Synthesis of spiro-fused heterocyclic scaffolds through multicomponent reactions involving isatin

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Abstract

Isatin has been utilized in many heterocyclic preparations and considered as an important building block in organic synthesis. There is a wide range of multi-component reactions that include isatin in the synthesis of heterocyclic compounds. This review highlights the advances in the use of isatin as starting material in the synthesis of various organic compounds and drugs during the period from 2012 to 2015.

Keywords: Isatin, spiro-fused compounds, multi-component reactions, heterocyclic synthesis

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1. Introduction

Isatin is a natural product found in plants of the genus *Isatis*[1] that was first obtained by Erdmann[2] and Laurent[3] in 1840 as a product from the oxidation of indigo dye by nitric acid and chromic acid. Substituted isatin analogues constitute valuable building blocks for potential pharmaceuticals with a wide range of biological properties such as antimicrobial,[4] antitumor,[5-8] antitubercular,[9-10] antimalaria,[11] anti-HIV,[12] and antibacterial.[13]

Furthermore, isatin is a core constituent of many drugs. For example, spirotetrahydro β-carboline is amenable to a single or low dose oral treatment for malaria,[14] *N*-methylisatin-*β*,4′,4′-diethylthiosemicarbazone (M-IBDET) specifically inhibits formation of Moloney leukemia virus structural proteins,[15] and the indenoquinoline compounds, NSC 706744, NSC 725776 and NSC 724998 show prominent antitumor activities (Figure 1).[16]

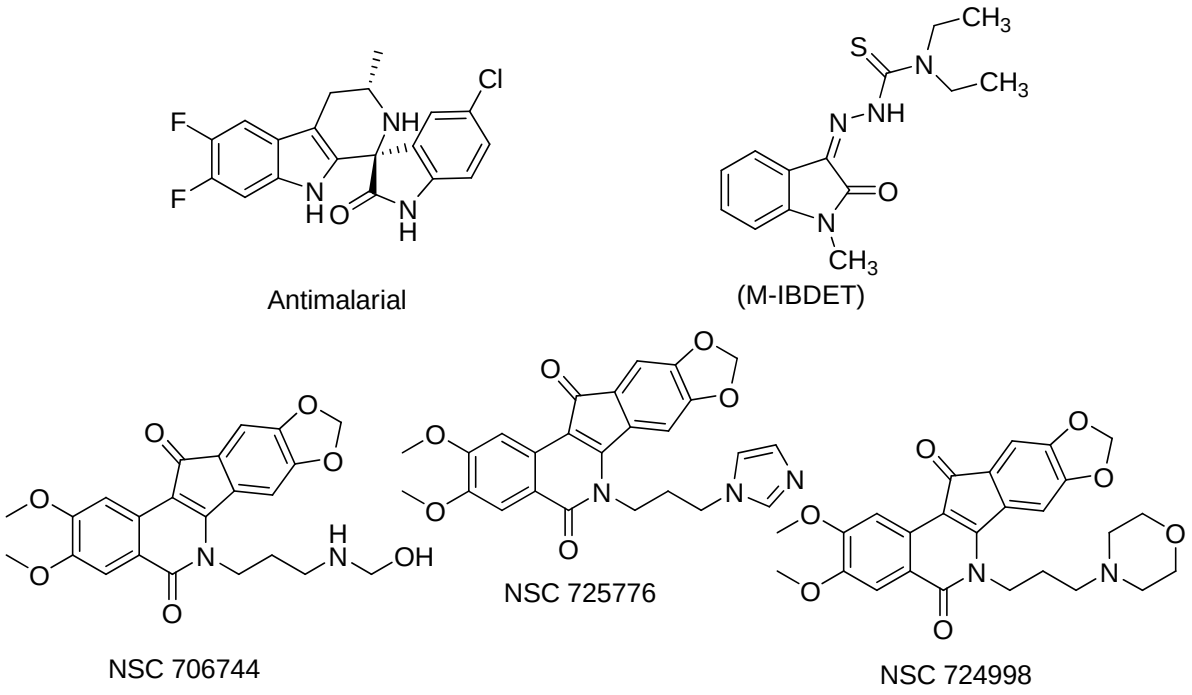


Figure 1

Isatin and its derivatives accomplish various reactions for the synthesis of organic compounds; Schiff bases of isatin are used for their pharmaceutical properties[17] and spirooxindoles have significant biological activities.[18,19] The chemistry of isatins was reviewed for the first time by Sumpter[20] and later updated by Popp[21] and da Silva *et al*.[22] In recent years isatin-related review articles have been published on enantioselective reactions with isatin,[23-25] biochemical and pharmacological characterization of isatin and its derivatives,[26] isatins as privileged molecules in design and synthesis of spiro-fused cyclic frameworks,[27] recent progress on routes to spirooxindole systems derived from isatin,[28] synthesis of spiro[29] and multispiro[30]

heterocyclic compounds from isatin, the use of water in the synthesis of isatin based spirocyclic compounds,[31] and synthesis of heterocyclic compounds based on isatin through 1, 3-dipolar cycloaddition reactions.[32]

Considering the importance of isatin as a building block in organic synthesis, and since there is a wide range of reactions that include isatin in the synthesis of heterocyclic compounds, this review gives an overview of the synthesis of different types of spiro-fused heterocyclic scaffolds through multicomponent reactions from the year 2012 to 2015 in which one of the starting materials is isatin.

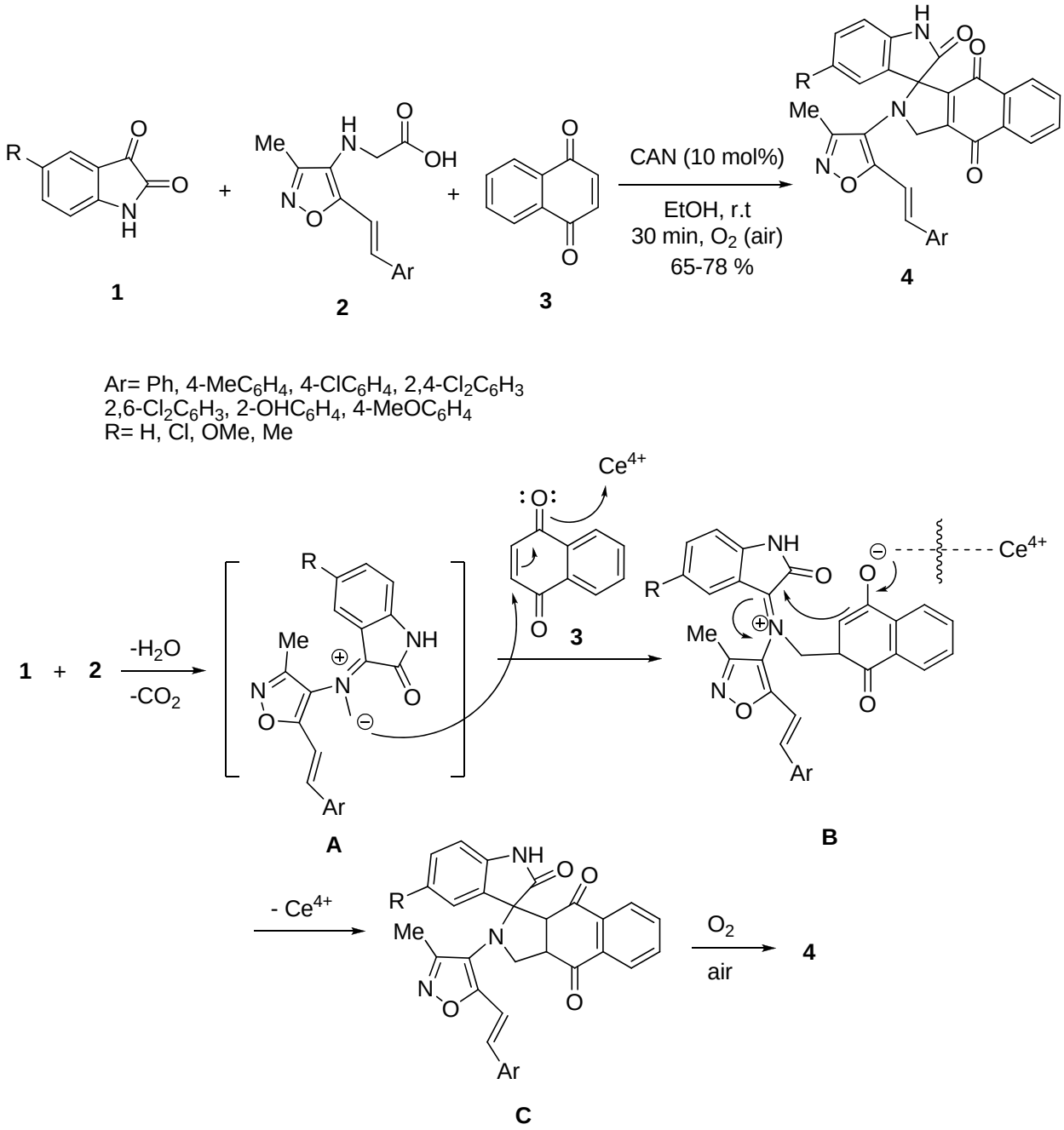
2. Synthesis of Isatin-Based Spiro-Fused Frameworks

Isatins have been employed in the architecture of different types of spiro-heterocyclic frameworks. This section involves a range of multi-component reactions involving isatin, starting with the synthesis of five-membered spiro-fused compounds trouth three-component reactions. Then, the synthesis of six-membered spiro-fused compounds, four-component and five-component reactions of isatin are presented.

2.1. Synthesis involving three-component reactions of isatins

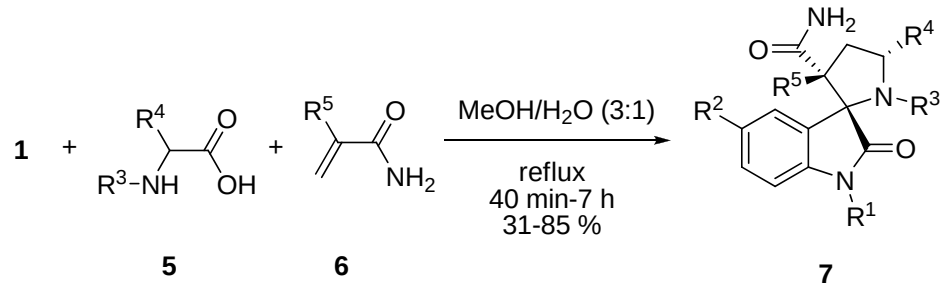
The design of reactions involving three or more different starting materials, usually referred to as multicomponent reactions (MCRs) has become an important area of research in organic, medicinal, and combinatorial chemistry.[33-36] Some advantages of MCRs involve minimization of the reagents, solvents, cost, and time. Other advantages, which make MCRs an effective tool for synthetic chemists, are ease of separation thus avoiding the complicated purification procedures and also minimizing the formation of chemical waste.

2.1.1. Five-membered spiro-fused compounds. Rajanarendar's group synthesized a series of isoxazoles **4** by the three component reaction of isoxazole acetic acid **2** with substituted isatins **1** and 1,4-naphthoquinone **3** using Ceric ammonium nitrate (CAN) catalyst under aerial oxidation condition (Scheme 1).[37] The plausible mechanism involves the 1,3-dipolar cycloaddition of azomethine ylide, generated *in situ* via decarboxylative condensation of isatin with isoxazole acetic acid to 1,4-naphthoquinone activated by CAN, followed by dehydrogenation under aerial oxidation condition affords the desired compound. The compounds were evaluated for their anti-inflammatory and analgesic activity.



Scheme 1

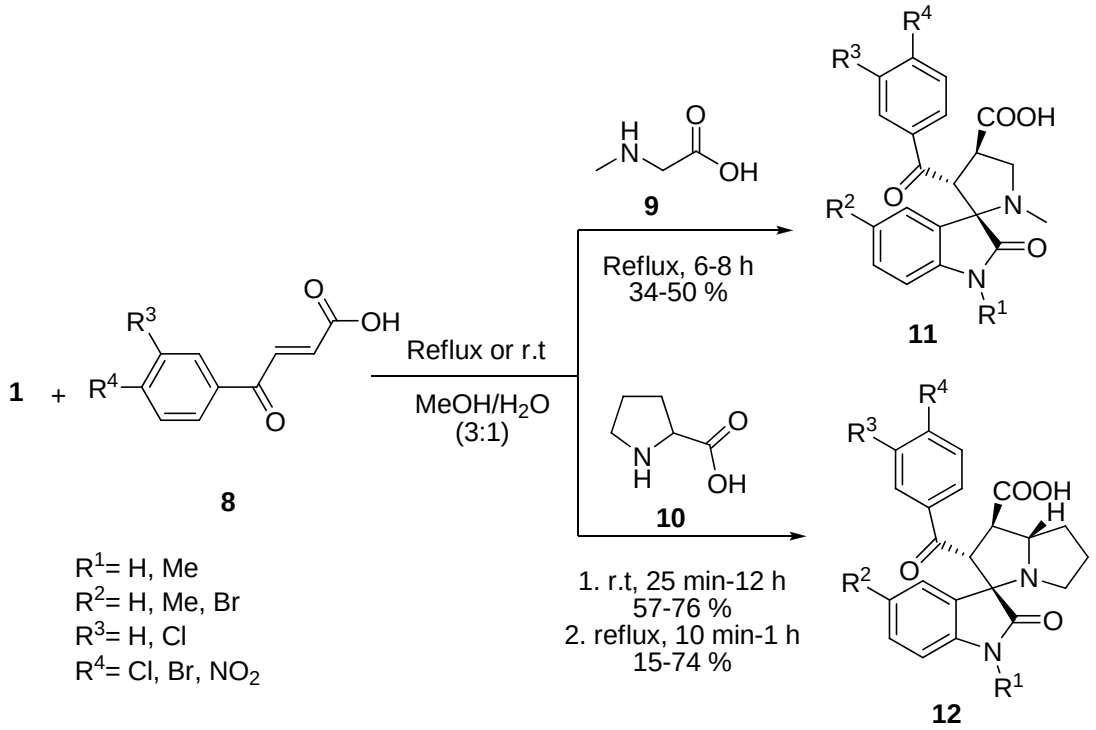
The synthesis of spirooxindolopyrrolidines **7** and **11** and spiropyrrolizidines **12** by utilizing a 1,3-dipolar cycloaddition of hitherto uninvestigated acrylamides **6** and aroylacrylic acids **8** with azomethine ylides, generated *in situ* via decarboxylative condensation of isatins **1** and *N*-substituted α-amino acids **5**, **9**, and **10** in a three-component fashion was reported by Lipson and co-workers (Schemes 2 and 3).[38]



5 **6** **7**

R^1= H, Me, 4-$ClC_6H_4CH_2$
R^2= H, Br, NO_2
R^3= Me, $CH_2CH_2CH_2$, CH_2SCH_2
R^4= H, $CH_2CH_2CH_2$, CH_2SCH_2
R^5= H, Me

Scheme 2



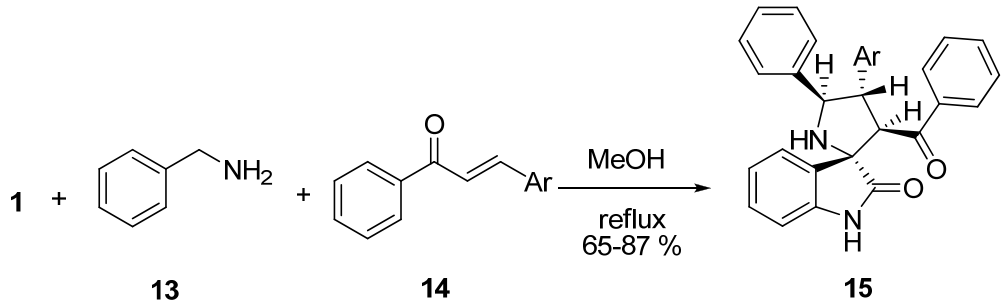
8 **9** **10** **11** **12**

R^1= H, Me
R^2= H, Me, Br
R^3= H, Cl
R^4= Cl, Br, NO_2

Scheme 3

Synthesis of some biologically interesting spiro-indolone-pyrrolidine derivatives **15** was accomplished by 1,3-dipolar cycloaddition reaction of azomethine ylide generated *in situ* from isatin **1** and benzylamine **13** with the substituted α,β-unsaturated carbonyl compounds **14** as dipolarophile, leading to the formation of new 4-aryl-3-benzoyl-5-phenylspiro[pyrrolidine-2.3′-indolin]-2′-one derivatives **15** stereoselectively in excellent yields (Scheme 4).[39] The synthesized compounds have been screened for their advanced glycation end (AGE) product formation

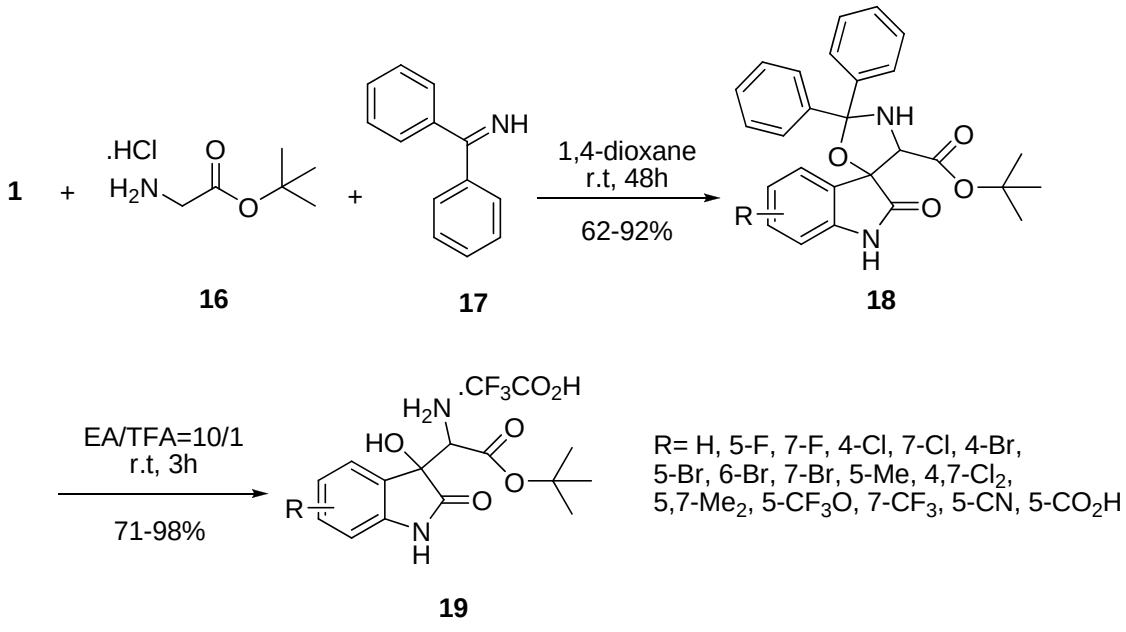
inhibitory activity. In another study, the molecular mechanism of this cycloaddition has been investigated by means of a density functional theory (DFT) method.[40]



Ar= Ph, 4-ClC_6H_4, 4-$OMeC_6H_4$, 4-$NO_2C_6H_4$, 4-OHC_6H_4, 4-$NMe_2C_6H_4$, 3,4-$(OMe)_2C_6H_3$, 2-ClC_6H_4, CH=CH-C_6H_5

Scheme 4

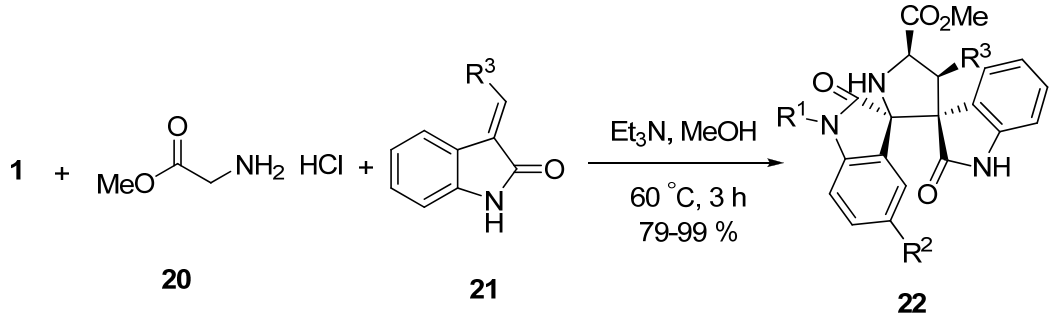
Huang *et al*. conducted a catalyst-free, one-pot, three-component process employing isatins **1**, *tert*-butyl 2-aminoacetate hydrochloride **16**, and benzophenone imine **17** for the synthesis of biologically interesting unnatural amino-acids containing 3-hydrooxindole skeleton **19** (Scheme 5).[41] The strategy involves the formation of two new quaternary centers in high yields and with a broad substrate scope.



Scheme 5

The three-component 1,3-dipolar cycloaddition reaction of substituted isatins **1** and primary *α*-amino acid methyl ester **20** with the Knoevenagel adducts of substituted isatin **21** resulted in

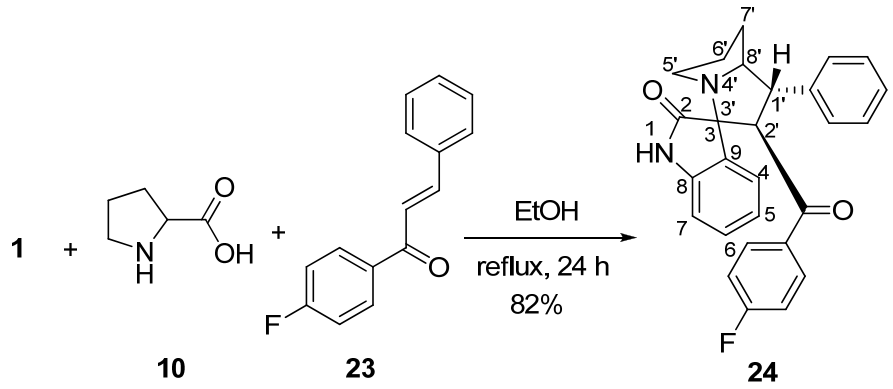
the formation of novel spiropyrrolidine bisoxindoles **22** in high yields (up to 99%) (Scheme 6).[42]



R^1= H, Bn, Et
R^2= H, Br, Me
R^3= Ph, 4-FC_6H_4, 4-BrC_6H_4,
3,4-$(MeO)_2C_6H_3$, Pyridin-3-yl

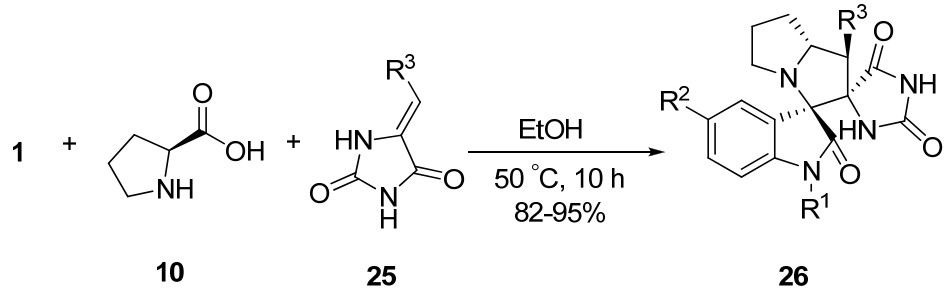
Scheme 6

A new spiro[indole-3,3′-pyrrolizine] derivative **24** was regioselectively synthesized by the multicomponent reaction of isatin **1**, 1-(4-fluorophenyl)-3-phenylprop-2-en-1-one **23**, and *L*-proline **10** (Scheme 7).[43] The possible mechanism of this reaction was investigated using a B3LYP/6-311G level of theory, and the results show that the regioselection depends on the energy barrier between the stacking state and the regioisomer.[44]



Scheme 7

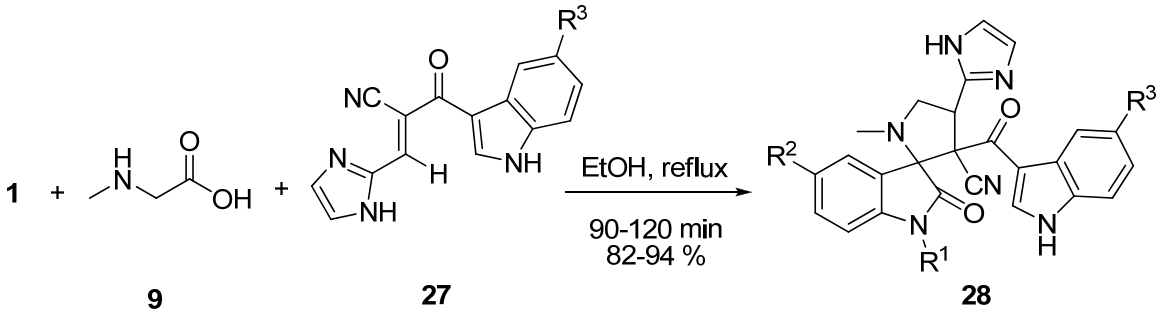
A synthetic route for the preparation of novel dispirooxindoles **26** has been achieved via 1,3-dipolar cycloaddition of azomethine ylides generated *in situ* by the decarboxylative condensation of isatins **1** and L-proline **10** with the dipolarophile 5-benzylideneimidazolidine-2,4-dione **25** (Scheme 8).[45]



R^1= H, Me, Bn
R^2= H, F, Cl, Br
R^3= Ph, 3,4-$Cl_2C_6H_3$, 4-BrC_6H_4, 3-ClC_6H_4, 4-$CF_3C_6H_4$, 4-$OMeC_6H_4$

Scheme 8

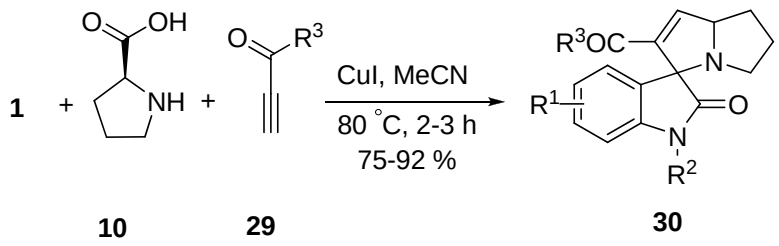
Novel spirooxindole-pyrrolidine compounds **28** have been synthesized through 1,3-dipolar cycloaddition of azomethine ylides generated from isatin **1** and sarcosine **9** with the dipolarophile 3-(1*H*-imidazol-2-yl)-2-(1*H*-indole-3-carbonyl)acrylonitrile **27** under the optimised reaction condition (Scheme 9).[46] Synthesized compounds were evaluated for their anticancer activity against A549 human lung adenocarcinoma cancer cell line.



R^1= H, Me
R^2= H, F, Cl, Br, I, NO_2, Me
R^3= H, OMe

Scheme 9

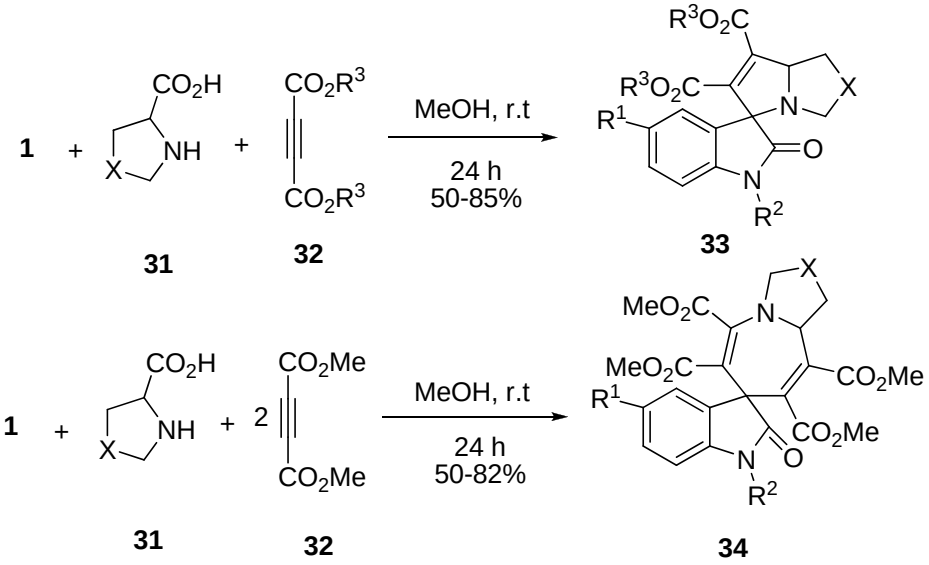
CuI facilitated three component reaction of isatins **1**, *L*-proline **10**, and terminal alkynes containing ester or amide substituents **29** in acetonitrile to prepare the spiropyrrolidine oxindoles **30** (Scheme 10).[47]



R^1= H, 5-Br, 5,7-$(NO_2)_2$, 5-F
R^2= H, $CH_2C_6H_4Cl$-*m*
R^3= NH_2, NHMe, NHEt, OEt

Scheme 10

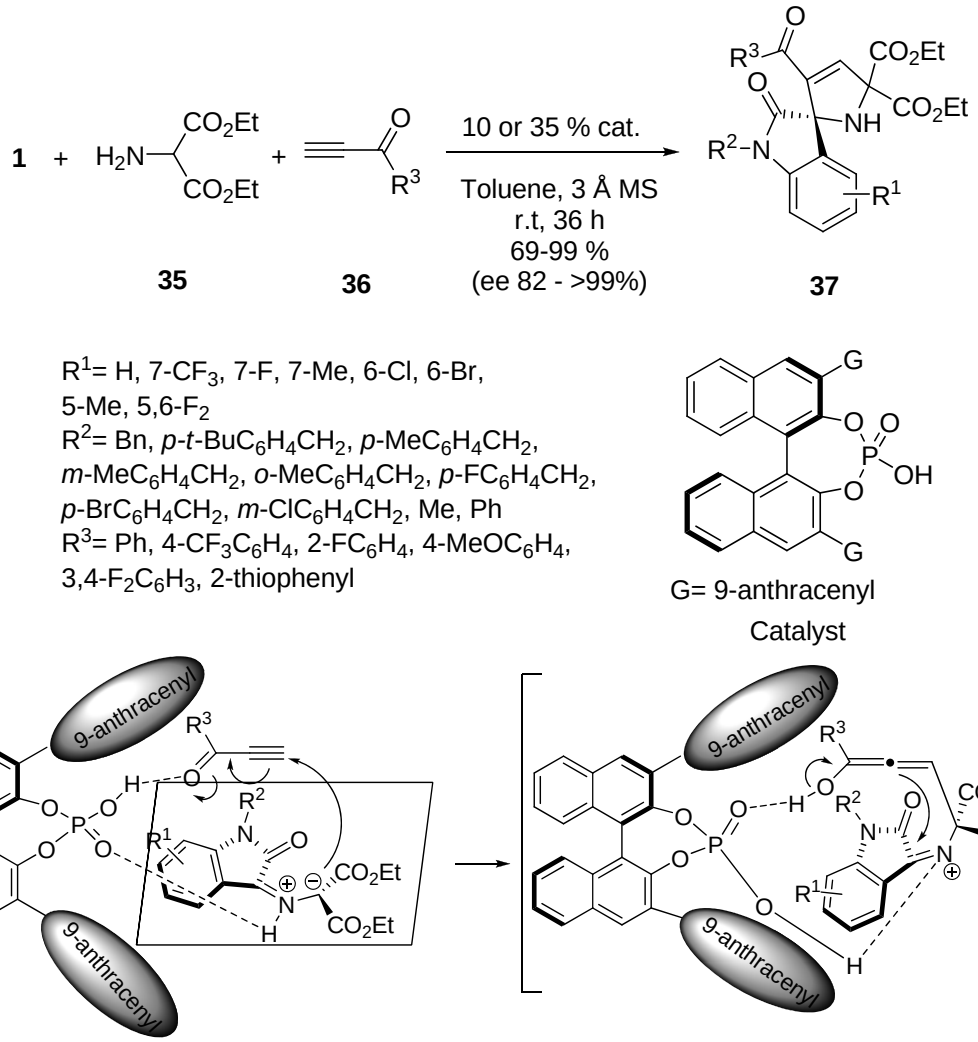
The three-component reaction of α-amino acids such as L-proline or thiazolidine-4-carboxylic acid **31**, isatins **1**, and acetylenedicarboxylates **32** proceeded with normal 1,3-dipolar cycloaddition reaction of azomethine ylide to give spiro[indoline-3,3′-pyrrolizines] **33**. More importantly, the reaction of α-amino acid **31**, and isatins **1** with two molecular acetylenedicarboxylates **32** in methanol afforded unprecedented spiro[indoline-3,7′-pyrrolo[1,2-*a*]-azepines] **34** as main products (Scheme 11).[48]



R^1= H, Me, F, Cl
R^2= H, Bn, *n*-C_4H_9
R^3= Me, Et
X= CH_2, CH(OH), S

Scheme 11

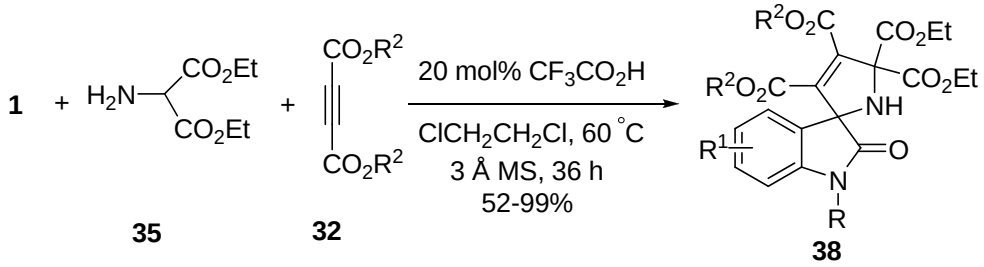
Catalytic asymmetric cycloaddition of isatins **1**, terminal alkynes **36**, and diethyl 2-amino-malonate **35** using the binaphthol derived phosphoric acid as catalyst afforded spiro[indoline-3,2´-pyrroles] **37** with quaternary stereogenic centers in high yields and excellent enantioselectivities (up to 99% yield, >99% ee) (Scheme 12).[49] According to possible reaction pathway and transition states, the 1,3-dipolar cycloadditions of alkynes with isatin-derived azomethine ylides might proceed via a sequential Michael addition and Mannich-type cyclization rather than a concerted pathway. By forming two hydrogen bonds with the substrates, the catalyst served as a Brønsted acid/Lewis base bifunctional catalyst to simultaneously activate both alkynes and isatin-derived azomethine ylides.



