Synthesis of heterocyclic compounds based on isatin through 1, 3-dipolar cycloaddition reactions

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Abstract

This review gives an overview of the advances in the use of isatin in the synthesis of various heterocyclic compounds via 1,3-dipolar cycloaddition reactions during the period from 2000 to 2011.

Keywords: Isatin, 1,3-dipolar cycloaddition reaction, heterocycles, spirooxindole pyrrolidine

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1. Introduction

The biological and pharmacological properties of isatin and its derivatives have led to extensive use of these compounds as key intermediates in organic synthesis.[1] Isatin is a core constituent of many alkaloids[2] and drugs[3] as well as dyes,[4] pesticides and analytical reagents. Literature surveys reveal that various derivatives of isatin possess diverse activities such as antibacterial,[5]

antifungal,[6] antiviral,[7] anti-HIV,[8] anti-mycobacterial,[9] anticancer,[10] anti-inflammatory[11] and anticonvulsant activities.[12]

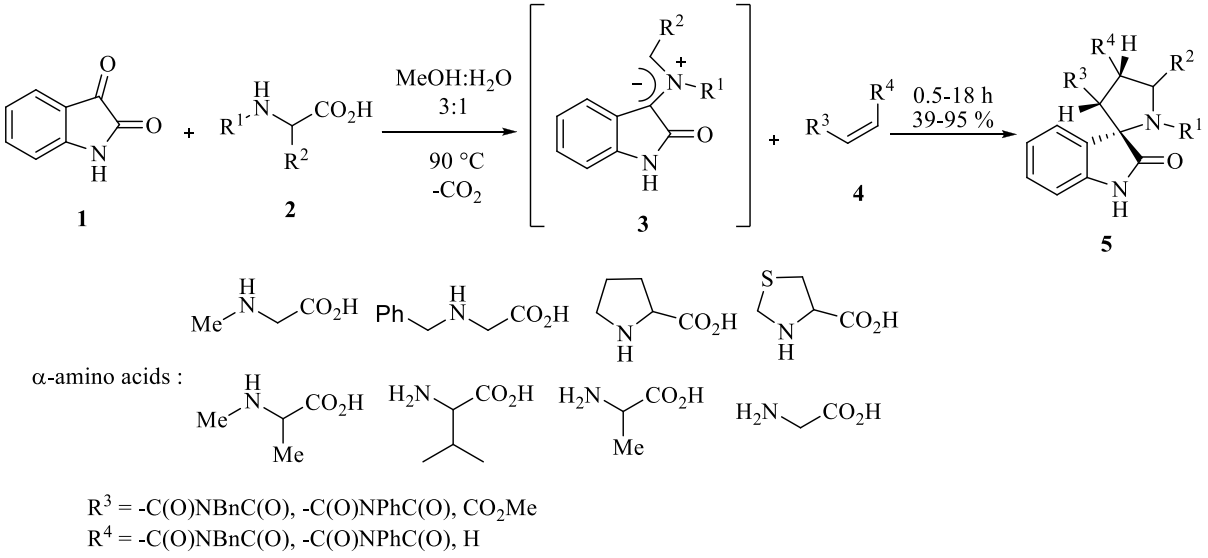
Furthermore, isatins with their multifunctionality and diversity of transformations are synthetically versatile substrates and many efforts have been made toward the synthesis of these compounds.

1,3-Dipolar cycloaddition, also known as the Huisgen reaction,[13] is regarded as one of the most attractive methods for the formation of pharmacologically important five-membered N-heterocyclic compounds. 1,3-Dipolar cycloaddition of ylidic species such as azomethine ylides with dipolarophiles provides an efficient and convergent approach for constructing pyrrolidine rings which are classes of compounds with significant biological activities.

Considering isatin as an important building block in organic synthesis, and since there is a wide range of reactions that include isatin in the synthesis of heterocyclic compounds, in the present review the focus is on applications of isatin in 1,3-dipolar cycloaddition reactions from reports that have been published after 2000.

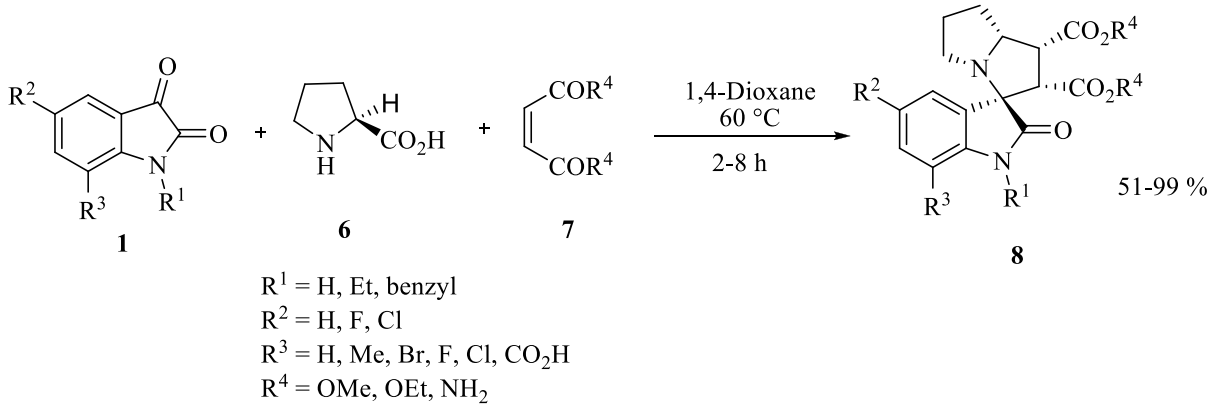
2. Synthesis of Monospiropyrrolo/pyrrolizidino-oxindole Ring Systems

Bergman and coworkers condensed isatin **1** with a number of α-amino acid derivatives **2** in a methanol/water medium. Formation of the anti-azomethine ylides **3** followed by the 1,3-dipolar addition of the dipolarophiles **4** yielded the pyrrolidine-2-spiro-3-(2-oxindole)s **5** (Scheme 1).[14]



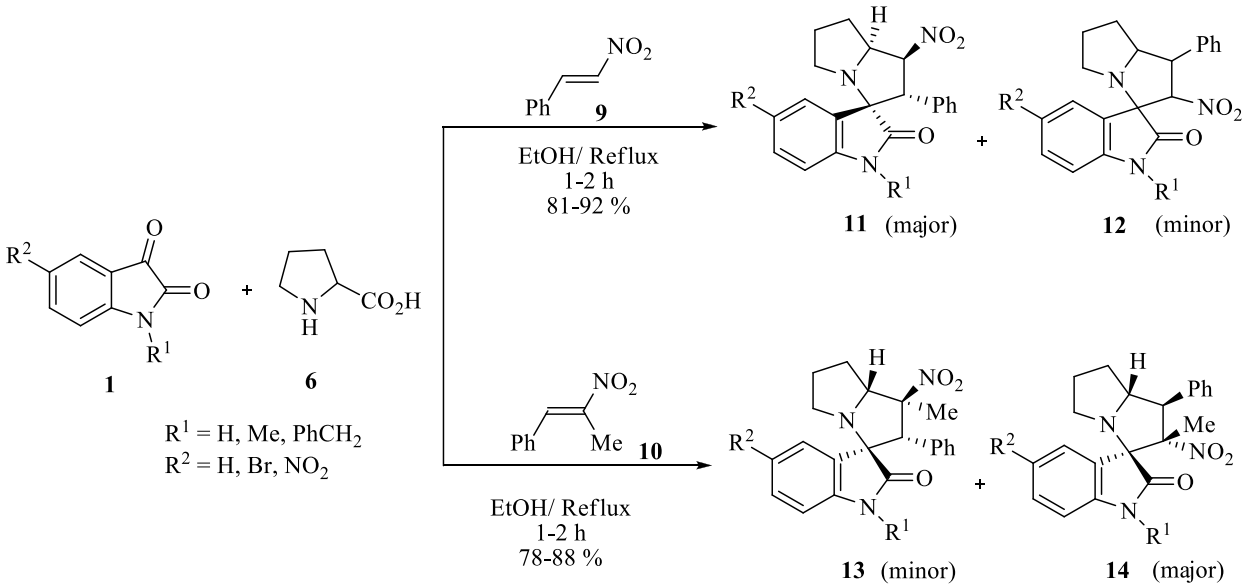
Scheme 1

The synthesis of spiropyrrolizidine oxindoles **8** containing two ester groups or two amide groups has been reported. In this reaction maleates or maleamides **7** act as dipolarophiles (Scheme 2).[15]

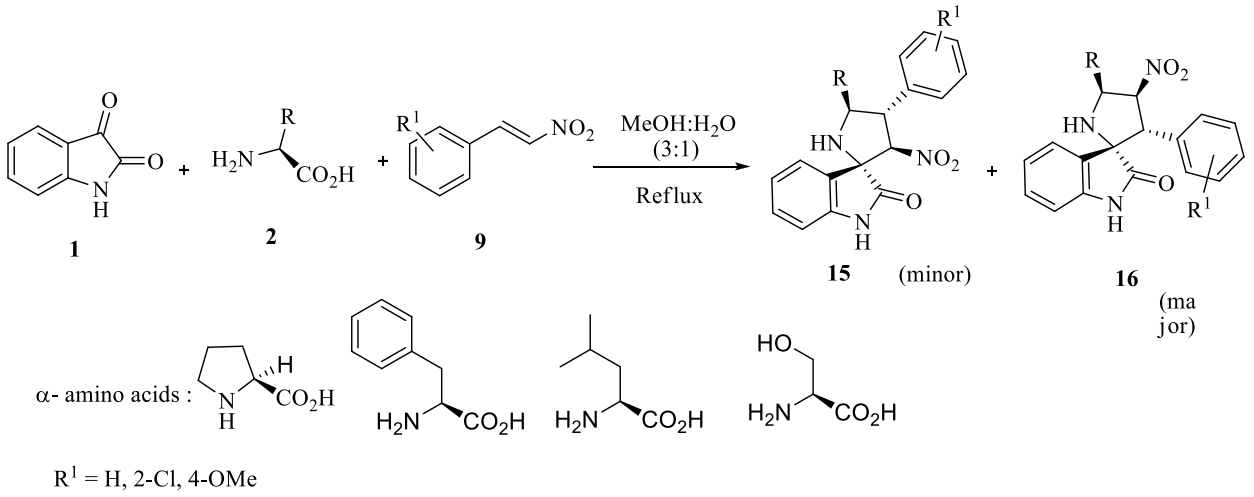


Scheme 2

The regio- and stereochemical 1,3-dipolar cycloaddition reaction of the azomethine ylides, which were generated *in situ* by the reaction of isatin derivatives and proline, with trans-β-nitrostyrene **9** and (*E*)-1-phenyl-2-nitropropene **10** were studied both experimentally and theoretically (Scheme 3).[16] In a related study, Chen and coworkers reported their new findings in the 1,3-dipolar cycloaddition reactions of isatin, α-amino acids **2**, and (*E*)-β-nitro-styrenes **9** with different regioselectivity (Scheme 4).[17] Perumal and coworkers evaluated these compounds for their *in vitro* activity against *Mycobacterium tuberculosis* H37Rv (MTB).[18]

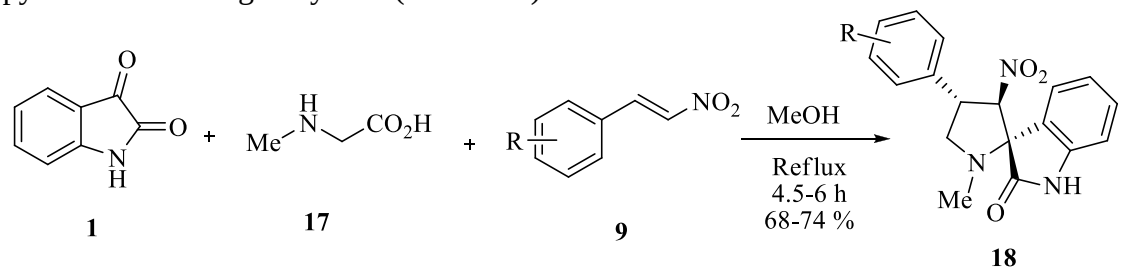


Scheme 3



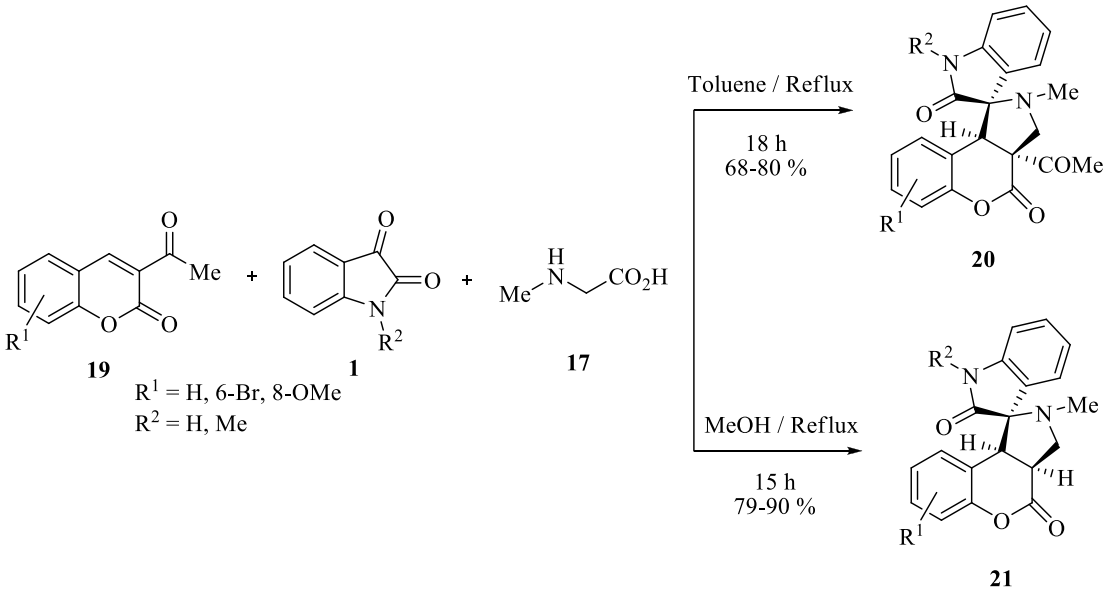
Scheme 4

β-Nitrostyrene **9** was also used in reaction with non-stabilized azomethine ylides generated from isatin **1** with sarcosine **17**, resulting in the formation of a series of spiro-oxindolo-nitropyrrolidines **18** in good yields (Scheme 5).[19]



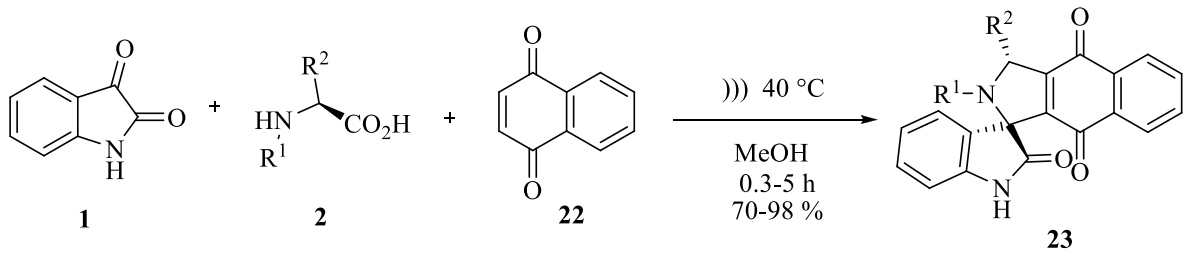
Scheme 5

The [3+2]-cycloaddition reaction of 3-acetylcoumarins **19** with azomethine ylides in toluene under reflux for 18 h afforded chromene bearing novel spiropyrrolidine-oxindoles **20**. The products **21** were surprisingly obtained when the reactions were carried out in methanol under reflux conditions for 15 h (Scheme 6).[20] The results show that the reaction in methanol was accompanied by deacetylation, presumably by nucleophilic attack of methanol at the COMe group.



Scheme 6

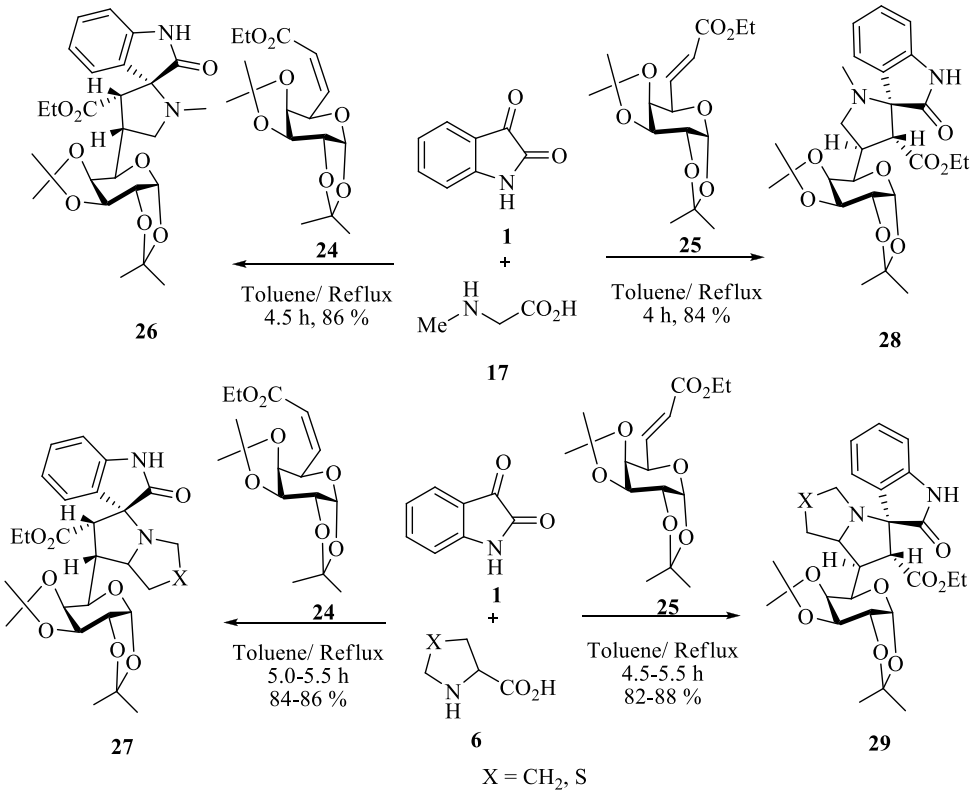
Chen and coworkers published a study of reactions of isatin, α-amino acids and 1,4-naphthoquinone **22** using ultrasound in methanol at about 40 °C to afford a series of 3-spiro[pyrrolidino-oxindoles] derivatives **23** (Scheme 7).[21]



amino acids : L-Proline, L-Isoleucine, L-Penylalanine, L-Tryptophan, L-Valine

Scheme 7

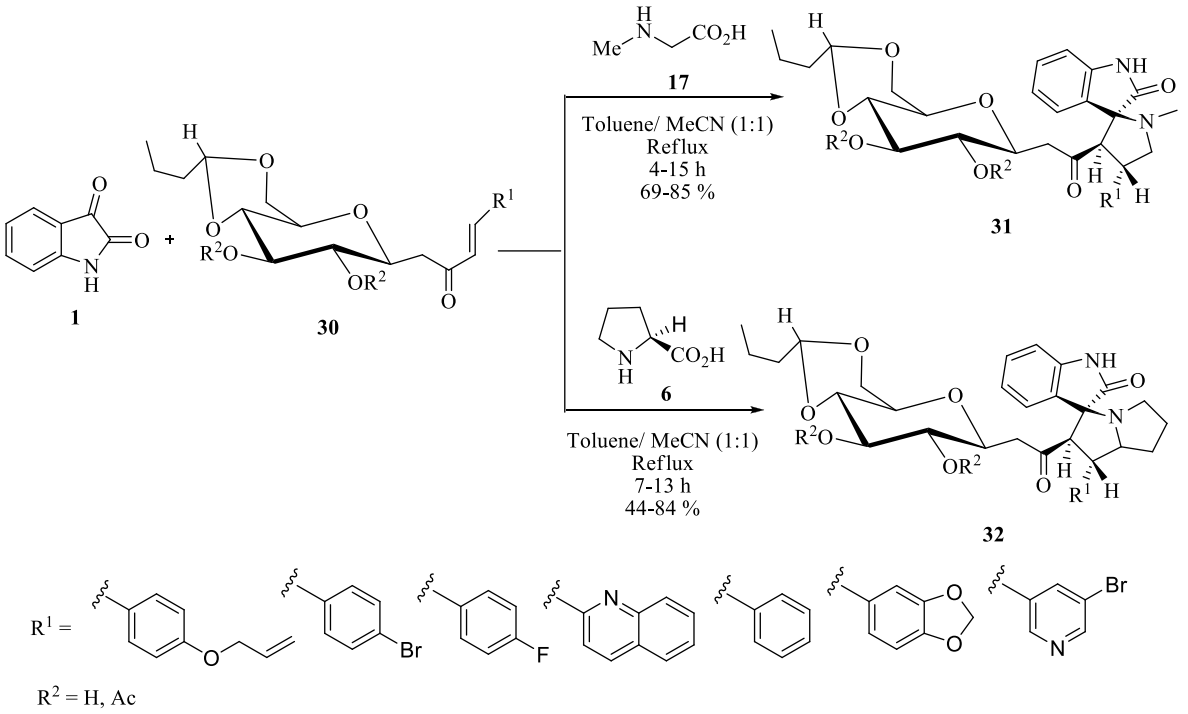
Dipolarophiles **24** and **25** derived from galactose have been reacted with azomethine ylides generated from isatin and secondary amino acids to give the corresponding spiro-glycoheterocycles **26-29** in good yields (Scheme 8).[22]



