that report the basic physical and chemical properties of SAIQ were studied in detail. In addition, blue/green/red and green/red phosphorescent organic light-emitting diodes were fabricated with SAIQ as host materials and showed a relatively high device performance with maximum external quantum efficiencies.



Scheme 72 Synthesis of dihydrospiro[indeno[2,1-*b*]quinoxaline-11,2′-perimidine] **133**.

5.7. Spiroindenoquinoxaline-perimidines

Bazgir *et al.*[119] reported the synthesis of 1′,3′-dihydrospiro [indeno[2,1-*b*]quinoxaline-11,2′-perimidine] **133** *via* the cyclic condensation reaction of naphthalene-1,8-diamine **132** and indeno[2,1-*b*]quinoxalinone **3** using water as a "green" reaction medium at room temperature under mild reaction conditions (Scheme 72).

6. Conclusions

This review summarizes the use of indenoquinoxalinone as a building block in the synthesis of the diverse spirocyclic frameworks of heterocyclic compounds to date. Indenoquinoxalinone has been utilized in the construction of spiro-β-lactams, spirofurans, mono- and dispiropyrrolidines/pyrrolizidines, spirothiazolidinones, and spiropyran skeletons grafted with other bioactive moieties. Most reactions described in this review involve multiple components and cycloaddition, and interesting examples of the regio- and stereoselective synthesis of biologically relevant compounds have also been presented. Many synthetic compounds also exhibit potential antimicrobial, anticancer and other interesting activities.

We think that this review will draw the attention of researchers in the field of synthetic organic chemistry and biology for the design and development of new viable spirocyclic frameworks to deliver new drug candidates in the future.

Conflicts of interest

There are no conflicts to declare.

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