Scheme 12

The construction of a spirooxindole-based 2,5-dihydropyrrole scaffold **38** has been also established by the same group via the reaction of isatins **1**, diethyl 2-aminomalonate **35** and alkynes **32** (Scheme 13).[50] The authors proposed a possible pathway and transition state of the

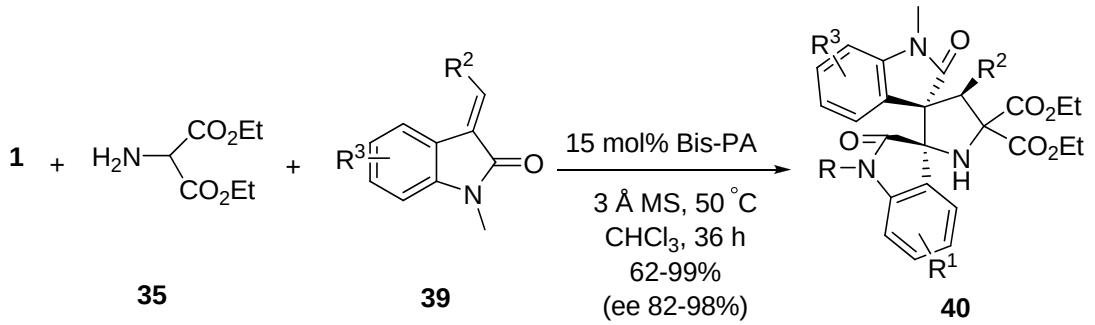
reaction based on the condensation of isatins and diethyl 2-aminomalonate in the presence of trifluoroacetic acid. The corresponding azomethine ylides then participated in 1,3-dipolar cycloadditions with alkynes to afford related products via a sequential Michael addition and Mannich-type cyclization. This reaction was also developed using chiral phosphoric acids as catalysts.[51]



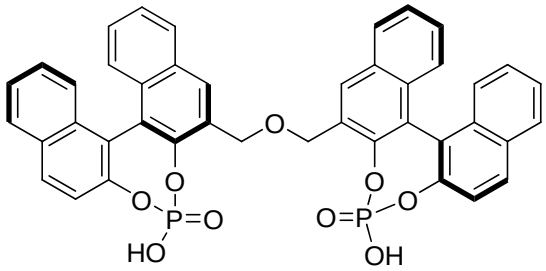
Scheme 13

The first catalytic enantioselective construction of a 3,3′-pyrrolidinyldispirooxindole scaffold **40** has been established via organocatalytic asymmetric 1,3-dipolar cycloadditions of isatin-derived azomethine ylides with methylene indolinones **39**, which afforded structurally complex bis-spirooxindoles (Scheme 14).[52]

In a related study, Shi and co-workers established the first catalytic asymmetric 1,3-dipolar cycloadditions of isatin-derived azomethine ylide with allenes **41**, which efficiently assembly isatins, amino-esters and 2,3-allenoate into enantioenriched spiro[indoline-3,2'-pyrrole] derivatives **42** with a quaternary stereogenic center in generally excellent enantioselectivities (80%-98% ee) (Scheme 15).[53]

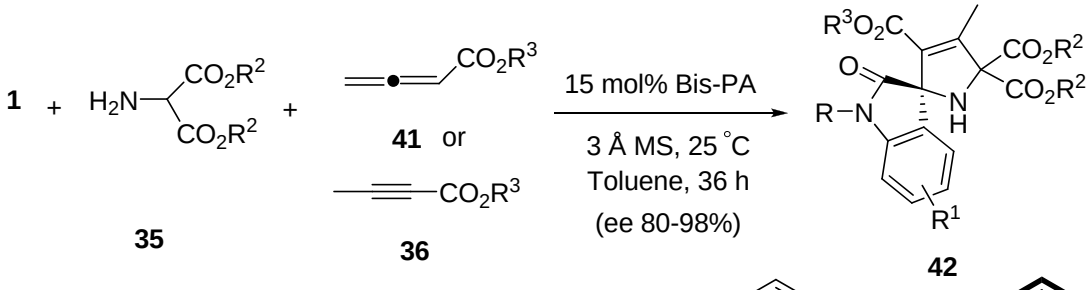


R= Bn, *p*-*t*Bu$C_6H_4CH_2$, *p*-Br$C_6H_4CH_2$, *m*-Cl$C_6H_4CH_2$, *o*-Cl$C_6H_4CH_2$, Ph, Me
R^1= H, 5-F, 6-MeO, 6-Cl, 6-Br, 7-CF_3, 7-F 5-F, 6-Br, 7-Br, 7-CF_3, 5,6-F_2
R^2= CO_2Et, COPh, CN
R^3= H, 5-Me, 5-Cl, 6-MeO, 6-Br, 6-Cl, 7-Me, 7-F

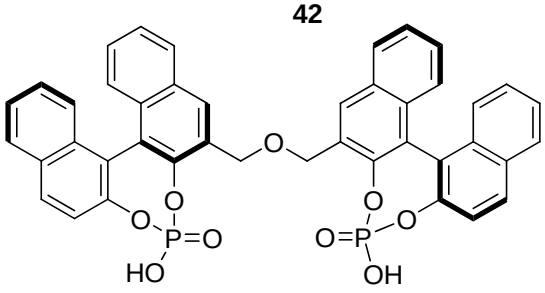


Bis-phosphoric acid (Bis-PA)

Scheme 14



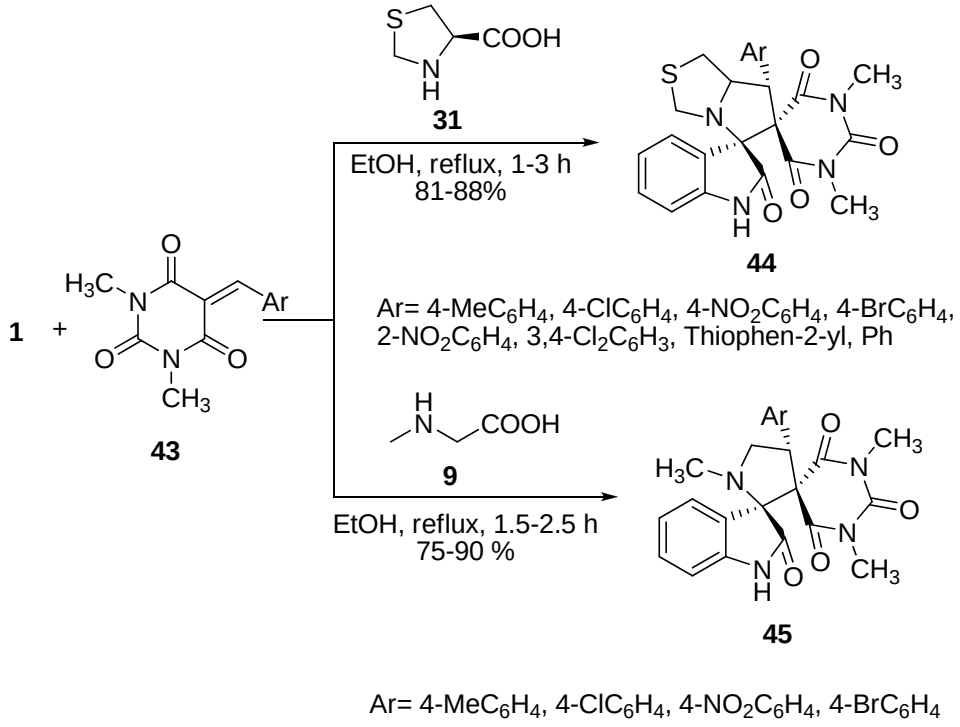
R= Bn, *p*-*t*Bu$C_6H_4CH_2$, *p*-Br$C_6H_4CH_2$, *m*-Me$C_6H_4CH_2$, *o*-Me$C_6H_4CH_2$, *p*-Me$C_6H_4CH_2$, *m*-Cl$C_6H_4CH_2$, *o*-Cl$C_6H_4CH_2$, Ph, Bn
R^1= H, 5-Me, 5,6-F_2, 6-Br, 6-Cl, 7-Me, 7-F, 7-CF_3
R^2= Me, Et
R^3= CH_2-9-anthracenyl



Bis-phosphoric acid (Bis-PA)

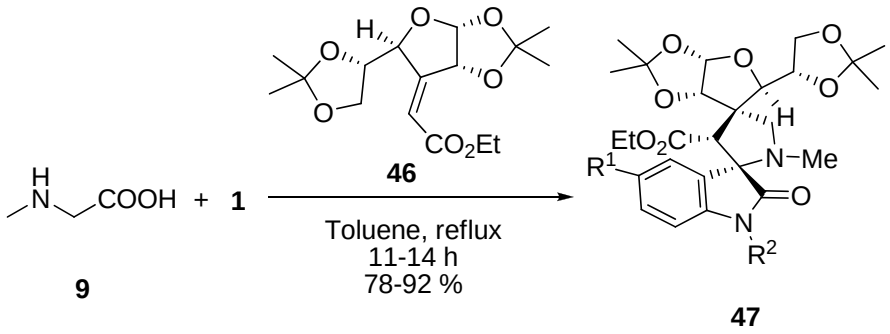
Scheme 15

1,3-Dipolar cycloaddition reaction between isatin **1** and *L*-thioproline **31**/ sarcosine **9** with the dipolarophile 5-benzylidene-1,3-dimethylpyrimidine-2,4,6-trione **43** was carried out and a series of novel dispirooxindoles **44-45** were synthesized (Scheme 16).[54]



Scheme 16

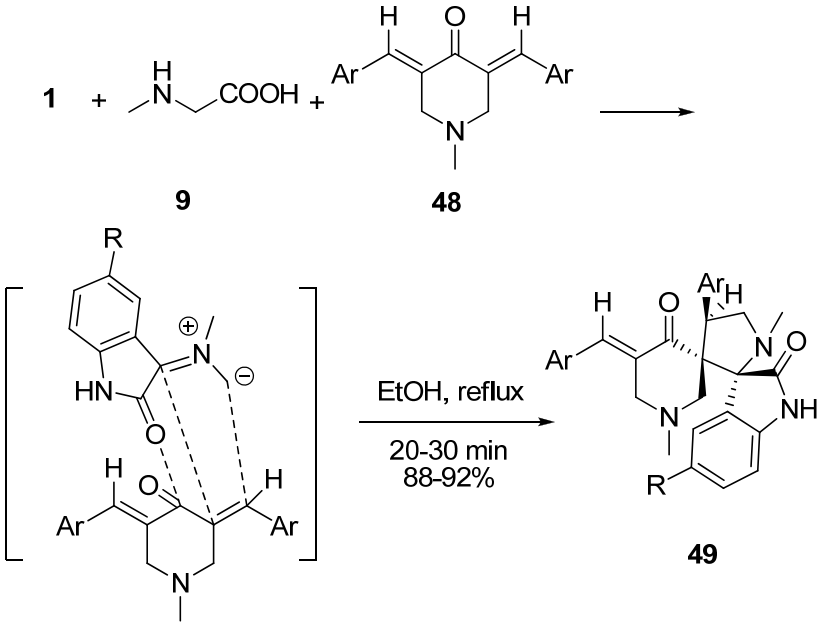
Barman *et al*. described the azomethine cycloaddition reactions to synthesize bispiropyrrolidines containing oxindoles **47** using sarcosine **9**, isatin **1**, and sugar-derived exocyclic olefin **46** and the sugar-derived olefin precursor (Scheme 17).[55]



Scheme 17

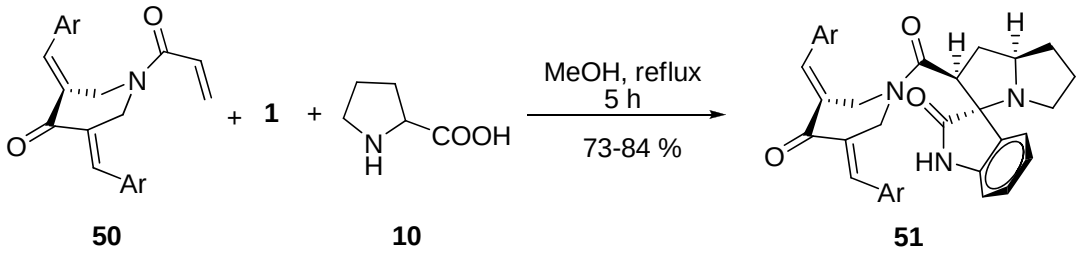
Dispiro[3*H*-indole-3,2′-pyrrolidine-3′,3″-piperidine]-2(1*H*),4″-dione derivatives **49** were synthesized by the reaction of substituted isatins **1**, sarcosine **9**, and 1-methyl-3,5-bis[(*E*)-arylidene]piperidin-4-ones **48** with high degree of chemo-, regio- and stereoselectivity (Scheme 18).[56] The regioselectivity in the product formation can be explained by considering the

secondary orbital interaction (SOI) of the orbital of the carbonyl group of dipolarophile **48** with those of the ylide as shown in Scheme 18.



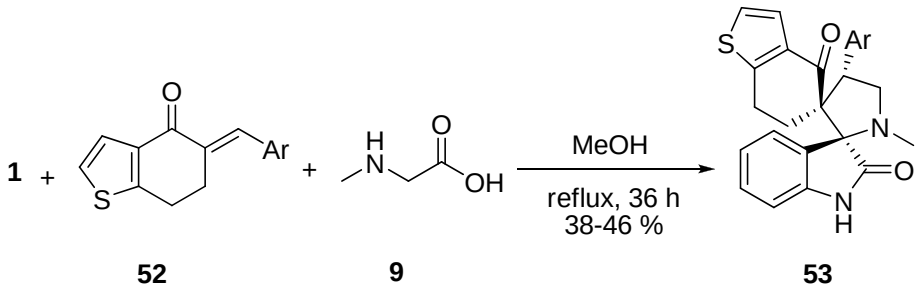
Scheme 18

A series of piperidone-grafted novel mono-spiropyrrolizines **51** has been synthesized by the [3+2]-cycloaddition reactions of 1-acryloyl-3,5-bisbenzylidenepiperidin-4-ones **50**, isatin **1**, and *L*-proline **10** (Scheme 19).[57] The *in vitro* evaluation of cholinesterase enzymes inhibitory activity of these cycloadducts was performed. Application of sarcosine[58] and phenylglycine[59] in this reaction was also investigated by the same group.



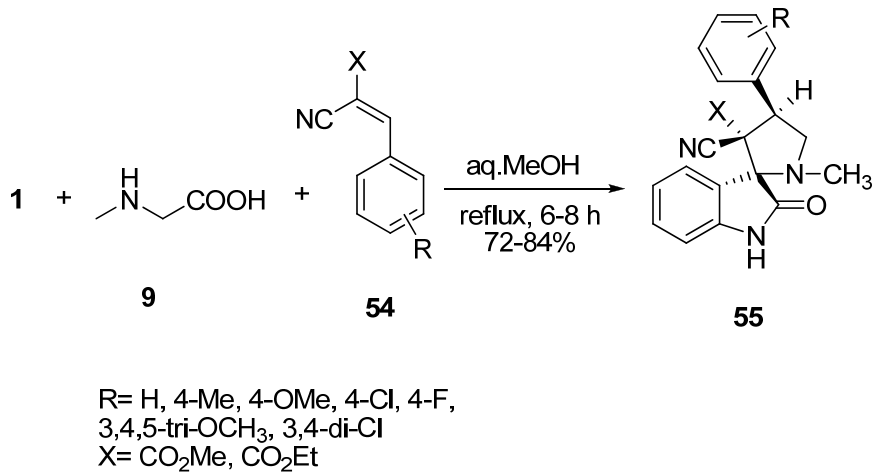
Scheme 19

The 1,3-dipolar cycloaddition reaction of azomethine ylide generated *in situ* from isatin **1** and sarcosine **9** to 5-arylmethylene-6,7-dihydro-1-benzothiophen-4(5*H*)-ones **52** gave novel 1′-methyl-4′-aryl-6,7-dihydro-4H-dispiro[1-benzothiophene-5,3′-pyrrolidine-2′,3″-indole]-2″,4-(1″*H*)-diones **53** in moderate yields (Scheme 20).[60]



Scheme 20

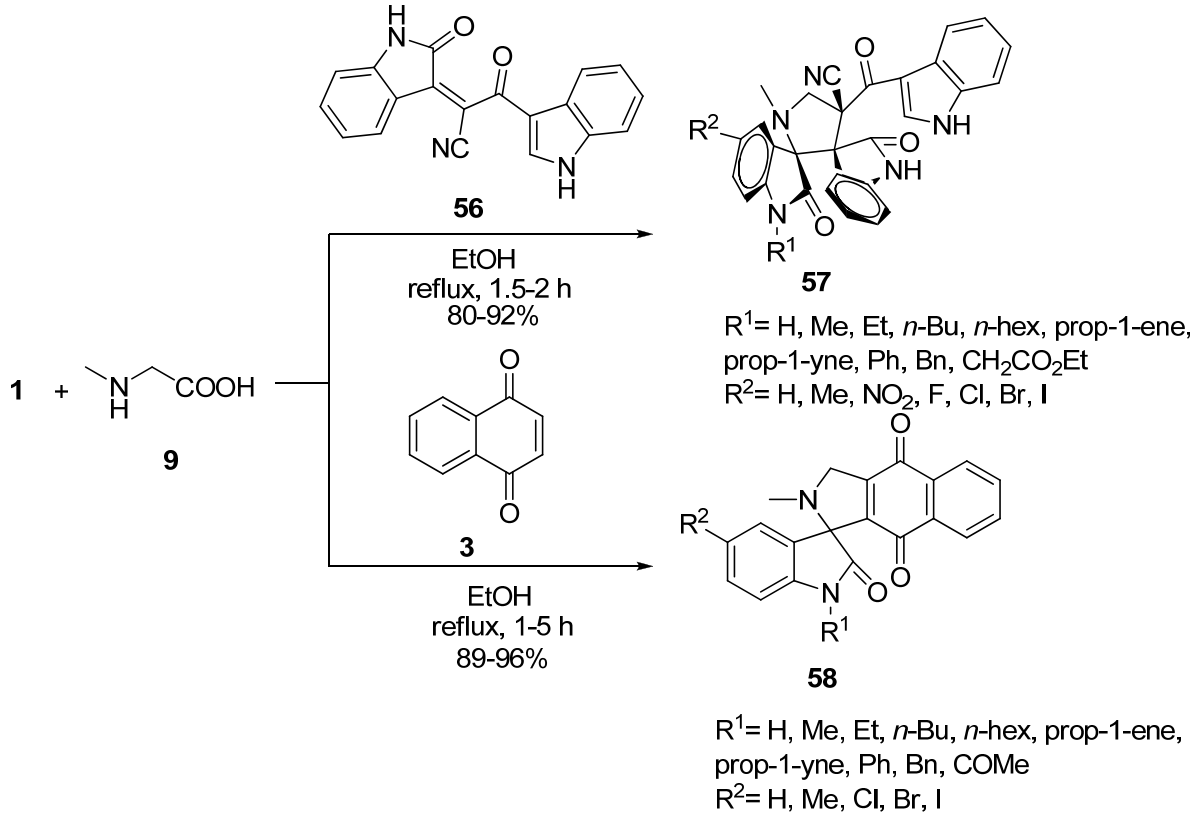
A series of novel spiro[indoline-3,2′-pyrrolidine] derivatives containing cyano group **55** were synthesized via a cycloaddition reaction of isatin **1**, sarcosine **9**, and Knoevenagel adducts **54** in refluxing aqueous methanol (Scheme 21).[61]



Scheme 21

Perumal and co-workers prepared novel dispirooxindole-pyrrolidine derivatives **57** by 1,3-dipolar cycloaddition of isatins **1** and sarcosine **9** with the dipolarophile 3-(1*H*-indol-3-yl)-3-oxo-2-(2-oxoindolin-3-ylidene)propanenitrile **56** (Scheme 22).[62] Synthesized compounds were evaluated for their antimicrobial activity and all the compounds showed significant activity.

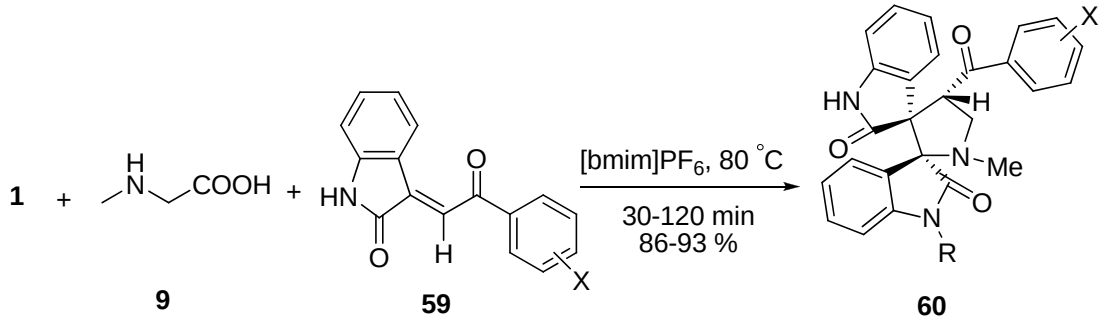
Anticancer activity was also evaluated against A549 human lung adenocarcinoma cancer cell lines. In another study, the same authors conducted this reaction using 1,4-naphthoquinone **3** as dipolarophile with sarcosine **9** or L-proline for the synthesis of novel spirooxindoles **58** (Scheme 22).[63] Ethyl lactate as an invaluable bio based solvent was also demonstrated as the medium for this 1,3-dipolar cycloaddition reaction.[64]



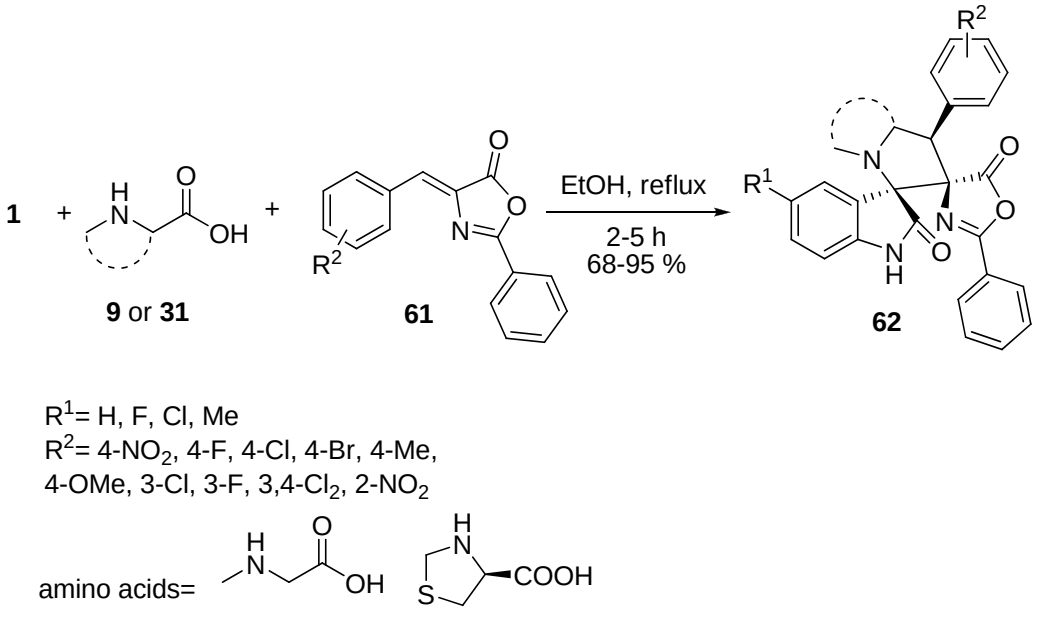
Scheme 22

A one-pot, three-component procedure for the synthesis of novel dispiropyrrolidine-bisoxindole derivatives **60** by cycloaddition trapping of azomethine ylides generated *in situ* from isatin **1** and sarcosine **9**, and 3-aroylmethyleneindol-2-ones **59** has been reported in [bmim]PF_6, as a recyclable solvent in excellent yield without using any catalyst (Scheme 23).[65]

Highly functionalized dispiropyrrolizidine derivatives **62** were synthesized via a three-component [3+2] cycloaddition reaction of azomethine ylides with (*Z*)-4-benzylidene-2-phenyloxazol-5(4*H*)-ones **61** as dipolarophiles (Scheme 24).[66] Many of these compounds were evaluated for their antiproliferative properties in vitro against cancer cells and several compounds were found to have good activities.



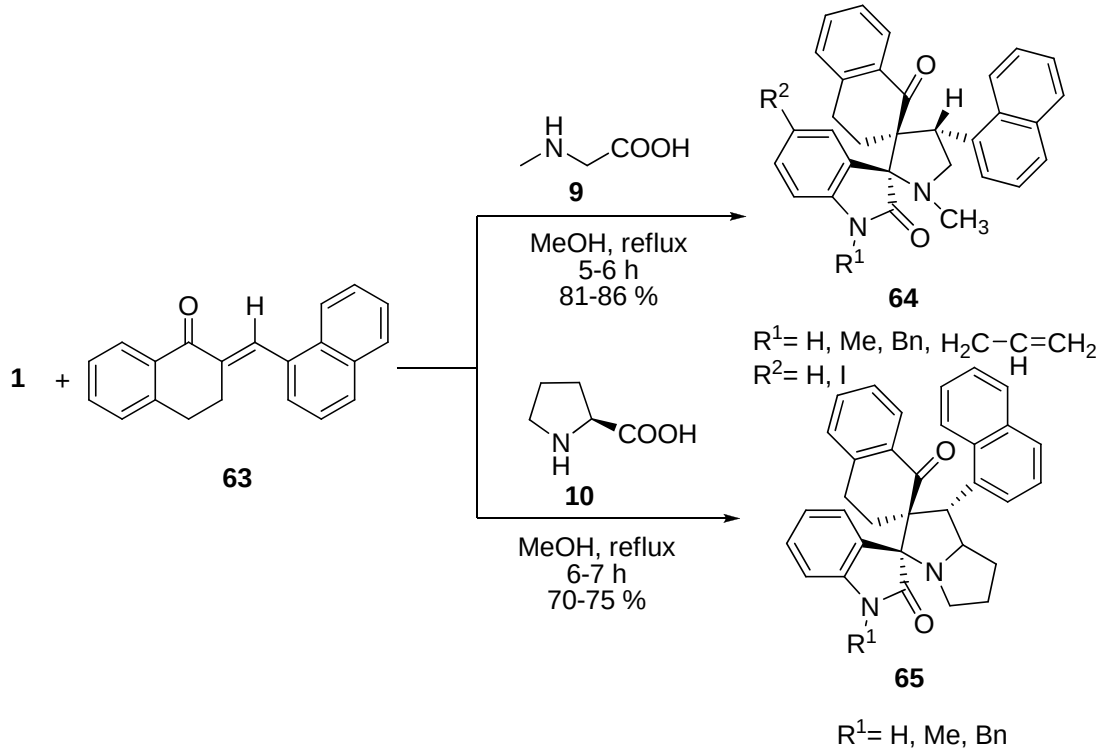
Scheme 23



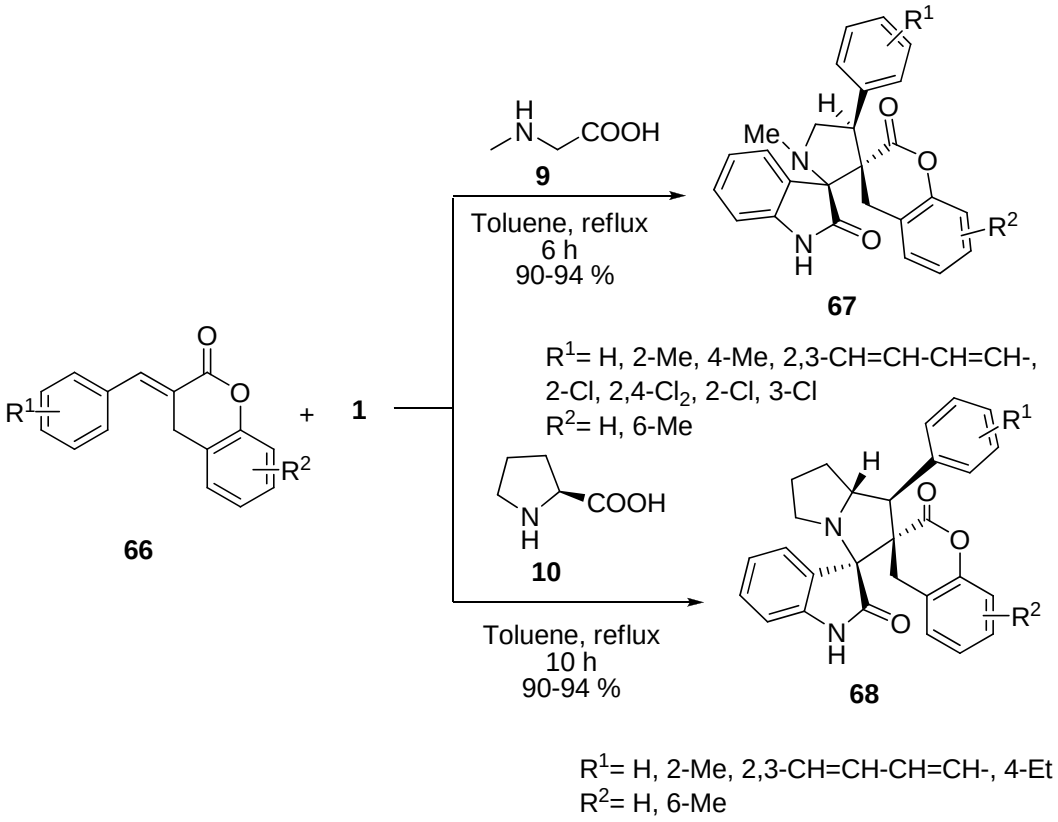
Scheme 24

Synthesis of naphthyl pyrrolidine/pyrrolizidine-spirooxindoles **64-65** has been achieved by a one pot three component 1,3-dipolar cycloaddition reaction. The azomethine ylides generated *in situ* from isatin/*N*-substituted isatin **1** and sarcosine **9**/L-proline **10** reacted with naphthylidene tetralone **63** as a dipolarophile to give naphthyl dispiro heterocycles (Scheme 25).[67]

The reaction of (*E*)-3-benzylidenechroman-2-one **66** with isatin **1** and sarcosine **9** or *L*-proline **10** synthesized the hybrid oxindole-functionalized dispiropyrrolidines and dispiropyrrolizidines **67-68**. The dispiro compounds are obtained via [3+2]-cycloaddition reactions between (*E*)-3-benzylidenechroman-2-one **66** and the adduct generated from isatin and sarcosine or *L*-proline (Scheme 26).[68]

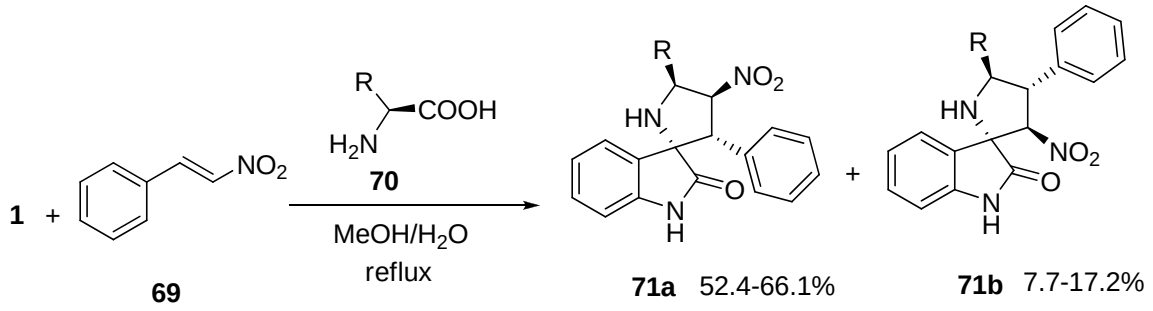


Scheme 25

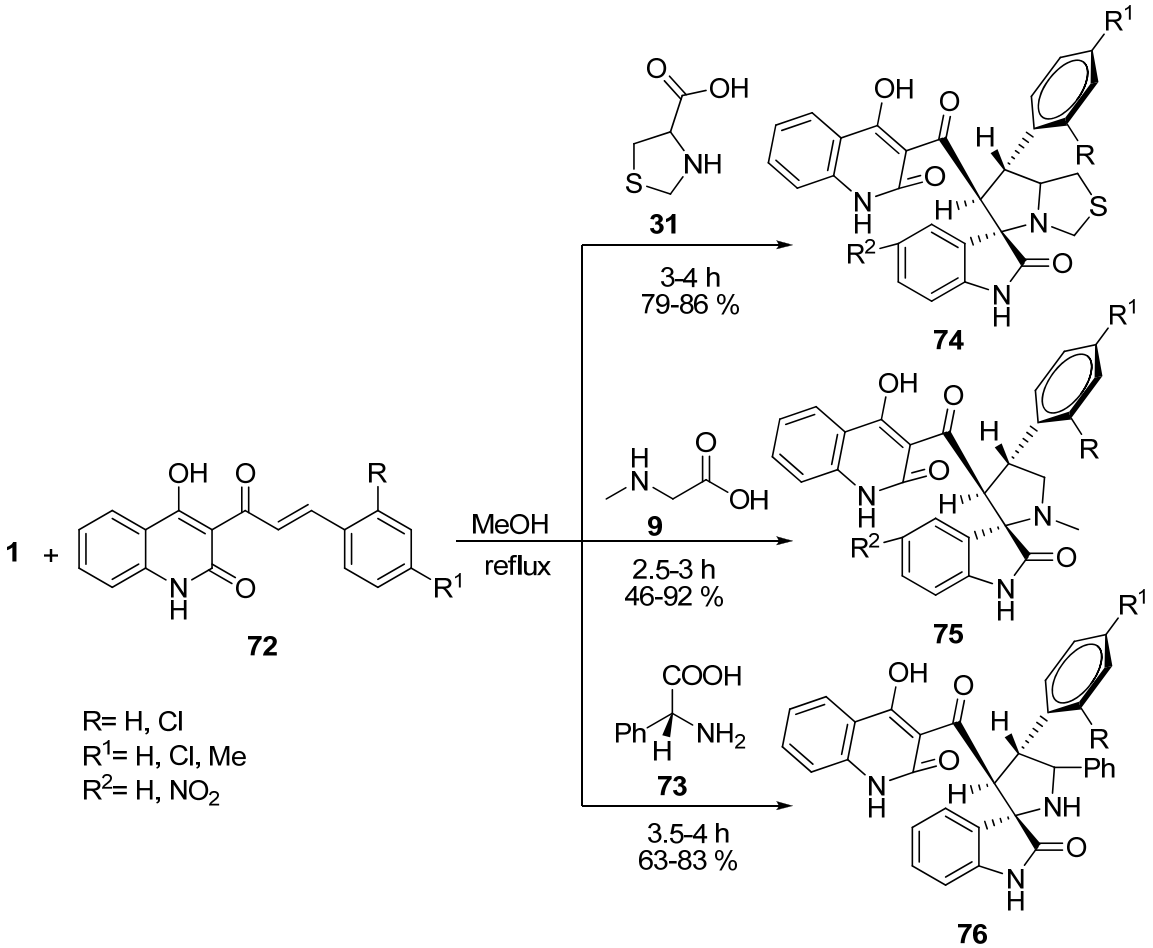


Scheme 26

The regioselectivity of the Huisgen reaction of isatin **1**, α-amino acids **70**,[69-70] and (*E*)-β-phenyl nitroolefins **69** was studied by Chen and co-workers (Scheme 27). Regioisomers **71a-b** were produced in each reaction and the major products showed different regioselectivity compared to previously reported spirooxindole derivatives.