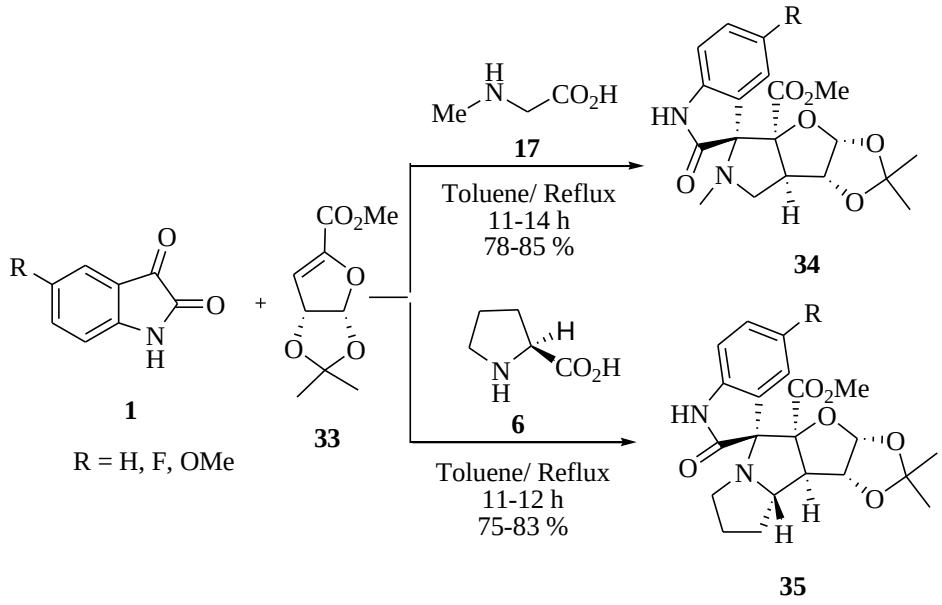
Scheme 8

One-pot reactions of various α,β-unsaturated β-C-glycosidic ketones **30** with the azomethine ylides resulted in the formation of novel sugar-based monospirooxindole-pyrrolidines **31** and **32** in 69–85% yields (Scheme 9).[23]

In another study, application of the 1,3-dipolar cycloaddition reaction of an azomethine ylide with a carbohydrate-derived olefin **33** has been reported by Banerjee and coworkers. In this study, a series of sugar-fused spiro-pyrrolidine, -pyrrolizidine, and -indolizidine heterocycles **34** and **35** were synthesized (Scheme 10).[24]



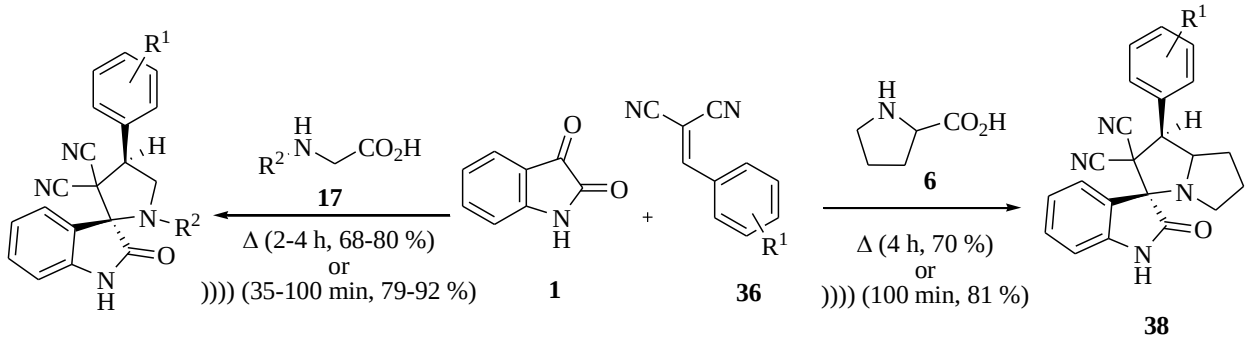
Scheme 9



Scheme 10

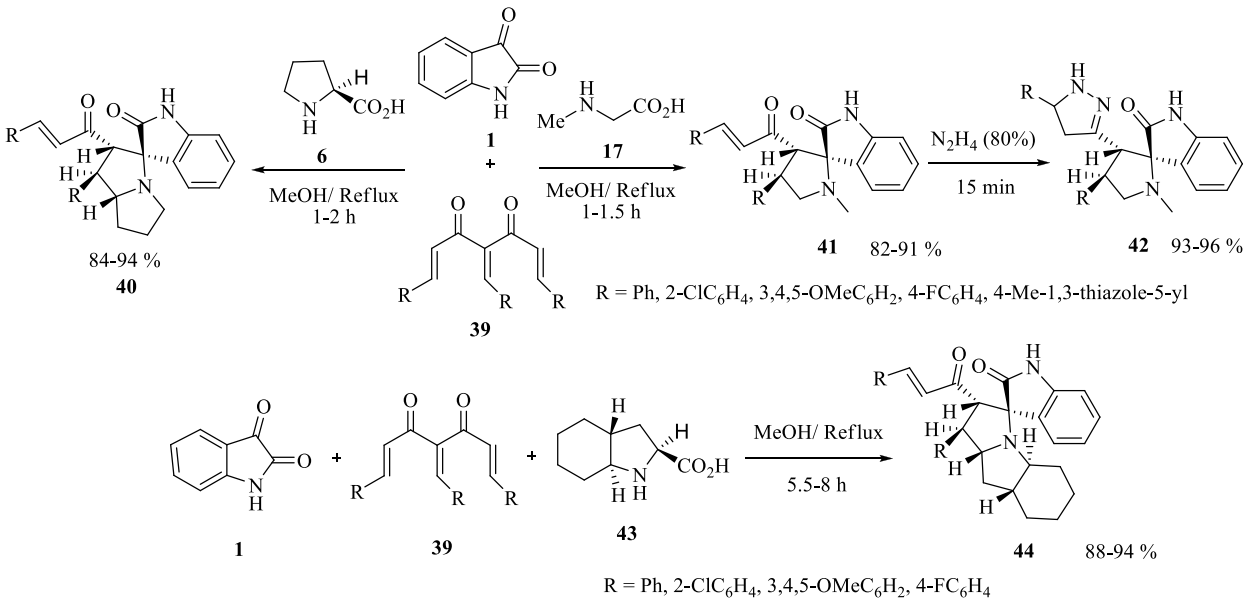
A synthetic route for the preparation of a novel class of dicyano- functionalised spiropyrrolidine **37** and spiropyrrolizidine **38** from the reaction of various arylidenemalononitrile Knoevenagel adducts **36** with non-stabilized azomethine ylides generated from isatin and α-

amino acids (sarcosine/*N*-phenylglycine/proline) has been developed (Scheme 11).[25] The reactions were carried out under both conventional heating and ultrasonic irradiation conditions.



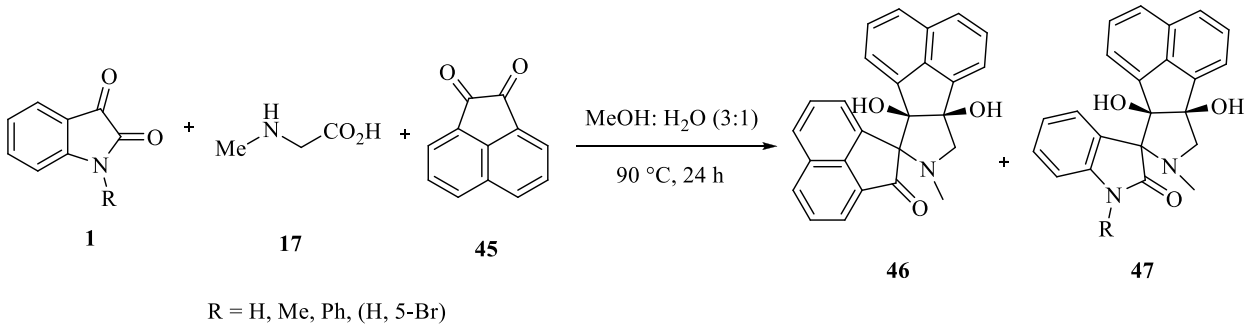
Scheme 11

When various derivatives of trisbenzylidene acetylacetone **39** as unusual dipolarophiles were subjected to 1,3-dipolar cycloaddition with the azomethine ylides, novel spiroheterocycles **40, 41,** and **44** with high regio- and stereoselectivity were obtained (Scheme 12).[26]



Scheme 12

Acenaphthoquinone **45** as a 1,2-dione in reaction with isatin and sarcosine afforded a mixture of two products, **46** and **47** (Scheme 13).[27]

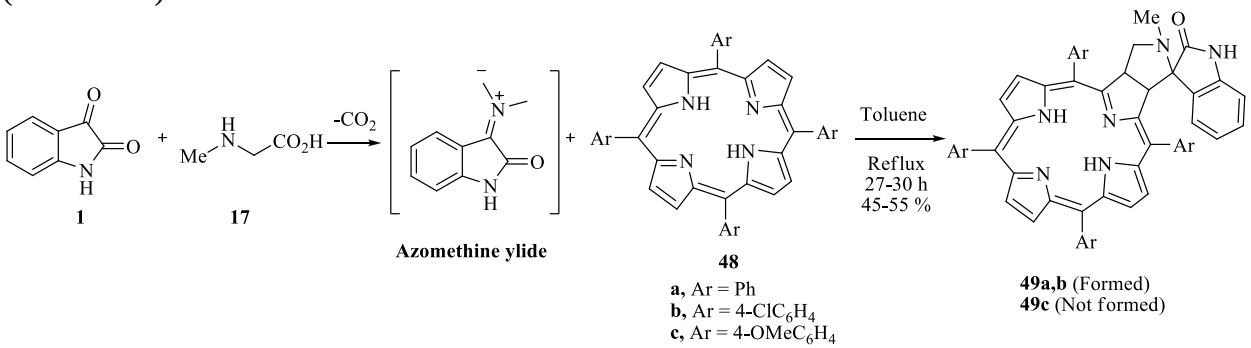


1 **17** **45** **46** **47**

R = H, Me, Ph, (H, 5-Br)

Scheme 13

The reaction of various porphyrin derivatives **48** with the azomethine ylide generated from isatin/*N*-benzylisatin and sarcosine in refluxing toluene afforded a series of novel chlorin-fused monospirooxindolopyrrolidines **49** in good yield via a facile [3+2]-cycloaddition reaction (Scheme 14).[28]



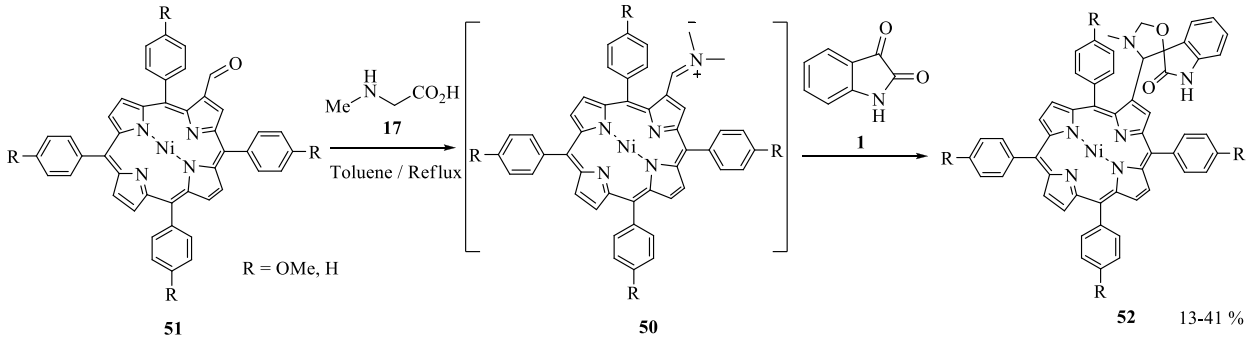
1 **17** **Azomethine ylide** **48**

a, Ar = Ph
b, Ar = 4-ClC_6H_4
c, Ar = 4-$OMeC_6H_4$

49a,b (Formed)
49c (Not formed)

Scheme 14

The intermediate azomethine ylide **50** (derived from Ni(II) β-formyl-*meso*-tetraphenyl-porphyrin in the presence of *N*-methylglycine) and its 1,3-dipolar cycloaddition with isatin to give the porphyrin derivatives **52** was also reported (Scheme 15).[29]



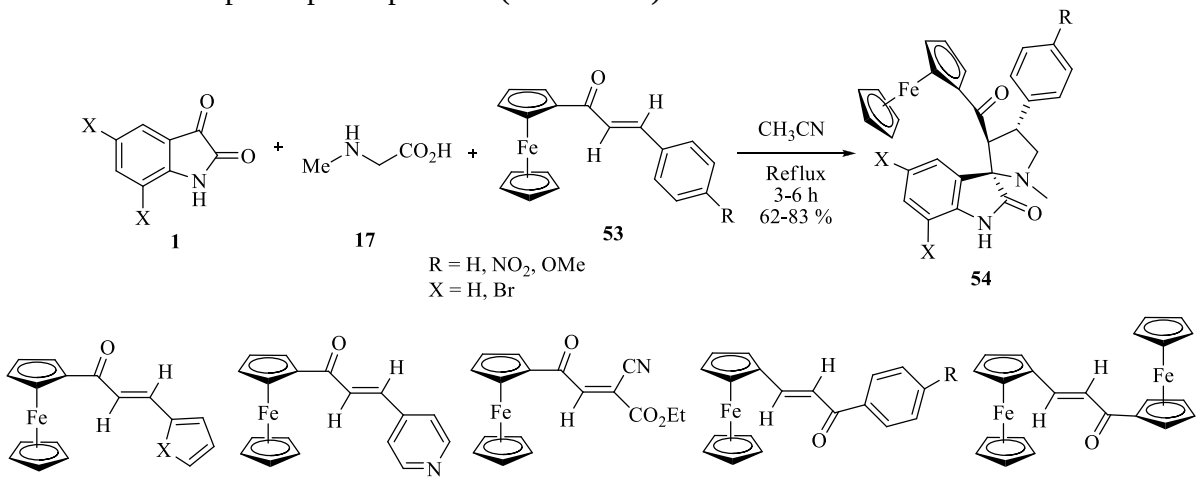
R = OMe, H

51 **50** **52** 13-41 %

Scheme 15

One-pot synthesis of novel ferrocenyl monospirooxindolopyrrolidines **54** has been accomplished in good yield via a facile [3+2]-cycloaddition reaction of several azomethine

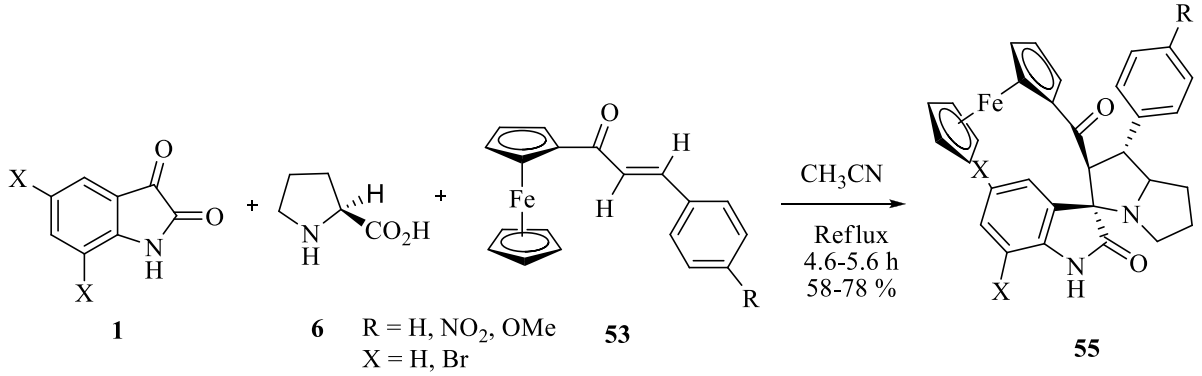
ylides, derived from isatin/5,7-dibromoisatin and sarcosine, with various unusual ferrocene derivatives **53** as dipolarophilic partners (Scheme 16).[30]



1 17 53 54

Scheme 16

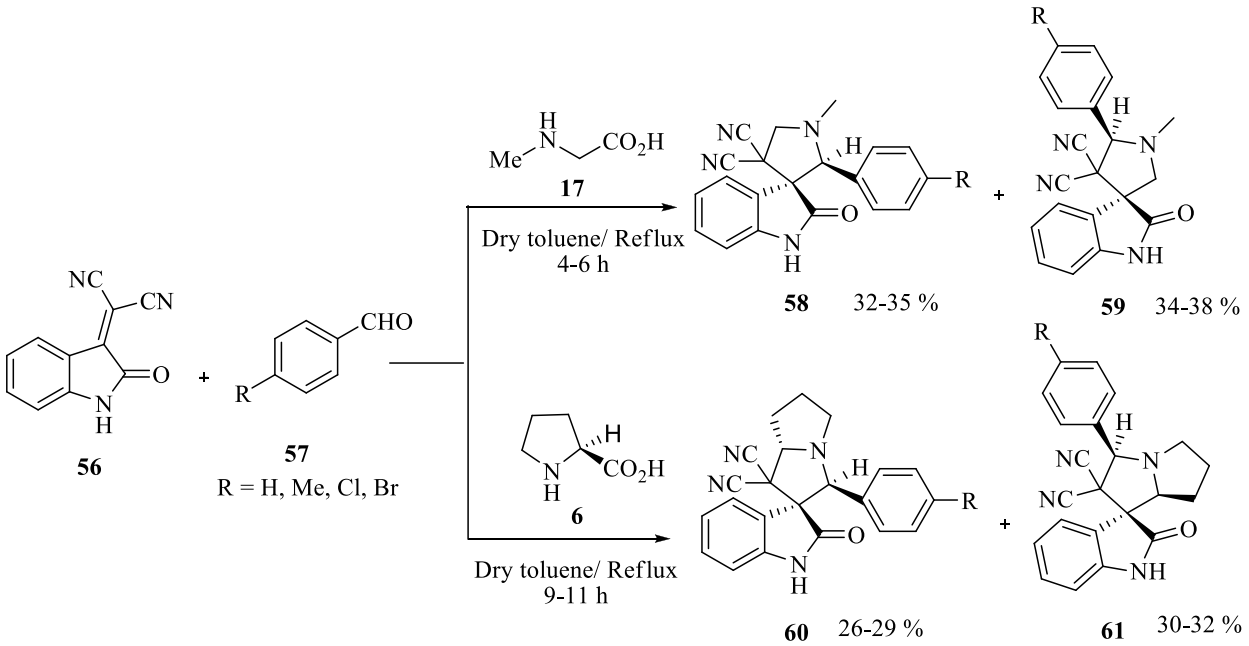
This reaction was also carried out with L-proline **6** in place of sarcosine (Scheme 17).[31]



1 6 53 55

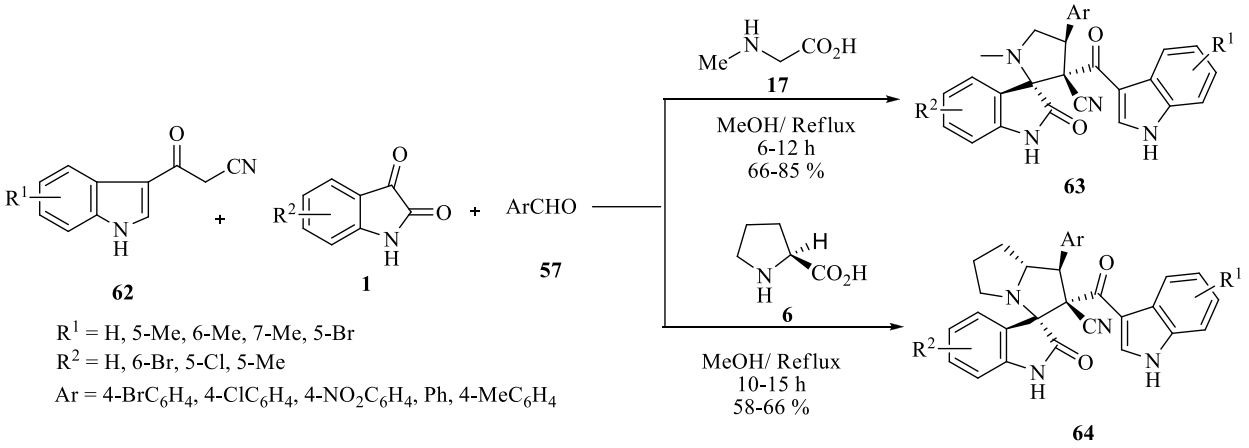
Scheme 17

The one-pot, three-component condensation of sarcosine or proline Schiff bases with several aromatic aldehydes **57** and the Knoevenagel adduct 2-(2-oxoindolin-3-ylidene)malononitrile derivatives **56** successfully afforded spiropyrrolidine-oxindoles **58** and **59** and spiropyrrolizine-oxindoles **60** and **61** (Scheme 18).[32]



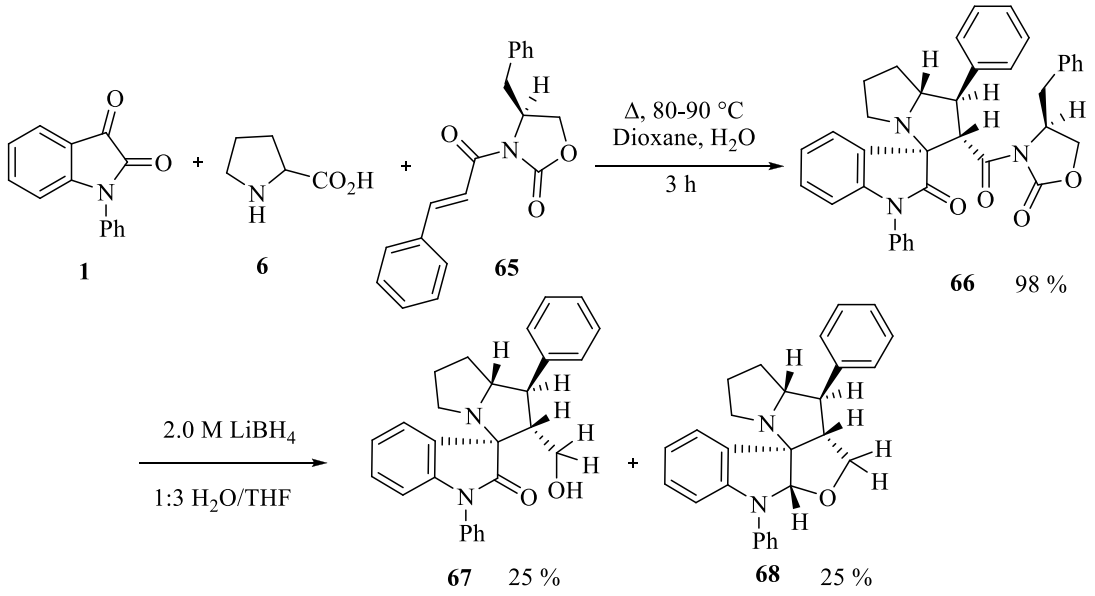
Scheme 18

A multicomponent [3+2] cycloaddition reactions of 3-cyanoacetylindoles **62**, aldehydes **57**, isatin **1** and amino acids **6** and **17** was reported by Xu and coworkers (Scheme 19).[33]