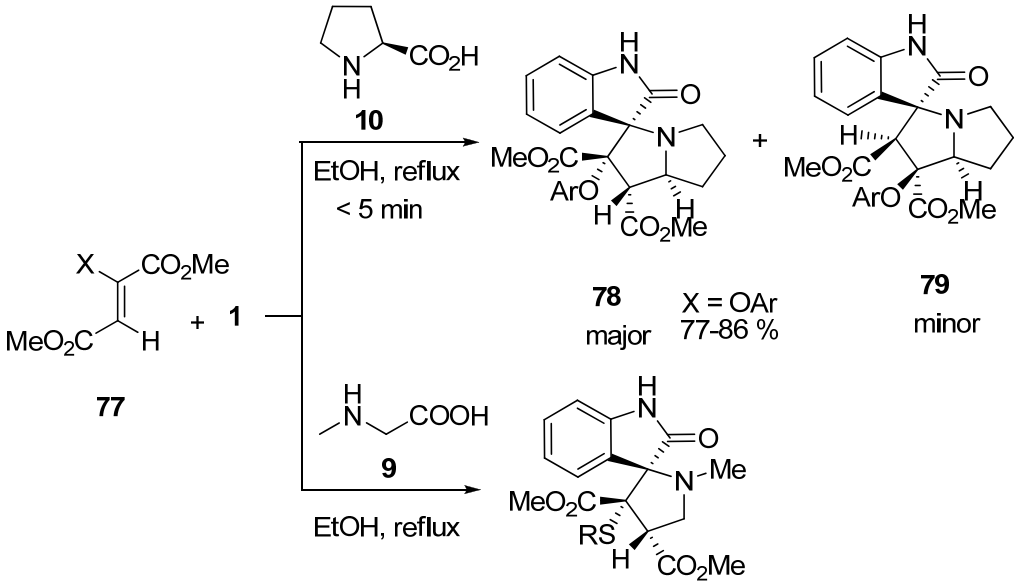
Scheme 27



Scheme 28

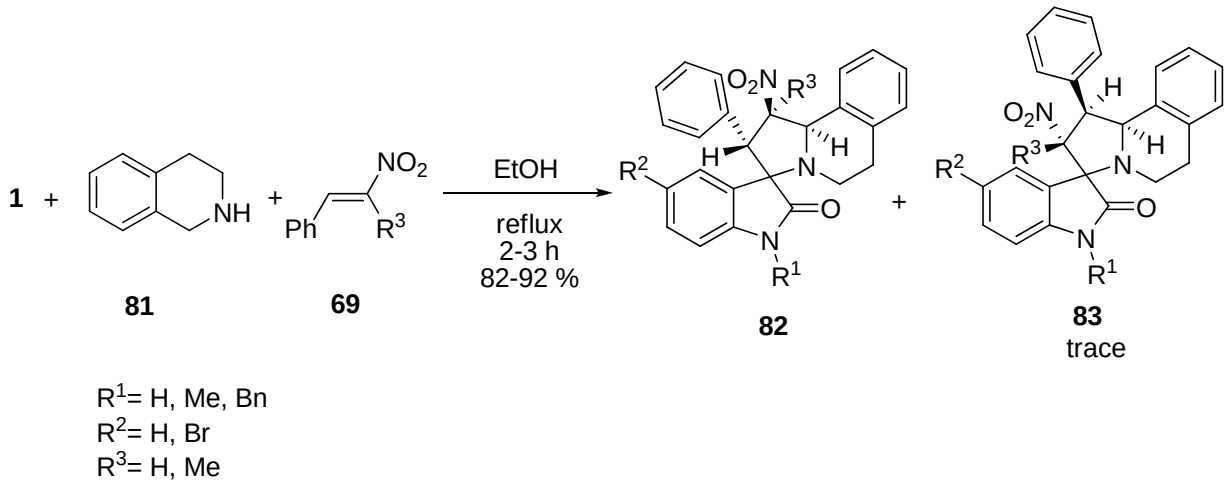
The synthesis of 4-hydroxyquinolone grafted spiropyrrolidines or pyrrolizidines **74-76** has been accomplished through 1,3-dipolar cycloaddition reaction of various azomethine ylides derived from isatin **1** and thioproline **31** /sarcosine **9** /phenylglycine **73** with 4-hydroxyquinolone derivatives **72** as dipolarophile (Scheme 28).[71] Cytotoxicity evaluation of selected compounds showed significant inhibition of cell proliferation against cervical as well as colon cancer cell lines.

Sarrafi and co-workers presented a condensation of dimethyl 2-(aryloxy)- or 2-(alkyl- or 2-arylthio)fumarate derivatives **77** as dipolarophiles in 1,3-dipolar cycloaddition reaction with azomethine ylides which are generated by the reaction of isatin **1** with the secondary amino acids proline **10** or sarcosine **9** to give novel spirooxindolopyrrolizidines/pyrrolidines **78-80** in high yields with excellent regioselectivities (Scheme 29).[72]

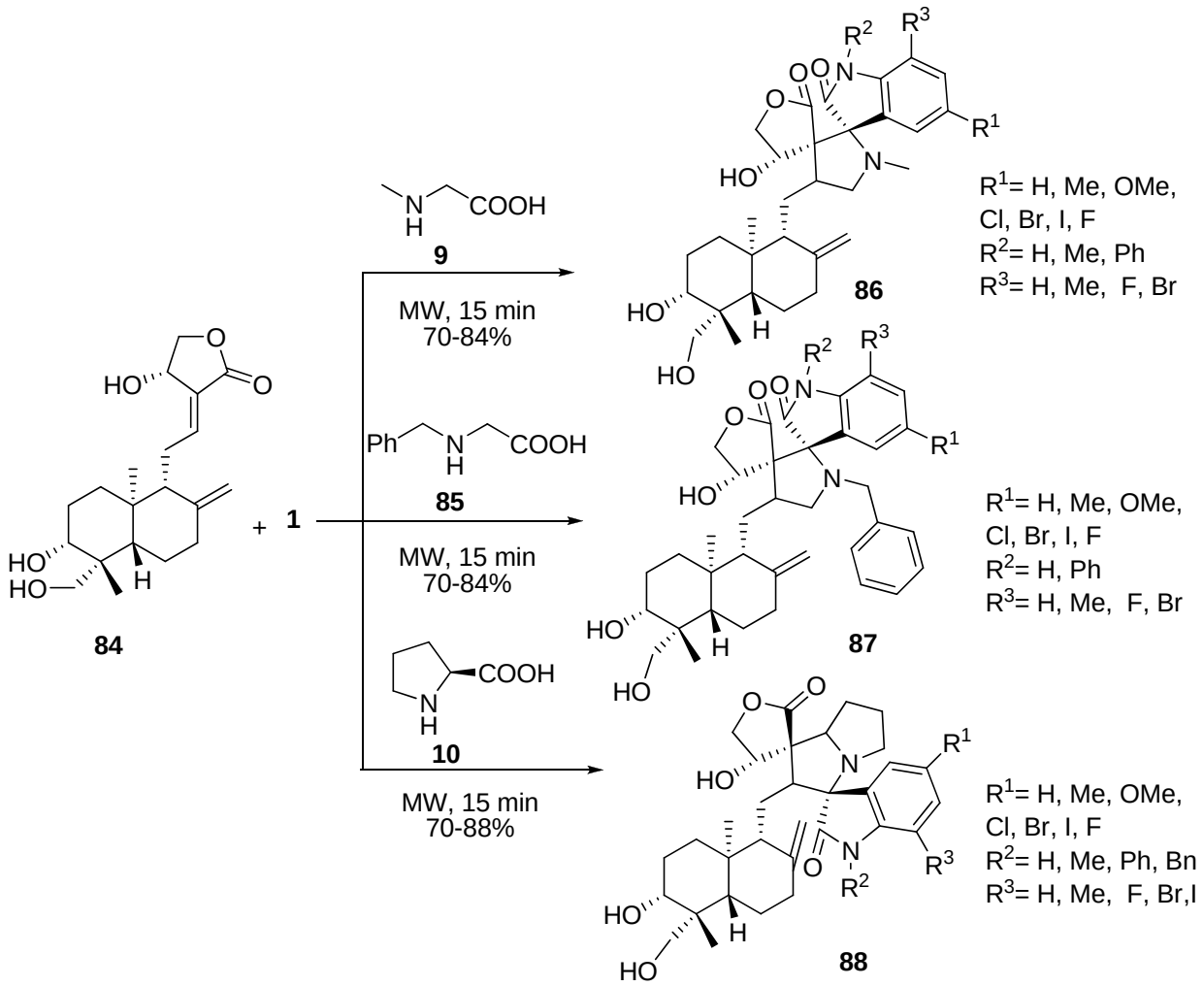


Scheme 29

The reaction of 1,2,3,4-tetrahydroisoquinoline **81** and isatin derivatives **1** with β-nitrostyrene and β-methyl-β-nitrostyrene **69** was investigated in a one-pot three-component process (Scheme 30).[73] The reaction afforded a series of novel spiroindolizidines **82** as major products in a similar regio- and stereocontrolled manner.



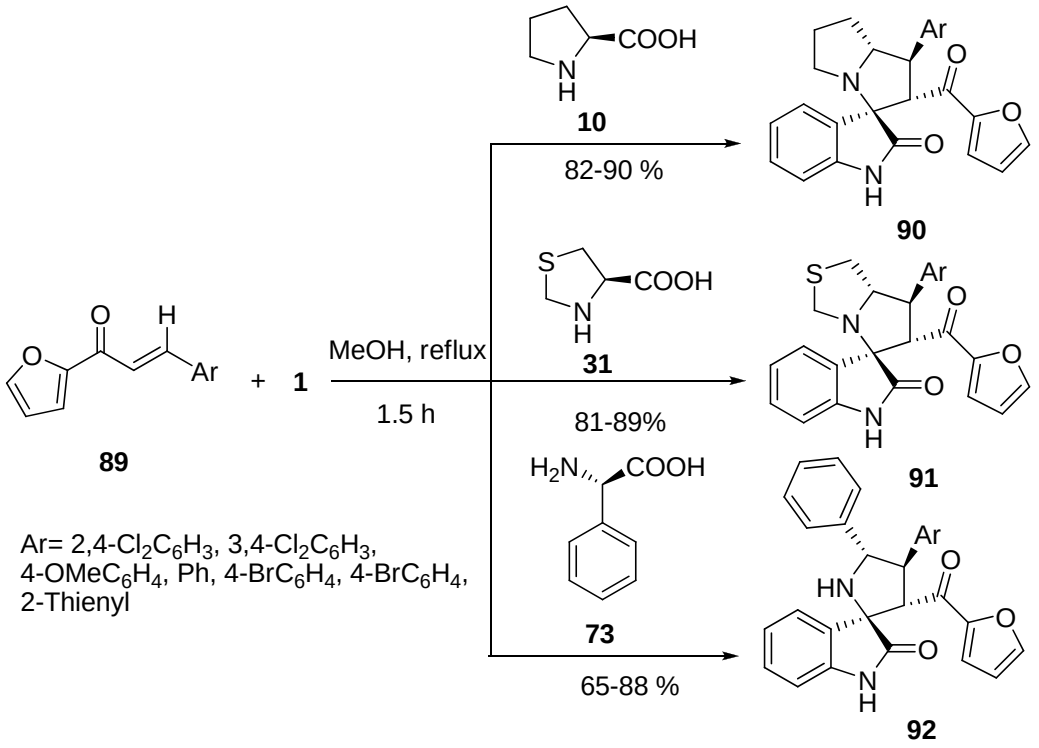
Scheme 30



Scheme 31

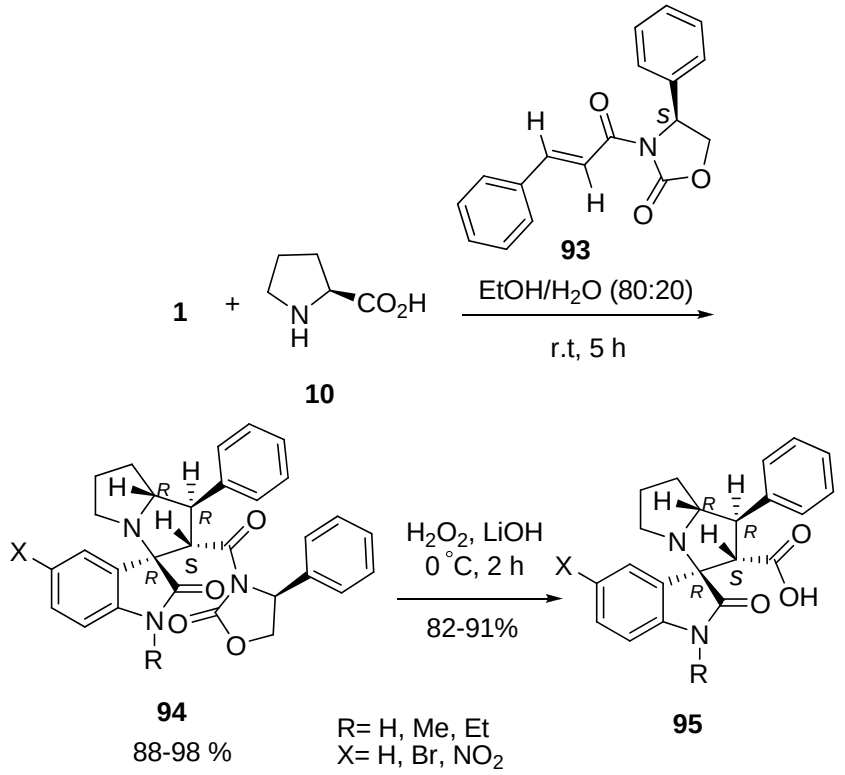
Dispiro-pyrrolidino/pyrrolizidino fused oxindoles **86-88** have been derived from andrographolide **84** via azomethine ylide cycloaddition to the conjugated double-bond under microwave irradiation (Scheme 31).[74] The reactions are chemo-, stereo-, and regioselective in nature. Change in amino acid from sarcosine **9**/*N*-benzyl glycine **85** to *L*-proline **10** changes the regiochemistry.

Wu *et al.* studied the regiosteselective synthesis of spirooxindolo-pyrrolidines, pyrrolizidines, and pyrrolothiazole frameworks containing a furanyl moiety **90-92** via the multicomponent condensation of azomethine ylides (generated *in situ* from amino acids and isatin) with the Knoevenagel adduct derivatives **89** (preformed by the reaction of 2-acetyl furan with substituted benzaldehydes) (Scheme 32).[75] Corresponding compounds were screened for their antibacterial activities.



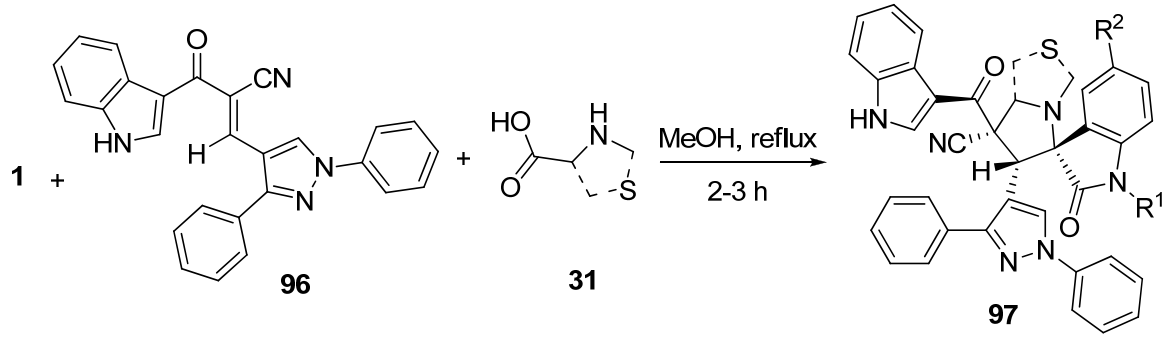
Scheme 32

The [3+2] cycloaddition of chiral dipolarophile **93** with azomethine ylide, generated from isatin **1** derivatives and (*S*)-proline **10**, resulted in the formation of new chiral spirooxindolopyrrolizidine **94** which contains four contiguous stereogenic centers (Scheme 33).[76] It was observed that the chiral auxiliary was removed easily with hydrogen peroxide in the presence of lithium hydroxide and cleanly produced products **95** in excellent to quantitative yields.



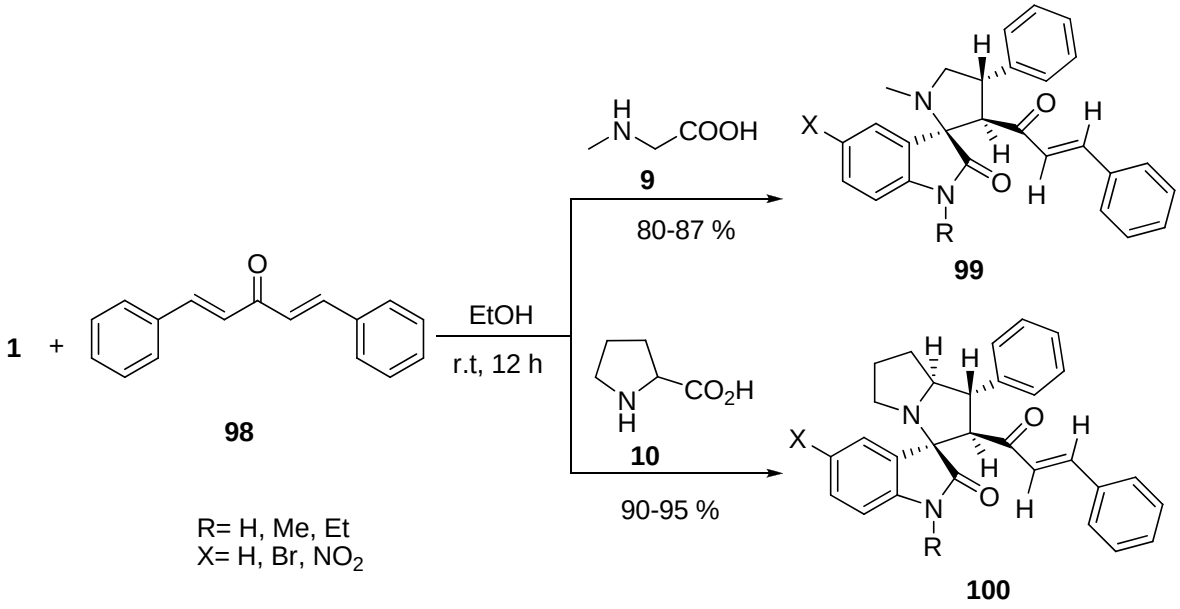
Scheme 33

A series of novel highly functionalized spiropyrrolidine-oxindoles **97** have been synthesized through 1,3-dipolar cycloaddition of an azomethine ylide formed from isatin **1** and various amino acids such as sarcosine, proline and thioproline **31** with the dipolarophile (*E*)-3-(1,3-diphenyl-1*H*-pyrazol-4-yl)-2-(1*H*-indole-3-carbonyl)acrylonitrile **96** under optimized conditions (Scheme 34).[77]



Scheme 34

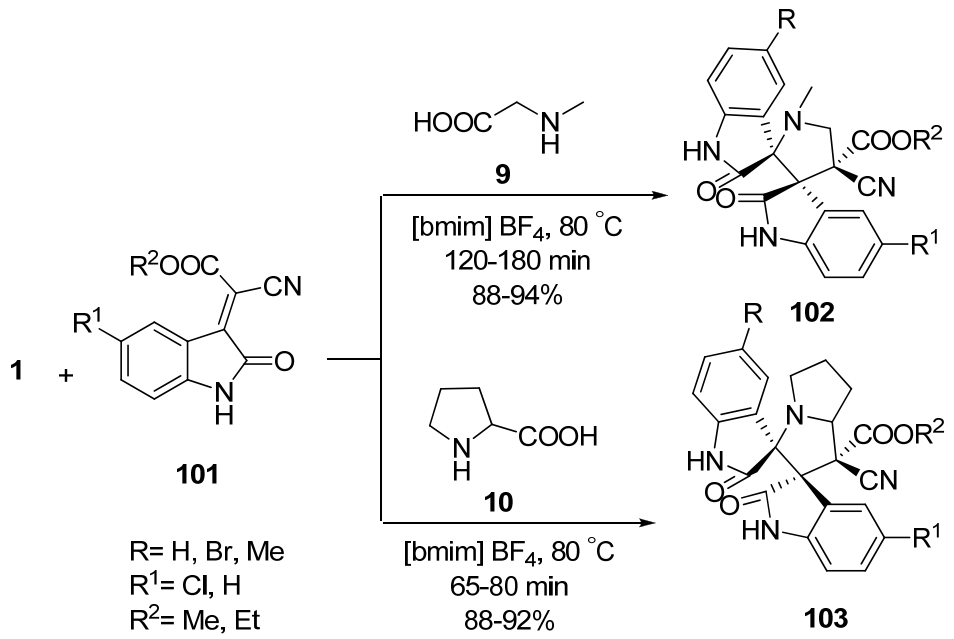
The synthesis of novel spirooxindolo(pyrrolizidine/pyrrolidine) ring systems **99-100** by the cycloaddition reaction of azomethine ylides generated from sarcosine **9**/proline **10** and isatin **1** with dibenzylideneacetone **98** was described by Javidan *et al*. (Scheme 35).[78]



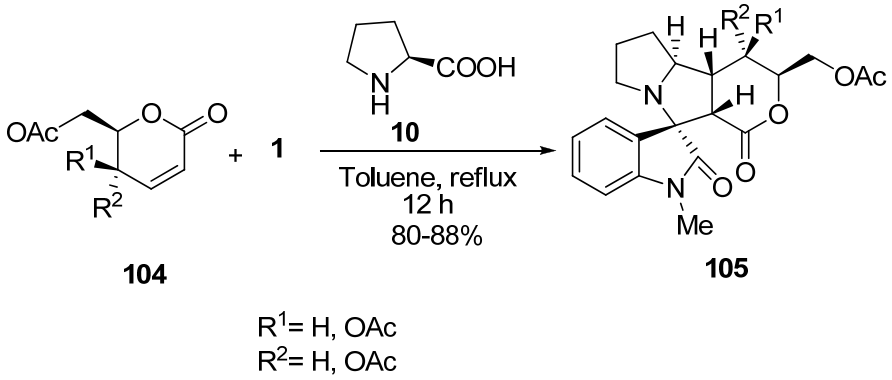
Scheme 35

The reactivity pattern of *E*/*Z* isomerized alkyl 2-cyano-2-(2-oxoindolin-3-ylidene)acetate **101** was studied with azomethine ylide generated *in situ* from decarboxylative condensation of isatins **1** and sarcosine **9**, yielding stereochemically different novel dispirobisoxindole derivatives through [3+2] cycloaddition reaction. Investigating the reaction with azomethine ylide of sarcosine **9**, *E* isomer is taking part as a dipolarophile producing dispiropyrrolidinebisoxindoles **102** exclusively, while in case of azomethine ylide of proline **10**, *Z* isomer is participating to generate the dispiropyrrolizidine-bisoxindoles **103** as single product (Scheme 36).[79]

Synthesis of pyrrolidinyl-spirooxindoles fused to sugar lactone **105** has been achieved by 1,3-dipolar cycloaddition reaction. A unique dipolarophile (*α,β*-unsaturated lactone) derived from D-glucose/D-galactose **104**, reacted with azomethine ylide generated *in situ* from isatin **1** and proline **10** to give the corresponding cycloadducts (Scheme 37).[80] The cycloaddition was found to be highly regio- and diastereoselective.

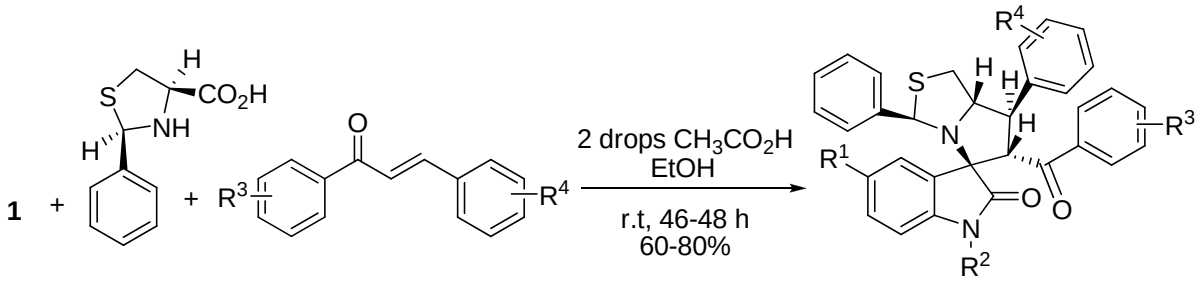


Scheme 36



Scheme 37

Kumar and co-workers prepared diastereoselective spiropyrrolidine-oxindole derivatives **107** from isatins **1**, 2-phenylthiazolidine-4-carboxylic acid **106** and chalcones **23** (Scheme 38).[81] These derivatives exhibited promising anti-cancer activity against the human breast cancer cell lines.

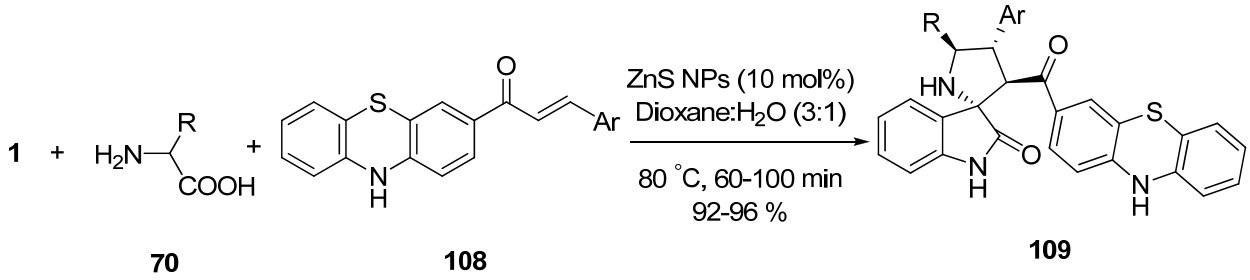


106 **23** **107**

R^1= H, Cl, F
R^2= H, Et
R^3= H, 4-NO_2, 3-OMe
R^4= H, 4-Cl, C_4H_4

Scheme 38

Through the reaction of isatin **1**, *α*-amino acid **70**, and phenothiazinyl chalcones **108**, using the ZnS-nanoparticles, the spiro[pyrrolidine-2,3′-oxindole] derivatives **109** were synthesized (Scheme 39).[82]

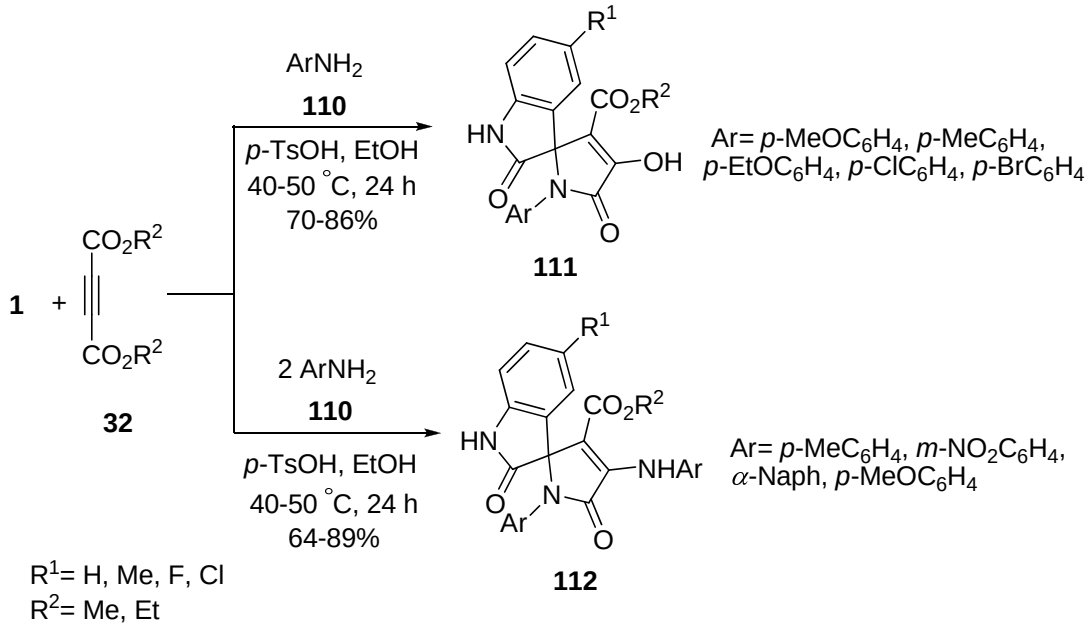


70 **108** **109**

R= $CH_2CH(CH_3)_2$
Ar= 2,4-$Cl_2C_6H_3$, 4-MeC_6H_4, C_4H_4N,
3-ClC_6H_4, 4-OHC_6H_4, 3-OH,4-$OMeC_6H_3$
C_5H_4N, C_4H_3S, C_4H_3O

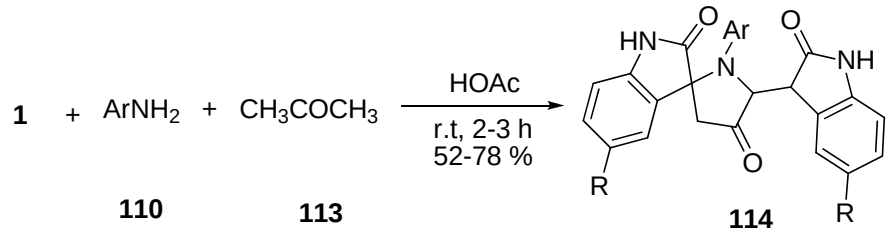
Scheme 39

The reactions of arylamines **110**, acetylenedicarboxylates **32**, and isatins **1** in the presence of *p*-toluenesulfonic acid as the catalyst, showed very interesting molecular diversity. When equal amount of arylamine was used, the three-component reaction resulted in high yields of functionalized 3′-hydroxyspiro[indoline-3,5′-pyrroline]-2,2′-dione derivatives **111**. On the other hand, the functionalized 3′-*N*-arylaminospiro[indoline-3,5′-pyrroline]-2,2′-diones **112** were successfully prepared in satisfactory yields by using 2 M arylamine **110** in the reaction (Scheme 40).[83] TiO_2-nanoparticles[84] and Et_3N[85] were also used as catalysts in this reaction.



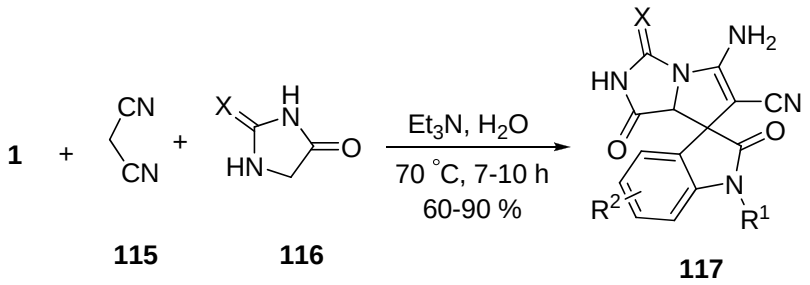
Scheme 40

Novel functionalized 1′-aryl-2′-(2-oxoindolin-3-yl)spiro[indoline-3,5′-pyrroline]-2,3′-diones **114** were prepared in the reaction of arylamines **110**, acetone **113**, and isatins **1** (Scheme 41).[86]



Scheme 41

Reaction of isatin **1**, malononitrile **115**, and hydantoin or thiohydantoin derivatives **116** using Et_3N as catalyst afforded spiro[indoline-3,7′-pyrrolo[1,2-*c*]imidazole]-6′-carbonitrile derivatives **117** in good yields (Scheme 42).[87]

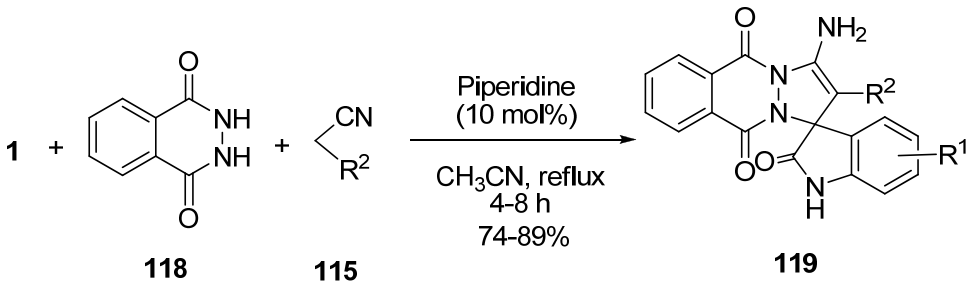


115 116 117

R^1= H, Me
R^2= H, 5-Cl, 5-Br, 5-F, 5-I, 5-OMe, 7-Cl
X= O, S

Scheme 42

Spiro[indoline-3,1′-pyrazolo[1,2-*b*]phthalazine] derivatives **119** were synthesized by the reaction of phthalhydrazide **118**, isatins **1**, and malononitriles **115** using piperidine in CH_3CN (Scheme 43).[88] In another study, application of ultrasound in this reaction was investigated.[89]

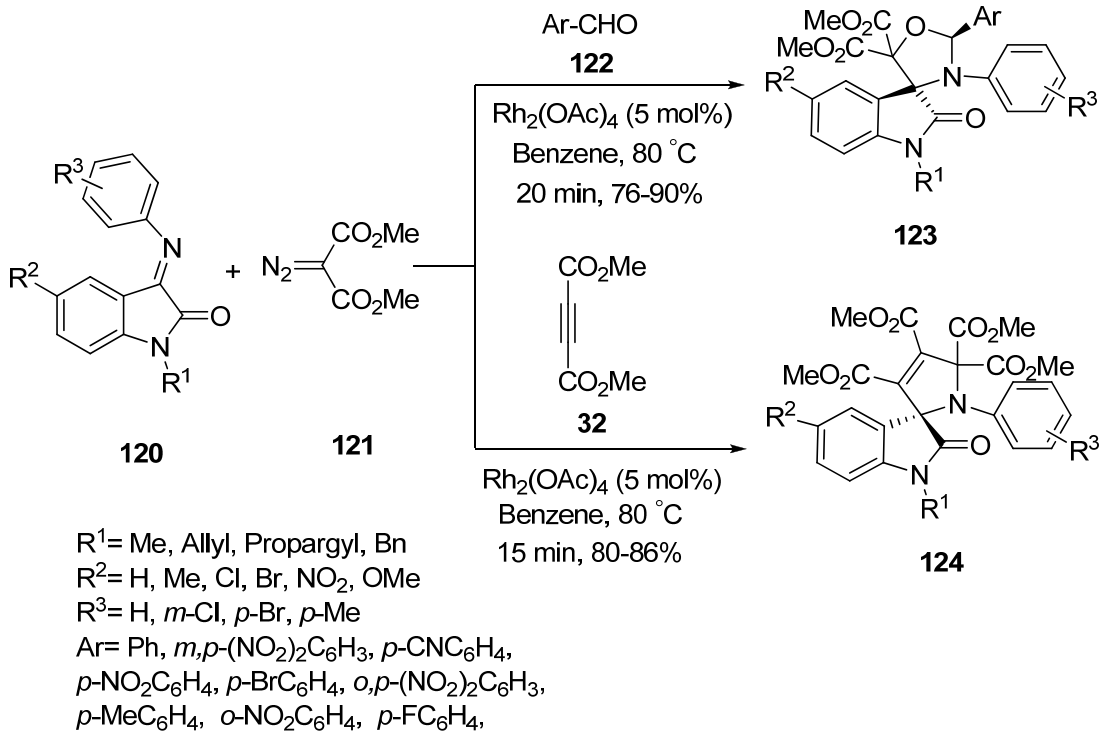


118 115 119

R^1= H, 4-Br, 5-F, 5-Cl, 5-Br, 4-Cl, 6-Br
R^2= CN, CO_2Et, CO_2Me, CO_2*i*Pr

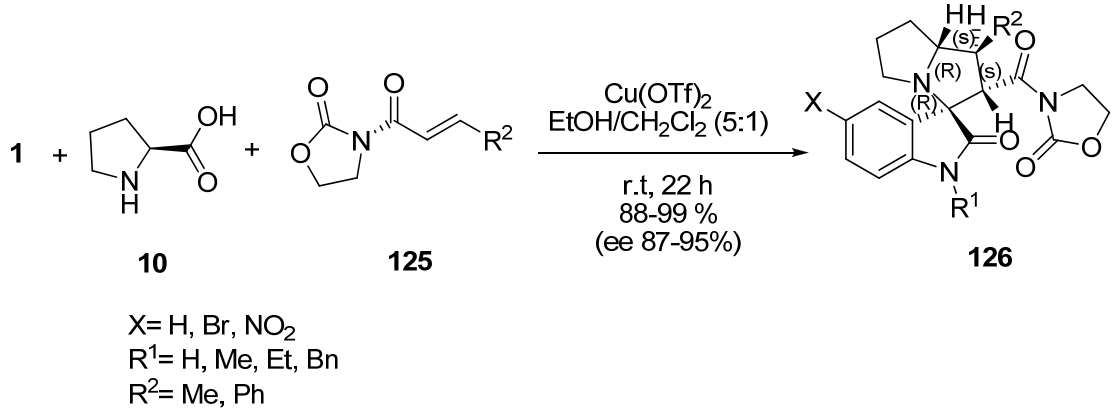
Scheme 43

A highly chemoselective method has been devised for the synthesis of a wide range of spirooxindolyl oxazolidines **123** via an intermolecular 1,3-dipolar cycloaddition of carbonyl ylides generated from dimethyl diazomalonate **121** and aromatic aldehydes **122**, with cyclic ketimines **120** using $Rh_2(OAc)_4$ under mild conditions (Scheme 44).[90] Similarly, highly functionalized spirooxindolyl pyrrolines **124** have been prepared through 1,3-dipolar cycloaddition of azomethine ylides generated from dimethyl diazomalonate **121** and cyclic ketimines **120**, with dimethyl acetylenedicarboxylate **32** (Scheme 44).[90]



Scheme 44

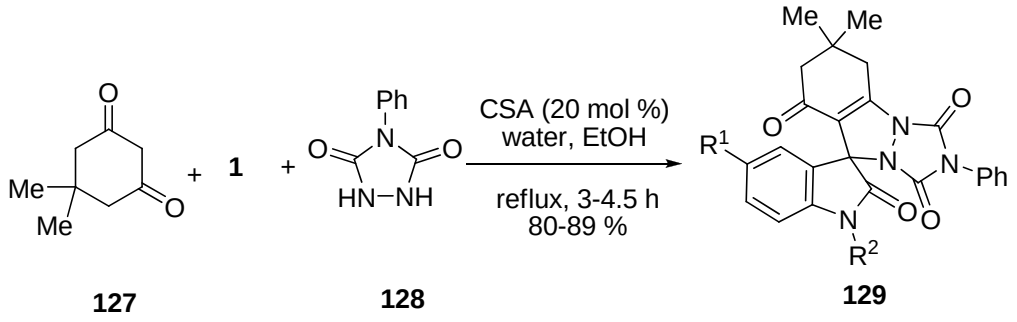
An asymmetric 1,3-dipolar cycloaddition reaction of azomethine ylides with electron-deficient dipolarophiles, 3-(2-alkenoyl)-1,3-oxazolidin-2-ones **125**, to give optically active spiropyrrolizidineoxindoles **126** in good yields with high regio-, diastereo-, and enantioselectivities (up to 93% ee) was described by Salahi *et al*. (Scheme 45).[91]



Scheme 45

Chandam *et al*. reported the synthesis of spiro triazolo[1,2-*a*]indazole-tetraones **129** by condensation reaction of dimedone **127** urazole **128** and isatins **1** in the presence of (±)-camphor-

10-sulfonic acid (CSA) as a Bronsted acid catalyst (Scheme 46).[92]

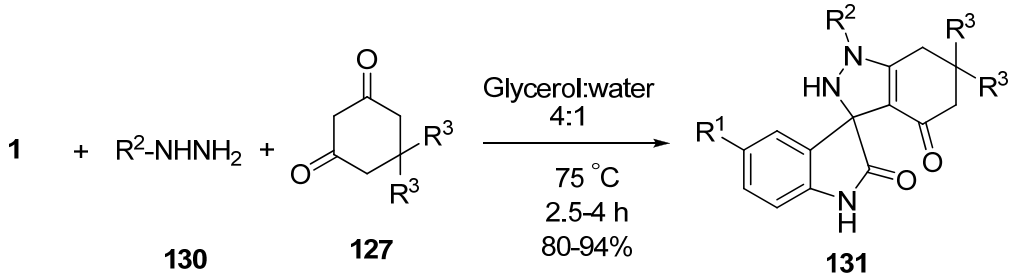


127 **128** **129**

R^1= H, Cl, Br, NO_2
R^2= H, Me, Ph

Scheme 46

Singh and co-workers have developed a versatile one pot catalyst-free multicomponent-tandem strategy for assembly of spirooxindole-indazolones **131** *via* the reaction of isatins **1**, hydrazines **130**, and dimedones **127** in glycerol-water solvent system (Scheme 47).[93] In all the cases the desired products were obtained in high yields and short reaction times.

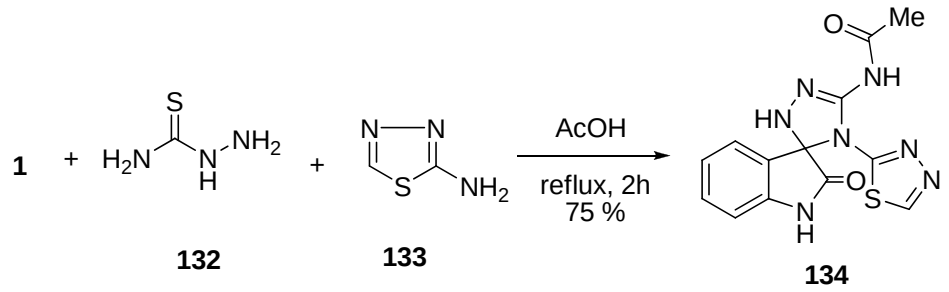


130 **127** **131**

R^1= H, Br, Cl
R^2= H, C_6H_5, 2,4-$(NO_2)_2C_6H_3$
R^3= H, Me

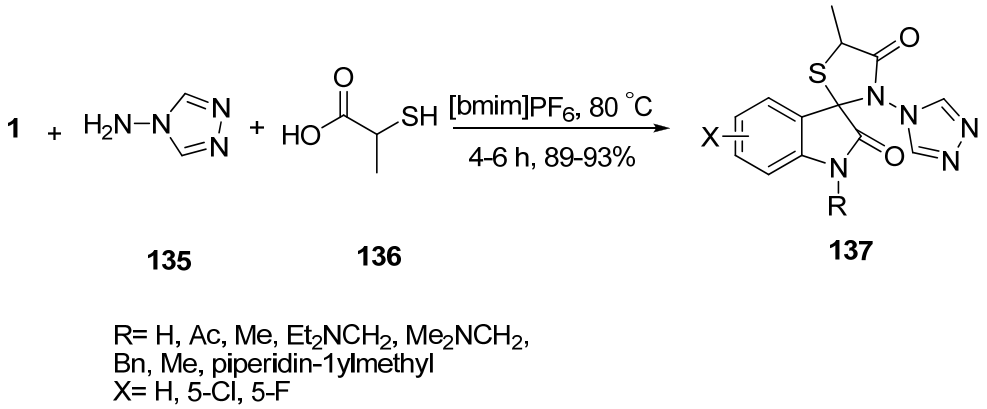
Scheme 47

Hamama's group reported the synthesis of spirotriazoles **134** by the reaction of isatin **1**, thiosemicarbazide **132** and 2-amino-1,3,4-thiadiazole **133** in acetic acid (Scheme 48).[94] These compounds were evaluated as antitumor agents.



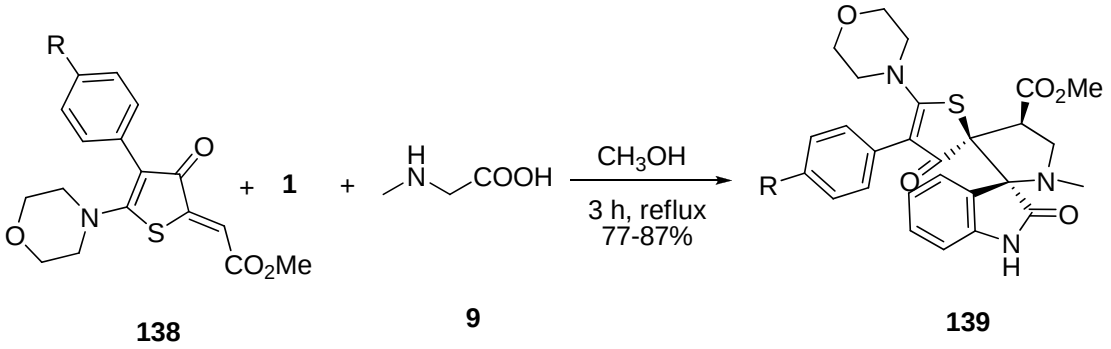
Scheme 48

Spiro[3*H*-indole-3,2′-thiazolidine]-2,4′(1*H*)-diones **137** were synthesized by a facile one-pot, three-component protocol using isatins **1**, 4*H*-1,2,4-triazol-4-amine **135**, and 2-sulfanylpropanoic acid **136** in [bmim]PF_6 (1-butyl-3-methyl-1*H*-imidazolium hexafluorophosphate) as a recyclable ionic-liquid (Scheme 49).[95]



Scheme 49

The synthesis of new dispiropyrrolidines containing a thiophenone ring **139** has been achieved by Moghaddam and co-workers. Unsaturated thiophenone dipolarophiles **138** were reacted with azomethine ylides, generated *in situ* from sarcosine **9** and isatins **1**, to produce the corresponding cycloadducts (Scheme 50).[96] The cycloaddition reaction was found to be highly regio- and diastereoselective.

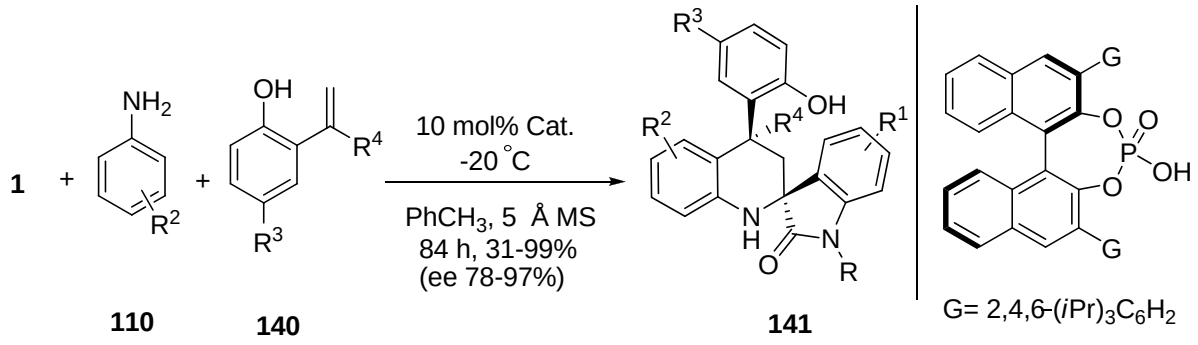


138 **9** **139**

R= H, Br, Me, Ph

Scheme 50

2.1.2. Six-membered spiro-fused compounds. Enantioselective isatin-involved Povarov reaction, which is applicable to a variety of reaction components, was used for the synthesis of new spiro-[indolin-3,2′-quinolines] **141** with concomitant creation of two quaternary stereogenic centers in high yields and excellent stereoselectivities. This transformation was created by isatins **1**, anilines **110**, and *α*-alkyl *o*-hydroxystyrenes **140** in the presence of the chiral catalyst (binaphthol derived phosphoric acid) (Scheme 51).[97]



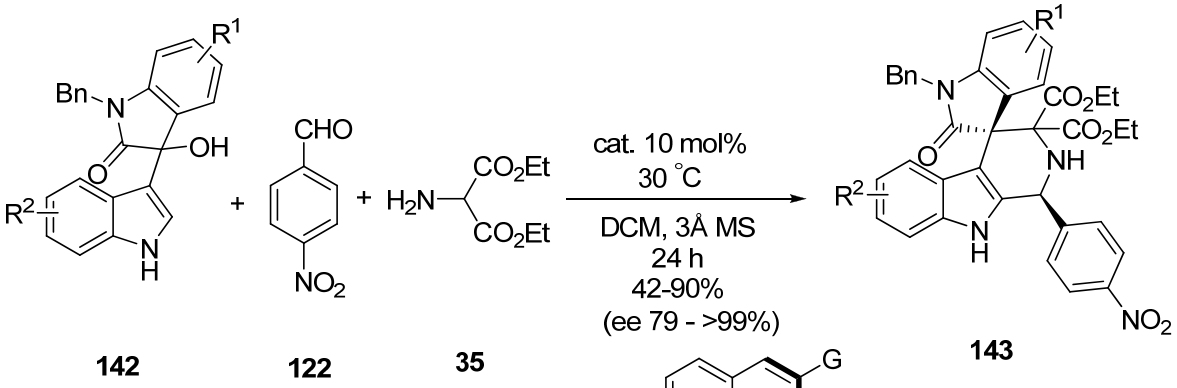
110 **140** **141**

R= H, Bn, *p*-tBuC$_6$H$_4$CH$_2$, C$_6$F$_5$CH$_2$, *i*Pr, Ph
R^1= H, 5-Cl, 5,6-F$_2$, 6-Cl, 6-Br, 6-Me, 7-F, 7-Br, 7-Me, 7-CF$_3$
R^2= H, 4-OMe, 4-OEt, 4-OPh, 4-F
R^3= Me, H, OMe
R^4= Me, Et

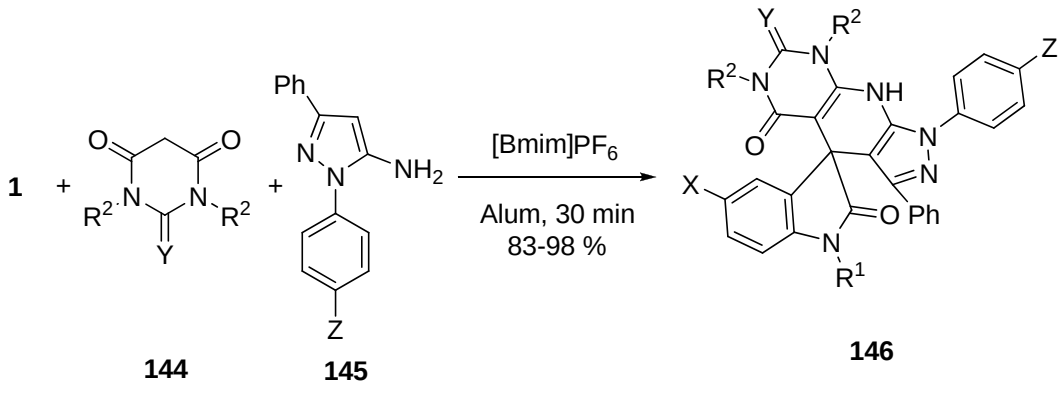
Scheme 51

The same group employed isatin-derived 3-indolylmethanols **142** as dipolarophiles to undergo catalytic asymmetric formal [3+3] cycloadditions with 4-nitrobenzaldehyde **122**, and diethyl 2-amino-malonate **35** in the presence of a chiral catalyst, affording stereoselective

spiro[indoline-3,4′-pyridoindoles] **143**, in which a six-membered piperidine framework would be constructed (Scheme 52).[98] Replacement of 4-nitrobenzaldehyde **122** with isatins in this reaction leads to the synthesis of a new class of bispirooxindole scaffold-containing tetrahydro-β-carboline moiety in excellent stereoselectivities (all >95:5 diastereomeric ratio (d.r.), up to 98:2 enantiomeric ratio (e.r.)).[99]



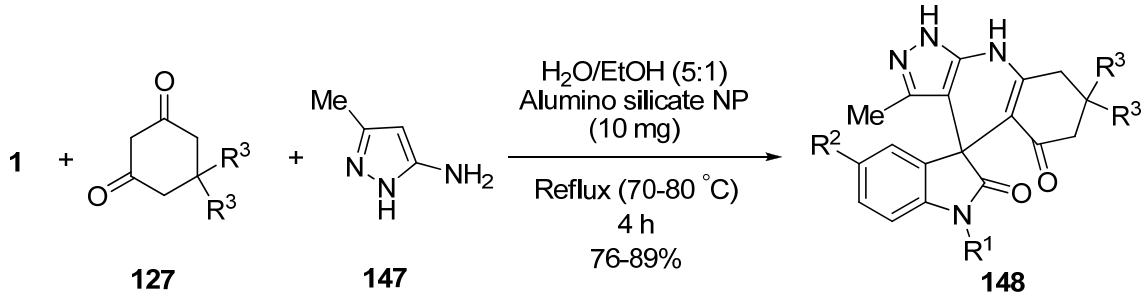
Scheme 52



Scheme 53

Synthesise of spiro[indoline-pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidine]trione derivatives **146** by a cyclocondensation reaction of isatins **1**, barbituric acids **144**, and 1,3-diphenyl-1*H*-pyrazol-5-amines **145** in [Bmim]PF_6 medium and in the presence of alum as a reusable catalyst was reported by Shirvan *et al*. (Scheme 53).[100] A simple and efficient method for the synthesis of pyrazolopyridine based spirooxindoles was also reported by Kamal and co-workers where isatins, 5-phenyl-1*H*-pyrazol-3-amine and 1,3-dicarbonyl compounds react in the presence of sulfamic acid (H_2NSO_3H) as a green catalyst.[101]

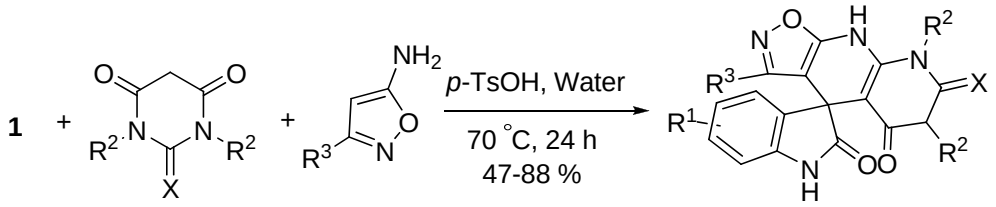
The three-component reactions of isatins **1**, cyclic-1,3-diones **127**, and pyrazol-5-amine **147** were successfully established and led to the formation of pyrazole-fused 1,4-dihydropyridine skeletons **148** using the heterogeneous aluminosilicate nanoparticle catalyst under eco-friendly conditions (Scheme 54).[102]



Scheme 54

Rahmati and Khalesi described the condensation reaction of isatins **1**, isoxazole **149**, and barbituric acids **144** in water to give spirooxindoles **150**, using a catalytic amount of *p*-toluene sulfonic acid (Scheme 55).[103] Reddy's group used dimedone instead of barbituric acid in an alternative strategy to obtain oxazolo[5,4-*b*]quinoline-fused spirooxindoles in the presence of microwave irradiation under solvent-free condition.[104]

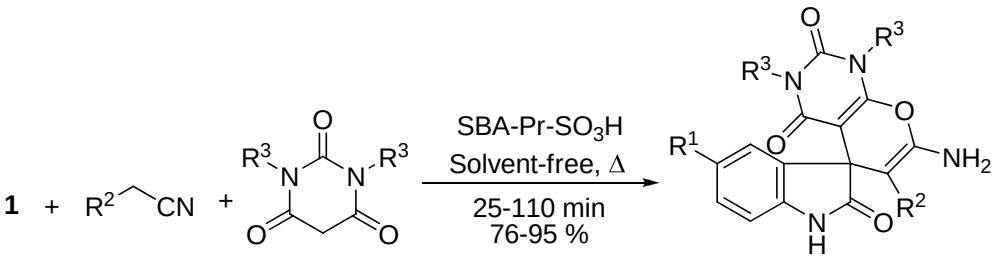
Sulfonic acid functionalized SBA-15 (SBA-Pr-SO_3H) as a new nanoporous solid acid catalyst was applied in the green one-pot synthesis of spiro[indole-tetrahydro-pyrano(2,3-*d*)pyrimidine] derivatives **151** via three-component reaction of isatins **1**, malononitrile or cyanoacetic esters **115** and barbituric acids **144** under solvent-free conditions (Scheme 56).[105]



144 **149** **150**

R= H, Me, COMe
R^1= H, 5-Me, 5-OMe, 5-Cl, 5-Br, 5-I, 5-NO_2, 5,7-Me_2
R^2= H, Me, Et
R^3= NH_2, Me
X= O, S

Scheme 55



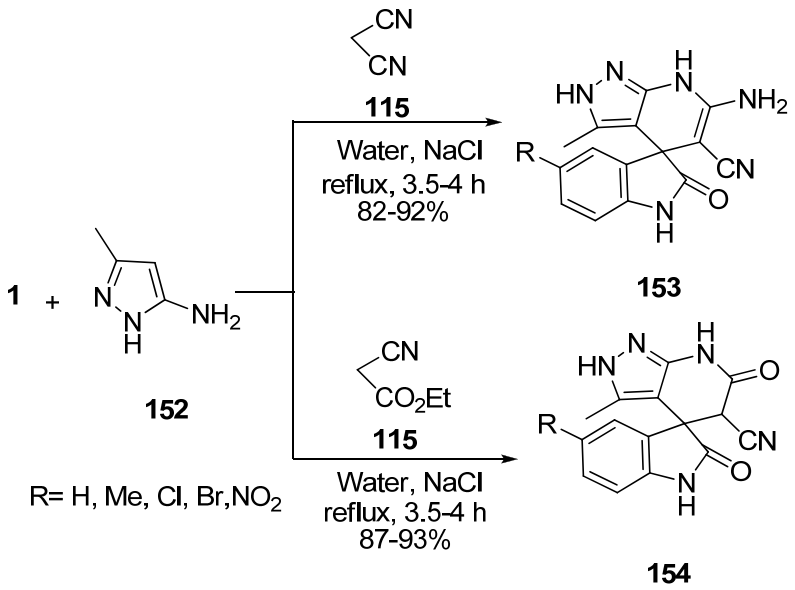
115 **144** **151**

R^1 = H, Cl, Br
R^2 = CN, CO_2Et, CO_2Me
R^3 = H, Me

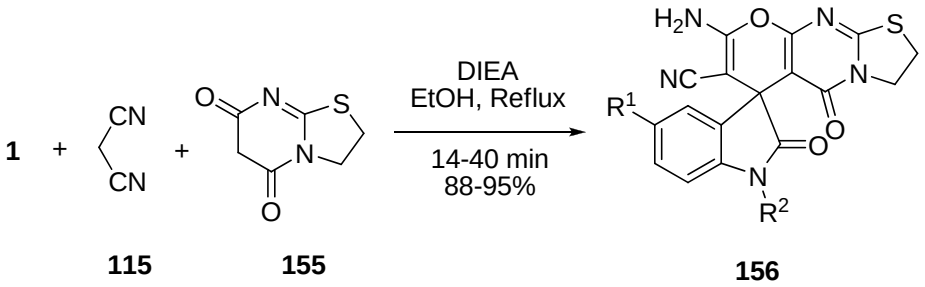
Scheme 56

Synthesis of pyrazolopyridinyl spirooxindoles **153-154** has been developed through a reaction of isatins **1**, malononitrile/ethyl cyanoacetate **115**, and 5-amino-3-methylpyrazole **152** catalyzed by sodium chloride in water (Scheme 57).[106] The product showed high diastereoselectivity in which the stereochemistry of major diastereomer was confirmed by X-ray diffraction analysis. In another study, Et_3N was used as the catalyst of this reaction.[107]

Isatin **1**, malononitrile **115**, and 2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-5,7(6*H*)-dione **155** in the presence of diisopropylethylamine (DIEA) yielded novel spirooxindole derivatives **156** in excellent yields (Scheme 58).[108]