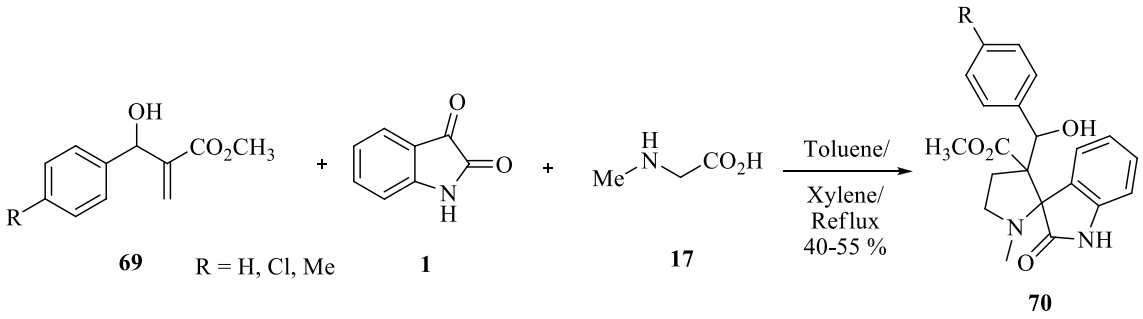
Scheme 19

The reaction of *N*-phenyl isatin with proline and **65** in aqueous dioxane at 80–90 °C for 3 h yielded **66** (98%) as the only diastereoisomer. Reduction of **66** with excess of lithium borohydride in aqueous tetrahydrofuran yielded a mixture of **67** (25%) and **68** (25%) (Scheme 20).[34]



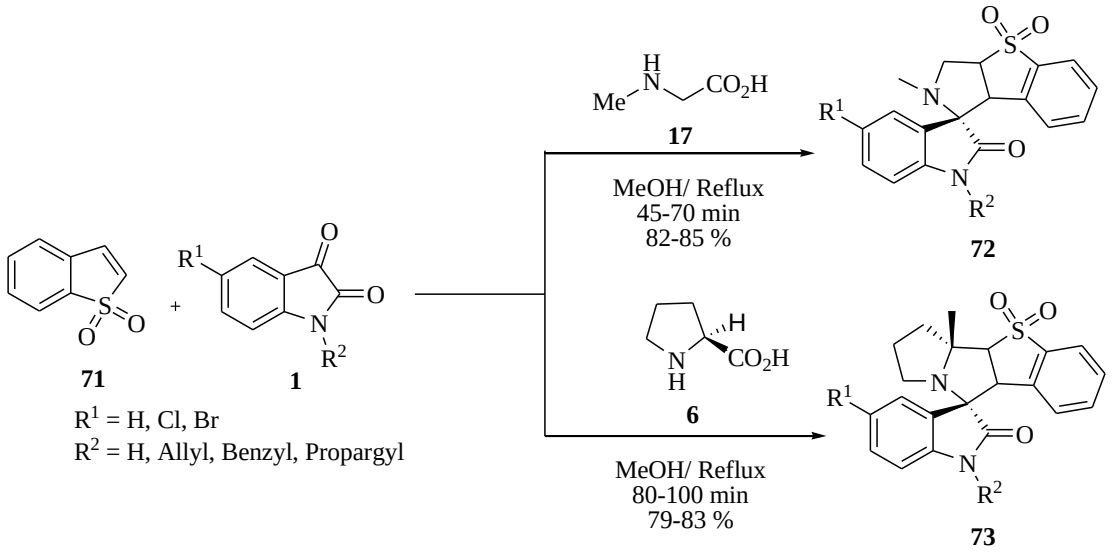
Scheme 20

The cycloaddition reaction of azomethine ylides generated by the reaction of isatin and sarcosine, with the olefinic bond of Baylis-Hillman adducts **69** gave the corresponding cycloadducts **70** as single regioisomers as disclosed by Raghunathan and coworkers (Scheme 21).[35]



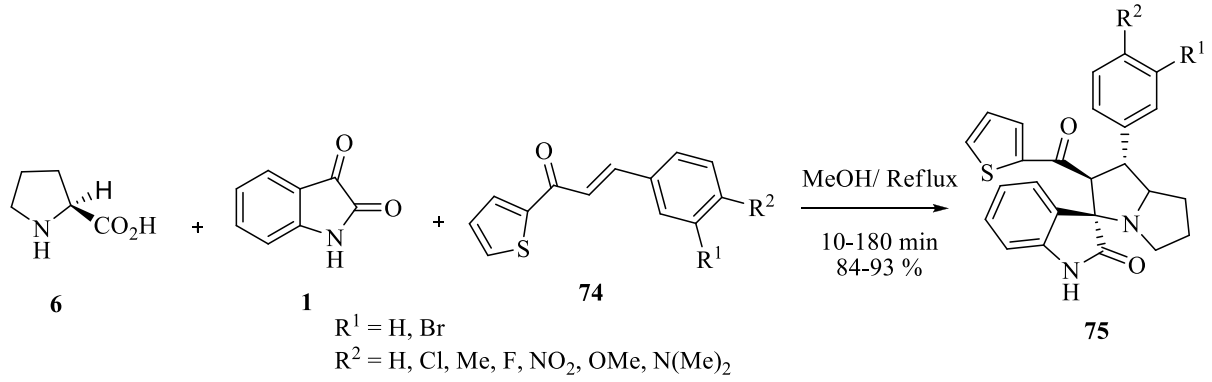
Scheme 21

A series of spirooxindoles containing tri- and tetracyclic fused pyrrolo-benzothiophene 1,1-dioxide derivatives **72** and **73** were synthesized regioselectively via a multicomponent 1,3-dipolar cycloaddition of isatin, 1-benzothiophene 1,1-dioxide **71** and sarcosine or L-proline (Scheme 22).[36]



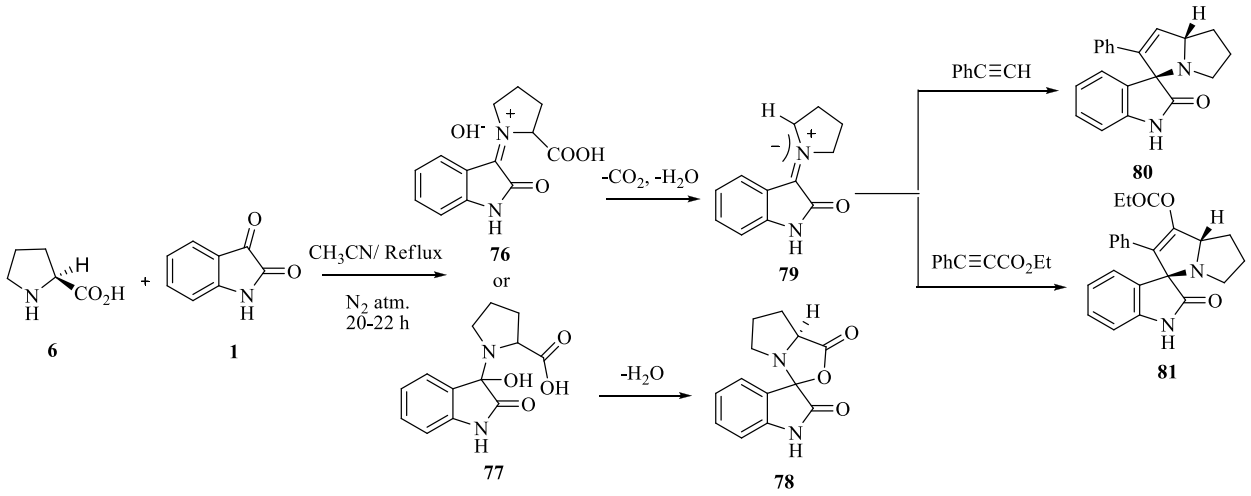
Scheme 22

Reaction of (*E*)-3-aryl-1-(thiophen-2-yl)prop-2-en-1-ones **74** with the azomethine ylide generated by the reaction of isatin and proline in refluxing methanol afforded the products **75** in a regiospecific manner (Scheme 23).[37] The compounds synthesized were screened for their antibacterial and antifungal activities.



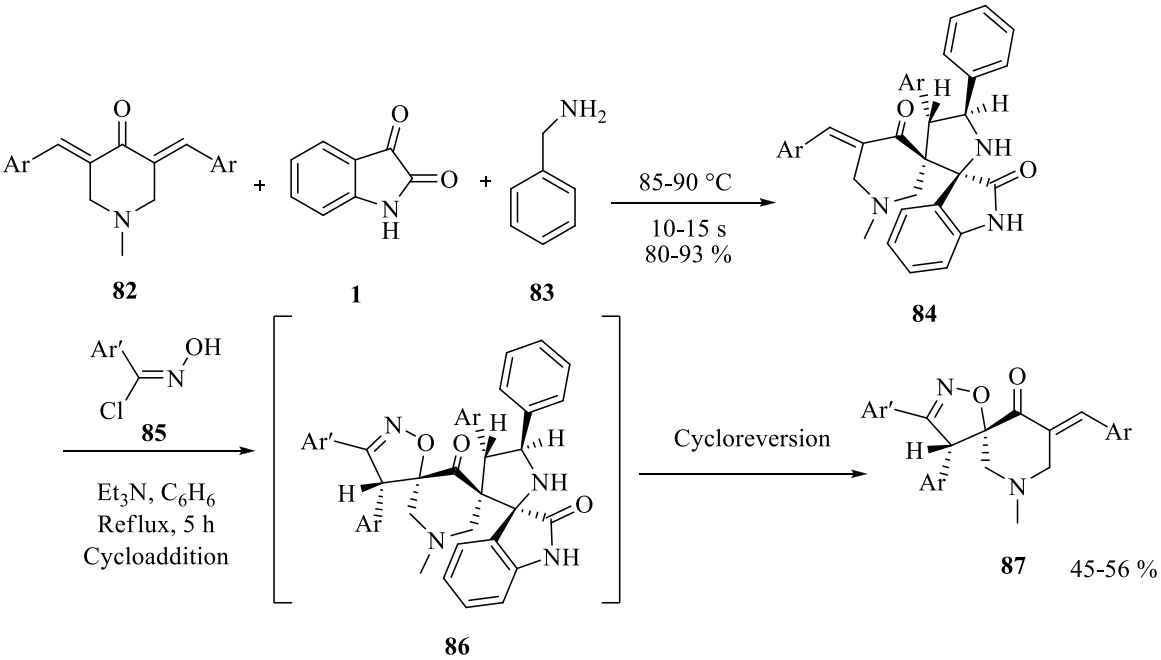
Scheme 23

Investigations by Pardasani and coworkers have shown that the oxazolidinone compound **78**, was derived from the condensation of isatin with L-proline, while in the presence of a dipolarophile, the intermediate iminium species **76** underwent decarboxylation to give the azomethine ylide **79** which subsequently underwent 1,3-dipolar cycloaddition reactions to give spiro-polycyclic compounds **80** and **81** (Scheme 24).[38]



Scheme 24

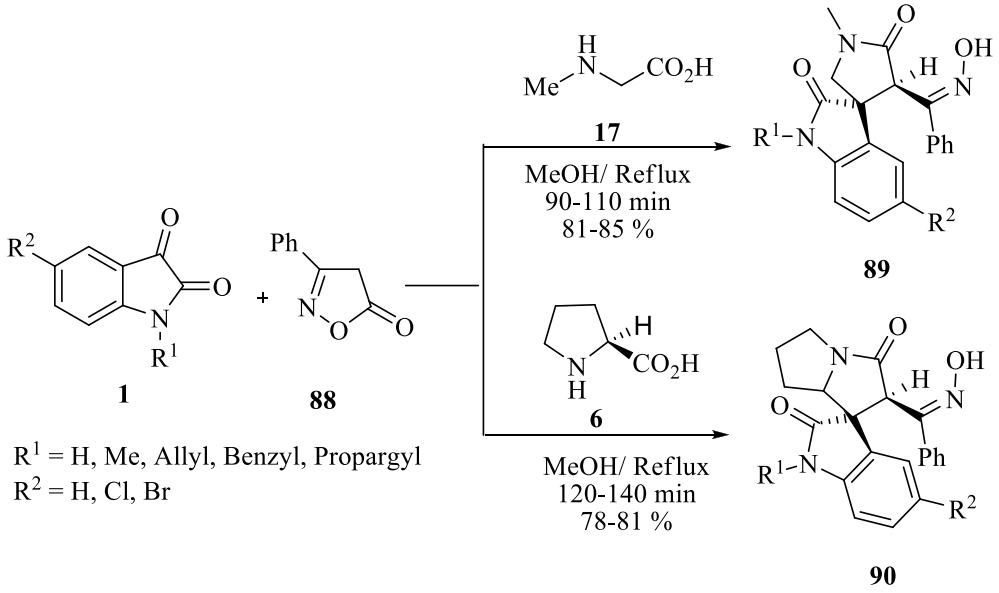
3,5-Bis(arylmethylidene)-*N*-methyl-4-piperidinone **82** in reaction with isatin and benzyl amine yielded the desired product **84** that was subsequently reacted with a nitrile oxide generated *in situ* from 4-chlorobenzohydroximoyl chloride **85** and triethylamine, with a view to obtaining trispiro-compounds **86**. However, this reaction furnished solely monospiroisoxazolines **87** in 45–56% yields (Scheme 25).[39]



Ar = C_6H_6, *p*-$MeOC_6H_4$, *p*-MeC_6H_4, *p*-FC_6H_4, *p*-ClC_6H_4, 1-Naphthyl, *o*-ClC_6H_4, 2-Thienyl, 2-Furyl
Ar′ = *p*-ClC_6H_4

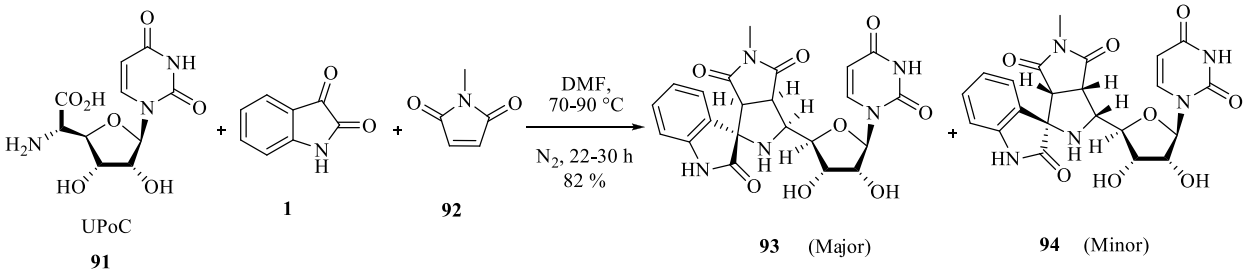
Scheme 25

The multicomponent reaction of isatin **1**, 3-phenyl-5-isoxazolone **88**, and sarcosine **17** or L-proline **6** in methanol under reflux has been reported (Scheme 26).[40] The reaction proceeded through an unusual mechanistic pathway resulting in the synthesis of spirooxindole derivatives **89** and **90**.



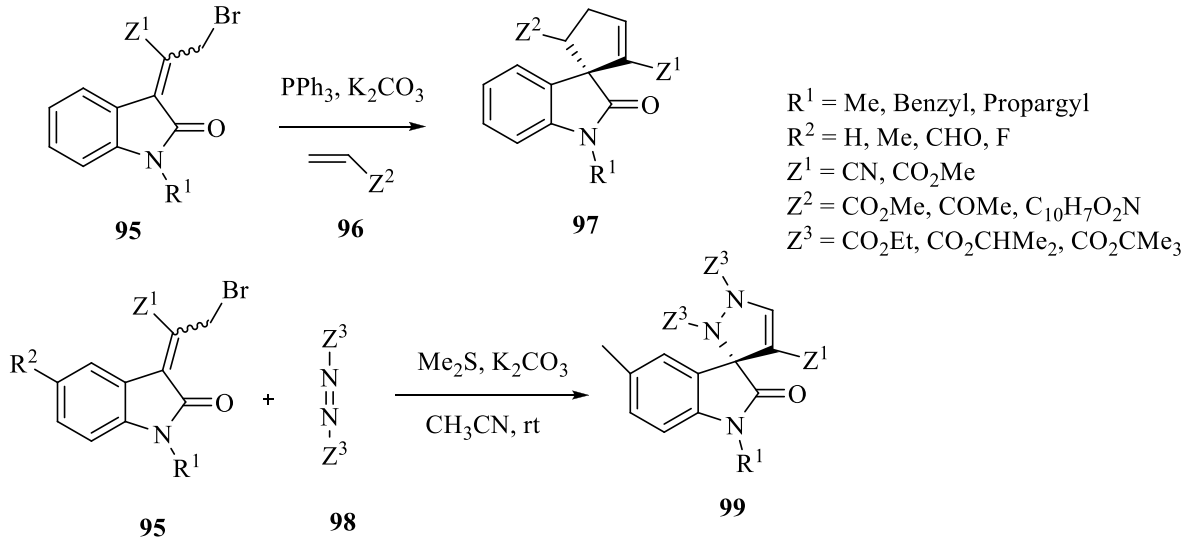
Scheme 26

Cascade thermal reactions of uracil polyoxin C (UPoC) **91** with isatin as a dicarbonyl compound in the presence of *N*-methylmaleimide (NMM) **92** leads, via an intermediate azomethine ylide, to polyoxin cycloadducts **93** and **94** in excellent yields (Scheme 27).[41]



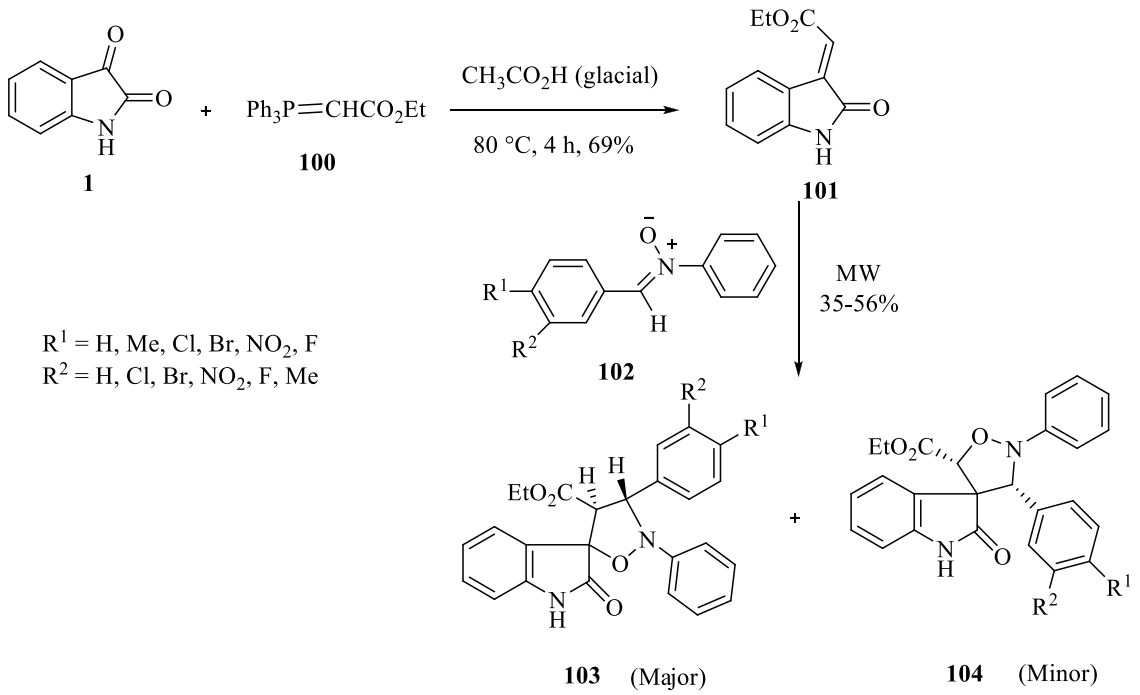
Scheme 27

The chemistry of phosphorus and sulfur ylides has been exploited for the reaction of various bromoallyl derivatives **95** with methyl acrylate, methyl vinyl ketone and *N*-phenylmaleimide **96** to afford the respective spirocyclic products **97** in good to moderate yields. The reaction of the bromoallyl derivatives of 1-methyl isatins **95** in acetonitrile with Me_2S, diazo compounds **98**, and K_2CO_3 at room temperature afforded 3-spiropyrazole-2-oxindoles **99** (Scheme 28).[42]



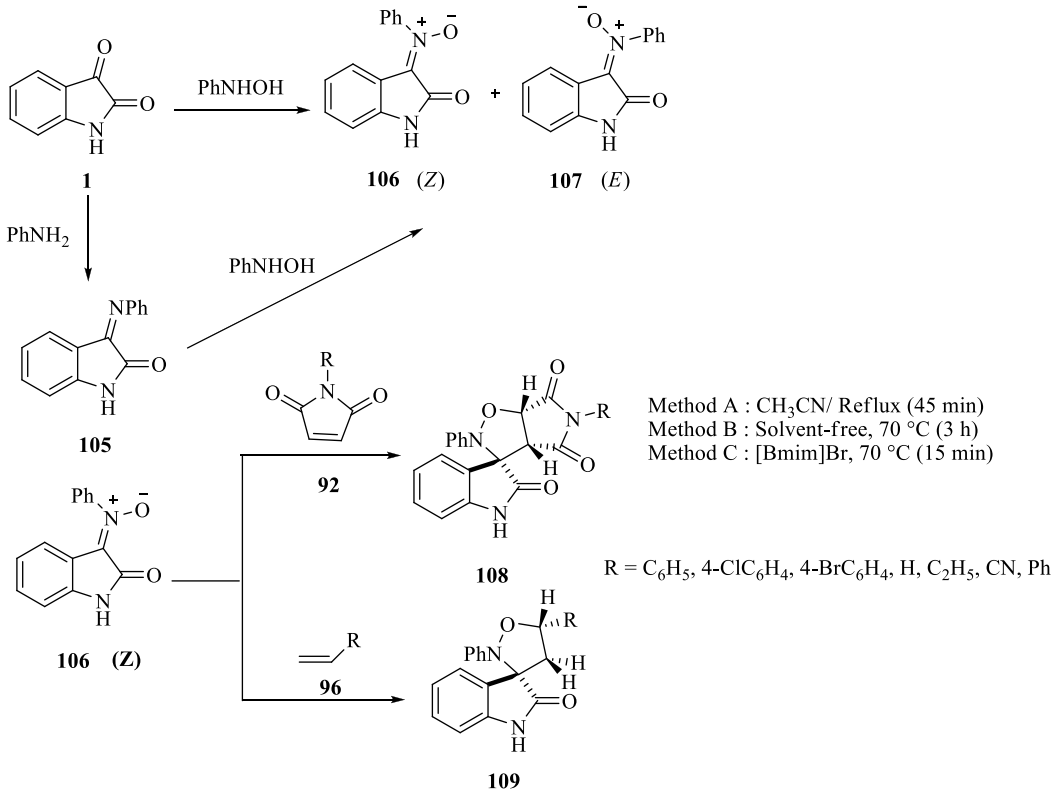
Scheme 28

Regioisomeric spiro(indoline-isoxazolidines) **103** and **104** have been synthesized in moderate yields by the cycloaddition reaction between ethyl (3-indolylidene)acetate **101** and various substituted α,*N*-diphenylnitrones **102**, using microwave irradiation (Scheme 29).[43]



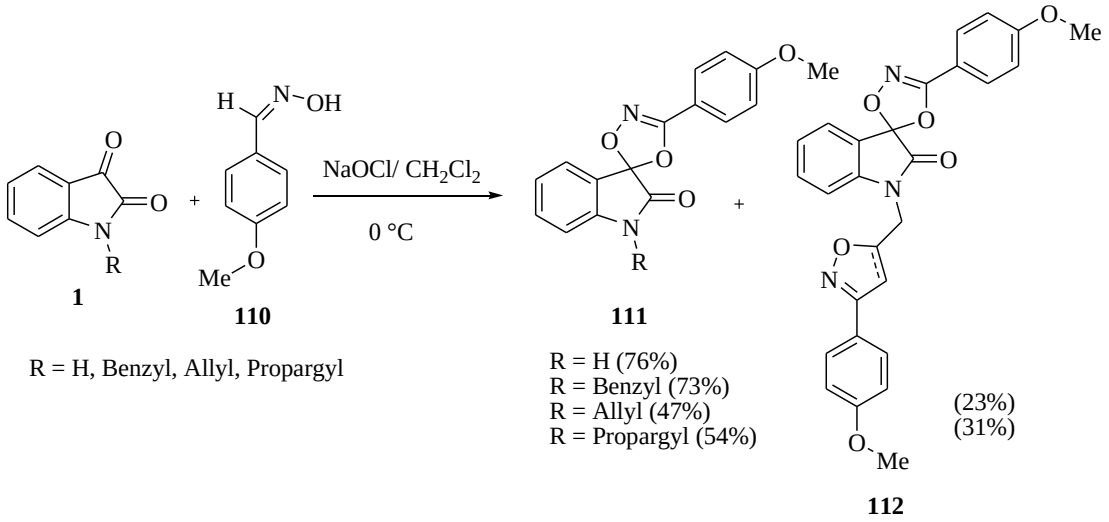
Scheme 29

The 1,3-dipolar cycloaddition of stable isatin ketonitrone **106** with various cyclic and acyclic dipolarophiles has been conducted under classical, ionic liquid and solvent-free conditions to give novel spiro[oxindole-isoxazolidine] derivatives **108** and **109** with similar diastereo-selectivity (Scheme 30).[44] Condensation of isatin **1** or isatin imine **105** with phenylhydroxylamine led to the formation of stable isatin ketonitrones **106** and **107** in high yields. It was found from ROESY and NOE investigations that the configuration of the stable isatin ketonitrone was *Z* and not *E*.