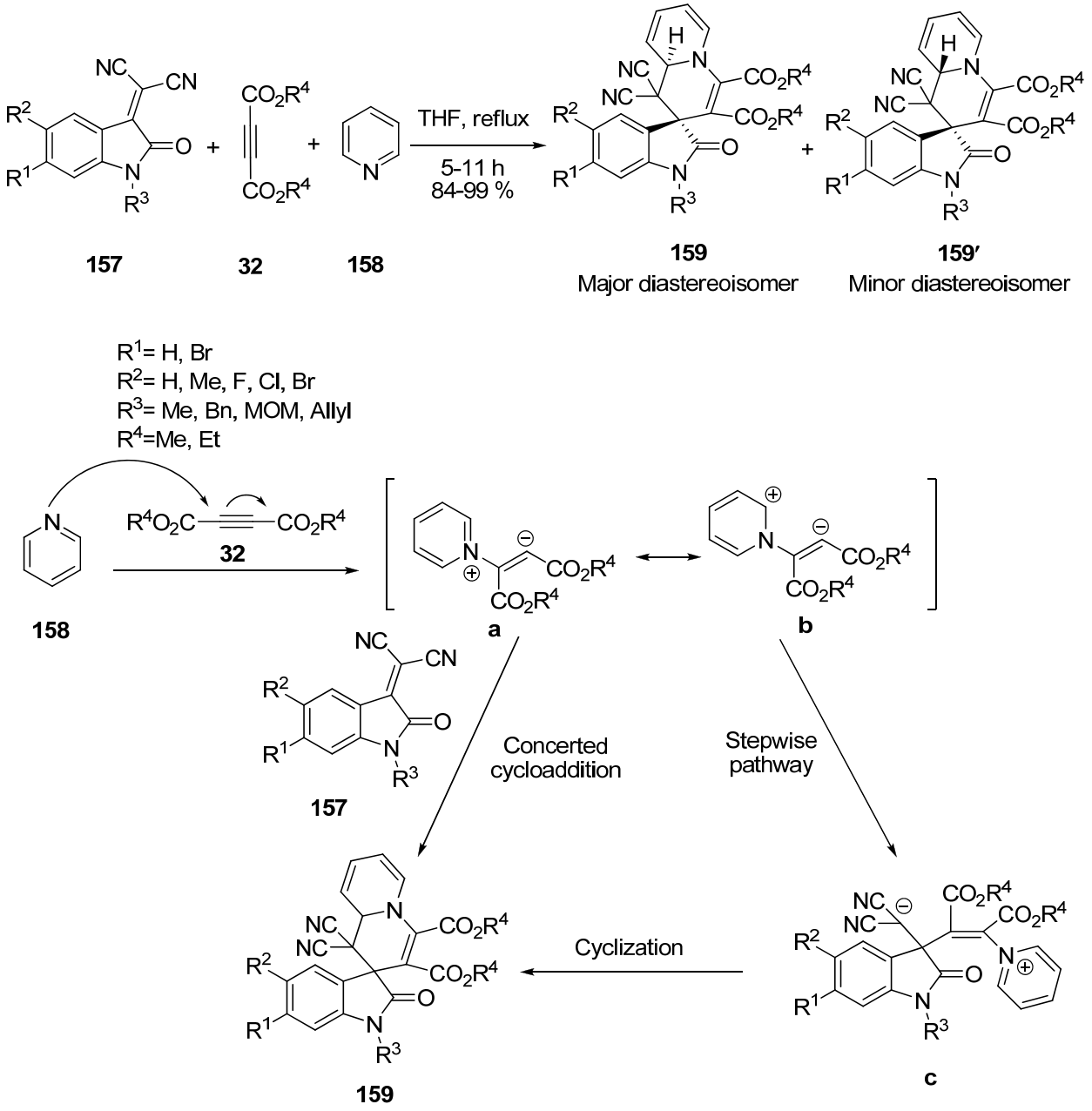


Scheme 57



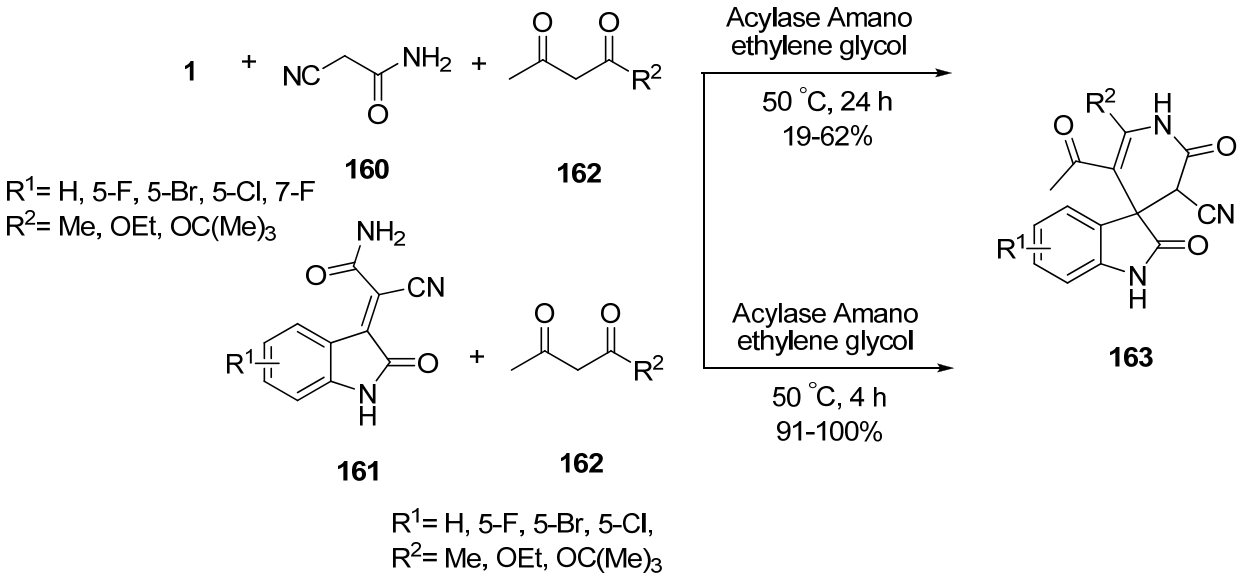
Scheme 58

Treatment of pyridine **158** and acetylenedicarboxylate esters **32** with *N*-substituted isatylidene derivatives **157** resulted in three-component condensations, affording spiro[indoline-3,3′-piperidin]-2-one derivatives **159** in high yields and with good diastereoselectivities through 1,4-dipolar cycloadditions (Scheme 59).[109] Based on a plausible mechanism, pyridine **158** could first attack activated alkyne **32** to afford inter mediates **a** or **b**. Intermediates **a** or **b**, acting as 1,3-dipole or 1,4-dipole, could then react with isatylidene **157** to give the product **159** in a concerted manner. Alternatively, 1,3-dipole **a** or 1,4-dipole **b** could attack the activated isatylidene C=C bond to give intermediate **c**, which could undergo cyclization to give the product **159** (stepwise pathway).



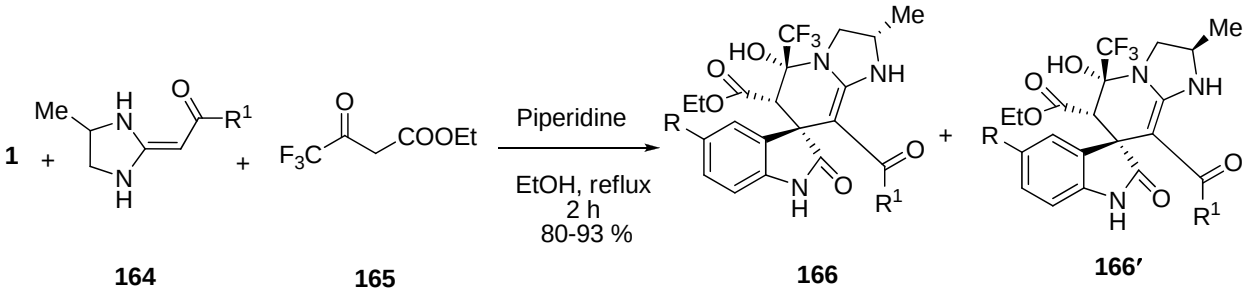
Scheme 59

A series of spirooxindole derivatives **163** were synthesized using isatin derivatives **1**, cyanoacetamide **160**, and 1,3-dicarbonyl compounds **162** as starting materials via one-pot three-component enzymatic or two-step chemo-enzymatic domino reactions, respectively (Scheme 60).[110] In the single Acylase 'Amano'-catalyzed one-pot reaction, moderate yields of the products were obtained while the developed chemo-enzymatic route in two steps was able to prepare the final products in nearly quantitative yields.



Scheme 60

Yu *et al*. synthesized spirooxindoles **166** by refluxing a mixture of ketene aminals **164**, isatins **1** and ethyl trifluoroacetate **165** in the presence of piperidine (Scheme 61).[111] The resulting compounds were generated with excellent regio- and diastereo-selectivity.

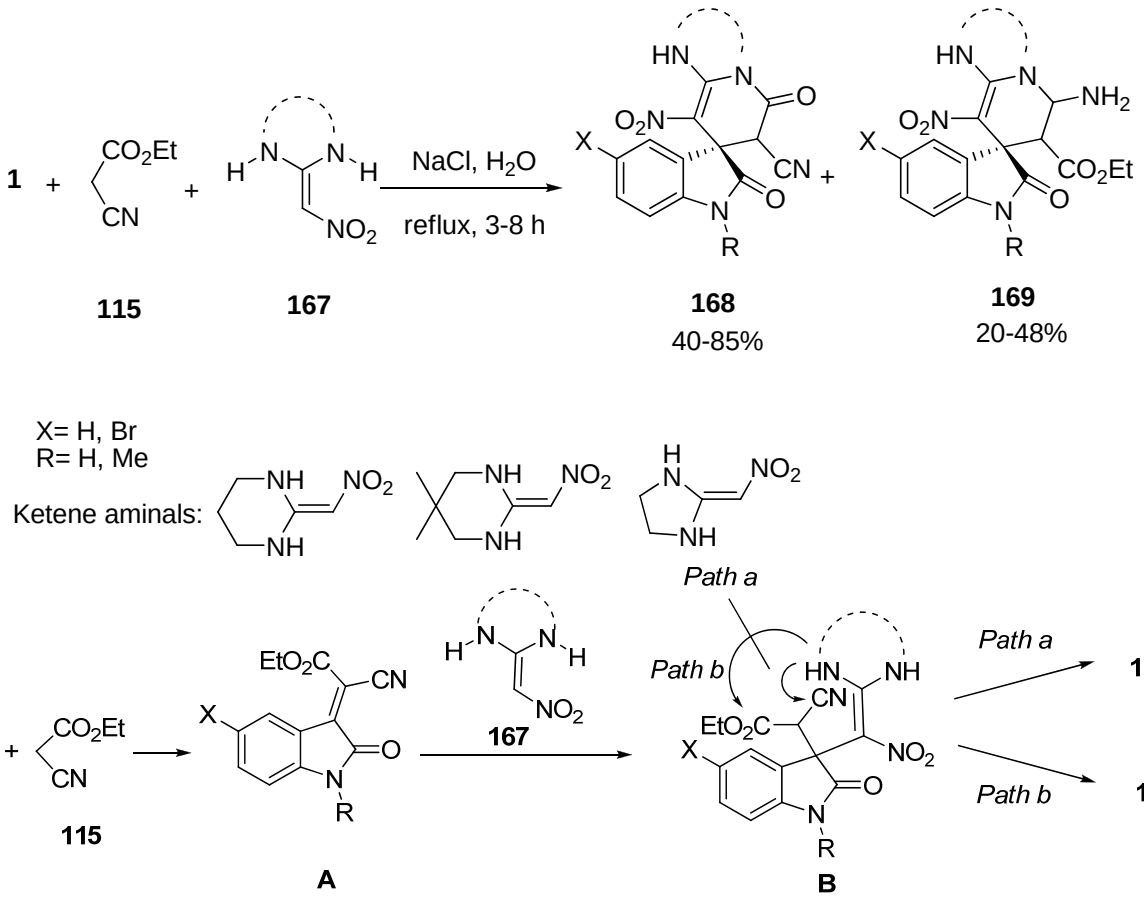


R= F, Cl, H
R^1= 4-ClC_6H_4, C_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$

Scheme 61

Reaction of isatin **1** with ethyl cyanoacetate **115** and hexahydro-2-(nitromethylidene)pyrimidine **167** in the presence of a catalytic amount of NaCl in H_2O resulted in the synthesis of spirooxindoles of type **168** (Scheme 62).[112] Utilizing NaCl as catalyst caused the ester group taking part in the cyclization, and, therefore, the yield of new spirooxindole **168** increased. It is conceivable that, initially, intermediate **A** is formed via the Knoevenagel condensation of isatin **1** and ethyl cyanoacetate **111**, followed by Michael addition of ketene aminal **163** to afford intermediate **B**. Intramolecular cyclization of **B** may proceed in two path

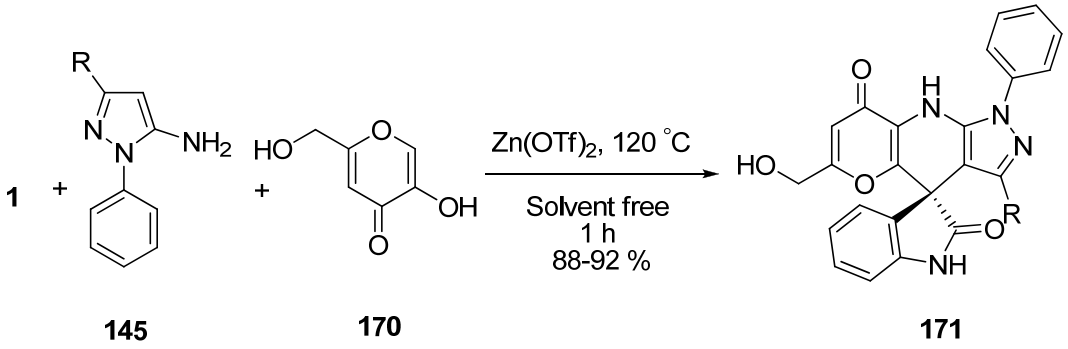
ways. Attack of the NH group to the ester or CN group generate spirooxindole **164** or **165**, respectively.



Scheme 62

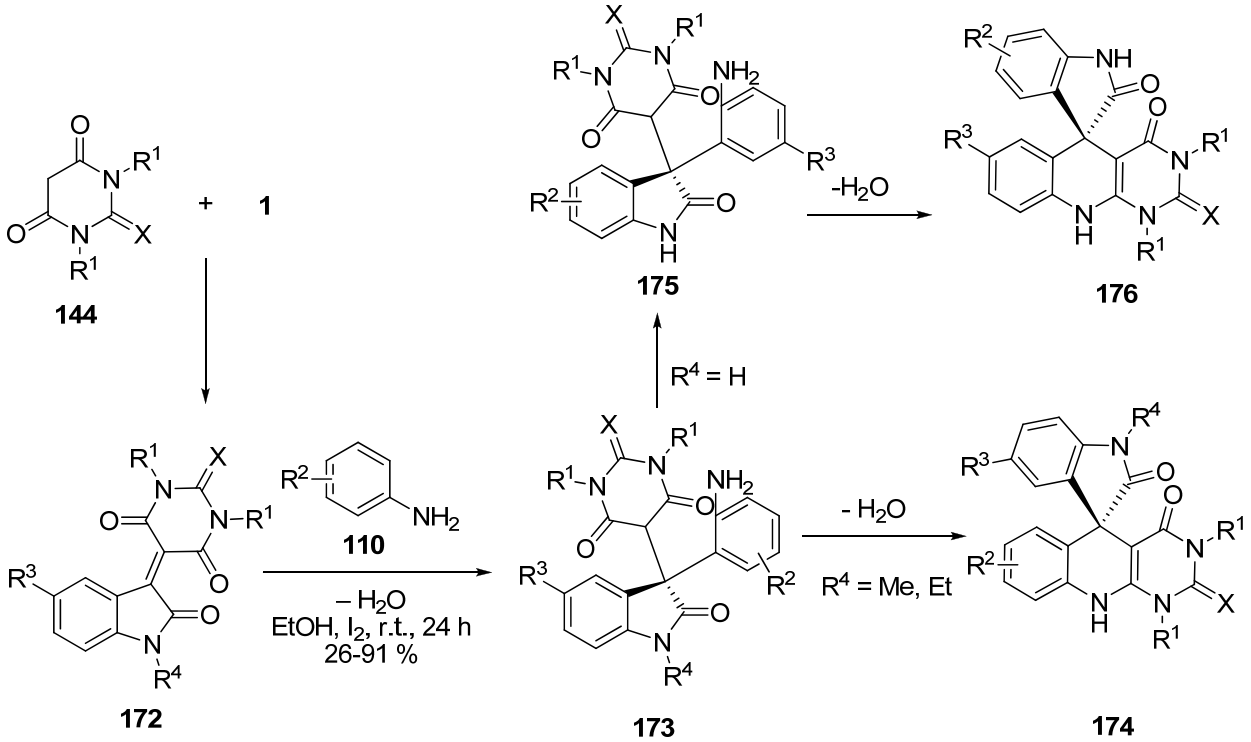
Mohammadpoor-Baltork and co-workers have established novel 1′*H*-spiro[indoline-3,4′-pyrano[2,3-*b*]pyrazolo[3,4-*e*]pyridine]-2,8′(9′*H*)-diones **171** via three-component condensation of isatin **1**, 1*H*-pyrazol-5-amines **145**, and kojic acid **170** in the presence of a catalytic amount of $Zn(OTf)_2$ (Scheme 63).[113]

Synthesis of spiroindolinones via the reaction of barbituric acids **144**, electron-rich anilines **110**, and isatins **1** was carried out in ethanol in the presence of iodine as catalyst (Scheme 64).[114] The *N*-unsubstituted isatin fragment facilitates the rearrangement of intermediate **172** into **173** toward formation of the thermodynamically favored amide bond in spiroindolinone moiety **176**.



R= Ph, Me

Scheme 63

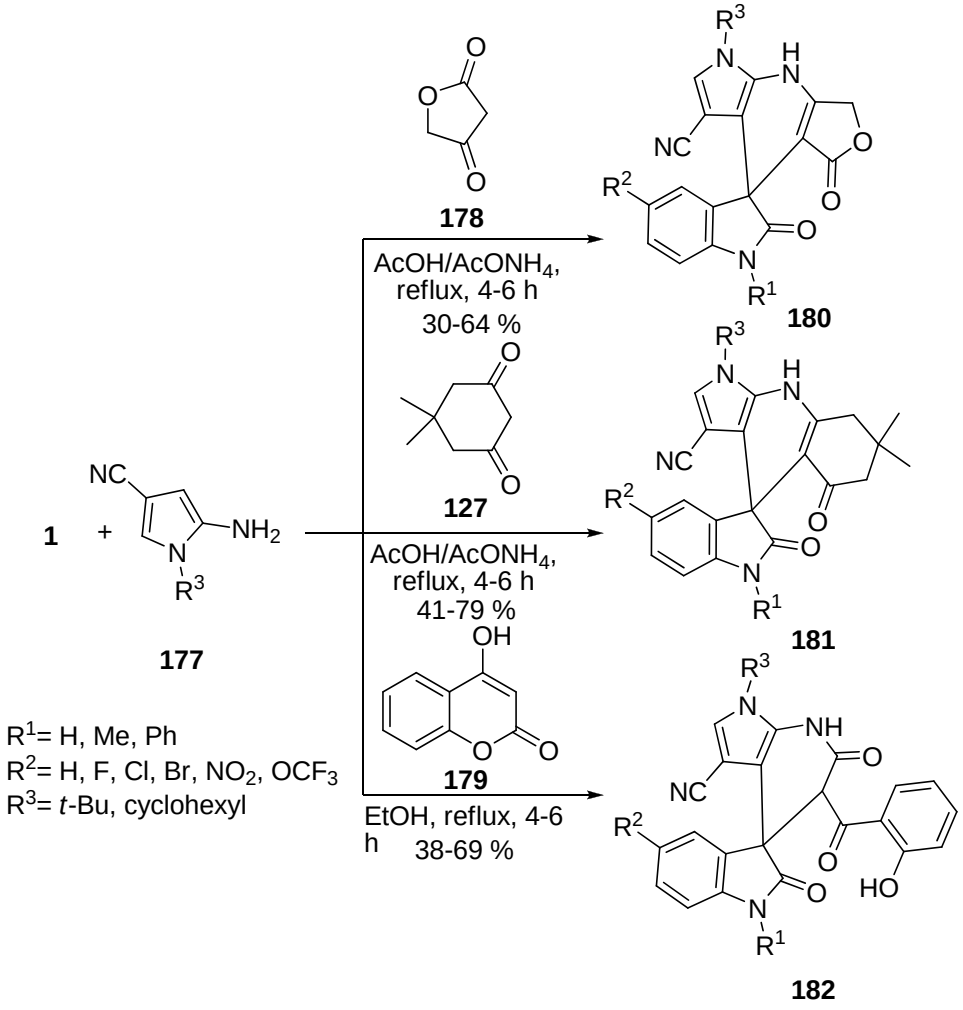


R^1= Me, Et, Pr
R^2= 3,5-$(MeO)_2$, 3,4,5-$(MeO)_3$, 2-anthraceneamine
R^3= H, Cl, F, NO_2
R^4= H, Me, Et
X= O, S

Scheme 64

Vilches-Herrera *et al.* studied the synthesis of 4-fused 4,7-dihydro-1*H*-pyrrolo[2,3-*b*]pyridines **180-182** from isatins **1**, *N*-substituted 5-amino-3-cyanopyrroles **177**, and a set of 1,3-

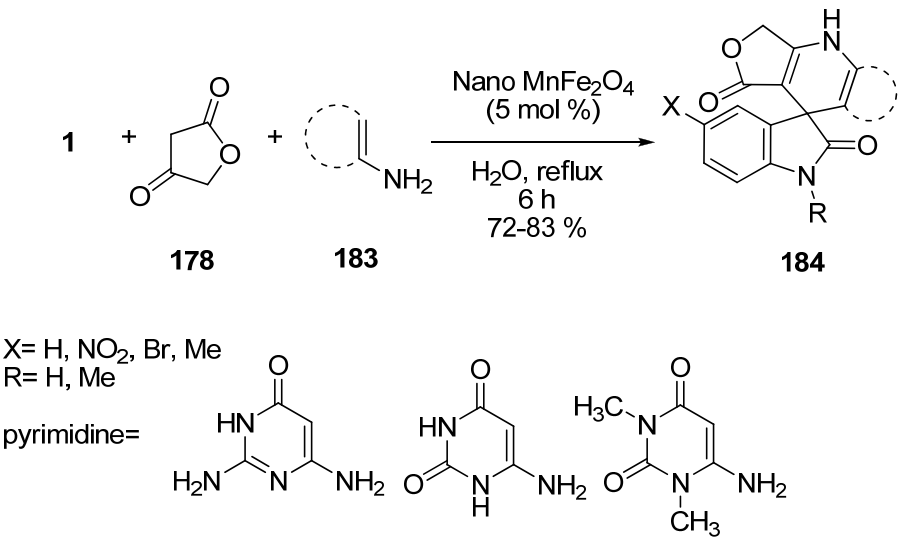
dicarbonyl compounds **127**, **178-179** (Scheme 65).[115] The reactions were carried out under mild conditions using ethanol and acetic acid as solvent.



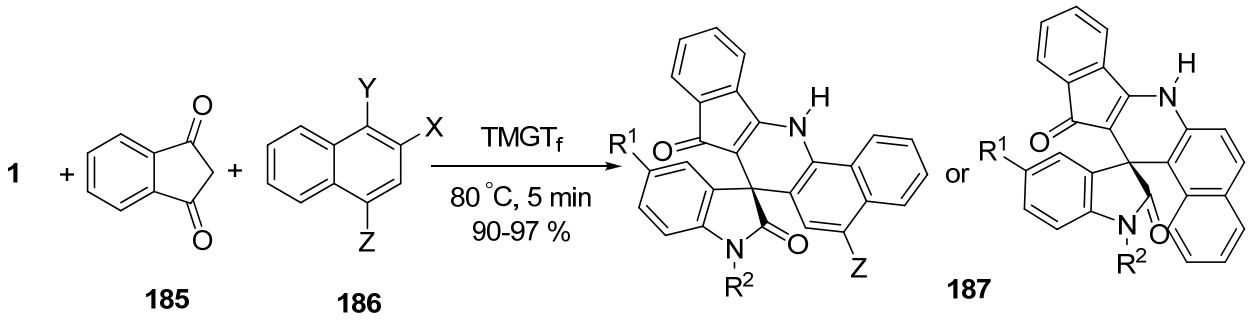
Scheme 65

In a similar way, Ghahremanzadeh and co-workers investigated three-component reaction of 2,6-diaminopyrimidine-4(3*H*)-one or uracils **183**, isatins **1**, and tetronic acid **178** in the presence of manganese ferrite nanoparticles as a magnetic catalyst in water (Scheme 66).[116]

Reaction of isatin derivatives **1**, 2*H*-indene-1,3-dione **185**, and 2-naphthalenamines **186** under catalysis of a *N,N,N′,N′*-tetramethylguanidinium triflate ionic liquid resulted in the formation of some fused spiro[1,4-dihydropyridine-oxindole] compounds **187** (Scheme 67).[117] Application of other CH-acids such as N,N-dimethylbarbituric acid, barbituric acid, and dimedone in this reaction was also investigated.[118]



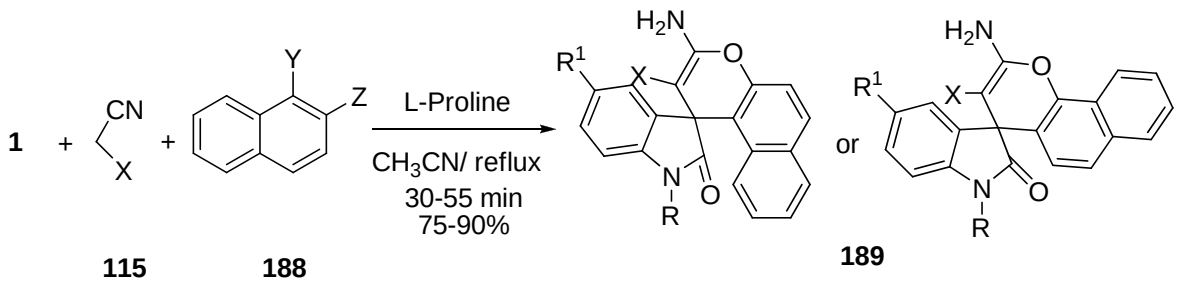
Scheme 66



R^1= I, Cl, NO_2, Me, OMe, Br, H
R^2= H, Bn
X= H, NH_2
Y= H, NH_2
Z= H, Br

Scheme 67

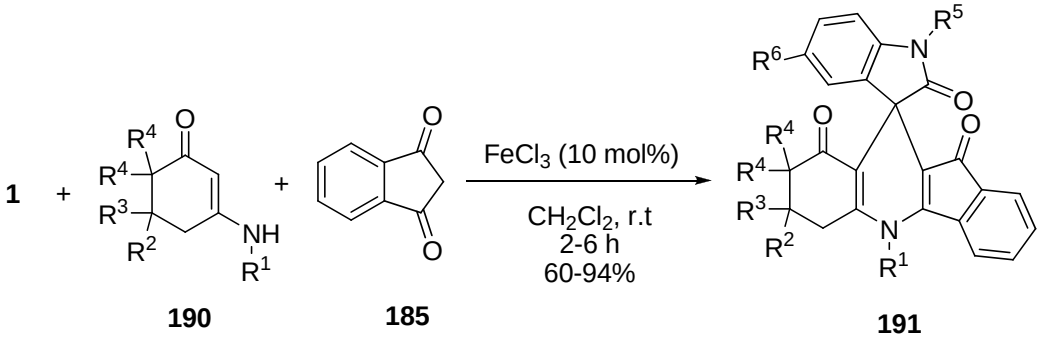
Synthesis of spiro-oxindole derivatives with fused 4*H*-chromenes **189** was accomplished by condensation of isatin **1**, malononitrile **115**, and naphthol **188** in the presence of *L*-proline as a catalyst (Scheme 68).[119] It is to be noted that the products obtained were racemic. *L*-proline did not take part in the generation of spiranic stereocenter. Hence, stereoselection was not achieved.



X= CN, CO_2Et
R= H, Me
R^1= H, Cl, Br
Y= H, Z= OH
Y= OH, Z= H

Scheme 68

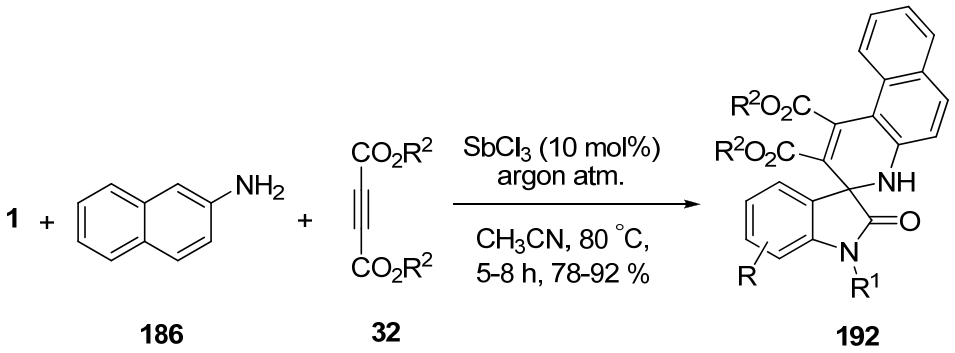
New spiro[indolo-3,10′-indeno[1,2-*b*]quinolin]-trione derivatives **191** were successfully obtained by means of a three-component process in which enaminones **190** are treated with *N*-substituted isatins **1** and indane-1,3-dione **185** in the presence of $FeCl_3$ as the catalyst in dichloromethane at room temperature (Scheme 69).[120]



R^1= H, *i*-Pr, Bu, Bn, 4-$OMeC_6H_4$, 4-MeC_6H_4, 2-*i*-PrC_6H_4, 2-MeC_6H_4, 3-MeC_6H_4, 3,4-$Me_2C_6H_3$, 3-$OMeC_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 2,5-$Cl_2C_6H_3$, 4-$CO_2HC_6H_4$, 3-$NO_2C_6H_4$
R^2, R^3= H, Me, Ph
R^4= H, Me
R^5= Allyl, Bn, *n*-Bu
R^6= H, Cl, Br, NO_2

Scheme 69

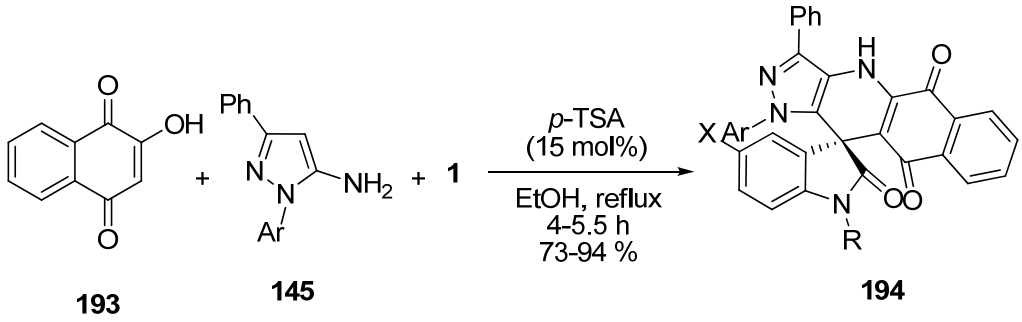
Maiti and co-workers developed an efficient procedure for the synthesis of the functionalized dimethyl-2′-oxo-4*H*-spiro[benzo[*f*]quinoline-3,3′-indoline]-1,2-dicarboxylate derivatives **192** via one-pot three-component reactions of 2-naphthylamine **186**, acetylenedicarboxylate **32**, and isatin **1** catalyzed by $SbCl_3$ in good to excellent yield (Scheme 70).[121]



R= H, 5-Cl, 5-Br, 5-I, 7-Cl, 5,7-Me_2
R^1= H, Me
R^2= Me, Et

Scheme 70

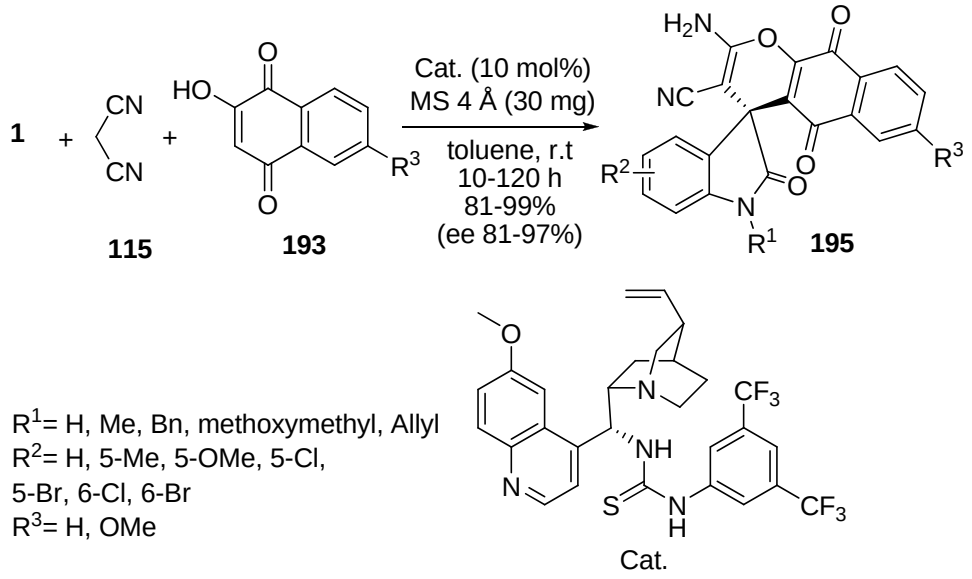
The condensation reaction of 2-hydroxynaphthalene-1,4-dione **193**, pyrazol-5-amines **145**, and isatins **1** in the presence of *p*-TSA afforded the spiro[11*H*-benzo[*g*]pyrazolo[4,3-*b*]quinoline-11,3′-[3*H*]indole]-2′,5,-10(1′*H*)-triones **194** (Scheme 71).[122]



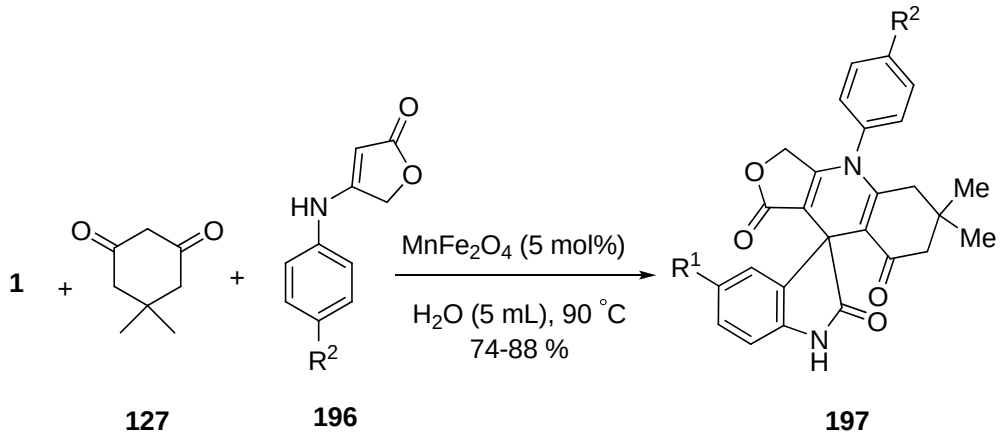
Ar= Ph, 4-$MeOC_6H_4$, 4-BrC_6H_4, 4-$NO_2C_6H_4$
X= H, Br, NO_2, Me
R= H, Et, Bn

Scheme 71

Three-component cascade reaction of isatins **1**, malononitrile **115**, and 2-hydroxy-naphthalene-1,4-diones **193** in the presence of cinchona-thiourea organocatalyst proceeded to furnish chiral pyranonaphthoquinone-fused spirooxindoles **195** in excellent yields and high enantioselectivities (Scheme 72).[123]



Scheme 72

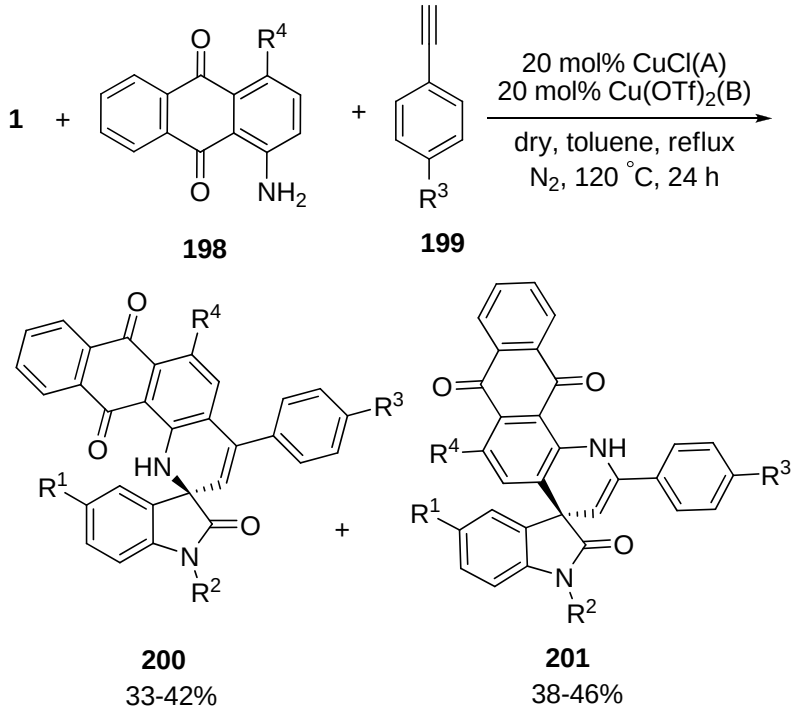


Scheme 73

4-Phenyl-6,7-dihydro-[spiro[furo]quinoline-indoline]-triones **197** were obtained via the reaction of isatins **1**, dimedone **127**, and anilinolactones **196** using $MnFe_2O_4$ nanoparticles as

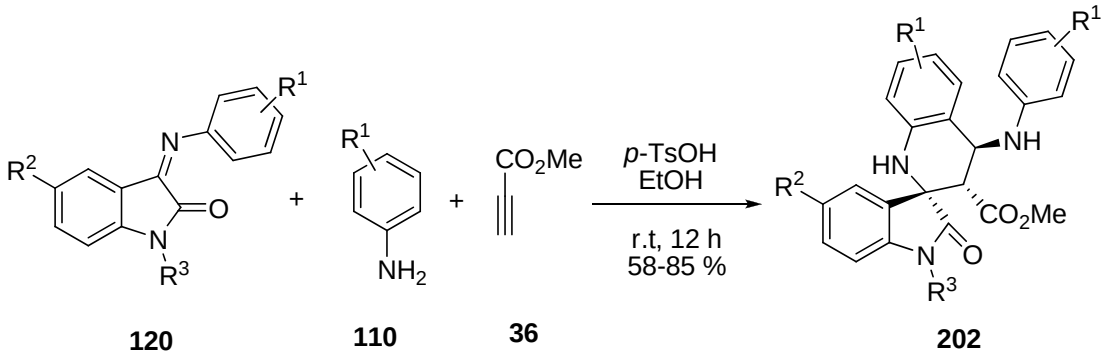
magnetically heterogeneous catalyst in water (Scheme 73).[124] Replacing dimedone with malononitrile in this reaction in the presence of a catalytic amount of Et_3N as a basic catalyst in THF under ultrasound irradiation has been also reported by the same group.[125]

Unusual reactivity of 1-aminoanthraquinone **198** with a number of isatins **1** and aryl alkynes **199** in a copper catalyzed multicomponent reaction afforded regioisomers of 3-spiroheterocyclic 2-oxindoles **200-201** (Scheme 74).[126] Both the regioisomers exhibited considerable optical properties and found as fluorescence materials.



Scheme 74

The *p*-toluenesulfonic acid catalyzed Povarov reaction of isatin-3-imines **120** with β-enamino esters, which were generated *in situ* by the reaction of arylamines **110** and methyl propiolate **36** in ethanol, afforded the polysubstituted spiro[indoline-3,2′-quinolines] **202** in high yields and with high diastereoselectivity (Scheme 75).[127]

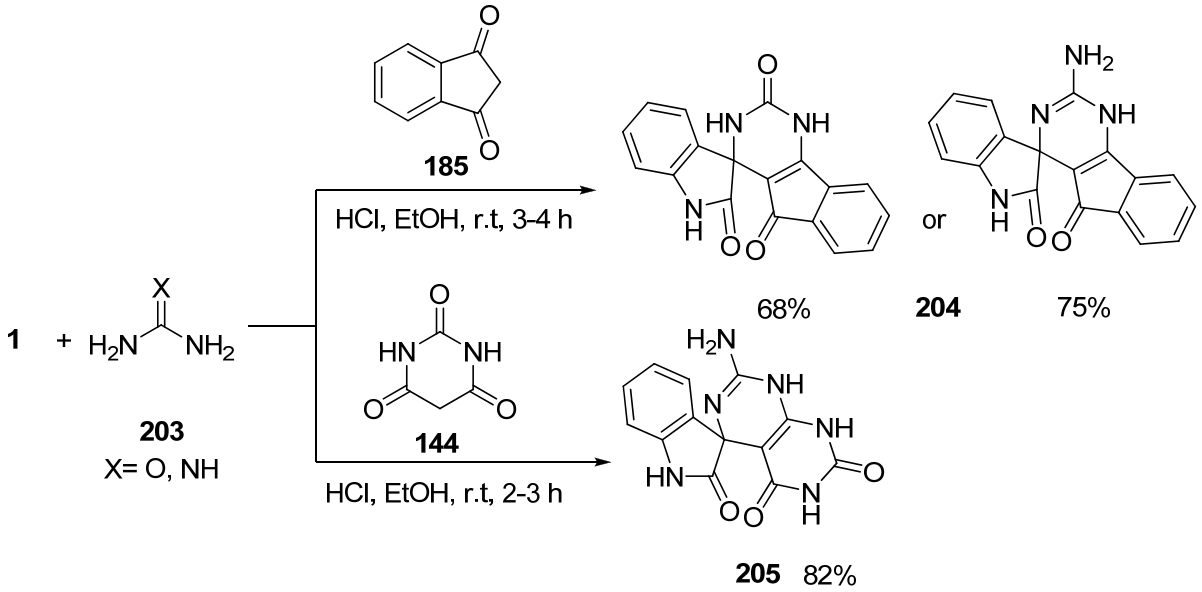


120 **110** **36** **202**

R^1= H, 4-Me, 4-*t*-Bu, 3-Me, 4-*i*-Pr, 4-MeO
R^2= H, Me, F, Cl
R^3= H, Bn, *n*-Bu

Scheme 75

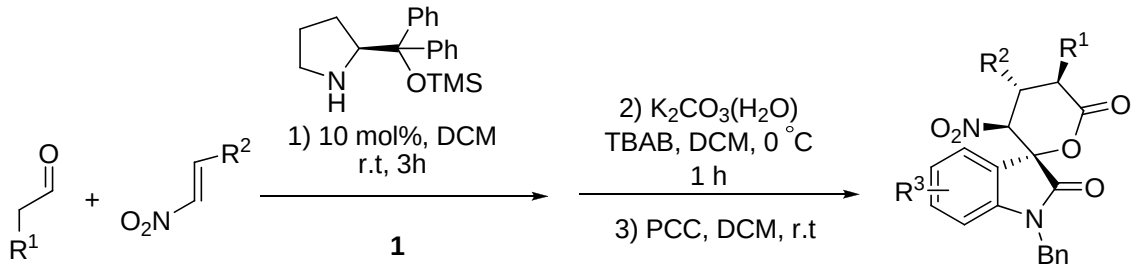
Meshram's group reported a method for the synthesis of spiro[quinazoline/pyrimidine]ones scaffold **204-205** by the reaction of isatin **1**, 1,3-dione **185/144** and urea or guanidine compounds **203** (Scheme 76).[128] In another study Baghernejad and Khorshidi established the reaction between isatin, urea and 1,3-dicarbonyl compounds for the preparation of spirooxindoles in the presence of nano-ZnO as a catalyst.[129]



Scheme 76

An organocatalytic cascade reaction involving a Michael–aldol–acetalization relay to achieve the asymmetric assembly of aldehydes **206**, nitroolefins **69**, and isatins **1** into six-

membered oxa-spirooxindole backbones **207** with high diastereo- and enantioselectivity was developed by Xie *et al*. (Scheme 77).[130]



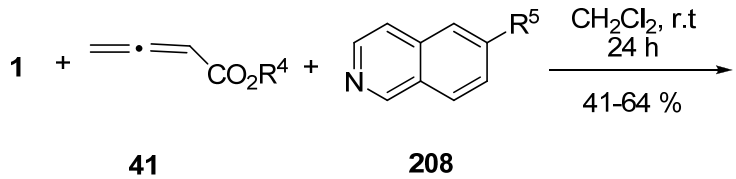
206 **69** **1** **207**

68-84%
(ee 94-99%)

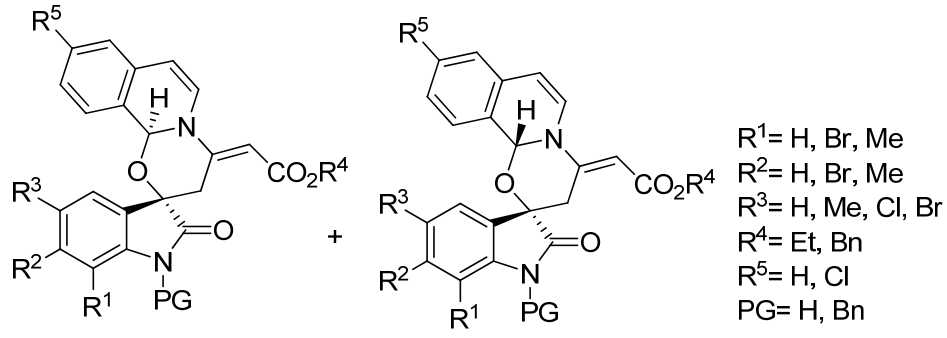
R^1= Me, Et, Pr
R^2= Ph, 3-BrC_6H_4, 4-FC_6H_4, 2-ClC_6H_4, 3,4-$(OMe)_2C_6H_3$, 2-furyl
R^3= H, 5-Cl, 5-Br, 5- NO_2
DCM: dichloromethane
PCC=pyridinium chlorochromate

Scheme 77

[1,3]Oxazino[2,3-*a*]isoquinoline derivatives **209** were prepared from isoquinoline **208**, allenoates **41**, and isatin derivatives **1** via 1,4-dipolar cycloaddition reaction (Scheme 78).[131] The X-ray diffraction showed that products were synthesized in moderate diastereoselectivities.



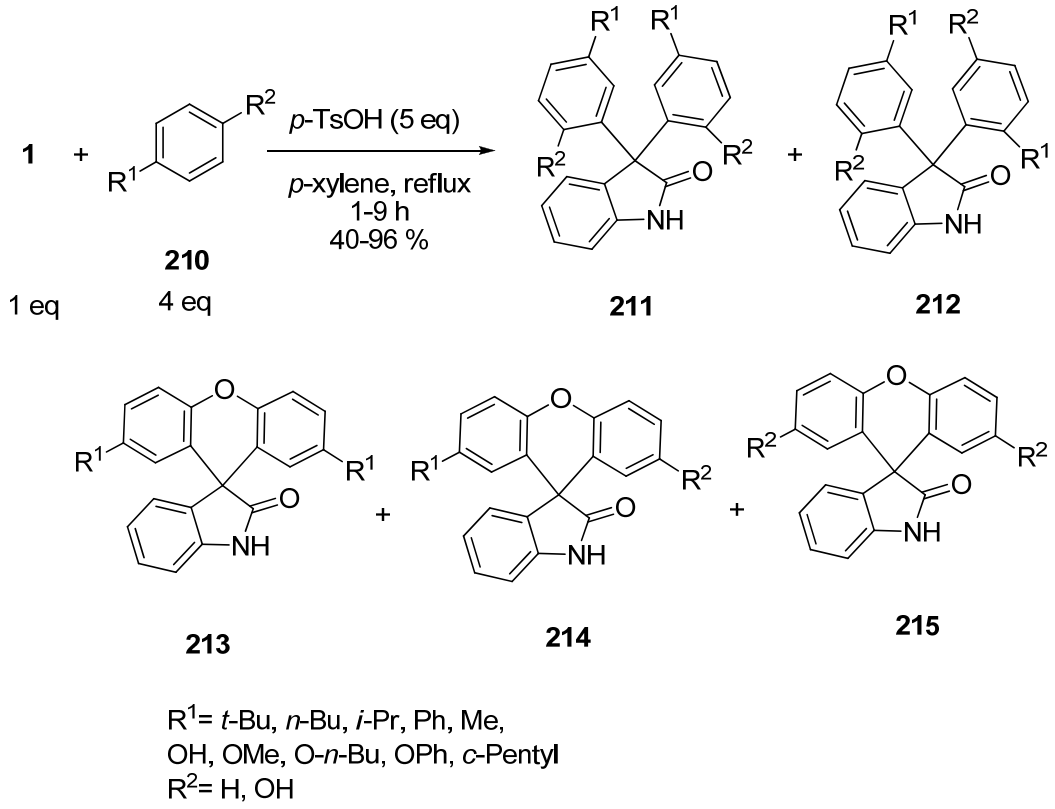
41 **208**



209 Major **209′** Minor

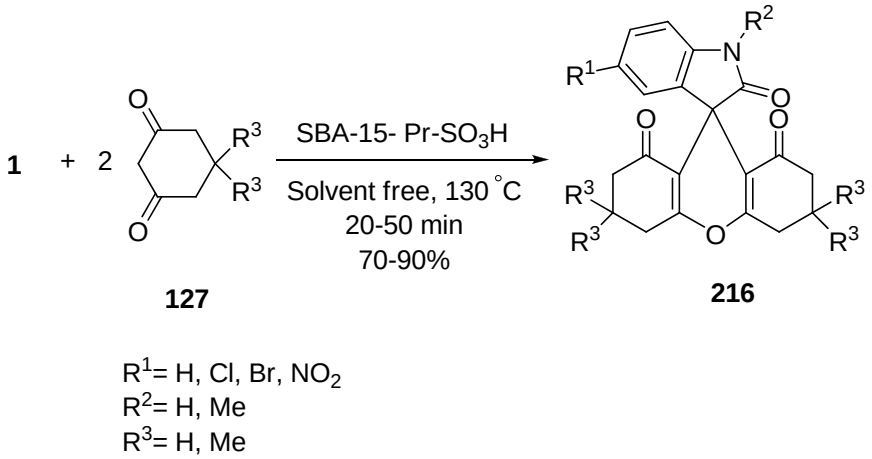
Scheme 78

Reaction of isatin **1** with *p*-substituted phenols **210** in the presence of *p*-TsOH as catalyst in refluxing *p*-xylene, afforded 3,3-bis-(2-hydroxy-5-alkylphenyl)oxindoles (**211, 212**) and their *in situ* conversion into 2′,7′-dialkylspiro[indoline-3,9′-xanthen]-2-ones (**213, 214, 215**) (Scheme 79).[132]



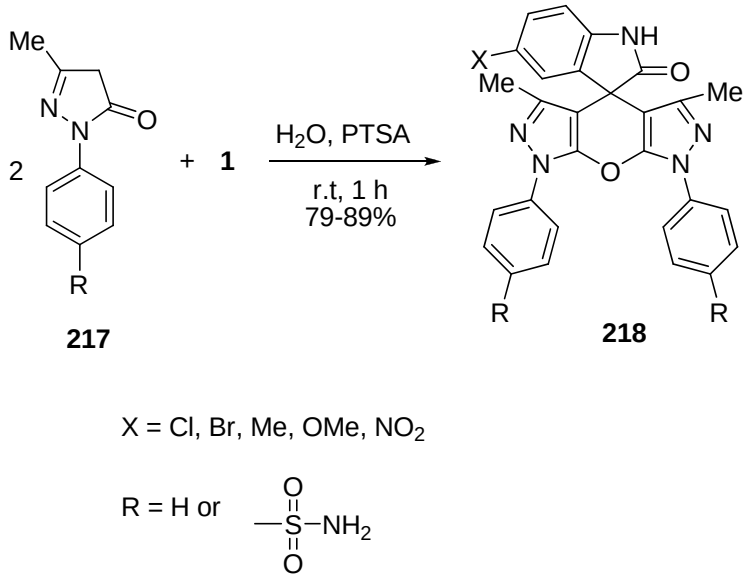
Scheme 79

Mohammadi Ziarani and co-workers carried out a method for the synthesis of spiro[indoline-3,9′-xanthene]trione derivatives **216** through the condensation reaction of isatins **1** and two moles of dimedone or 1,3-cyclohexanedione **127** under solvent-free conditions in the presence of SBA-15-Pr-SO_3H as a heterogeneous nano catalyst (Scheme 80).[133]



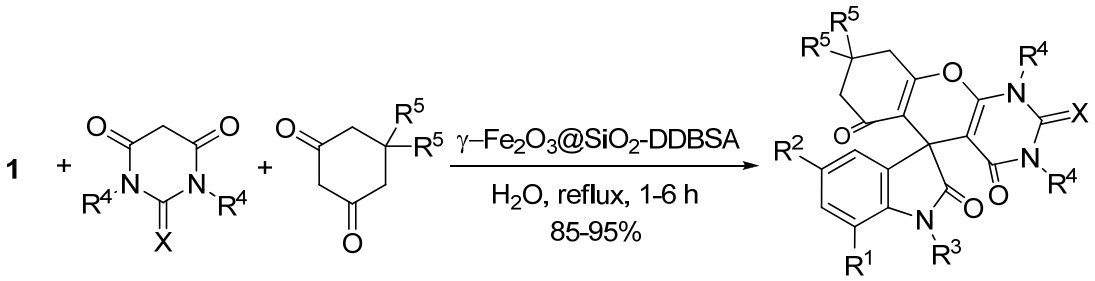
Scheme 80

Rahmati *et al*. prepared the spirooxindole scaffold by the reaction of isatin **1** with activated pyrazolones **217** in the presence of a catalytic amount of *p*-toluenesulfonic acid (Scheme 81).[134] A variety of symmetrical spirooxindole derivatives **218** were obtained with excellent yields within short reaction time.



Scheme 81

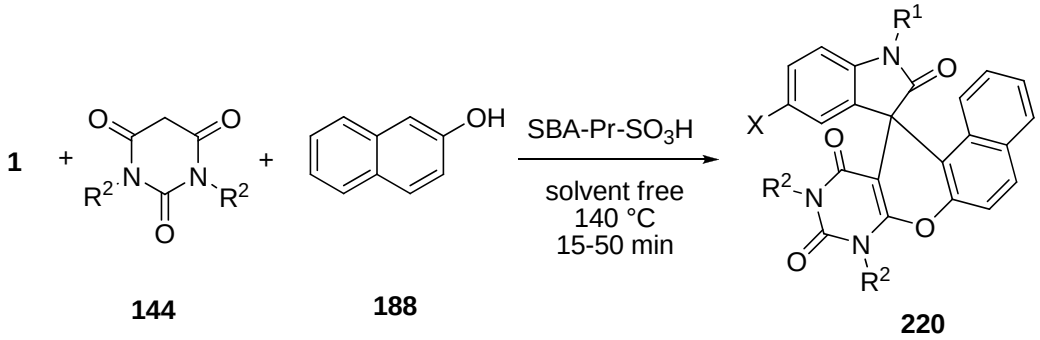
The reaction of substituted isatins **1**, barbituric acids **144**, and cyclohexane-1,3-diones **127** for the direct construction of a library of spirooxindole-pyrimidine derivatives **219** was catalyzed by nano magnetically silica-supported dodecyl benzenesulfonic acid (γ-Fe_2O_3@SiO_2-DDBSA) in water (Scheme 82).[135] This reaction was also accomplished in the presence of alum ($KAl(SO_4)_2 \cdot 12H_2O$)[136] and gluconic acid aqueous solution (GAAS) as catalysts.[137]



R^1= H, Me
R^2= H, Me, F, Cl, Br, I
R^3= H, Me, Et, Bz
R^4= H, Me
R^5= H, Me
X= O, S

Scheme 82

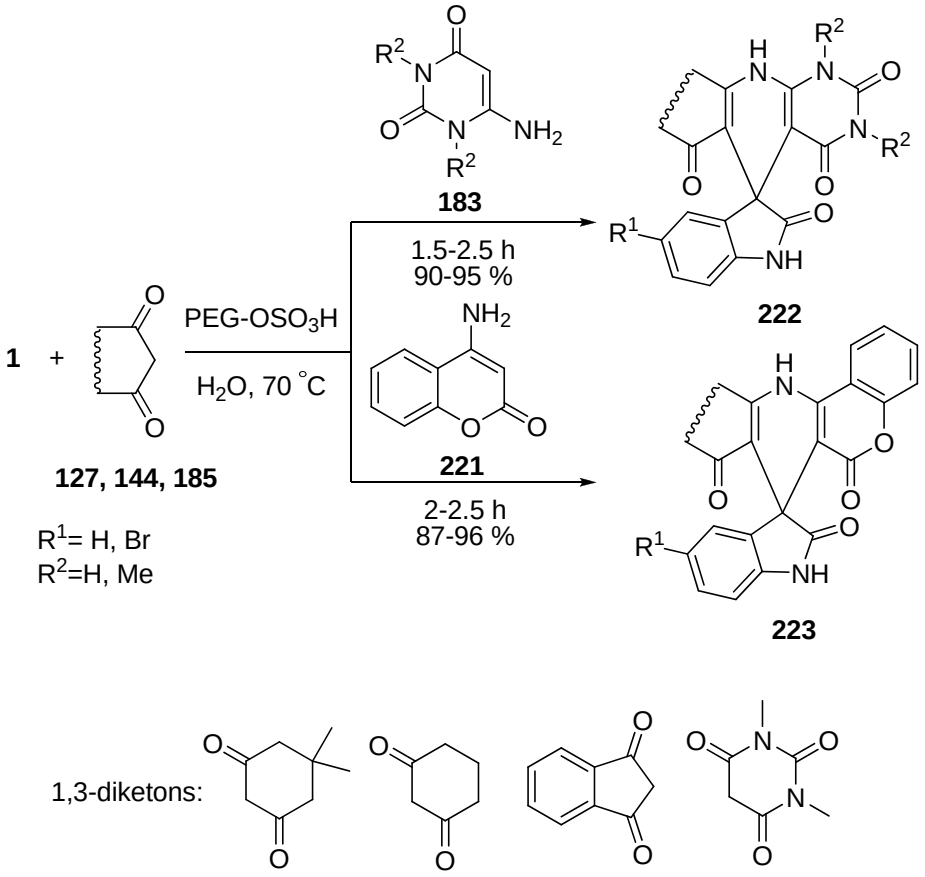
A green one-pot synthesis of spironaphthopyrano[2,3-*d*]pyrimidine-5,3′-indoline derivatives **220** by a three-component reaction of isatins **1**, 2-naphthol **188**, and barbituric acids **144** under solvent-free conditions in the presence of SBA-Pr-SO_3H has been accomplished (Scheme 83).[138] Replacement of barbituric acid with 1,3-indanedione in this reaction leads to the synthesis of spironaphthopyrano[1,2-*b*]indeno-7,3′-indolines.[139]



R^1= H, Me
R^2= H, Me
X= Cl, Br, NO_2

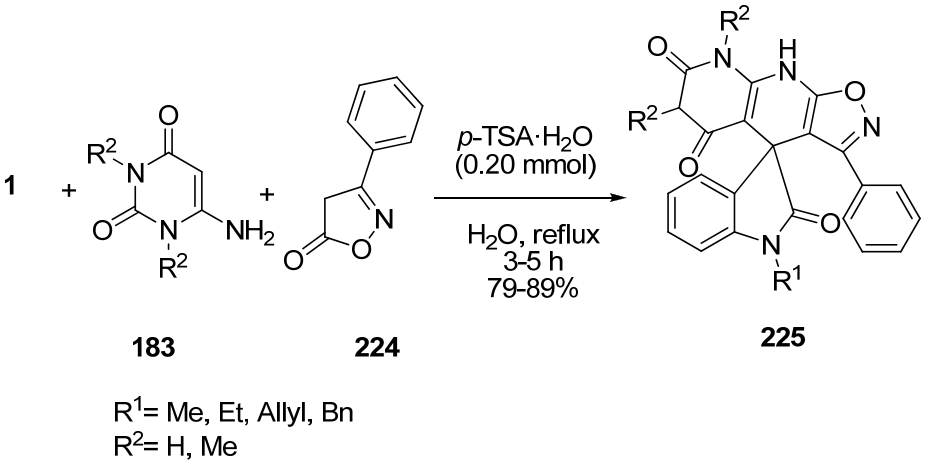
Scheme 83

Paul and Das applied PEG-OSO_3H as a catalyst in reactions involving the domino coupling of 1,3-diketo compounds **127, 144, 185**, 6-aminouracil **183**/4-aminocoumarin **221**, and isatins **1** for the synthesis of uracil **222** and coumarin **223** fused spirooxindole derivatives, respectively. (Scheme 84).[140]



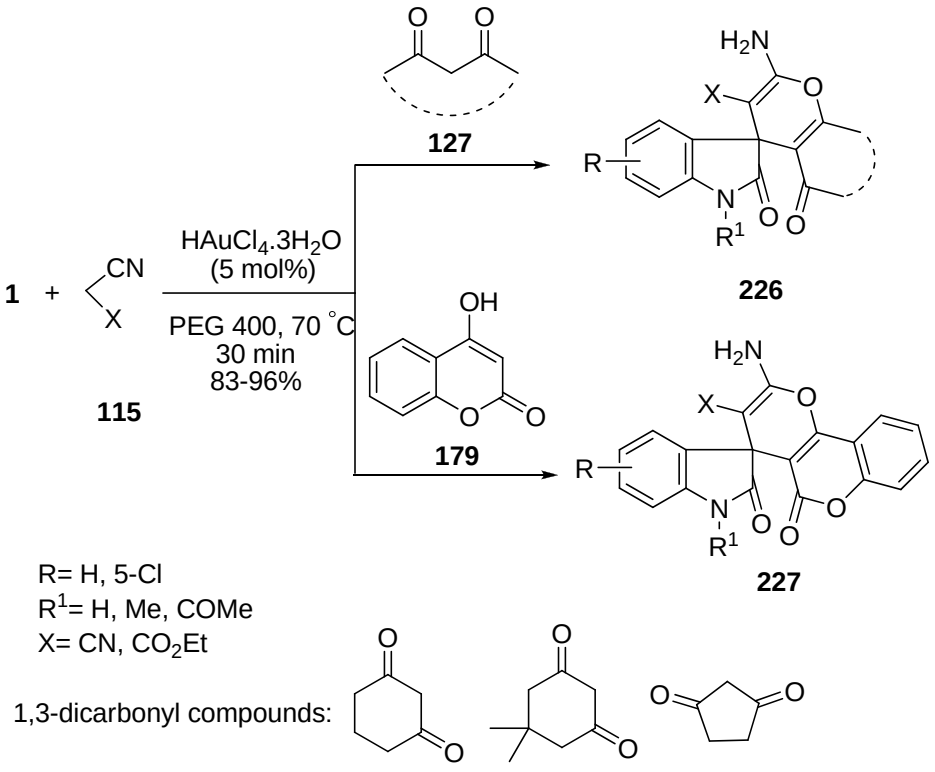
Scheme 84

A *p*-toluenesulfonic acid-catalyzed three-component reaction of isatins **1**, aminouracils **183**, and isoxazolones **224** as coupling partners for the synthesis of spiroxindole derivatives **225** was reported by Perumal and co-workers (Scheme 85).[141]



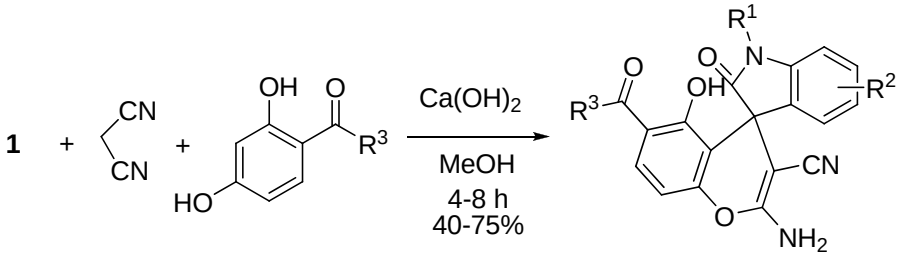
Scheme 85

The synthesis of spirochromene derivatives **226-227** was carried out using isatins **1**, malononitrile **115**, and cyclic 1,3-diketones **127**/4-hydroxycoumarin **179** as a model substrate in the presence of gold(III) chloride ($HAuCl_4 \cdot 3H_2O$) as catalyst in PEG (Scheme 86).[142] Moreover, silica-bonded 5-*n*-propyl-octahydro-pyrimido[1,2-*a*]azepinium chloride (SB-DBU)C,[143] DBU in water,[144] $Mg(ClO_4)_2$,[145] DABCO,[146] [γ-Fe_2O_3@HAp-Si$(CH_2)_3SO_3H$],[147] SBA-Pr-SO_3H,[148-149] SBA-Pr-NH_2,[150, 151] SBA-15@DABCO,[152] $CaCl_2$,[153] PEG-Ni nanoparticle,[154] triphenylphosphine (PPh_3),[155] mesoporous silica nanoparticles (MSNs),[156] nanocrystalline MgO in aqueous condition,[157] glycerol-based carbon-sulfonic acid,[158] α-amylase,[159] and hexamethylenetetramine (HMT) in water[160] were also used as catalyst in this reaction. Kidwai and co-workers analyzed these compounds for their cytotoxic activity against U87 human glioma cells.[161] Wu *et al*. used an aqueous media without any catalysts under microwave irradiation.[162] In another study, glycerol as a biodegradable and reusable promoting medium was applied under catalyst-free conditions.[163] This reaction was also conducted under catalyst-free condition in deep eutectic solvent (DES based choline chloride)[164] or under catalyst-free conditions in DMSO at 70 °C.[165] Elinson's group reported thermal non-catalytic reaction in water or alcohols in high yields.[166] A similar reaction has been reported by Zakeri and co-workers under microwave irradiation in the presence of 4-dimethylaminopyridine (DMAP).[167]



Scheme 86

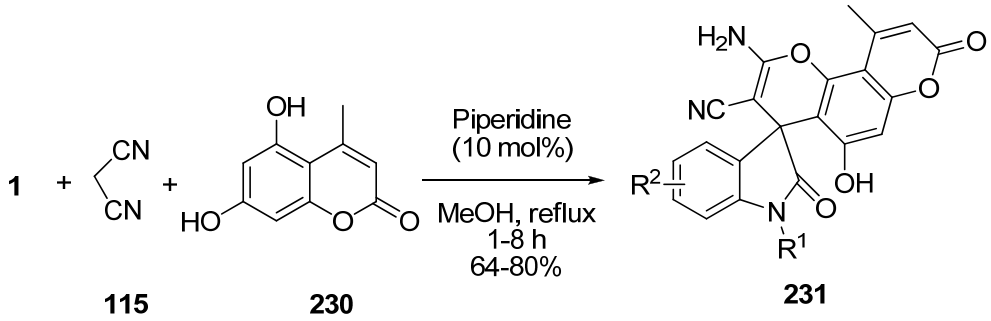
Lee and co-workers made a series of novel 2-amino-5-hydroxy-4*H*-chromene derivatives **229** with a spirooxindole nucleus using $Ca(OH)_2$-mediated three-component reactions of substituted resorcinols **228** with isatins **1** and malononitrile **115** (Scheme 87).[168]



R^1= H, Me, Ph
R^2= H, 5-Me, 5-Br, 5-NO_2, 5-Cl, 7-Cl
R^3= Me, Et, Benzyl, Ph

Scheme 87

Synthesis of pyranocoumarin fused spirooxindole derivatives **231** from the one-pot three-component reaction of isatin **1**, malononitrile **115**, and 5,7-dihydroxy-4-methyl-2*H*-chromen-2-one **230** using piperidine as organocatalyst has been reported by Choudhury and co-workers (Scheme 88).[169] When ethyl cyanoacetate was employed in the reaction instead of malononitrile, transesterified product was formed in methanol.