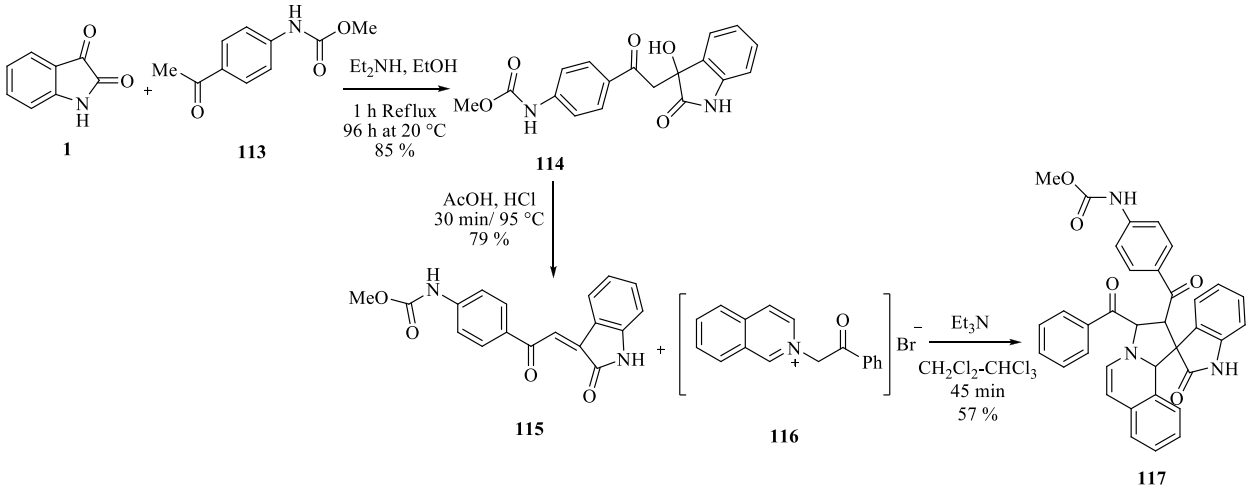
Scheme 30

The 1,3-dipolar cycloaddition reaction of isatin derivatives with the nitrile oxide generated *in situ* from 4-methoxybenzaldoxime **110** and sodium hypochlorite for synthesis of novel spiro[1,4,2-dioxazole-5,3′-indolin]-2′-one derivatives **111** and **112** was studied (Scheme 31).[45] It was found that, besides the C=O participating in the formation of the 1,4,2-dioxazole ring, the C-C alkene (allyl) or alkyne (propargyl) bond also underwent 1,3-dipolar cycloaddition reaction with the nitrile oxide to form an isoxazole linked to the indole nitrogen by a methylene group.



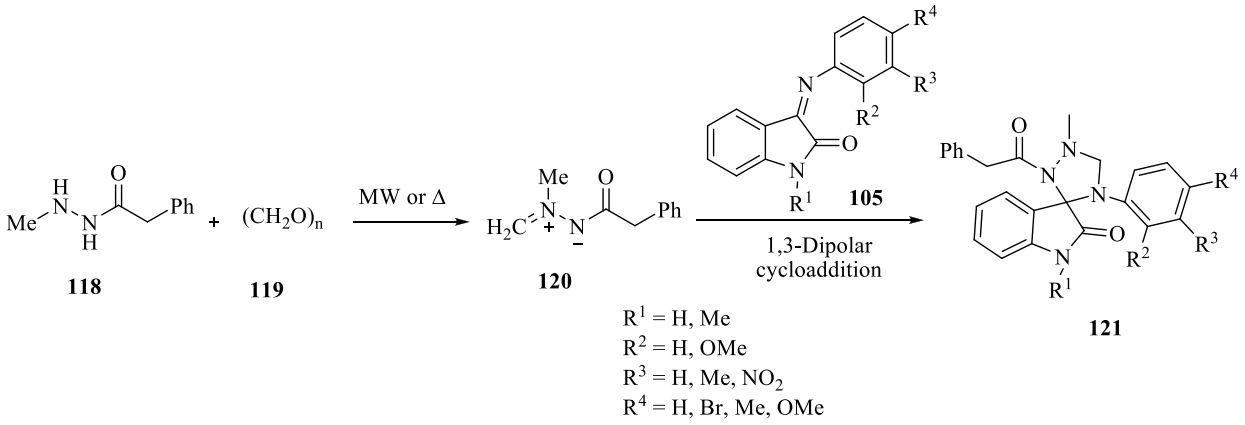
Scheme 31

Condensation of methyl 4-acetylphenylcarbamate **113** with isatin afforded **114** which was converted into the corresponding chalcone **115**. 1,3-Dipolar cycloaddition to that chalcone of the azomethine ylide generated from 2-phenacylisoquinolinium bromide **116** by the action of triethylamine gave **117** (Scheme 32).[46]



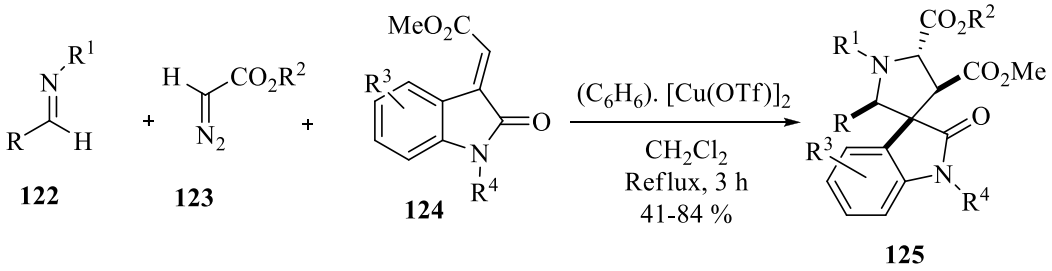
Scheme 32

Spiroindoles **121** were prepared readily via a one-pot, 1,3-dipolar cycloaddition reaction of azomethine imines **120** with isatin imines **105** under microwave irradiation and classical heating (Scheme 33).[47] By using microwave irradiation, the reaction time was reduced greatly from 9–14 hours to 6–8 min and the yield of the reaction was enhanced by 10–20% compared to the conventional heating method.



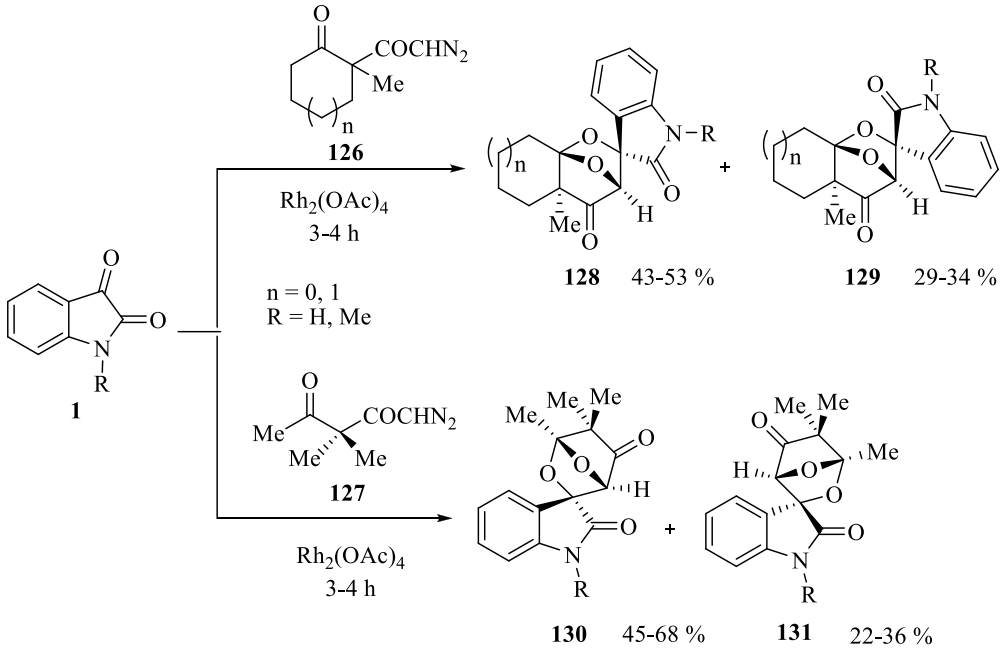
Scheme 33

The combination of an α-diazoester **123** and an imine **122** in the presence of a Cu(I) catalyst generated a transient azomethine ylide which underwent a highly diastereoselective cycloaddition with dipolarophile **124** to afford highly substituted spiropyrrolidinyloxindoles **125** in a convergent, three-component assembly reaction (Scheme 34).[48]



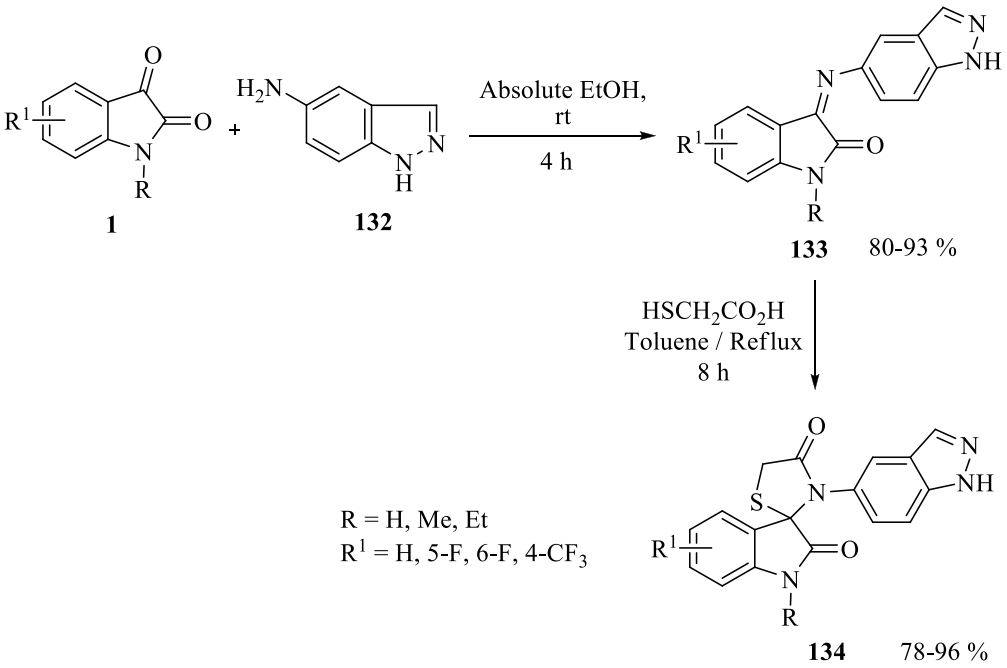
Scheme 34

α-Diazo ketones **126** or **127** and isatin in the presence of 1 mol% of $Rh_2(OAc)_4$ led to novel spiro dioxa-bridged indole derivatives as a mixture of diastereomers (Scheme 35).[49]



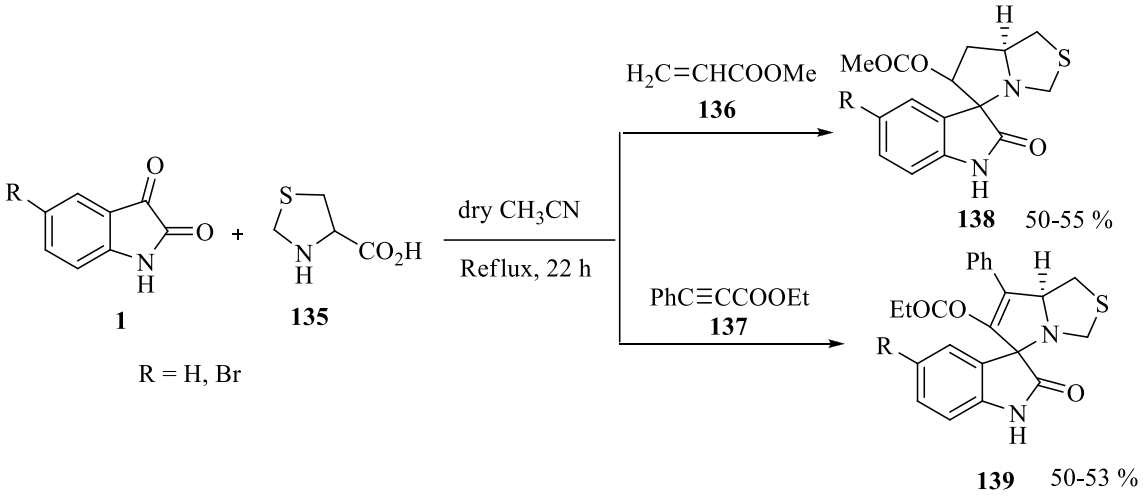
Scheme 35

Treatment of isatin with 5-aminoindazole **132** and mercaptoacetic acid provided the desired spiro systems containing three heterocyclic moieties namely indole, thiazolidine, and indazole **134** (Scheme 36).[50]



Scheme 36

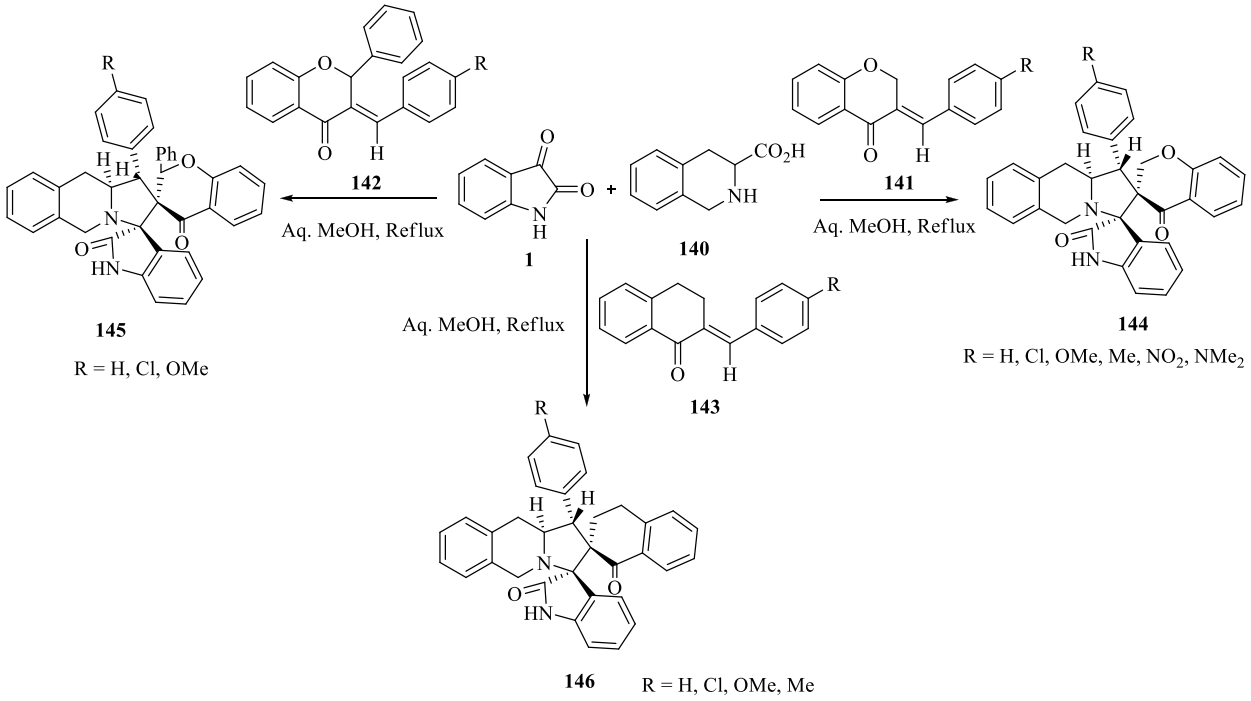
1,3-Dipolar cycloaddition of ylides generated *in situ* by the decarboxylative condensation of isatin with 1,3-thiazolane-4-carboxylic acid **135** with ethyl phenyl propiolate **137** or methyl acrylate **136** led to novel spiro compounds **138** or **139**, respectively (Scheme 37).[51]



Scheme 37

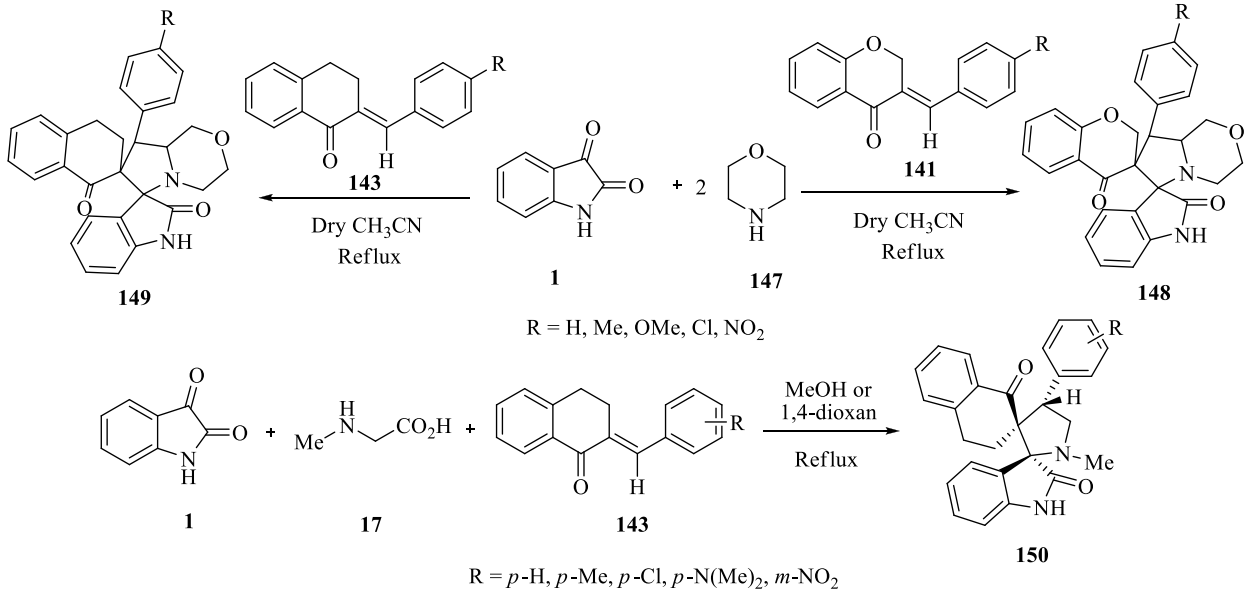
3. Synthesis of Dispiropyrrolo/pyrrolizidino-oxindole Ring Systems

An efficient synthesis of novel dispiroheterocycles containing the oxindole ring has been accomplished by 1,3-dipolar cycloaddition reaction of azomethine ylides generated by the decarboxylative route from tetrahydroisoquinoline-3-carboxylic acid **140** and isatin with unusual dipolarophiles such as 3-arylidene-4-chromanone **141**, 3-arylidene-4-flavanone **142** and 2-arylidenetetrahydro-1-naphthalenone **143** (Scheme 38).[52]



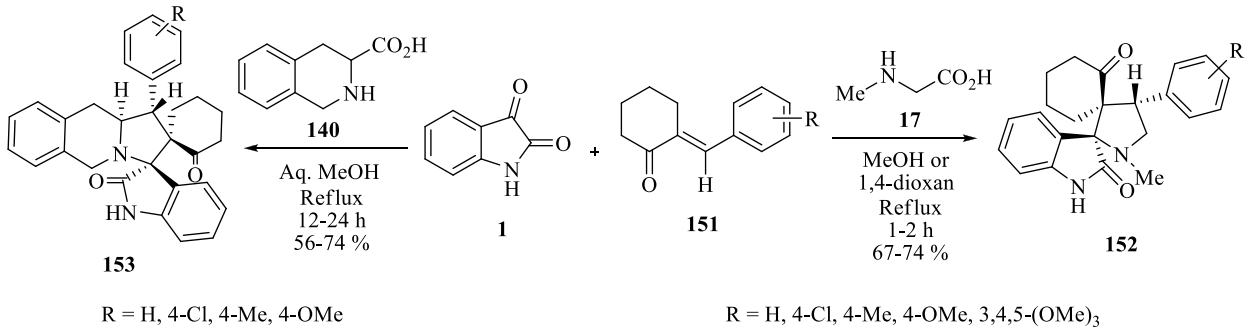
Scheme 38

Similarly, the secondary amines morpholine **147**[53] and sarcosine **17** (Scheme 39),[54] were used in the above reaction.



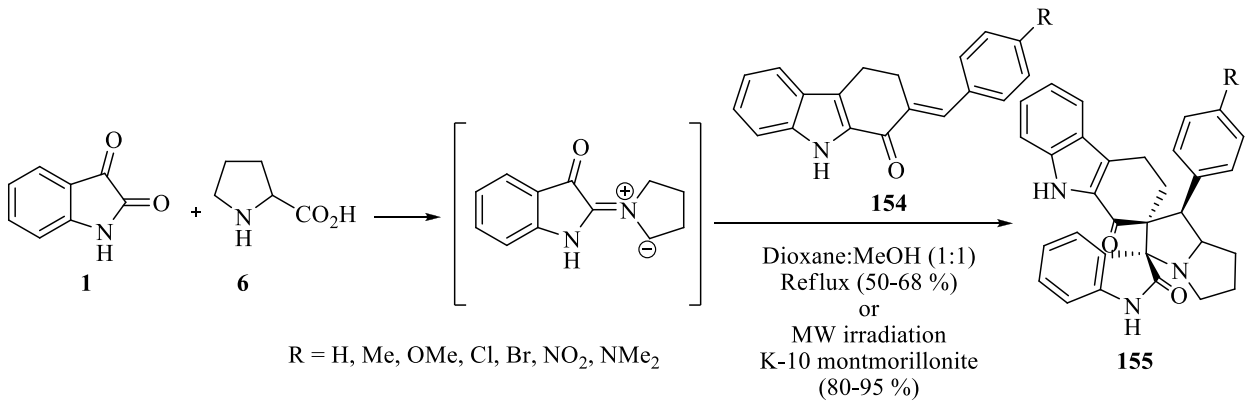
Scheme 39

Use of (*E*)-2-benzylidene-1-cyclohexanones **151** as dipolarophiles was also described, leading to the formation of novel dispiro[oxindole-cyclohexanone]pyrrolidines **152**,[55] and dispiro[oxindole-cyclohexanone]pyrroloisoquinolines **153** (Scheme 40).[56]



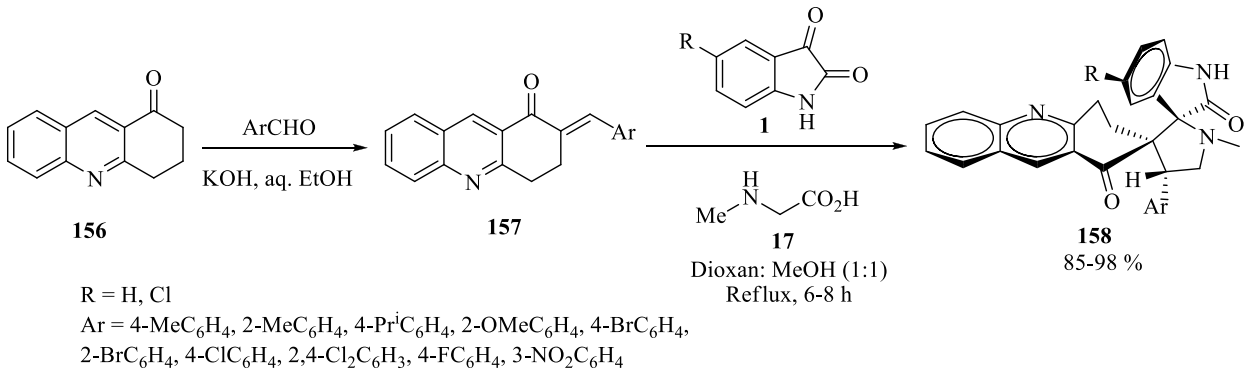
Scheme 40

Reaction of azomethine ylide generated from proline and isatin with the dipolarophile (*E*)-2-arylidine-1-ketocarbazoles **154** resulted in the formation of dispirooxindolopyrrolizidine derivatives **155** that possessed antibacterial and antifungal activities (Scheme 41).[57]



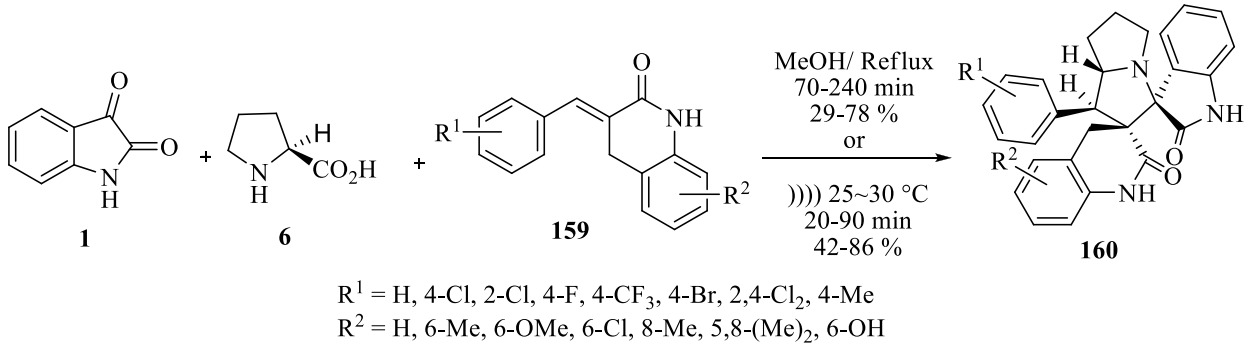
Scheme 41

In another study, the dipolarophiles, (*E*)-2-(arylmethylidene)-3,4-dihydro-1(2*H*)-acridinones **157,** prepared by the base-catalyzed condensation of 3,4-dihydroacridin-1(2*H*)-one **156** with substituted benzaldehydes, readily reacted with nonstabilized azomethine ylides, to afford dispirooxindolyl-[acridine-2',3-pyrrolidine]-10-ones **158** (Scheme 42).[58]



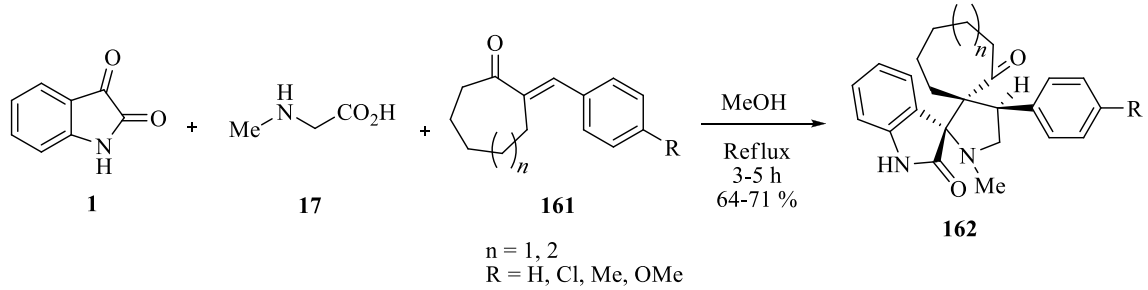
Scheme 42

A class of novel tetracyclic dispiropyrrolizidines **160** has been synthesized via the 1,3-dipolar cycloaddition of azomethine ylide with dipolarophiles **159** under conventional heating and ultrasound irradiation conditions (Scheme 43).[59]



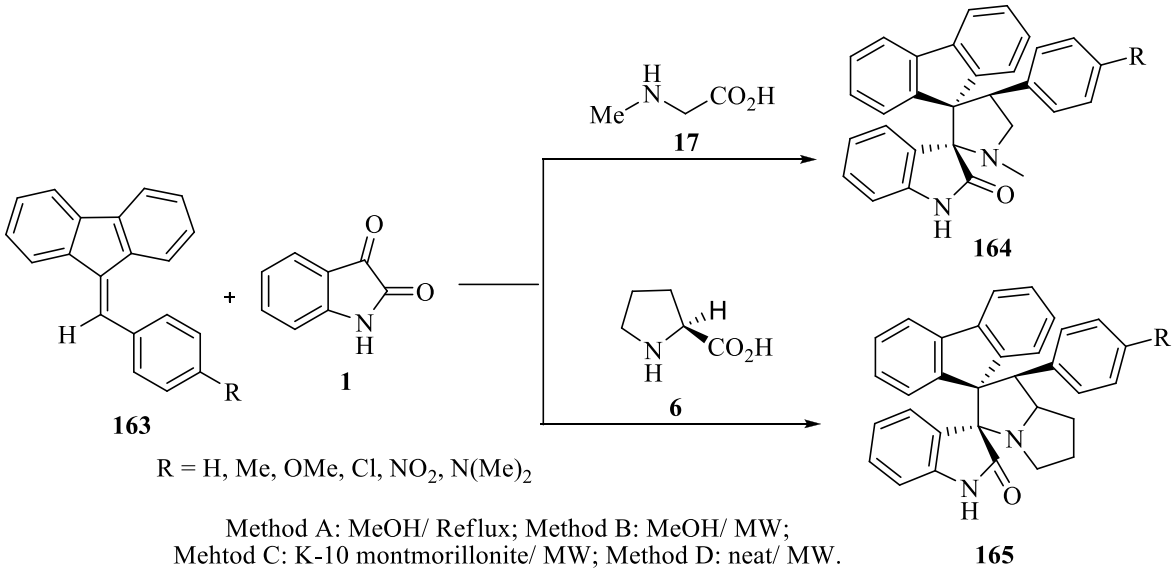
Scheme 43

Arylidene cycloheptanones and arylidene cyclooctanones **161** were used as dipolarophiles. It was observed that the isatin/sarcosine derived nonstabilized azomethine ylide added regioselectively across the exocyclic double bonds of the dipolarophiles to give novel spiroheterocycles **162** (Scheme 44).[60]



Scheme 44

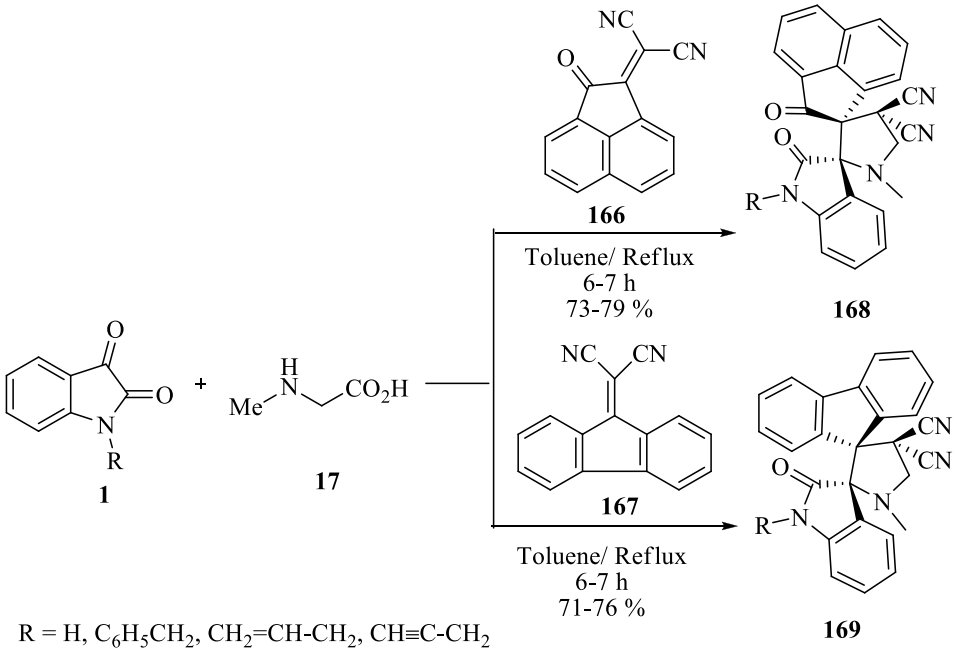
Synthesis of novel dispiro pyrrolo/pyrrolizidino ring systems by the cycloaddition of azomethine ylides with the dipolarophile 9-arylidine-fluorene **163** using four different methodologies has been described (Scheme 45).[61] A solvent-free microwave-assisted approach gave products with the highest yields in the shortest times.



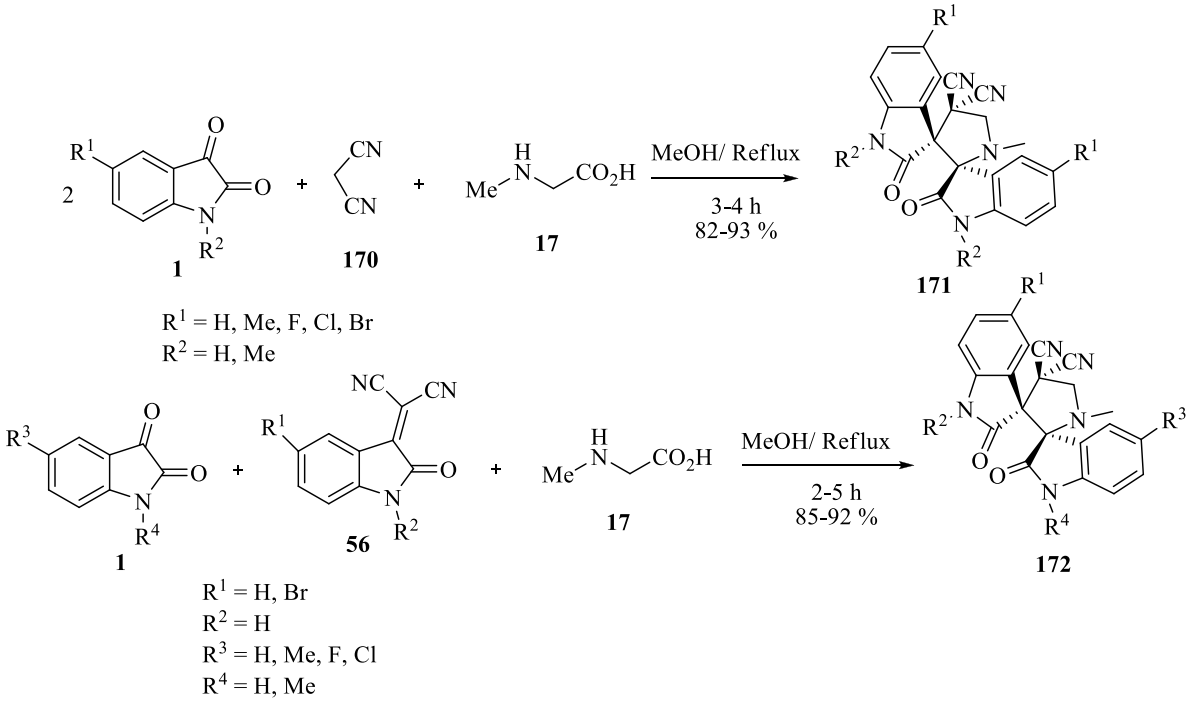
Scheme 45

Application of 2-oxo-(2*H*)-acenaphthylen-1-ylidene-malononitrile Knoevenagel adducts **166**, as dipolarophiles in 1,3-dipolar cycloaddition reaction of azomethine ylides has been studied. Under similar conditions, 2-fluoren-9-ylidene-malononitrile **167** has been applied to furnish the respective dispiropyrrolidine oxindole derivatives (Scheme 46).[62]

The synthesis of novel dispiropyrrolidine bisoxindole derivatives **172** via condensation of azomethine ylides with the Knoevenagel adduct **56**, prepared by the reaction of isatins with malononitrile, was reported (Scheme 47).[63] The pseudo-four-component reaction of isatin, malononitrile **170** and sarcosine afforded dispiropyrrolidine bisoxindoles containing two different indole rings **171**.

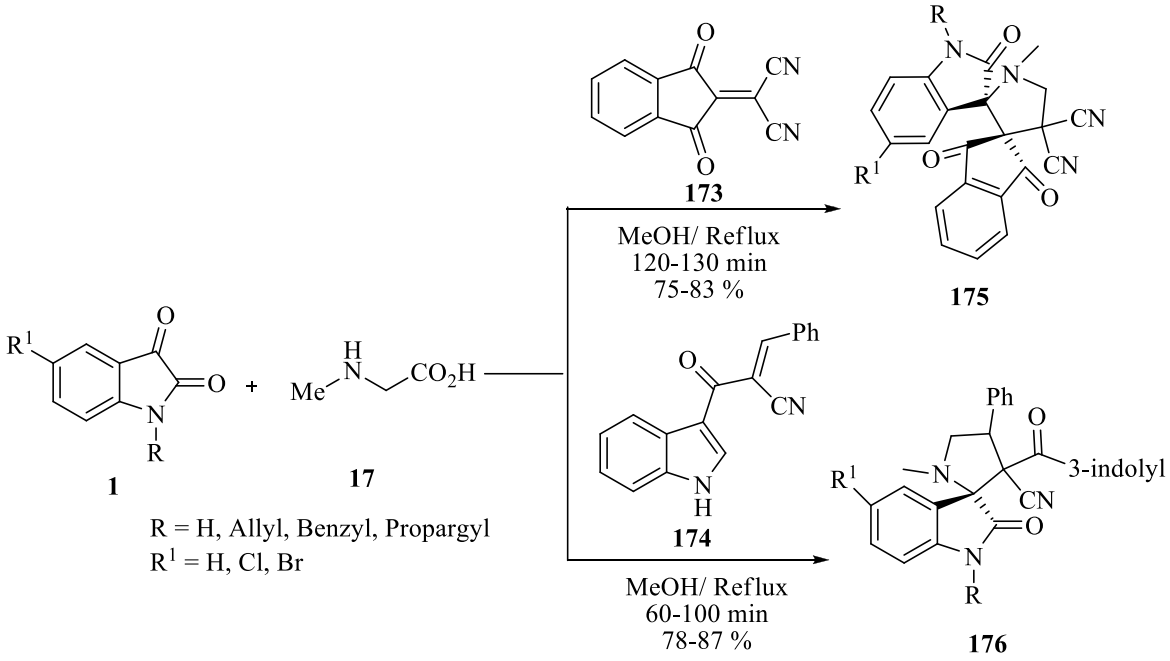


Scheme 46



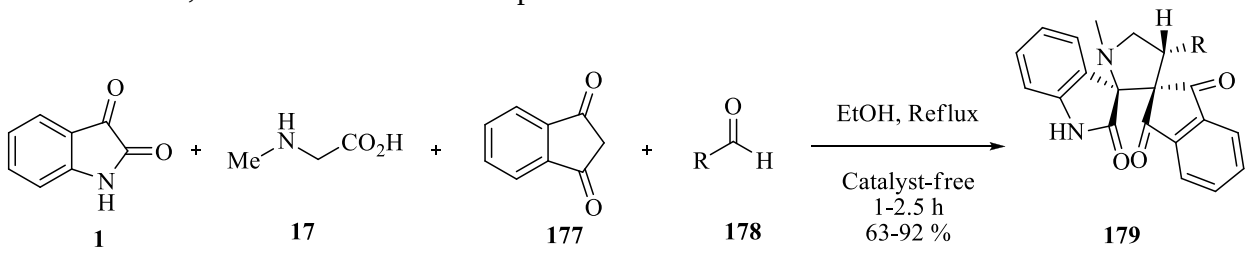
Scheme 47

Perumal and coworkers employed two dipolarophiles **173** and **174** to yield **175** and **176** respectively, as single products with good yields (Scheme 48).[64]



Scheme 48

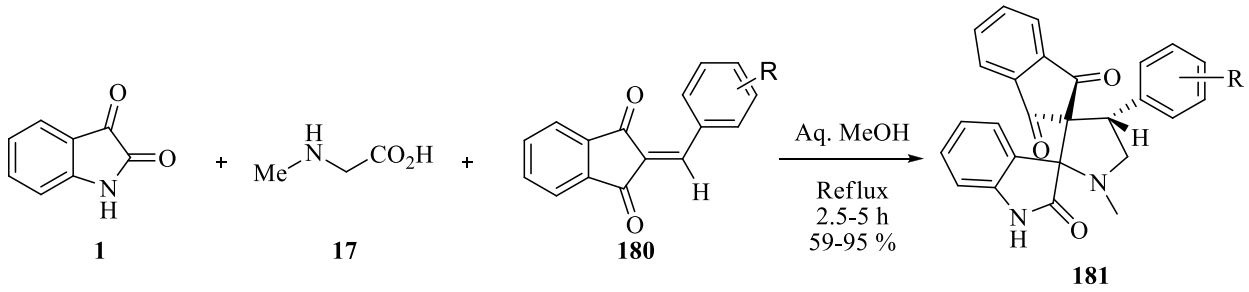
Novel dispiropyrrolidines **179** were synthesized by a tandem Knoevenagel-1,3-dipolar cycloaddition reaction sequence of isatin, sarcosine, 1,3-indanedione **177**, and an aldehyde **178** in the absence of catalyst (Scheme 49).[65] Ethanol as the solvent, and a mol ratio of 1 : 1.2 : 1.2 : 1, were deemed to be the optimum reaction conditions.