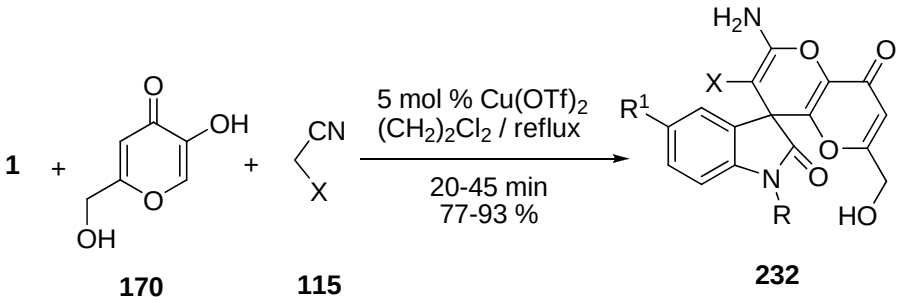


R^1= H, Me, Ph
R^2= 5-F, 5-Cl, 5-Br, 5-I, 5-OMe, 7-Cl

Scheme 88

Perumal's group used the $Cu(OTf)_2$ as catalyst for synthesis of spiropyrano[3,2-*b*]pyran-4(8*H*)-ones **232** in the reaction between isatin **1**, kojic acid **170**, and active methylenes **115** (Scheme 89).[170] Synthesized compounds were evaluated for their tumor cell growth inhibitory

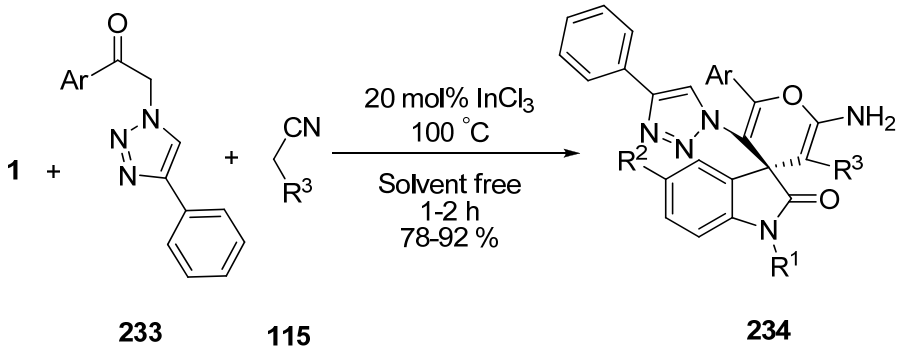
activity against the human lung cancer cell line (A549). Later, application of catalytic amount of DABCO in this reaction was also investigated.[171]



R= H, Me, Allyl, Bn, Propargyl
R^1= H, F, Cl, Br, Me, NO_2
X= CN, CO_2Me, CO_2Et

Scheme 89

Efficient synthesis of novel triazolylspiroxindolinopyrans **234** was achieved by reacting phenacyltriazole **233**, isatin **1**, and active methylene compounds **115** in the presence of $InCl_3$ under solvent-free conditions at 100 °C (Scheme 90).[172]

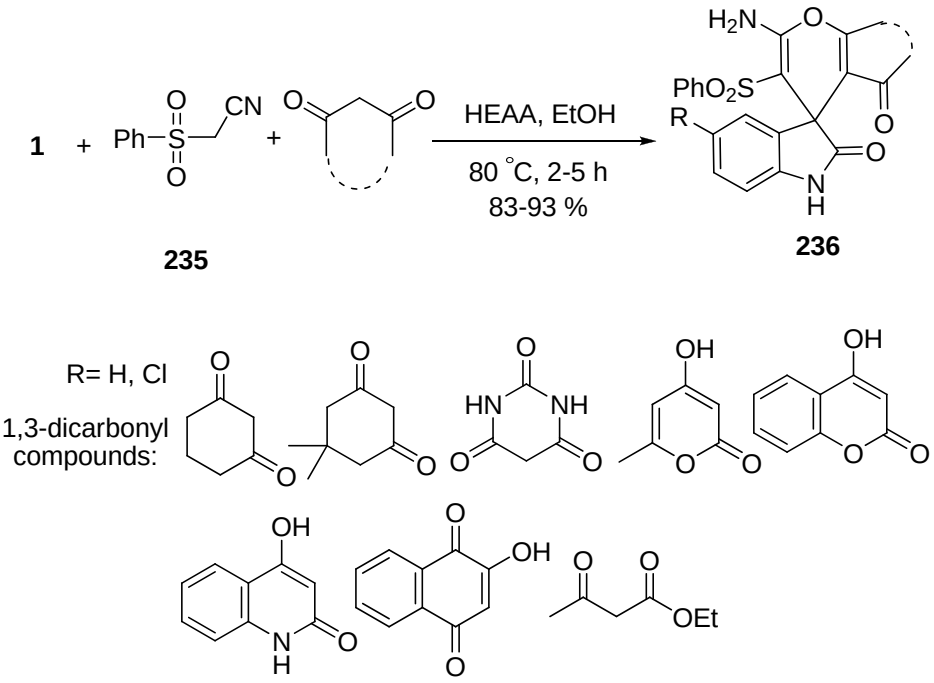


R^1= H, Me, Allyl, Propyne
R^2= H, F, Cl, Br
R^3= CN, CO_2Et
Ar= C_6H_5, 4-ClC_6H_4, 4-BrC_6H_4, naphthalene

Scheme 90

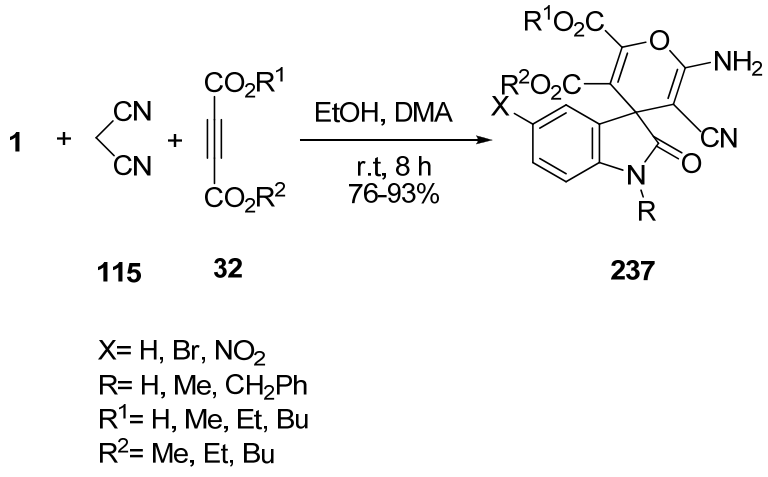
A series of spiro-2-amino-3-phenylsulfonyl-4*H*-pyran derivatives **236** were synthesized via the reaction of phenylsulfonylacetonitrile **235** and 1,3-dicarbonyl compounds with isatins **1** using

a novel basic ionic liquid 2-hydroxyethylammonium acetate $[H_3N^+CH_2CH_2OH][CH_3COO^-]$ (HEAA) as catalyst (Scheme 91).[173]



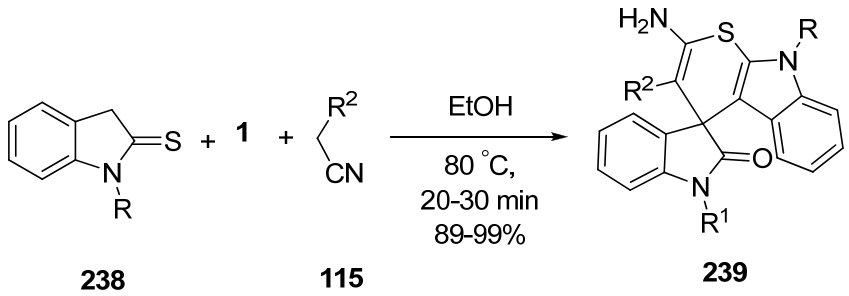
Scheme 91

Bazgir and co-workers reported a method for the synthesis of polyfunctionalized pyrano-fused spirooxindoles **237** via the condensation of isatins **1**, malononitrile **115**, and dialkyl acetylenedicarboxylates **32** in the presence of 3,4-dimethylaniline (DMA) as an organocatalyst (Scheme 92).[174]



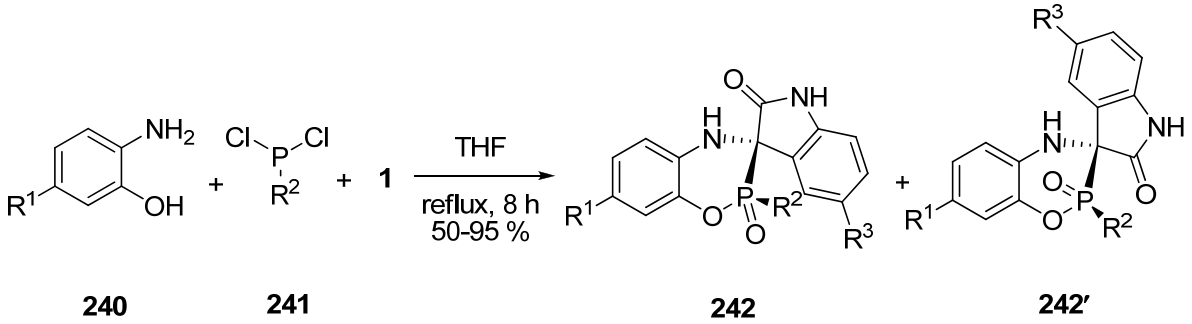
Scheme 92

The one-pot Knoevenagel condensation/Michael addition/cyclization reaction of indoline-2-thiones **238**, isatin derivatives **1**, and malononitriles **115** afforded the spirooxindole-annulated thiopyran derivatives **239** (Scheme 93).[175]



Scheme 93

Regioselective synthesis of structurally diverse spirooxindole-fused phosphorus heterocycle derivatives **242** and **242′** was constructed by means of a three-component domino reaction of isatins **1**, dichlorophenylphosphine or phenyl phosphorodichloridite **241**, and *o*-aminophenol **240** in tetrahydrofuran reflux (Scheme 94).[176]

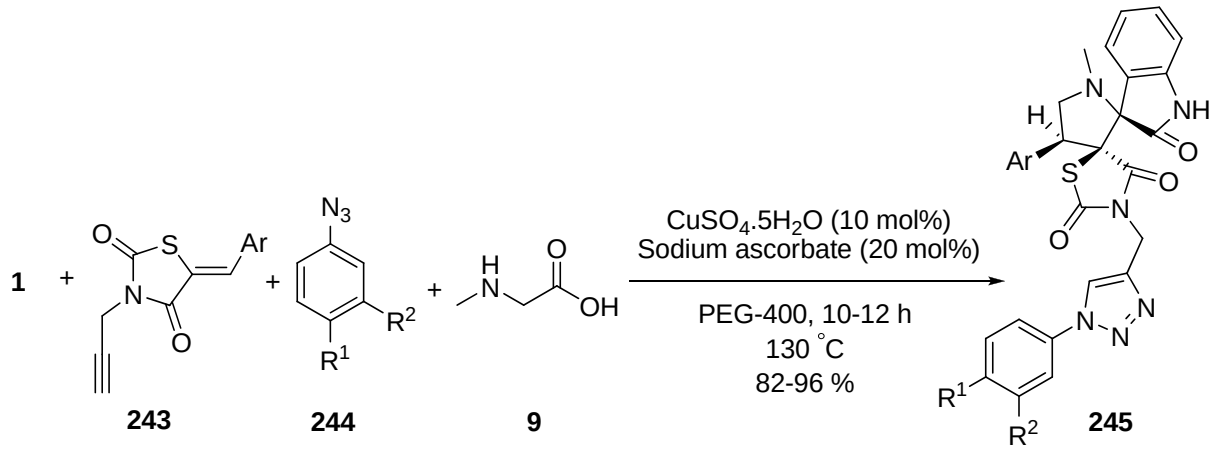


Scheme 94

2.2. Synthesis involving four-component reactions of isatins

2.2.1. Five-membered spiro-fused compounds. A series of novel dispiropyrrolidine-linked 1,2,3-triazole derivatives **245** have been prepared by one-pot, four-component protocol that employed 5-arylidene-3-(prop-2-ynyl)thiazolidine-2,4-dione **243**, isatin **1**, sarcosine **9**, and

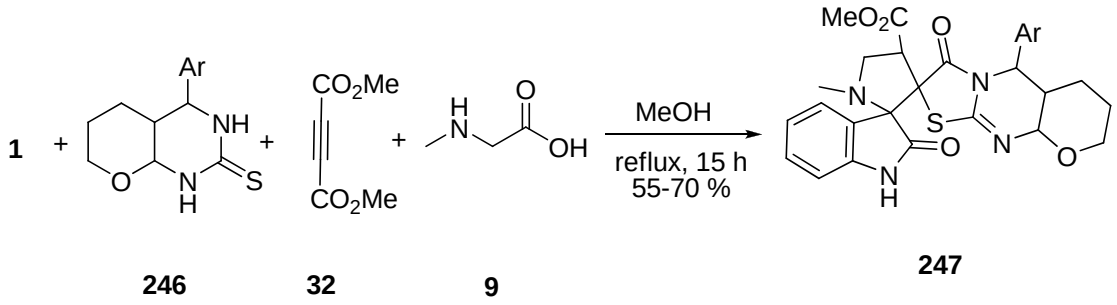
substituted azides **244** using Cu(I) generated *in situ* as catalyst in PEG-400 as a highly efficient and green medium (Scheme 95).[177]



Ar= 4-BrC_6H_4, 4-MeC_6H_4, 4-$NO_2C_6H_4$, 4-$OMeC_6H_4$, $C_7H_5O_2$
R^1= H, F, Me, OMe, Br
R^2= H, Cl

Scheme 95

The one-pot synthesis of a series of novel spiropyrano[2,3-*d*][1,3]thiazolo[3,2-*a*]pyrimidine derivatives **247** was achieved via the sequential reaction of 4-aryl-octahydro-pyrano[2,3-*d*]pyrimidine-2-thione **246**, dimethyl acetylenedicarboxylate **32**, and a mixture of isatin **1** and sarcosine **9** (Scheme 96).[178]

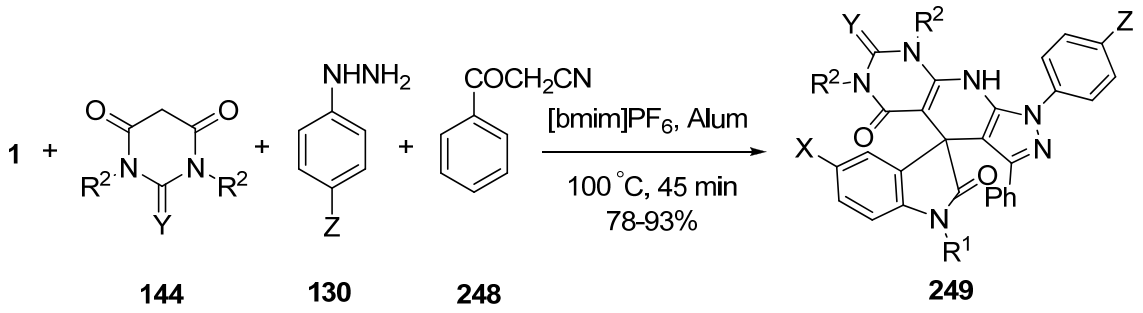


Ar= 4-ClC_6H_4, 4-$OMeC_6H_4$, 2,4-$Cl_2C_6H_3$,
3,4,5-$(MeO)_3C_6H_2$, 4-FC_6H_4, 4-$SMeC_6H_4$,
4-MeC_6H_4, 4-$CO_2MeC_6H_4$, C_6H_5

Scheme 96

2.2.2. Six-membered spiro-fused compounds. Ghahremanzadeh and co-workers developed a four-component reaction between isatins **1**, barbituric acids **144**, phenyl hydrazines **130**, and

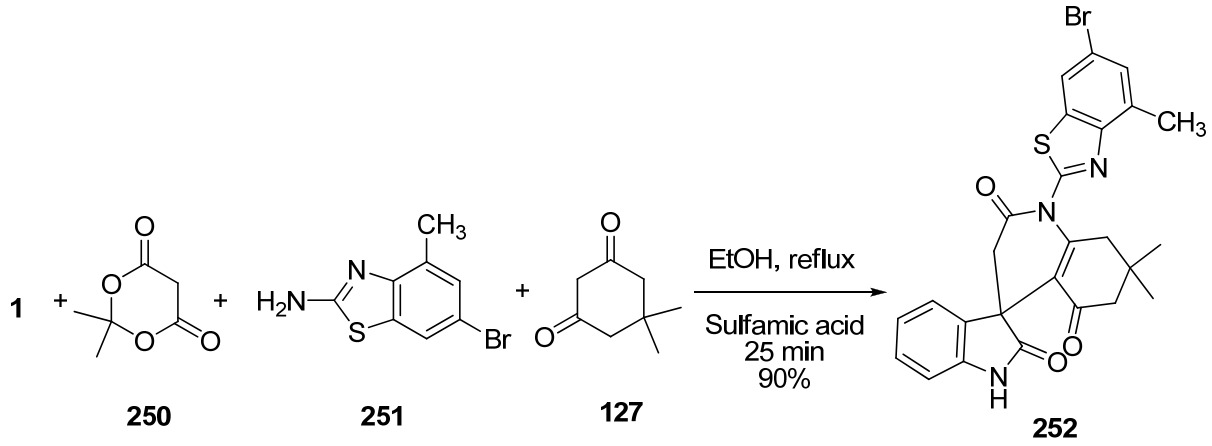
phenacyl cyanide **248** in the presence of alum [$KAl(SO_4)_2 \cdot 12H_2O$] as catalyst using the ionic liquid [Bmim]PF_6 as an effective green reaction medium (Scheme 97).[179]



R^1= H, Me, Et
R^2= H, Me
X= H, Br, NO_2, Me
Y= O, S
Z= H, NO_2

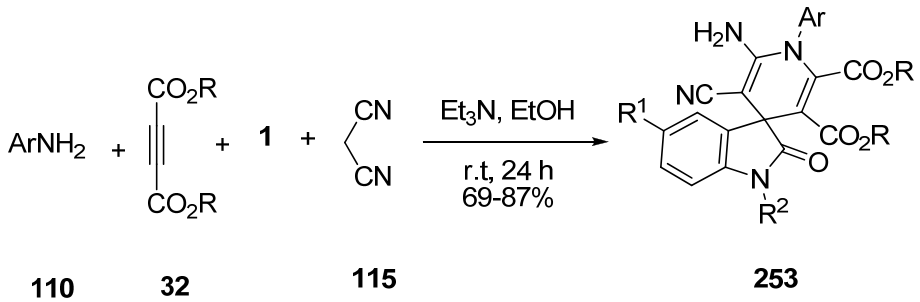
Scheme 97

Structurally diverse benzothiazolylquinoline-2,5-diones **252** were synthesized by a synthetic method involving sulfamic acid catalyzed one-pot four-component reaction of Meldrum's acid **250**, 2-aminobenzothiazoles **251**, dimedone **127**, and isatin **1** (Scheme 98).[180] Replacing Meldrum's acid with barbituric acid in this reaction using SO_3H-functionlized halogen-free ionic liquid 3-methyl-1-(butyl-4-sulfonyl)imidazolium hydrogen sulphate ([$MIM(CH_2)_4SO_3H$][HSO_4]) in aqueous medium was also reported by the same group.[181]



Scheme 98

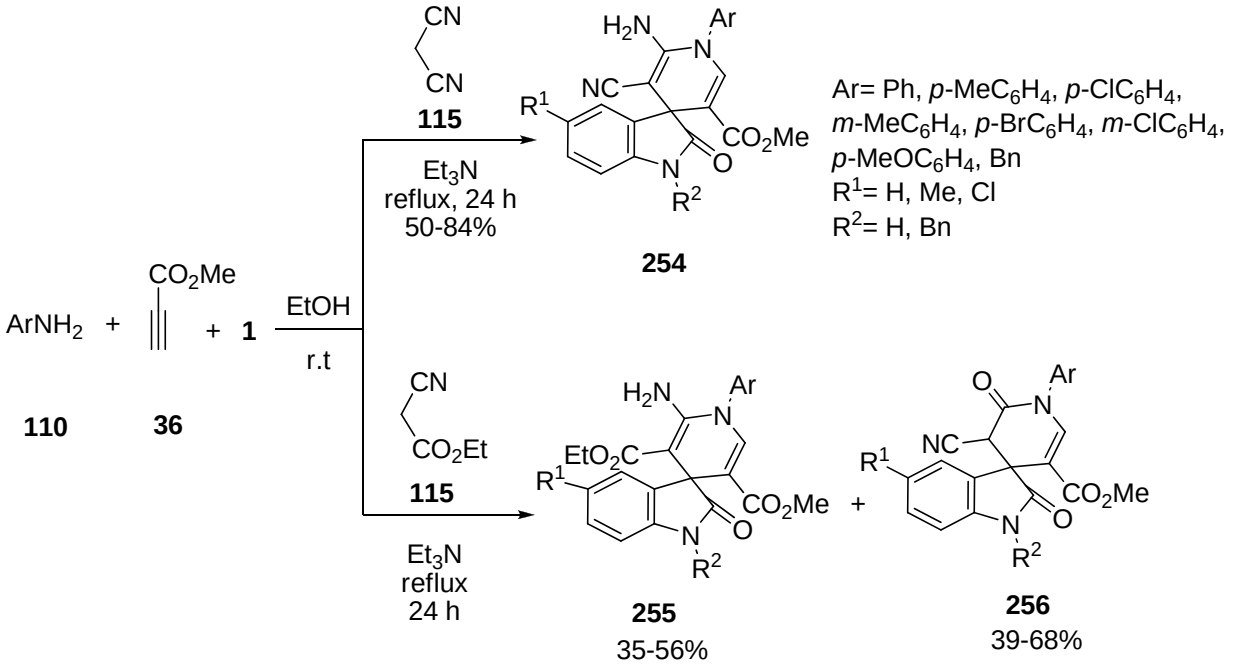
Yan's group developed a synthetic procedure for the synthesis of spiro[indoline-3,4′-pyridine] derivatives **253** via the four-component reaction of arylamines **110**, acetylenedicarboxylates **32**, isatins **1** and malononitrile **115** in the presence of triethylamine as the base catalyst (Scheme 99).[182]



110 **32** **115** **253**

Ar= *p*-MeC_6H_4, *p*-$MeOC_6H_4$, *p*-ClC_6H_4, *p*-$NO_2C_6H_4$, *m*-$NO_2C_6H_4$
R= Me, Et
R^1= H, Me, Cl
R^2= H, Bn

Scheme 99



110 **36**

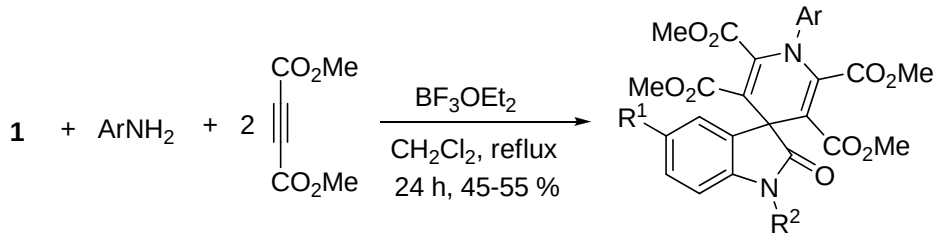
Ar= Ph, *p*-MeC_6H_4, *p*-ClC_6H_4, *m*-MeC_6H_4, *p*-BrC_6H_4, *m*-ClC_6H_4, *p*-$MeOC_6H_4$, Bn
R^1= H, Me, Cl
R^2= H, Bn

Ar= Ph, Bn, CH_2Bn, *p*-MeC_6H_4, *p*-ClC_6H_4, *p*-BrC_6H_4, *m*-ClC_6H_4, *p*-$MeOC_6H_4$
R^1= H, Me
R^2= H, Bn, C_4H_9

Scheme 100

The same group accomplished domino reaction of arylamines **110**, methyl propiolate **36**, isatin **1** and malononitrile/ethyl 2-cyanoacetate **115** with triethylamine for the synthesis of functionalized spiro[indoline-3,4′-pyridine] **254-255** and spiro[indoline-3,4′-pyridinone] derivatives **256**, respectively (Scheme 100).[183]

In a similar study, the $BF_3.OEt_2$-catalyzed reactions of acetylenedicarboxylates **32**, arylamines **110**, and isatins **1** afforded functionalized spiro[indoline-3,4′-pyridine]-2′,3′,5′,6′-tetracarboxylates **257** in moderate yields (Scheme 101).[184-185]



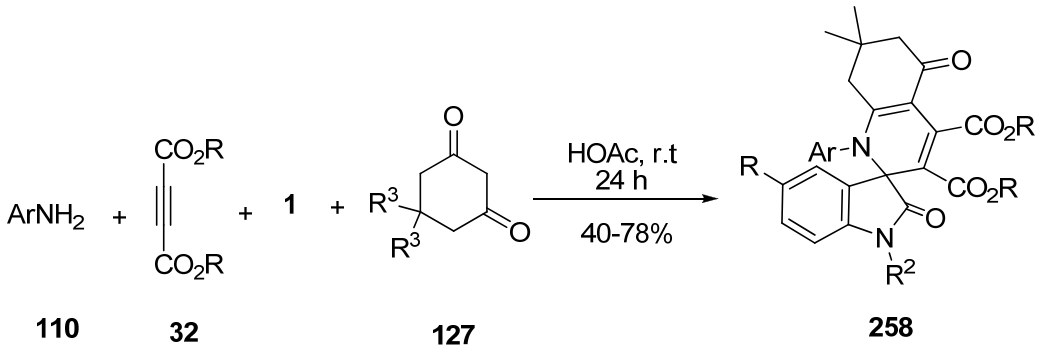
110 **32** **257**

R^1= H, Me
R^2= H, Bn
Ar= Ph, *p*-MeC_6H_4, *p*-$MeOC_6H_4$, *p*-EtC_6H_4

Scheme 101

The same group found that the four-component reactions of arylamines **110**, acetylenedicarboxylate derivatives **32**, isatins **1**, and dimedone **127** in acetic acid resulted in the novel functionalized tetrahydrospiro[indoline-3,2′-quinoline] derivatives **258** in moderate yields (Scheme 102).[186] In a similar study, Debnath and Pramanik used the bimetallic $ZnFe_2O_4$ nanopowder as a dual Lewis acid-base combined catalyst in this reaction.[187]

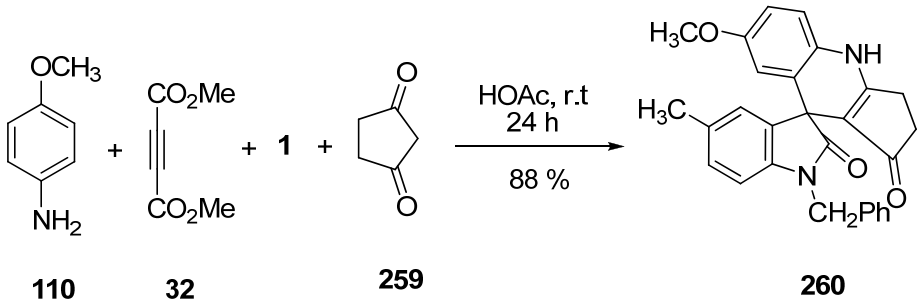
In an exploratory experiment, the four-component reaction of *p*-methoxyaniline **110**, dimethyl acetylenedicarboxylate **32**, 1-benzyl-5-methylisatin **1** and cyclopentane-1,3-dione **259** in acetic acid was carried out by the same authors and there was no unit of acetylenedicarboxylate in the obtained product **260** (Scheme 103).[188] This result indicated that the three-component reaction of arylamine **110**, isatin **1**, and cyclopentane-1,3-dione **259** gave the final spiro[dihydropyridine-oxindole] compounds **260**, while the acetylenedicarboxylate could not take part in the reaction.