R = C_6H_5, 4-ClC_6H_4, 4-BrC_6H_4, 4-OHC_6H_4, 4-MeC_6H_4, 4-$OMeC_6H_4$, 3-$NO_2C_6H_4$, 3-FC_6H_4, 3-OHC_6H_4, 3,4-$(OMe)_2C_6H_3$,2-ClC_6H_4, 2-FC_6H_4, $MeCH_2CH_2$

Scheme 49

2-Arylidene-1,3-indanediones **180** undergo regioselective 1,3-dipolar cycloaddition reaction with the azomethine ylide, affording a series of dispiro[oxindole/indanedione]pyrrolidine ring systems **181** (Scheme 50).[66]

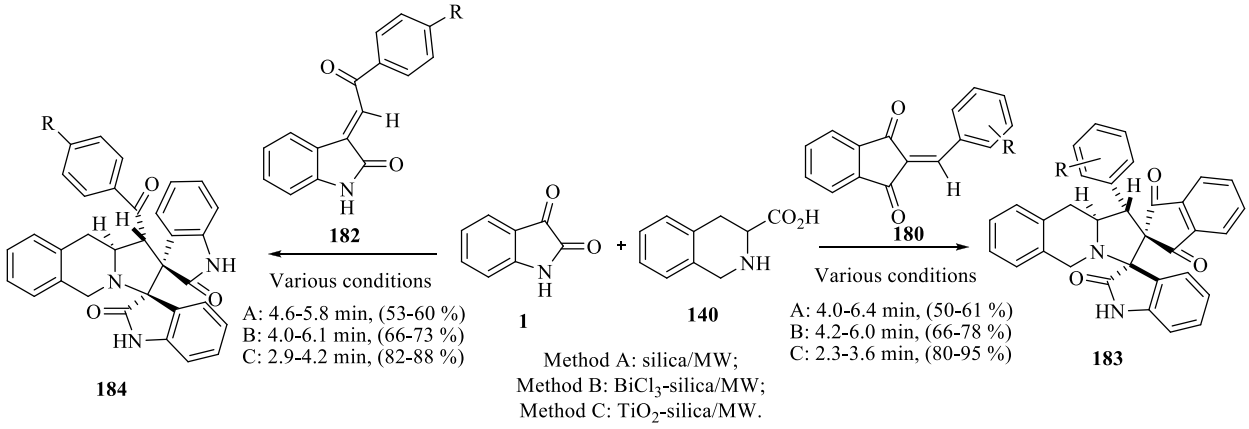


1 17 180 181

R= H, *p*-Cl, *p*-Me, *p*-OMe, *p*-NO_2, *m*-Cl, *m*-NO_2, *o*-Cl, *o*-NO_2, 3′,4′-OMe, 3′,4′,5′-OMe

Scheme 50

The reaction of tetrahydroisoquinoline-3-carboxylic acid **140** with **180** and isatin was reported, too. Compound **182** as an alternative dipolarophile, reacted with isatin and **140** in the presence of TiO_2–silica catalyst (Scheme 51).[67]

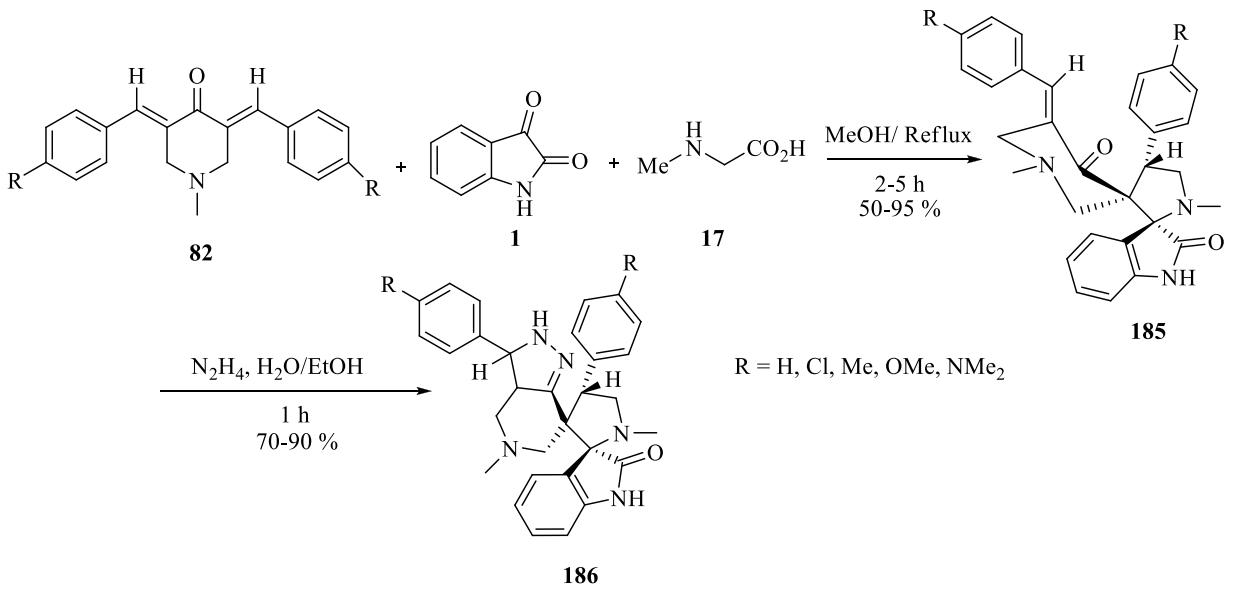


R= H, Cl, Me, OMe, Br

R= H, *p*-Cl, *p*-Me, *p*-OMe, *p*-NO_2, *p*-NMe_2, *m*-Cl, *m*-NO_2, *o*-Cl, *o*-NO_2

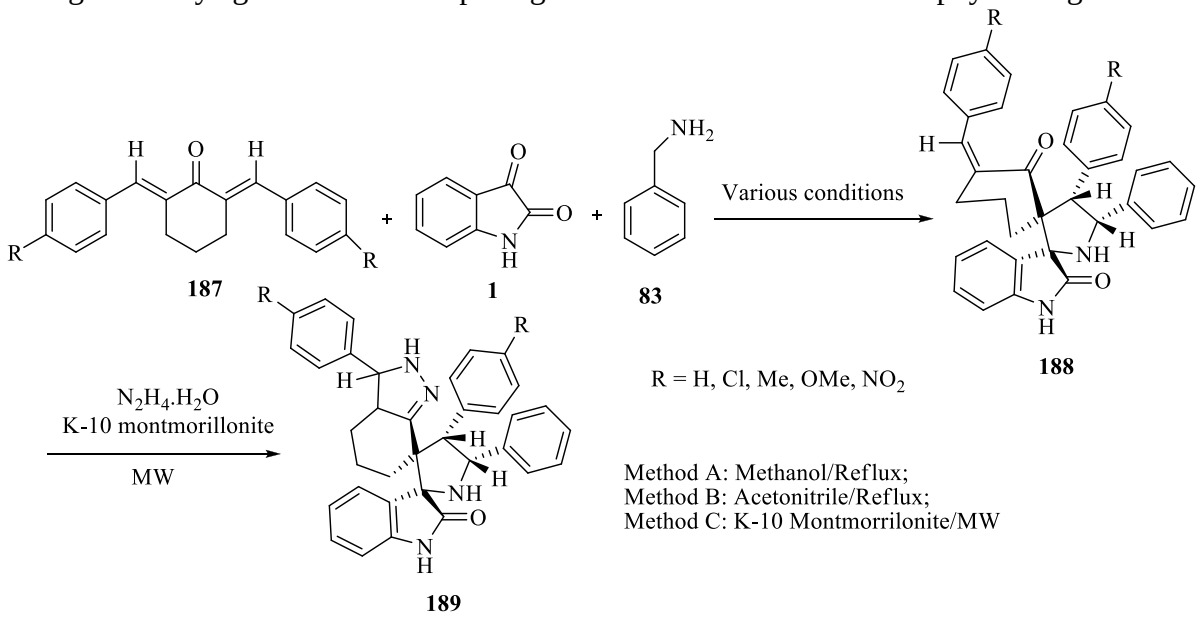
Scheme 51

Using 3,5-bis(arylmethylidene)-*N*-methyl-4-piperidinone **82**, in refluxing methanol, the synthesis of novel spiropyrrolidinyl oxindole derivatives **185** has been investigated. Subsequent reaction with hydrazine hydrate afforded annulated products **186** (Scheme 52).[68]



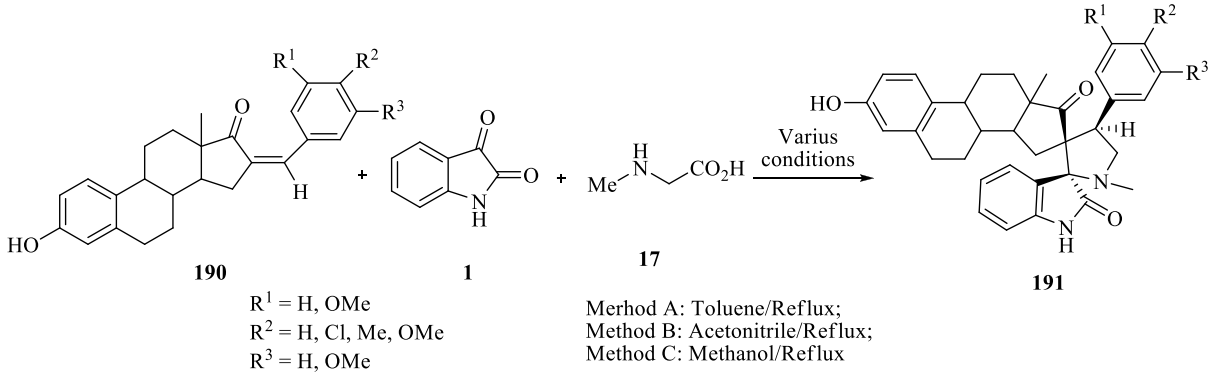
Scheme 52

Reaction of azomethine ylides with various *p*-substituted 2,6-bis(arylmethylidene)-cyclohexanones **187** under different conditions, proceeded regioselectively to give novel dispiroheterocycles **188**. The products, on subsequent annulation with hydrazine hydrate, afforded **189** in good yields (Scheme 53).[69] Replacing benzylamine with sarcosine in this reaction has also been reported.[70] The products were screened for their antibacterial and antifungal activity against ten human pathogenic bacteria and four dermatophytic fungi.[6a]



Scheme 53

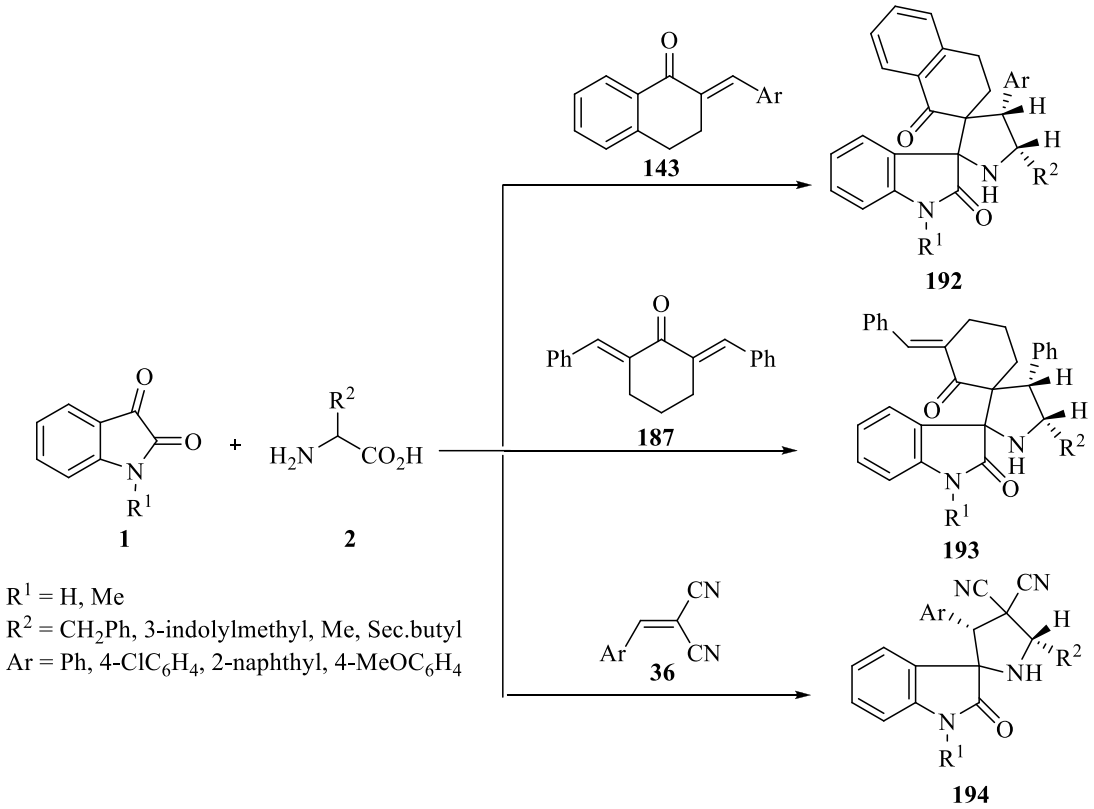
(*Z*)-16-arylidene-estrone derivatives **190** as 2π components were used in reactions with azomethine ylides for the synthesis of hitherto unknown steroidal dispiropyrrolidines **191** (Scheme 54).[71] The reactions were carried out using three different sets of conditions.



190 **1** **17** **191**

Scheme 54

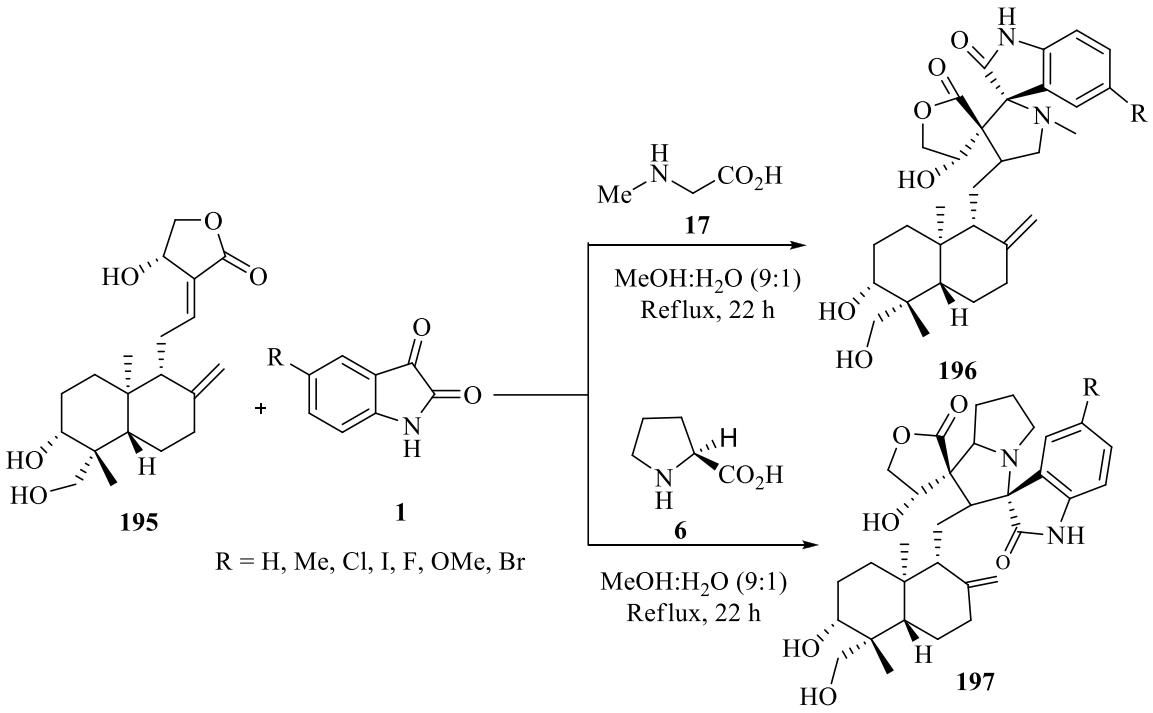
El-Ahl used **143**, **187**, and **36** as dipolarophiles in the reaction with isatin-derived azomethine ylides (Scheme 55).[72]



1 **2** **143** **187** **36** **192** **193** **194**

Scheme 55

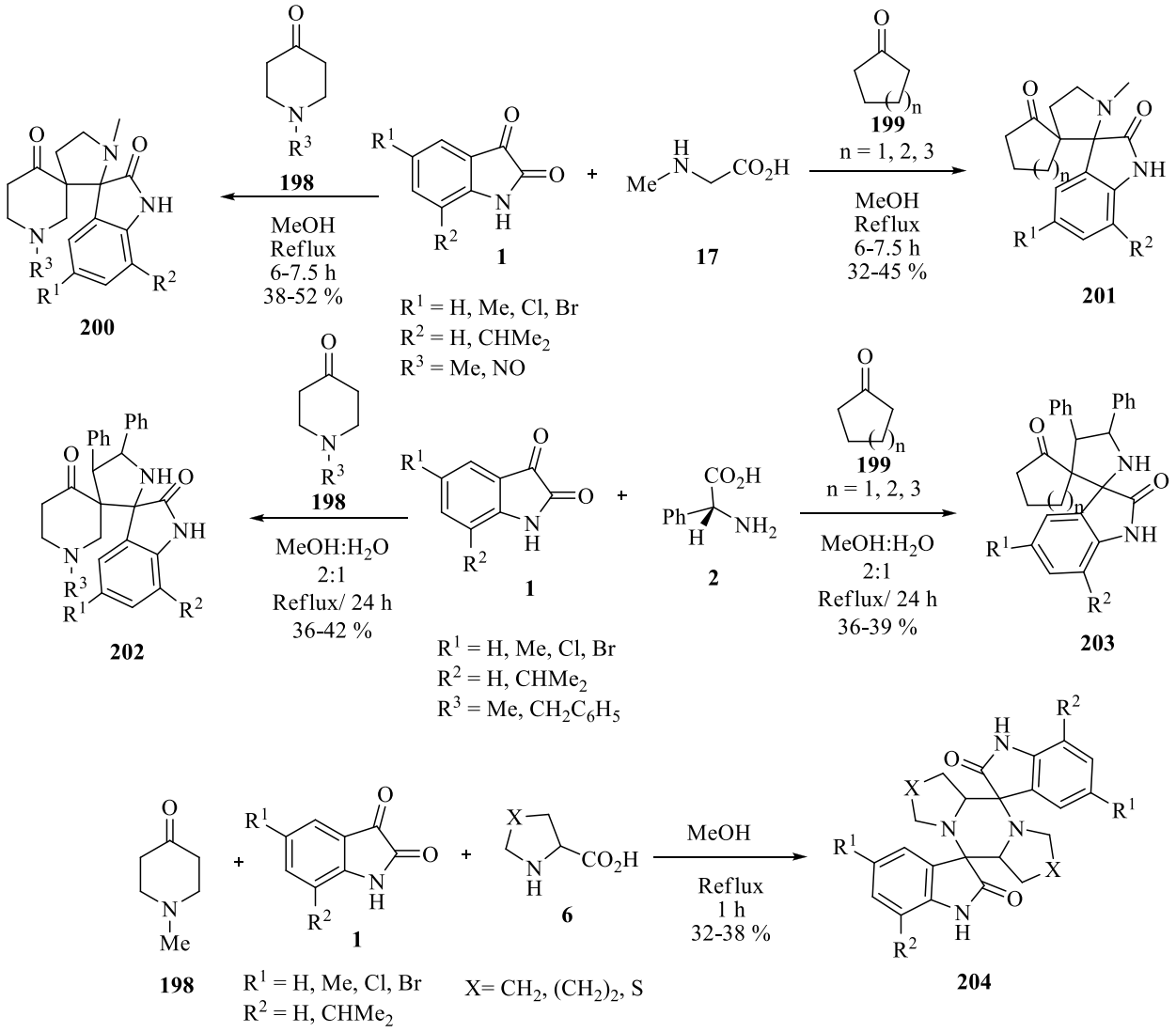
1,3-Dipolar cycloaddition of azomethine ylides to the conjugated double bond of andrographolide **195** yielded adducts of andrographolide **196** and **197** (Scheme 56).[73]



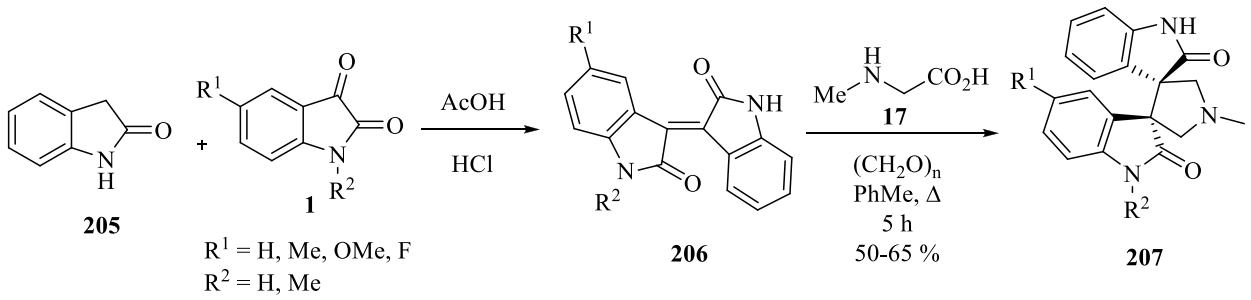
Scheme 56

Domino reactions of isatin, and sarcosine[74] or phenylglycine,[75] furnishing highly function-alised dispiropyrrolidines **200-203** in moderate yields, have been described. When the reaction was performed with L-proline and congeners it resulted in the dimeric azomethine ylides **204** (Scheme 57).[75] These compounds were screened for their antimycobacterial activities.

β,β′-Bis-spiro derivatives of oxindole **207** were prepared by dipolar [3+2] cycloaddition to isoindigo derivatives **206**, obtained from oxindole **205** and isatin derivatives. The azomethine ylide was generated *in situ* from sarcosine and paraformaldehyde (Scheme 58).[76] Both reactions proceed with high yield and are completely diastereoselective.

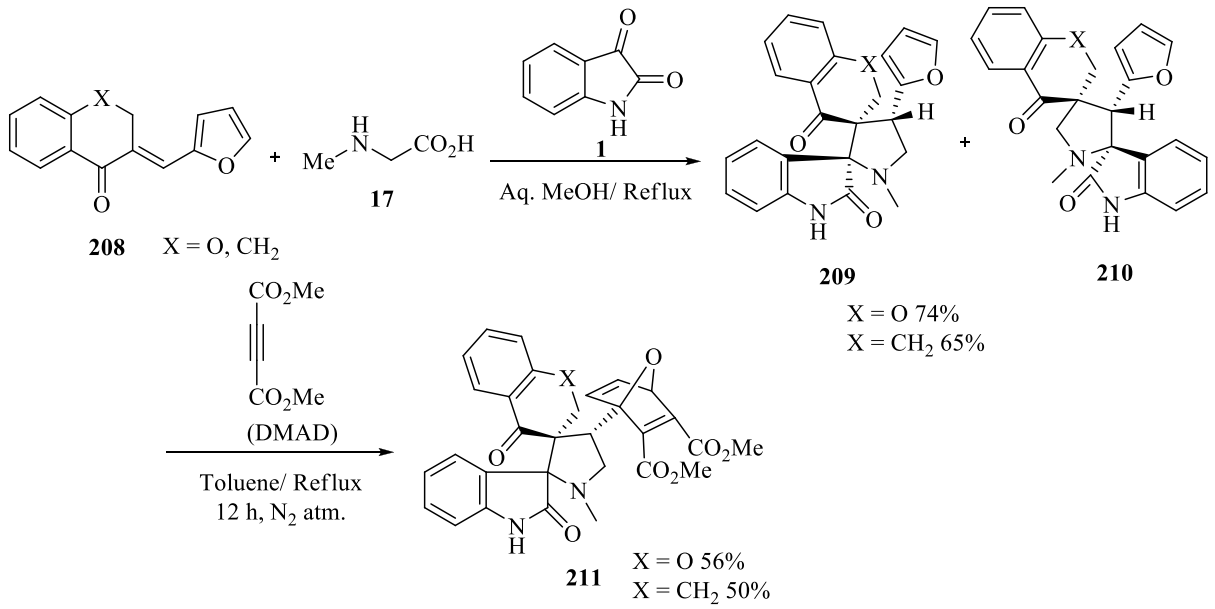


Scheme 57



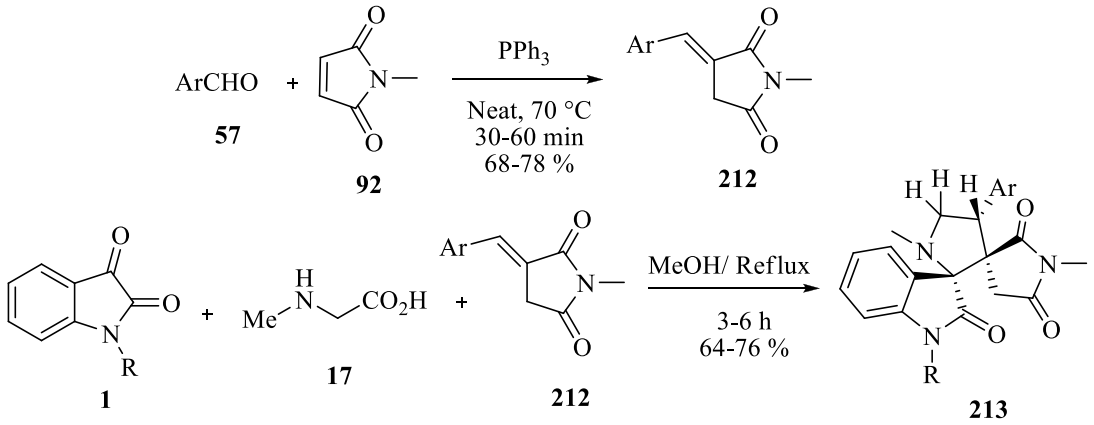
Scheme 58

A simple and efficient synthetic approach to spiropyrrolo-bicyclo[2.2.1]heptanes **209** and **210** involving 1,3-dipolar cycloaddition reaction of the azomethine ylide with (*E*)-3-furfurylidene-4-chromanone and (*E*)-2-furfurylidene-1-tetralone **208** in a regio- and stereo-controlled fashion has been developed. A subsequent intermolecular Diels–Alder cycloaddition of the spiropyrrolidines with dimethyl acetylenedicarboxylate (DMAD) provided adducts **211** (Scheme 59).[77]



Scheme 59

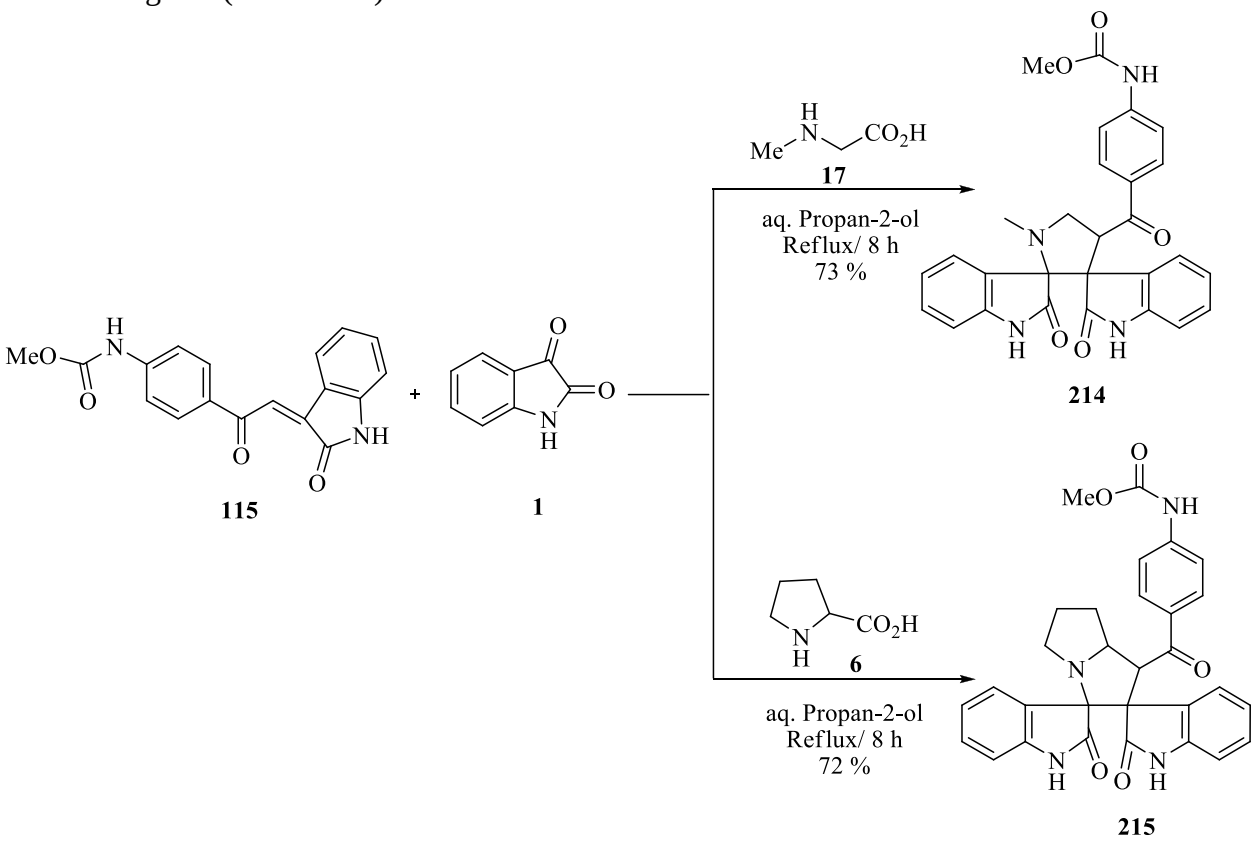
3-Benzylidene-1-methylpyrrolidine-2,5-diones **212**, prepared from *N*-methylmaleimide **92** and various substituted benzaldehydes **57**, were used for the synthesis of biologically active dispiropyrrolidines **213** (Scheme 60).[78]



Ar = 2-OHC$_6$H$_4$, 4-OMeC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-MeC$_6$H$_4$
R = H, Me, Bn, Propargyl

Scheme 60

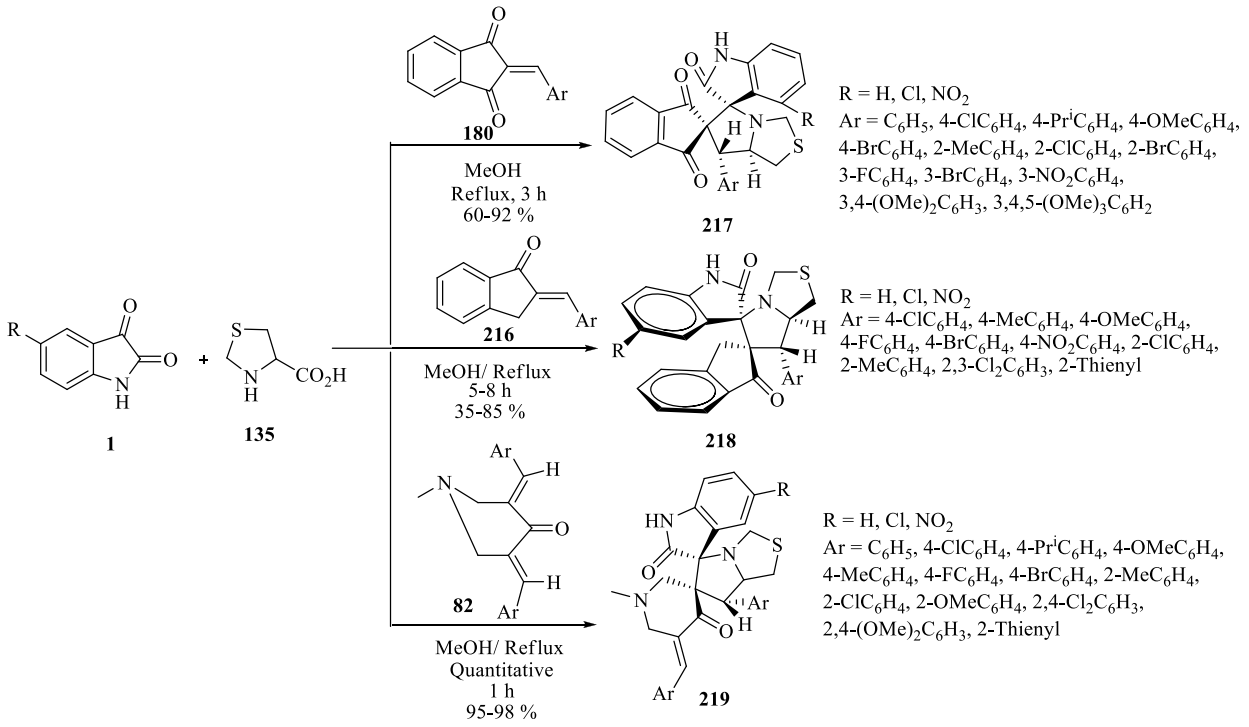
1,3-Dipolar cycloaddition reactions of **115** with azomethine ylides generated by thermal reaction of isatin with α-amino acids **6** and **17**, forming the diindoxyl products **214** and **215**, were also investigated (Scheme 61).[79]



Scheme 61

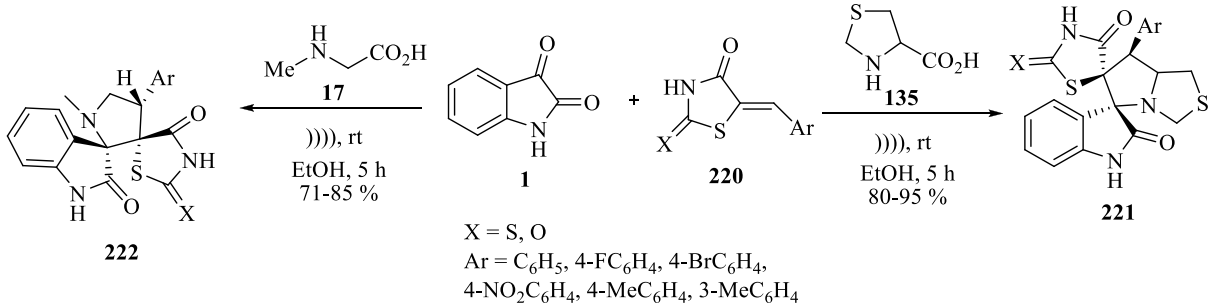
3.1. Synthesis of dispiropyrrolothiazolo-oxindoles

Synthesis of heterocyclic compounds having both thiazolone and spirooxindole moieties via 1,3-dipolar cycloaddition reaction of azomethine ylides generated *in situ* by the decarboxylative condensation of isatin with 1,3-thiazolane-4-carboxylic acid **135** with dipolarophiles such as **180**,[80] **216**,[81] and **82**[82] has been reported (Scheme 62).



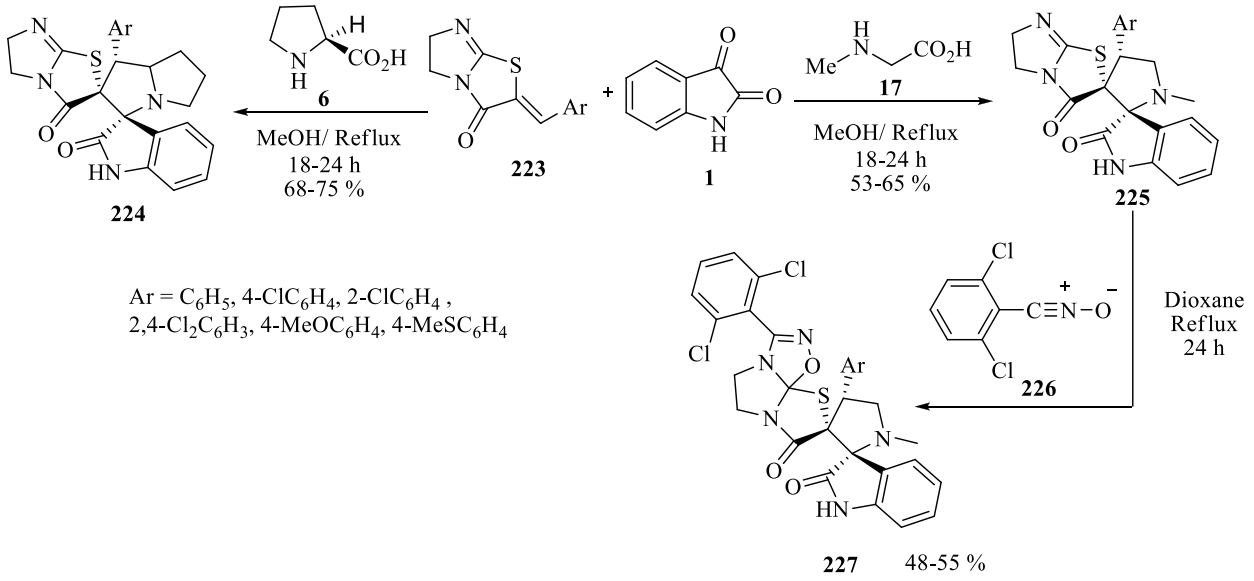
Scheme 62

Catalyst-free 1,3-dipolar cycloaddition reactions of azomethine ylides to 5-benzylidene-2-thioxothiazolidin-4-one or 5-benzylidenethiazolidine-2,4-dione **220** promoted by ultrasound has been reported (Scheme 63).[83] Application of sarcosine **17** and proline in this reaction was also investigated.[84] The compounds synthesized were screened for their antidiabetic activity on male Wistar rats.[85]



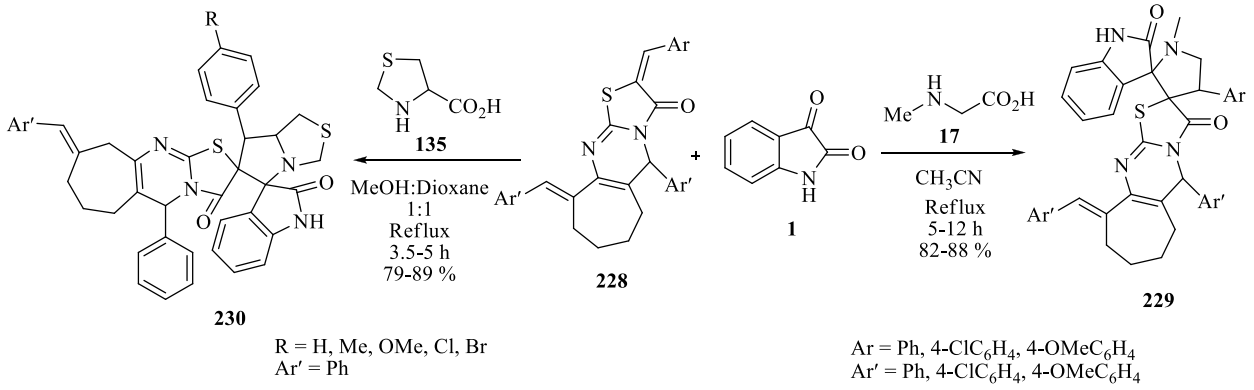
Scheme 63

Azomethine ylide cycloaddition to 2-arylmethylidene-6,7-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-3-ones **223** afforded novel products regio- and stereo-selectively in moderate yields (Scheme 64).[86] Further reaction of **225** with 2,6-dichlorobenzonitrile oxide **226** resulted in spirothiazolo-[3,2-*a*]pyrimidines **227**.[87]



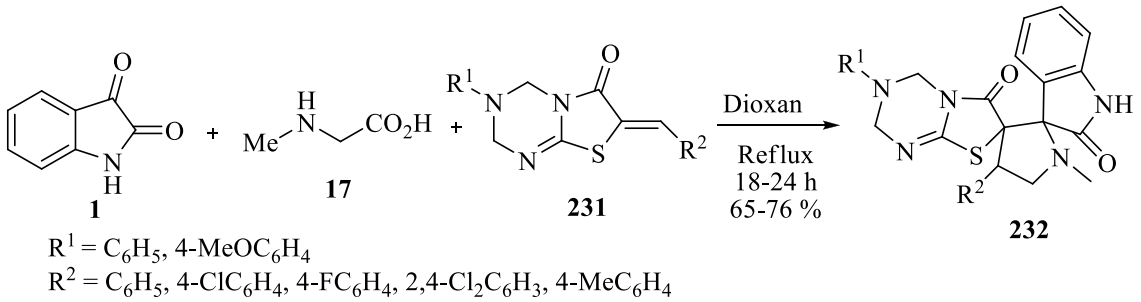
Scheme 64

Compound **228** as a dipolarophile undergoes regioselective 1,3-dipolar cycloaddition in different reaction conditions to give a new class of complex spiropyrrolidines **229**[88] and **230**[89] in good yields (Scheme 65).



Scheme 65

7-Arylmethylidene-3-aryl-3,4-dihydro-2*H*-thiazolo[3,2-*a*][1,3,5]triazin-6(7*H*)-one **231** was reacted with azomethine ylides to afford dispiro[oxindole-pyrrolidine]-thiazolo[3,2-*a*]-[1,3,5]triazines **232** in moderate yields (Scheme 66).[90]

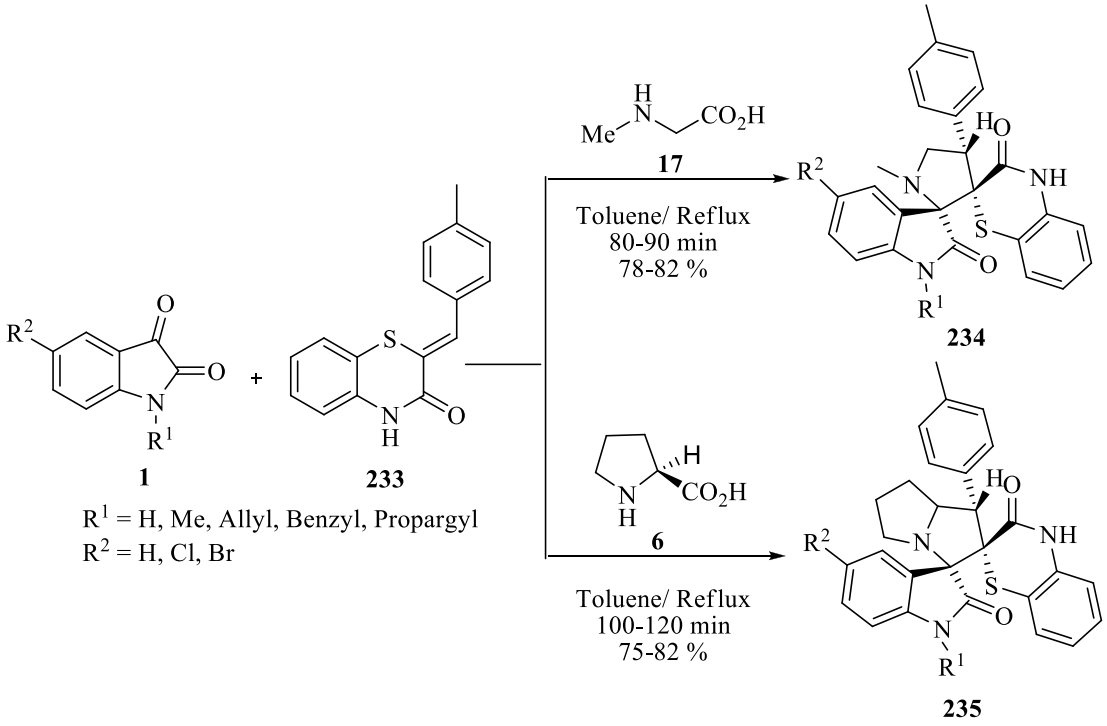


1 17 231 232

R^1 = C_6H_5, 4-$MeOC_6H_4$
R^2 = C_6H_5, 4-ClC_6H_4, 4-FC_6H_4, 2,4-$Cl_2C_6H_3$, 4-MeC_6H_4

Scheme 66

The preparation of a series of spirooxindole derivatives **234** and **235** containing a spirobenzo[1,4]thiazin-3-one ring using 2-(4-methylbenzylidene)-4*H*-benzo[1,4]thiazin-3-one **233** as dipolarophile has been reported (Scheme 67).[91]



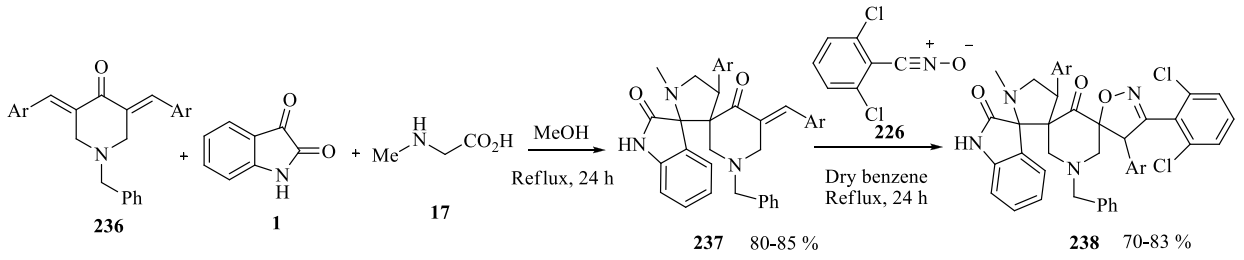
1 233 17 6 234 235

R^1 = H, Me, Allyl, Benzyl, Propargyl
R^2 = H, Cl, Br

Scheme 67

4. Synthesis of Trispiroheterocycles

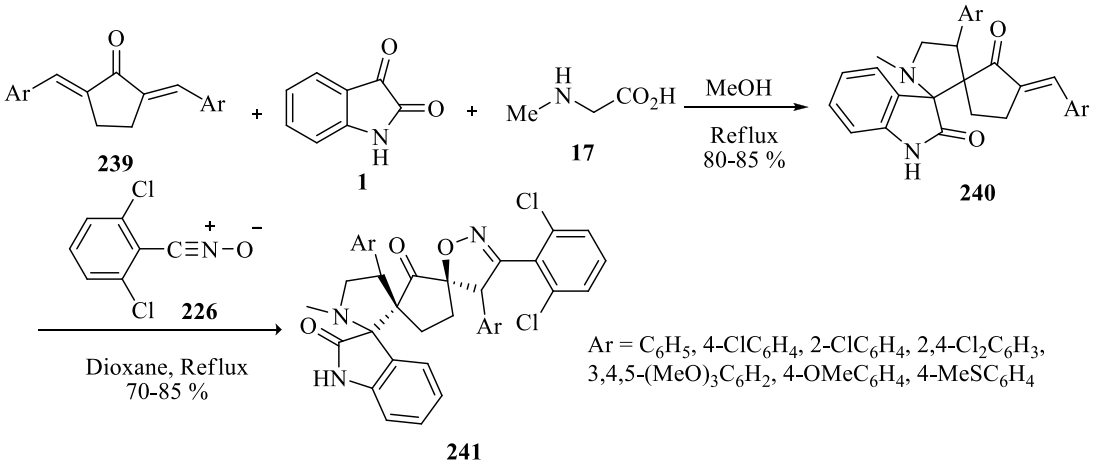
Li and coworkers investigated the synthesis of novel dispiropyrrolidines via azomethine ylide cycloaddition to 1-benzyl-3,5-diarylmethylidene-4-piperidinone **236** and subsequent cycloaddition with nitrile oxide **226** to obtain novel tri-spiro heterocycles **238** (Scheme 68).[92]



Ar = C_6H_5, 4-ClC_6H_4, 2-ClC_6H_4, 2,4-$Cl_2C_6H_3$, 4-$OMeC_6H_4$, 4-$MeSC_6H_4$

Scheme 68

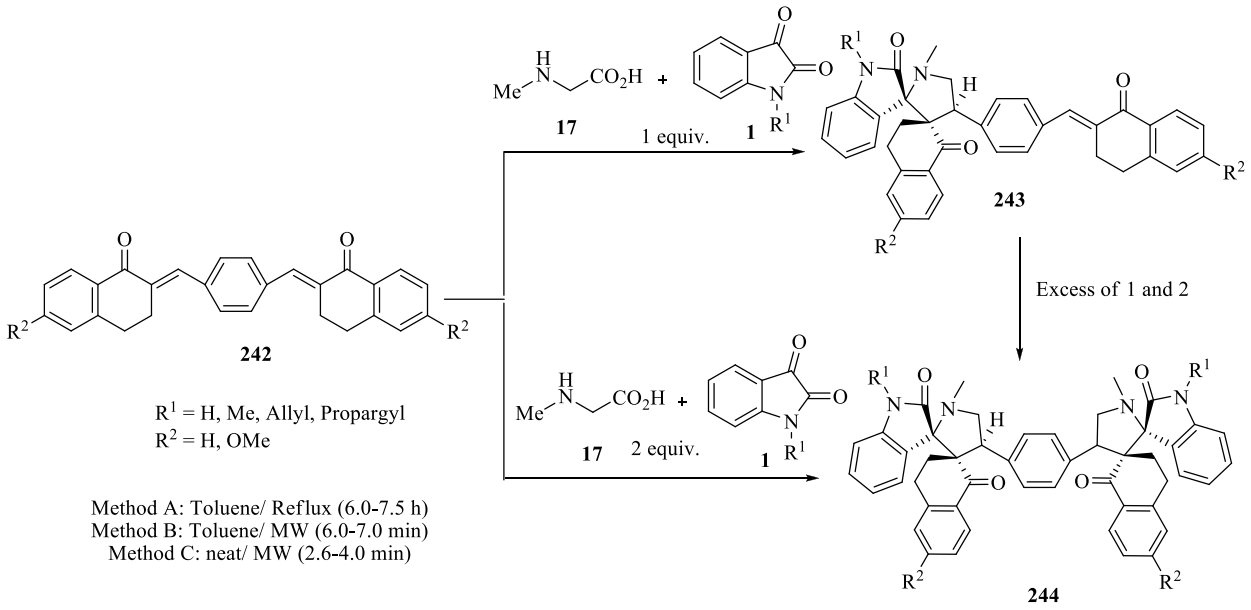
2,5-Bis(arylmethylidene)-cyclopentanones **239** as dipolarophiles have been used for the synthesis of novel dispiro oxindole/pyrrolidines in moderate yields. Further cycloaddition of compound **240** with nitrile oxide **226** afforded **241** with high regio- and stereoselectivity (Scheme 69).[93]



Scheme 69

5. Synthesis of Tetraspiroheterocycles

The facile synthesis of tetraspiro-bisoxindolopyrrolidine derivatives **244**, in a highly regio- and stereoselective manner through 1,3-dipolar cycloaddition of bis-dipolarophiles **242** with the 1,3-dipole generated from isatins and sarcosine, has been reported (Scheme 70).[94]



Scheme 70

6. Acknowledgements

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7. References

1. Da Silva, J. F. M.; Garden, S. J.; Pinto, A. C. *J. Braz. Chem. Soc.* **2001**, *12*, 273.
2. (a) Batanero, B.; Barba, F. *Tetrahedron Lett.* **2006**, *47*, 8201. (b) Deng, H.; Konopelski, J. P. *Org. Lett.* **2001**, *3*, 3001. (c) Jahng, K. C.; Kim, S. I.; Kim, D. H.; Seo, C. S.; Son, J. -K.; Lee, S. H.; Lee, E. S.; Jahng, Y. *Chem. Pharm. Bull.* **2008**, *56*, 607. (d) Kitajima, M.; Mori, I.; Arai, K.; Kogure, N.; Takayama, H. *Tetrahedron Lett.* **2006**, *47*, 3199. (e) Lee, E. S.; Park, J. -G.; Jahng, Y. *Tetrahedron Lett.* **2003**, *44*, 1883. (f) Overman, L. E.; Peterson, E. A. *Angew. Chem. Int. Ed.* **2003**, *42*, 2525. (g) Sun, C.; Lin, X.; Weinreb, S. M. *J. Org. Chem.* **2006**, *71*, 3159. (h) Torres, J. C.; Pinto, A. C.; Garden, S. J. *Tetrahedron* **2004**, *60*, 9889. (i) Trost, B.; Brennan, M. *Synthesis* **2009**, 3003.
3. (a) Aboul-Fadl, T.; Bin-Jubair, F. A. S.; Aboul-Wafa, O. *Eur. J. Med. Chem.* **2010**, *45*, 4578. (b) Gupta, L.; Sunduru, N.; Verma, A.; Srivastava, S.; Gupta, S.; Goyal, N.; Chauhan, P. M. S. *Eur. J. Med. Chem.* **2010**, *45*, 2359. (c) Shibinskaya, M. O.; Lyakhov, S. A.; Mazepa, A. V.; Andronati, S. A.; Turov, A. V.; Zholobak, N. M.; Spivak, N. Y. *Eur. J. Med. Chem.* **2010**, *45*, 1237. (d) Bandekar, P. P.; Roopnarine, K. A.; Parekh, V. J.; Mitchell, T. R.; Novak, M. J.; Sinden, R. R. *J. Med. Chem.* **2010**, *53*, 3558. (e) Bhattacharjee, A. K.; Skanchy, D. J.;

Jennings, B.; Hudson, T. H.; Brendle, J. J.; Werbovetz, K. A. *Bioorg. Med. Chem.* **2002**, *10*, 1979. (f) Nguyen, Q. -D.; Aboagye, E. O. *Integr. Biol.* **2010**, *2*, 483.
4. (a) Doménech, A.; Doménech-Carbó, M. T.; Sánchez del Río, M.; Vázquez de Agredos Pascual, M. L.; Lima, E. *New J. Chem.* **2009**, *33*, 237. (b) Ferreira, E. S. B.; Hulme, A. N.; McNab, H.; Quye, A. *Chem. Soc. Rev.* **2004**, *33*, 329.
5. (a) Kassab, S.; Hegazy, G.; Eid, N.; Amin, K.; El-Gendy, A. *Nucleosides, Nucleotides Nucleic Acids* **2010**, *29*, 72. (b) Sridhar, S. K.; Saravanan, M.; Ramesh, A. *Eur. J. Med. Chem.* **2001**, *36*, 615. (c) Singh, U. K.; Pandeya, S. N.; Singh, A.; Srivastava, B. K.; Pandey, M. *Int. J. Pharm. Sci. Drug Res.* **2010**, *2*, 151.
6. (a) Amal Raj, A.; Raghunathan, R.; SrideviKumari, M. R.; Raman, N. *Bioorg. Med. Chem.* **2003**, *11*, 407. (b) Rodríguez-Argüelles, M. C.; Mosquera-Vázquez, S.; Tourón-Touceda, P.; Sanmartín-Matalobos, J.; García-Deibe, A. M.; Belicchi-Ferrari, M.; Pelosi, G.; Pelizzi, C.; Zani, F. *J. Inorg. Biochem.* **2007**, *101*, 138. (c) Dandia, A.; Singh, R.; Khaturia, S.; Mérienne, C.; Morgant, G.; Loupy, A. *Bioorg. Med. Chem.* **2006**, *14*, 2409.
7. (a) Quenelle, D.; Keith, K.; Kern, E. *Antiviral Res.* **2006**, *71*, 24. (b) Jiang, T.; Kuhen, K. L.; Wolff, K.; Yin, H.; Bieza, K.; Caldwell, J.; Bursulaya, B.; Tuntland, T.; Zhang, K.; Karanewsky, D. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2109. (c) Jarrahpour, A.; Khalili, D.; De Clercq, E.; Salmi, C.; Brunel, J. M. *Molecules* **2007**, *12*, 1720.
8. (a) Bal, T. R.; Anand, B.; Yogeeswari, P.; Sriram, D. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4451. (b) Sriram, D.; Yogeeswari, P.; Myneedu, N. S.; Saraswat, V. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2127. (c) Pandeya, S. N.; Sriram, D.; Nath, G.; De Clercq, E. *Eur. J. Med. Chem.* **2000**, *35*, 249.
9. (a) Karalı, N.; Gürsoy, A.; Kandemirli, F.; Shvets, N.; Kaynak, F. B.; Özbey, S.; Kovalishyn, V.; Dimoglo, A. *Bioorg. Med. Chem.* **2007**, *15*, 5888. (b) Feng, L. -S.; Liu, M. -L.; Wang, B.; Chai, Y.; Hao, X. -Q.; Meng, S.; Guo, H. -Y. *Eur. J. Med. Chem.* **2010**, *45*, 3407. (c) Sriram, D.; Yogeeswari, P.; Basha, J. S.; Radha, D. R.; Nagaraja, V. *Bioorg. Med. Chem.* **2005**, *13*, 5774.
10. Gürsoy, A.; Karalı, N. *Eur. J. Med. Chem.* **2003**, *38*, 633.
11. Sridhar, S. K.; Ramesh, A. *Biol. Pharm. Bull.* **2001**, *24*, 1149.
12. Verma, M.; Pandeya, S. N.; Singh, K. N.; Stables, J. P. *Acta Pharm.* **2004**, *54*, 49.
13. (a) Huisgen, R. *Angew. Chem. Int. Ed.* **1963**, *2*, 633. (b) Huisgen, R. *Angew. Chem. Int. Ed.* **1963**, *2*, 565.
14. Rehn, S.; Bergman, J.; Stensland, B. *Eur. J. Org. Chem.* **2004**, *2004*, 413.
15. Xie, Y. M.; Yao, Y. Q.; Sun, H. B.; Yan, T. T.; Liu, J.; Kang, T. R. *Molecules* **2011**, *16*, 8745.
16. Alimohammadi, K.; Sarrafi, Y.; Tajbakhsh, M.; Yeganegi, S.; Hamzehloueian, M. *Tetrahedron* **2011**, *67*, 1589.
17. Chen, G.; Yang, J.; Gao, S.; He, H.; Li, S.; Di, Y.; Chang, Y.; Lu, Y.; Hao, X. *Mol. Divers.* **2012**, *16*, 151.
18. Rajesh, S. M.; Perumal, S.; Menéndez, J. C.; Yogeeswari, P.; Sriram, D. *Med. Chem. Commun.* **2011**, *2*, 626.

19. Poornachandran, M.; Muruganantham, R.; Raghunathan, R. *Synth. Commun.* **2006**, *36*, 141.
20. Ghandi, M.; Taheri, A.; Abbasi, A. *Tetrahedron* **2010**, *66*, 6744.
21. Chen, H.; Wang, S. Y.; Xu, X. P.; Ji, S. J. *Synth. Commun.* **2011**, *41*, 3280.
22. Prasanna, R.; Purushothaman, S.; Raghunathan, R. *Tetrahedron Lett.* **2010**, *51*, 4538.
23. Hemamalini, A.; Nagarajan, S.; Ravinder, P.; Subramanian, V.; Das, T. M. *Synthesis* **2011**, 2495.
24. Barman, P. D.; Sanyal, I.; Mandal, S. B.; Banerjee, A. K. *Synthesis* **2011**, 3563.
25. Tabatabaei Rezaei, S. J.; Nabid, M. R.; Yari, A.; Ng, S. W. *Ultrason. Sonochem.* **2011**, *18*, 49.
26. Murugan, R.; Raghunathan, R.; Narayanan, S. S. *Synth. Commun.* **2010**, *40*, 3135.
27. Nair, V.; Sheela, K. C.; Rath, N. P.; Eigendorf, G. K. *Tetrahedron Lett.* **2000**, *41*, 6217.
28. Saravanan, P.; Babu, A. R. S.; Raghunathan, R. *Synth. Commun.* **2010**, *40*, 2329.
29. Liu, X. G.; Feng, Y. Q.; Tan, C. J.; Chen, H. L. *Synth. Commun.* **2006**, *36*, 2655.
30. Suresh Babu, A. R.; Raghunathan, R. *Tetrahedron Lett.* **2008**, *49*, 4487.
31. Suresh Babu, A. R.; Raghunathan, R.; Baskaran, S. *Tetrahedron* **2009**, *65*, 2239.
32. Ghandi, M.; Yari, A.; Rezaei, S. J. T.; Taheri, A. *Tetrahedron Lett.* **2009**, *50*, 4724.
33. Ji, S. -J.; Xu, X. -P.; Zhao, K.; Zhu, S. -L.; Shi, D. -Q. *Synthesis* **2010**, 1793.
34. Ganguly, A. K.; Seah, N.; Popov, V.; Wang, C. H.; Kuang, R.; Saksena, A. K.; Pramanik, B. N.; Chan, T. M.; McPhail, A. T. *Tetrahedron Lett.* **2002**, *43*, 8981.
35. Jayashankaran, J.; Manian, R. D. R. S.; Sivaguru, M.; Raghunathan, R. *Tetrahedron Lett.* **2006**, *47*, 5535.
36. Lakshmi, N. V.; Thirumurugan, P.; Jayakumar, C.; Perumal, P. T. *Synlett* **2010**, 955.
37. Thangamani, A. *Eur. J. Med. Chem.* **2010**, *45*, 6120.
38. Pardasani, R. T.; Pardasani, P.; Chaturvedi, V.; Yadav, S. K.; Saxena, A.; Sharma, I. *Heteroat. Chem.* **2003**, *14*, 36.
39. Ranjith Kumar, R.; Perumal, S. *Tetrahedron* **2007**, *63*, 12220.
40. Lakshmi, N. V.; Arun, Y.; Perumal, P. T. *Tetrahedron Lett.* **2011**, *52*, 3437.
41. Dondas, H. A.; Fishwick, C. W. G.; Grigg, R.; Kilner, C. *Tetrahedron* **2004**, *60*, 3473.
42. Selvakumar, K.; Vaithiyanathan, V.; Shanmugam, P. *Chem. Commun.* **2010**, *46*, 2826.
43. Raunak; Kumar, V.; Mukherjee, S.; Poonam; Prasad, A. K.; Olsen, C. E.; Schäffer, S. J. C.; Sharma, S. K.; Watterson, A. C.; Errington, W. *Tetrahedron* **2005**, *61*, 5687.
44. Mehrdad, M.; Faraji, L.; Jadidi, K.; Eslami, P.; Sureni, H. *Monatsh. Chem.* **2011**, *142*, 917.
45. Bouhfid, R.; Joly, N.; Essassi, E. M.; Lequart, V.; Massoui, M.; Martin, P. *Synth. Commun.* **2011**, *41*, 2096.
46. Velikorodov, A. V.; Imasheva, N. M.; Kuanchalieva, A. K.; Poddubnyi, O. Y. *Russ. J. Org. Chem.* **2010**, *46*, 971.
47. Azizian, J.; Morady, A. V.; Soozangarzadeh, S.; Asadi, A. *Tetrahedron Lett.* **2002**, *43*, 9721.
48. Galliford, C. V.; Martenson, J. S.; Stern, C.; Scheidt, K. A. *Chem. Commun.* **2007**, 631.
49. Muthusamy, S. *Tetrahedron* **2003**, *59*, 8117.

50. Jain, S.; Khanna, P.; Bhagat, S.; Jain, M.; Sakhuja, R. *Phosphorus, Sulfur, Silicon Relat. Elem.* **2005**, *180*, 1829.
51. Pardasani, P.; Pardasani, R. T.; Sherry, D.; Chaturvedi, V. *Synth. Commun.* **2002**, *32*, 435.
52. Subramaniyan, G.; Raghunathan, R.; Nethaji, M. *Tetrahedron* **2002**, *58*, 9075.
53. Manian, R. D. R. S.; Jayashankaran, J.; Raghunathan, R. *Synth. Commun.* **2003**, *33*, 4053.
54. Amal Raj, A.; Raghunathan, R. *Synth. Commun.* **2003**, *33*, 1131.
55. Amal Raj, A.; Raghunathan, R. *Synth. Commun.* **2003**, *33*, 421.
56. Subramaniyan, G.; Raghunathan, R. *Synth. Commun.* **2004**, *34*, 1825.
57. Periyasami, G.; Raghunathan, R.; Surendiran, G.; Mathivanan, N. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2342.
58. Maheswari, S. U.; Perumal, S.; Almansour, A. I. *Tetrahedron Lett.* **2012**, *53*, 349.
59. Ge, S.; Hua, Y.; Xia, M. *Ultrason. Sonochem.* **2009**, *16*, 232.
60. Poornachandran, M.; Jayagobi, M.; Raghunathan, R. *Synth. Commun.* **2010**, *40*, 551.
61. Jayashankaran, J.; Manian, R. D. R. S.; Raghunathan, R. *Tetrahedron Lett.* **2004**, *45*, 7303.
62. Dandia, A.; Jain, A. K.; Bhati, D. S. *Tetrahedron Lett.* **2011**, *52*, 5333.
63. Liu, H.; Dou, G.; Shi, D. *J. Comb. Chem.* **2010**, *12*, 292.
64. Lakshmi, N. V.; Thirumurugan, P.; Perumal, P. T. *Tetrahedron Lett.* **2010**, *51*, 1064.
65. Li, M.; Yang, W. -L.; Wen, L. -R.; Li, F. -Q. *Eur. J. Org. Chem.* **2008**, *2008*, 2751.
66. Suresh Babu, A. R.; Raghunathan, R.; Gayatri, G.; Sastry, G. N. *J. Heterocycl. Chem.* **2006**, *43*, 1467.
67. Suresh Babu, A. R.; Raghunathan, R. *Tetrahedron* **2007**, *63*, 8010.
68. Sridhar, G.; Raghunathan, R. *Synth. Commun.* **2006**, *36*, 21.
69. Jayashankaran, J.; Manian, R. D. R. S.; Venkatesan, R.; Raghunathan, R. *Tetrahedron* **2005**, *61*, 5595.
70. Amal Raj, A.; Raghunathan, R. *Tetrahedron* **2001**, *57*, 10293.
71. Babu, A. R. S.; Raghunathan, R. *Tetrahedron Lett.* **2008**, *49*, 4618.
72. El-Ahl, A. S. *Heteroat. Chem.* **2002**, *13*, 324.
73. Hazra, A.; Paira, P.; Sahu, K. B.; Naskar, S.; Saha, P.; Paira, R.; Mondal, S.; Maity, A.; Luger, P.; Weber, M.; Mondal, N. B.; Banerjee, S. *Tetrahedron Lett.* **2010**, *51*, 1585.
74. Suresh Kumar, R.; Perumal, S. *Tetrahedron Lett.* **2007**, *48*, 7164.
75. Kumar, R. S.; Rajesh, S. M.; Perumal, S.; Banerjee, D.; Yogeeswari, P.; Sriram, D. *Eur. J. Med. Chem.* **2010**, *45*, 411.
76. Shvets, A. A.; Kurbatov, S. V. *Chem. Heterocycl. Compd.* **2009**, *45*, 866.
77. Manian, R. D. R. S.; Jayashankaran, J.; Kumar, S. S.; Raghunathan, R. *Tetrahedron Lett.* **2006**, *47*, 829.
78. Karthikeyan, K.; Sivakumar, P. M.; Doble, M.; Perumal, P. T. *Eur. J. Med. Chem.* **2010**, *45*, 3446.
79. Velikorodov, A. V.; Poddubnyi, O. Y.; Krivosheev, O. O.; Titova, O. L. *Russ. J. Org. Chem.* **2011**, *47*, 402.

80. Maheswari, S. U.; Balamurugan, K.; Perumal, S.; Yogeeswari, P.; Sriram, D. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7278.
81. Prasanna, P.; Balamurugan, K.; Perumal, S.; Yogeeswari, P.; Sriram, D. *Eur. J. Med. Chem.* **2010**, *45*, 5653.
82. Karthikeyan, S. V.; Bala, B. D.; Raja, V. P. A.; Perumal, S.; Yogeeswari, P.; Sriram, D. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 350.
83. Hu, Y.; Zou, Y.; Wu, H.; Shi, D. *Ultrason. Sonochem.* **2012**, *19*, 264.
84. (a) Liu, H.; Zou, Y.; Hu, Y.; Shi, D. Q. *J. Heterocycl. Chem.* **2011**, *48*, 877. (b) Ponnala, S.; Kumar, R.; Maulik, P. R.; Sahu, D. P. *J. Heterocycl. Chem.* **2006**, *43*, 1635.
85. Murugan, R.; Anbazhagan, S.; Sriman Narayanan, S. *Eur. J. Med. Chem.* **2009**, *44*, 3272.
86. Li, X.; Zheng, A.; Liu, B.; Yu, X.; Yi, P. *Chin. J. Chem.* **2010**, *28*, 1207.
87. Li, X.; Zheng, A.; Liu, B.; Li, G.; Yu, X.; Yi, P. *J. Heterocycl. Chem.* **2011**, *48*, 776.
88. Hu, X. F.; Feng, Y. Q. *Synth. Commun.* **2005**, *35*, 1747.
89. Poornachandran, M.; Raghunathan, R. *Tetrahedron* **2006**, *62*, 11274.
90. Li, X.; Li, Z.; Zheng, A.; Li, G.; Yu, X.; Yi, P. *J. Heterocycl. Chem.* **2011**, *48*, 836.
91. Lakshmi, N. V.; Tamilisai, R.; Perumal, P. T. *Tetrahedron Lett.* **2011**, *52*, 5301.
92. Li, X.; Yu, X.; Yi, P. *Chin. J. Chem.* **2010**, *28*, 434.
93. Li, X.; Zheng, A.; Liu, B.; Yu, X.; Yi, P. *J. Heterocycl. Chem.* **2010**, *47*, 1157.
94. Rajesh, R.; Raghunathan, R. *Tetrahedron Lett.* **2010**, *51*, 5845.

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