110 **32** **127** **258**

Ar= *p*-MeC_6H_4, Ph, *p*-ClC_6H_4, *p*-$MeOC_6H_4$, *m*-$NO_2C_6H_4$
R= Me, Et
R^1= H, Me, Cl
R^2= H, CH_2Ph, *n*-C_4H_9
R^3= H, Me

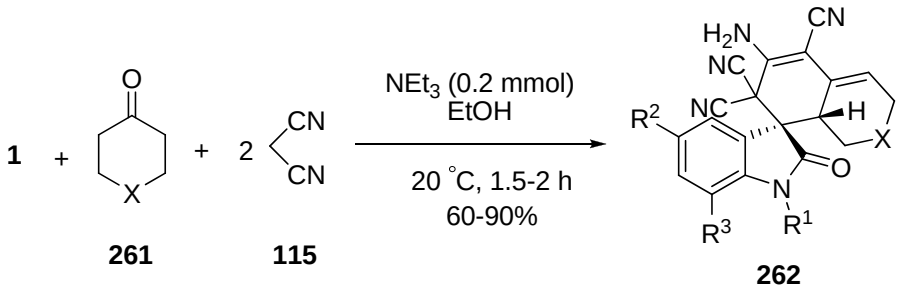
Scheme 102



110 **32** **259** **260**

Scheme 103

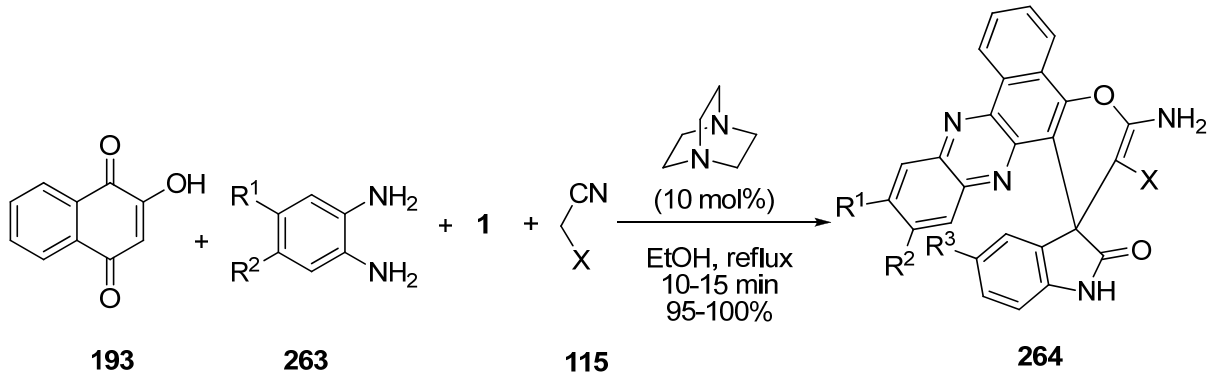
A new type of catalytic stereoselective cascade pseudo four-component reaction was discovered by Elinson and co-workers. In this study, reaction of isatins **1** and cyclic ketones **261** with two molecules of malononitrile **115** catalyzed by triethylamine at ambient temperature stereoselectively resulted in the formation of tetracyclic spirooxindoles **262** in 60-90% yields (Scheme 104).[189]



R^1= H, Et, Bn, Ac, CH_2CO_2Et
R^2= H, Me, Cl, Br
R^3= H, Me, Br
X= CH_2, CHMe, CHPh, NAc, NCO_2Et, O, S

Scheme 104

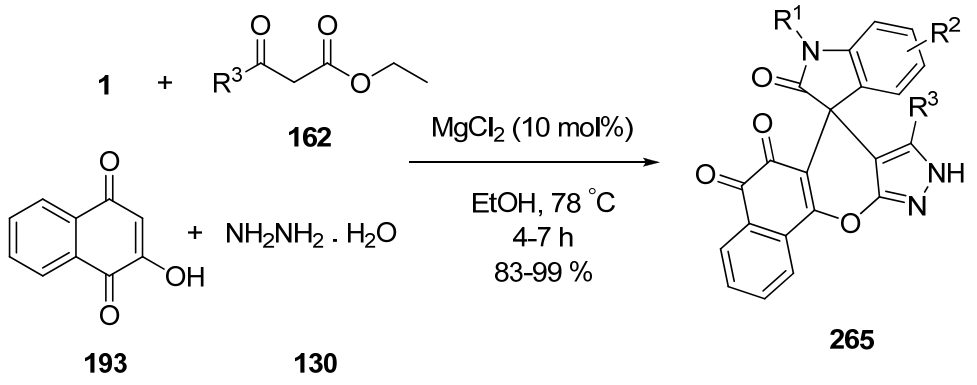
An efficient regio- and chemoselective method for the synthesis of novel 3-amino-2′-oxospiro[benzo[*c*]pyrano[3,2-*a*]phenazine-1,3′-indoline]-2-carbonitrile derivatives **264** has been developed via domino coupling of 2-hydroxynaphthalene-1,4-dione **193**, benzene-1,2-diamines **263**, isatins **1**, and malononitrile **115** in the presence of DABCO (Scheme 105).[190] The merit of this cascade formation of two C=N bonds/Knoevenagel condensation/Michael addition/cyclization sequence is highlighted by its high atom-economy, efficiency of producing five new bonds (two C–N, two C–C, and one C–O), and one stereocenter in a single operation.



R^1= H, Me
R^2= H, Me
R^3= H, Br, Cl
X= CN, CO_2Et

Scheme 105

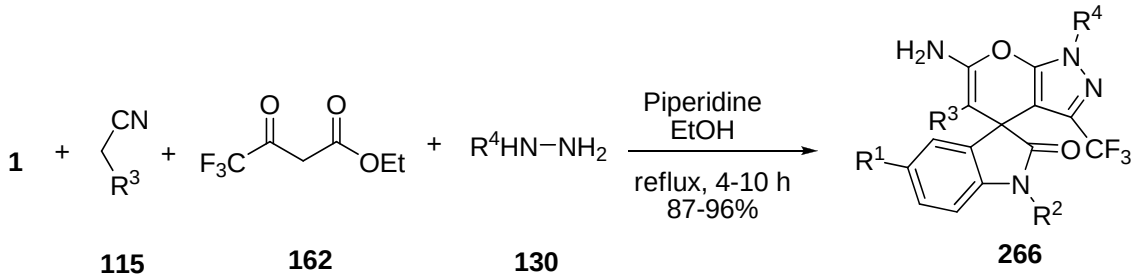
An efficient one-pot synthesis of 5*H*-spiro[benzo[7,8]chromeno[2,3-*c*]pyrazole-7,3′-indoline]-2′,5,6-(9*H*)-trione derivatives **265** via a four-component reaction of hydrazine hydrate **130**, β-keto esters **162**, isatins **1**, and 2-hydroxynaphthalene-1,4-dione **193** catalyzed by $MgCl_2$ in ethanol was reported by Song and co-workers (Scheme 106).[191]



Scheme 106

A reaction for the synthesis of trifluoromethylated spirocyclic [indole-3,4-pyrano[2,3-*c*]-pyrazole] derivatives **266** by reaction of isatins **1**, malononitrile, ethyl cyanoacetate or cyanoacetamide **115**, ethyl 4,4,4-trifluoroacetoacetate **162**, and hydrazine **130** in the presence of a catalytic amount of piperidine was described (Scheme 107).[192] Application of *L*-proline,[193] piperidine under ultrasound irradiation,[194] and propylamine functionalized nanoporous silica (SBA-Pr-NH_2)[195] was also investigated in this reaction. In similar studies, one-pot reaction of isatins, malononitrile (or ethyl cyanoacetate), hydrazine hydrate (or phenylhydrazine), and 1,3-dicarbonyl compounds was conducted under catalyst-free conditions,[196] in the presence of 4-dimethylaminopyridine (4-DMAP) catalyst,[197] or using uncapped SnO_2 quantum dots.[198] Replacing malononitrile with naphthylamines in this reaction has been also investigated.[199]

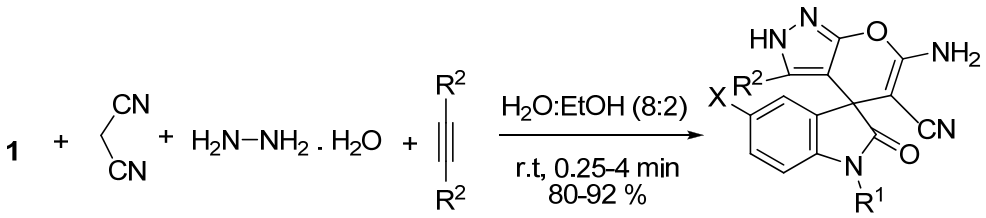
The spiro pyranopyrazole derivatives **267** were synthesized by the reaction of isatins **1**, malononitrile **115**, hydrazine hydrate **130**, and acetylenedicarboxylate derivatives **32** in catalyst-free condition. At first pyrazolones were *in situ* formed from acetylenedicarboxylates and hydrazine hydrate and then reacted with another two components (Scheme 108).[200] Et_3N was also investigated as catalyst in this reaction.[201-202]



115 **162** **130** **266**

R^1= H, Cl, Br, Me, NO_2
R^2= H, Me
R^3= CN, CO_2Et, $CONH_2$
R^4= H, Ph

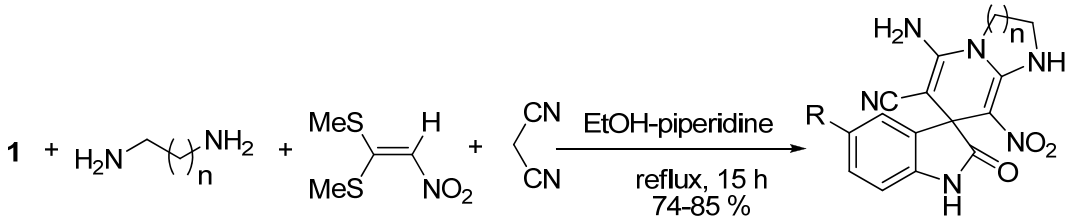
Scheme 107



115 **130** **32** **267**

X= H, Cl, I, Me, OMe
R^1= H, Me, Et
R^2= CO_2Me, CO_2Et

Scheme 108



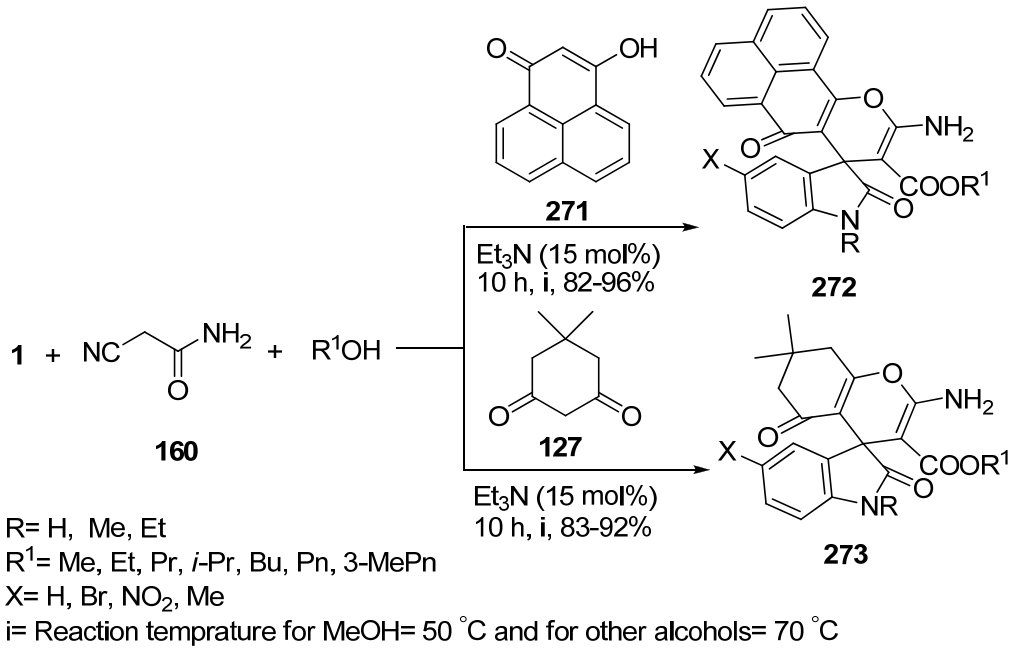
268 **269** **115** **270**

R= H, Br, NO_2
Diamine= 1,2-ethanediamine, 1,3-propanediamine,
1,4-butanediamine, 2,2-dimethyl-1,3-propanediamine

Scheme 109

Spirooxindole derivative containing 1,4-dihydropyridine-fused 1,3-diazaheterocycle fragments **270** were synthesized from the one-pot four-component reaction of 1,1-bis(methylthio)-2-nitroethylene **269**, 1,n-diamine **268**, isatin or its derivatives **1**, and malononitrile **115** (Scheme 109).[203]

A novel four-component reaction of isatins **1**, 2-cyanoacetamide **160**, cyclic 1,3-diketones **271** or **127** and alcohols was reported by Bazgir and co-workers (Scheme 110).[204] The reaction gave the unexpected spirooxindole ethyl carboxylates **272** and **273** in excellent yields and the spirooxindole carboxamide was not observed.

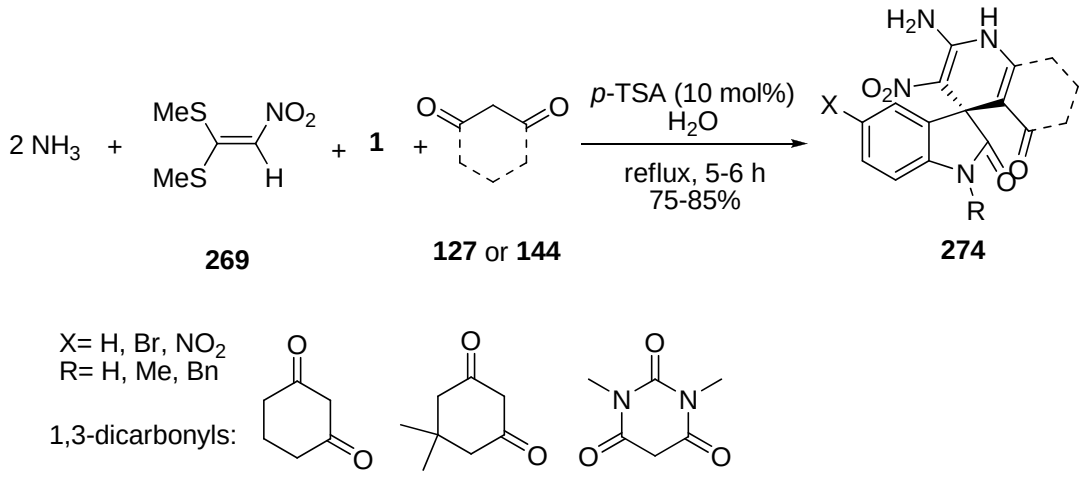


Scheme 110

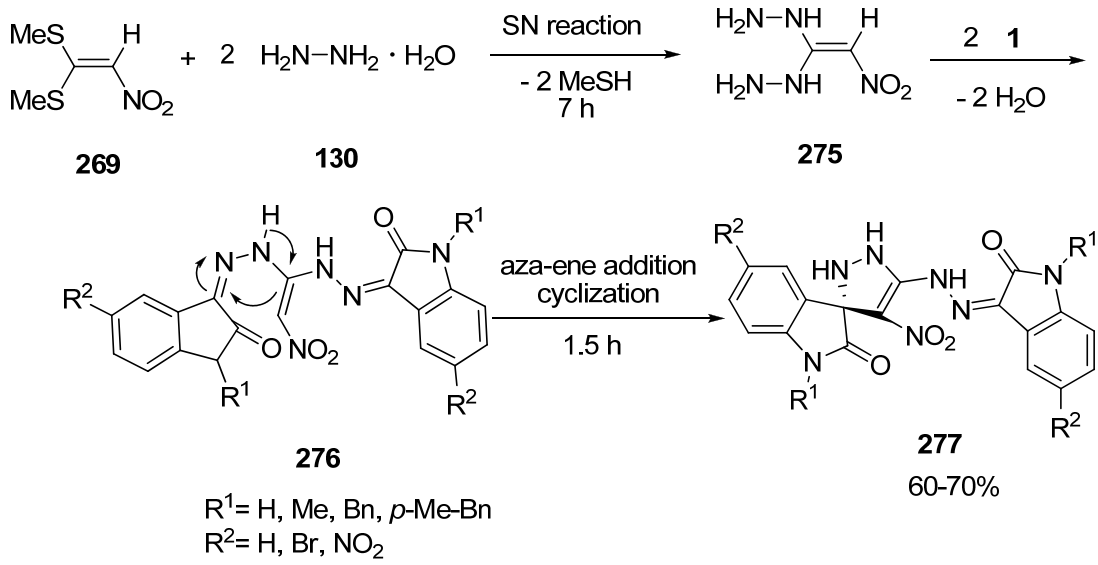
2.3. Synthesis involving five-component reactions of isatins

A five-component reaction between 1,1-bis(methylthio)-2-nitroethylene **269**, two equivalents of ammonia, isatin or its derivatives **1**, and 1,3-dicarbonyl compounds **127** or **144** in the presence of 10 mol% *p*-toluenesulfonic acid (*p*-TSA) generated spirooxindole heterocycles **274** (Scheme 111).[205]

A previously unknown class of highly substituted pyrazoline-spirooxindoles **277** was prepared by an uncatalyzed approach incorporating a domino nucleophilic substitution / condensation / aza-ene addition cyclization reaction sequence. 1,1-Dihydrazino-2-nitroethylene **275**, which was generated *in situ* from the nucleophilic substitution reaction of hydrazine **130** and 1,1-bis(methylthio)-2-nitroethylene **269**, was isolated and allowed to condense with isatins **1** followed by an intramolecular aza-ene addition cyclization (Scheme 112).[206] A pseudo-five-component reaction was also used in similar condition for the synthesis of the same products. This procedure avoided the isolation of the intermediate **275**.[207]



Scheme 111



Scheme 112

3. Conclusions

Isatins, as a type of unsymmetrical cyclic ketone with high reactivity, have proven to be important privileged building blocks in the synthesis of spiro-heterocycles with potential bioactivities. The most commonly used isatin derivatives were employed in design of the spirocyclic scaffolds. This review surveyed the last 4-year progress on the construction of spiro-fused heterocyclic scaffolds derived from isatin with typical examples.

Acknowledgements

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References

1. Guo, Y.; Chen, F. *Zhongcaoyao* **1986**, *17*. *Chem. Abstr.* **104**, 213068f.
2. Erdmann, O. L. *J. Prakt. Chem.* **1840**, *19*, 321.
3. Laurent, A. *Ann. Chim. Phys.* **1840**, *3*, 393.
4. Kumar, M.; Ramasamy, K.; Mani, V.; Mishra, R. K.; Majeed, A. B. A.; Clercq, E. D.; Narasimhan, B. *Arabian. J. Chem.* **2014**, *7*, 396. http://dx.doi.org/10.1016/j.arabjc.2012.12.005
5. Havrylyuk, D.; Zimenkovsky, B.; Vasylenko, O.; Gzella, A.; Lesyk, R. *J. Med. Chem.* **2012**, *55*, 8630. http://dx.doi.org/10.1021/jm300789g
6. Kumar, S. B.; Ravinder, M.; Kishore, G.; Rao, V. J.; Yogeeswari, P.; Sriram, D. *Med. Chem. Res.* **2014**, *23*, 1934. http://dx.doi.org/10.1007/s00044-013-0787-x
7. Han, K.; Zhou, Y.; Liu, F.; Guo, Q.; Wang, P.; Yang, Y.; Song, B.; Liu, W.; Yao, Q.; Teng, Y.; Yu, P. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 591. http://dx.doi.org/10.1016/j.bmcl.2013.12.001
8. Liang, C.; Xia, J.; Lei, D.; Li, X.; Yao, Q.; Gao, J. *Eur. J. Med. Chem.* **2014**, *74*, 742. http://dx.doi.org/10.1016/j.ejmech.2013.04.040
9. Kumar, K.; S. Carrere-Kremer; Kremer, L.; Gueerardel, Y.; Biot, C.; Kumar, V. *Organometallics* **2013**, *32*, 5713. http://dx.doi.org/10.1021/om301157z
10. Mondal, P.; Jana, S.; Balaji, A.; Ramakrishna, R.; Kanthal, L. *J. Young Pharm.* **2013**, *4*, 38. http://dx.doi.org/10.4103/0975-1483.93574
11. Raj, R.; Singh, P.; Singh, P.; Gut, J.; Rosenthal, P. J.; Kumar, V. *Eur. J. Med. Chem.* **2013**, *62*, 590. http://dx.doi.org/10.1016/j.ejmech.2013.01.032
12. Paul, B. K.; Ray, D.; Guchhait, N. *Phys. Chem. Chem. Phys.* **2013**, *15*, 1275. http://dx.doi.org/10.1039/C2CP42539D
13. Kiran, G.; Maneshwar, T.; Rajeshwar, Y.; Sarangapani, M. *J. Chem.* **2013**, *2013*, 1. http://dx.doi.org/10.1155/2013/192039
14. Yeung, B. K. S.; Zou, B.; Rottmann, M.; Lakshminarayana, S. B.; Ang, S. H.; Leong, S. Y.; Tan, J.; Wong, J.; Keller-Maerki, S.; Fischli, C.; Goh, A.; Schmitt, E. K.; Krastel, P.; Francotte, E.; Kuhen, K.; Plouffe, D.; Henson, K.; Wagner, T.; Winzeler, E. A.; Petersen, F.; Brun, R.; Dartois, V.; Diagana, T. T.; Keller, T. H. *J. Med. Chem.* **2010**, *53*, 5155. http://dx.doi.org/10.1021/jm100410f

15. Ermut, G.; Karal, N.; Cetin, I.; Topcul, M.; Birteksoz, S. *Marmara Pharm. J.* **2013**, *17*, 147. http://dx.doi.org/10.12991/201317383
16. Song, Y.; Fu, X.; Qi, Y. EP Patent 2011/2573072 A1, 2011.
17. Jarrahpour, A. A.; Khalili, D. *Molbank* **2005**, *4*, M437. http://dx.doi.org/10.3390/M437
18. Basabe-Desmonts, L.; Reinhoudt, D. N.; Crego-Calama, M. *Chem. Soc. Rev.* **2007**, *36*, 993. http://dx.doi.org/10.1039/b609548h
19. Ding, K.; Lu, Y.; Nikolovska-Coleska, Z.; Wang, G.; Qiu, S.; Shangary, S.; Gao, W.; Qin, D.; Stuckey, J.; Krajewski, K.; Roller, P. P.; Wang, S. *J. Med. Chem.* **2006**, *49*, 3432. http://dx.doi.org/10.1021/jm051122a
20. Sumpter, W. C. *Chem. Rev.* **1944**, *34*, 393. http://dx.doi.org/10.1021/cr60109a003
21. Popp, F. D. *Adv. Heterocycl. Chem.* **1975**, *18*, 1. http://dx.doi.org/10.1016/S0065-2725(08)60127-0
22. da Silva, J. F. M.; Garden, S. J.; Pinto, A. C. J. *J. Braz. Chem. Soc.* **2001**, *12*, 273. http://dx.doi.org/10.1590/S0103-50532001000300002
23. Ball-Jones, N. R.; Badillo, J. J.; Franz, A. K. *Org. Biomol. Chem.* **2012**, *10*, 5165. http://dx.doi.org/10.1039/c2ob25184a
24. Floresa, M.; Pena, J.; Garcia-García, P.; Garrido, N. M.; Díez, D. *Curr. Org. Chem.* **2013**, *17*, 1957. http://dx.doi.org/10.2174/13852728113179990092
25. Liu, Y.; Wang, H.; Wan, J. *Asian J. Org. Chem.* **2013**, *2*, 374. http://dx.doi.org/10.1002/ajoc.201200180
26. Pakravan, P.; Kashanian, S.; Khodaei, M.; Harding, F. J. *Pharm. Rep.* **2013**, *65*, 313. http://dx.doi.org/10.1016/S1734-1140(13)71007-7
27. Singh, G. S.; Desta, Z. Y. *Chem. Rev.* **2012**, *112*, 6104. http://dx.doi.org/10.1021/cr300135y
28. Xia, M.; Ma, R.-Z. *J. Heterocycl. Chem.* **2014**, *51*, 539. http://dx.doi.org/10.1002/jhet.1114
29. Borad, M. A.; Bhoi, M. N.; Prajapati, N. P.; Patel, H. D. *Synth. Commun.* **2014**, *44*, 897. http://dx.doi.org/10.1080/00397911.2013.843196
30. Borad, M. A.; Bhoi, M. N.; Prajapati, N. P.; Patel, H. D. *Synth. Commun.* **2014**, *44*, 1043. http://dx.doi.org/10.1080/00397911.2013.858361
31. Khanna, P.; Panda, S. S.; Khanna, L.; Jain, S. C. *Mini-Rev. Org. Chem.* **2014**, *11*, 73. http://dx.doi.org/10.2174/1570193X1101140402101831
32. Lashgari, N.; Mohammadi Ziarani, G. *Arkivoc* **2012**, *i*, 277. http://dx.doi.org/10.3998/ark.5550190.0013.108
33. Sunderhaus, J. D.; Martin, S. F. *Chem. Eur. J.* **2009**, *15*, 1300. http://dx.doi.org/10.1002/chem.200802140

34. Guillena, G.; Ramon, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2007**, *18*, 693. http://dx.doi.org/10.1016/j.tetasy.2007.03.002
35. Liu, H.; Dou, G.; Shi, D. *J. Comb. Chem.* **2010**, *12*, 633. http://dx.doi.org/10.1021/cc100035q
36. Litvinov, Y. M.; Shestopalov, A. A.; Rodinovskaya, L. A.; Shestopaqlov, A. M. *J.Comb. Chem.* **2009**, *11*, 914. http://dx.doi.org/10.1021/cc900076j
37. Rajanarendar, E.; Ramakrishna, S.; Reddy, K. G.; Nagaraju, D.; Reddy, Y. N. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 3954. http://dx.doi.org/10.1016/j.bmcl.2013.04.053
38. Pavlovskaya, T. L.; Yaremenko, F. G.; Lipson, V. V.; Shishkina, S. V.; Shishkin, O. V.; Musatov, V. I.; Karpenko, A. S. *Beilstein J. Org. Chem.* **2014**, *10*, 117. http://dx.doi.org/10.3762/bjoc.10.8
39. Kaur, A.; Singh, B.; Vyas, B.; Silakari, O. *Eur. J. Med. Chem.* **2014**, *79*, 282. http://dx.doi.org/10.1016/j.ejmech.2014.04.022
40. Sarrafi, Y.; Hamzehloueian, M.; Alimohammadi, K.; Yeganegi, S. *J. Mol. Struct.* **2012**, *1030*, 168. http://dx.doi.org/10.1016/j.molstruc.2012.04.013
41. Huang, H.; Xu, Y.; Mao, F.; Zhu, J.; Jiang, H.; Li, J. *Tetrahedron Lett.* **2015**, *56*, 586. http://dx.doi.org/10.1016/j.tetlet.2014.12.011
42. Liu, J.; Sun, H.; Liu, X.; Ouyang, L.; Kang, T.; Xie, Y.; Wang, X. *Tetrahedron Lett.* **2012**, *53*, 2336. http://dx.doi.org/10.1016/j.tetlet.2012.02.099
43. Sapnakumari, M.; Narayana, B.; Samshuddin, S.; Sarojini, B. K. *Molbank* **2013**, *M802*, 1. http://dx.doi.org/10.3390/M802
44. Chen, G.; Yang, J.; Gao, S.; Zhang, Y.; X-J., H. *Res. Chem. Intermed.* **2013**, *39*, 1245. http://dx.doi.org/10.1007/s11164-012-0680-0
45. He, J.; Ouyang, G.; Yuan, Z.; Tong, R.; Shi, J.; Ouyang, L. *Molecules* **2013**, *18*, 5142. http://dx.doi.org/10.3390/molecules18055142
46. Arun, Y.; Saranraj, K.; Balachandran, C.; Perumal, P. T. *Eur. J. Med. Chem.* **2014**, *74*, 50. http://dx.doi.org/10.1016/j.ejmech.2013.12.027
47. Singh, S. N.; Regati, S.; Paul, A. K.; Layek, M.; Jayaprakash, S.; Reddy, K. V.; Deora, G. S.; Mukherjee, S.; Pal, M. *Tetrahedron Lett.* **2013**, *54*, 5448. http://dx.doi.org/10.1016/j.tetlet.2013.07.126
48. Yang, F.; Sun, J.; Gao, H.; Yan, C. G. *RSC Adv.* **2015**, *5*, 32786. http://dx.doi.org/10.1039/c5ra04102c
49. Shi, F.; Zhu, R.-Y.; Liang, X.; Tua, S.-J. *Adv. Synth. Catal.* **2013**, *355*, 2447. http://dx.doi.org/10.1002/adsc.201300366
50. Tan, W.; Zhu, X.-T.; Zhang, S.; Xing, G.-J.; Zhu, R.-Y.; Shi, F. *RSC Adv.* **2013**, *3*, 10875. http://dx.doi.org/10.1039/c3ra40874d

51. Shi, F.; Tao, Z.-L.; Luo, S.-W.; Tu, S.-J.; Gong, L.-Z. *Chem. Eur. J.* **2012**, *18*, 6885. http://dx.doi.org/10.1002/chem.201200358
52. Dai, W.; Jiang, X.-L.; Wu, Q.; Shi, F.; Tu, S.-J. *J. Org. Chem*. **2015**, *80*, 5737. http://dx.doi.org/10.1021/acs.joc.5b00708
53. Wang, C.-S.; Zhu, R.-Y.; Zheng, J.; Shi, F.; Tu, S.-J. *J. Org. Chem.* **2015**, *80*, 512. http://dx.doi.org/10.1021/jo502516e
54. Huang, Z.; Zhao, Q.; Chen, G.; Wang, H.; Lin, W.; Xu, L.; Liu, H.; Wang, J.; Shi, D.; Wang, Y. *Molecules* **2012**, *17*, 12704. http://dx.doi.org/10.3390/molecules171112704
55. Barman, P. D.; Goyal, D.; Daravath, U. K.; Sanyal, I.; Mandal, S. B.; Banerjee, A. K. *Tetrahedron Lett.* **2013**, *54*, 3801. http://dx.doi.org/10.1016/j.tetlet.2013.05.027
56. Dandia, A.; Jain, A. K.; Laxkar, A. K. *RSC Adv.* **2013**, *3*, 8422. http://dx.doi.org/10.1039/c3ra00170a
57. Kia, Y.; Osman, H.; Suresh Kumar, R.; Murugaiyah, V.; Perumal, A. B. S.; Wahab, H. A.; Bing, C. S. *Bioorg. Med. Chem.* **2013**, *21*, 1696. http://dx.doi.org/10.1016/j.bmc.2013.01.066
58. Kia, Y.; Osman, H.; Suresh Kumar, R.; Basiri, A.; Murugaiyah, V. *Bioorg. Med. Chem.* **2014**, *22*, 1318. http://dx.doi.org/10.1016/j.bmc.2014.01.002
59. Kia, Y.; Osman, H.; Suresh Kumar, R.; Basiri, A.; Murugaiyah, V. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 1815. http://dx.doi.org/10.1016/j.bmcl.2014.02.019
60. Yan, J. *J. Chem. Res.* **2014**, *38*, 50. http://dx.doi.org/10.3184/174751914X13865875476588
61. Dandia, A.; Jain, A. K.; Laxkar, A. K.; Bhati, D. S. *Tetrahedron Lett.* **2013**, *54*, 3180. http://dx.doi.org/10.1016/j.tetlet.2013.04.033
62. Arun, Y.; Bhaskar, G.; Balachandran, C.; Ignacimuthu, S.; Perumal, P. T. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 1839. http://dx.doi.org/10.1016/j.bmcl.2013.01.023
63. Bhaskar, G.; Arun, Y.; Balachandran, C.; Saikumar, C.; Perumal, P. T. *Eur. J. Med. Chem.* **2012**, *51*, 79. http://dx.doi.org/10.1016/j.ejmech.2012.02.024
64. Dandia, A.; Jain, A. K.; Laxkar, A. K. *Tetrahedron Lett.* **2013**, *54*, 3929. http://dx.doi.org/10.1016/j.tetlet.2013.05.035
65. Jain, R.; Sharma, K.; Kumar, D. *Tetrahedron Lett.* **2012**, *53*, 1993. http://dx.doi.org/10.1016/j.tetlet.2012.02.029
66. Yang, J.-M.; Hu, Y.; Li, Q.; Yu, F.; Cao, J.; Fang, D.; Huang, Z.-B.; Shi, D.-Q. *ACS Comb. Sci.* **2014**, *16*, 139. http://dx.doi.org/10.1021/co400096c

67. Saravanan, P.; Pushparaj, S.; Raghunathan, R. *Tetrahedron Lett.* **2013**, *54*, 3449. http://dx.doi.org/10.1016/j.tetlet.2013.04.091
68. Bakthadoss, M.; Kannan, D.; Sivakumar, G. *Synthesis* **2012**, *44*, 793. http://dx.doi.org/10.1055/s-0031-1289704
69. Chen, G.; Yang, J.; Gao, S.; He, H.; Li, S.; Di, Y.; Chang, Y.; Lu, Y.; Hao, X. *Mol. Divers.* **2012**, *16*, 151. http://dx.doi.org/10.1007/s11030-011-9342-1
70. Chen, G.; Miao, Y.-Q.; Zhou, R.; Zhang, L.; Zhang, J.; Hao, X.-J. *Res. Chem. Intermed.* **2013**, *39*, 2445. http://dx.doi.org/10.1007/s11164-012-0770-z
71. Sankaran, M.; Uvarani, C.; Chandraprakash, K.; Lekshmi, S. U.; Suparna, S.; Platts, J.; Mohan, P. S. *Mol. Divers.* **2014**, *18*, 269. http://dx.doi.org/10.1007/s11030-013-9498-y
72. Sarrafi, Y.; Sadatshahabi, M.; Hamzehloueian, M.; Alimohammadi, K.; Tajbakhsh, M. *Synthesis* **2013**, *45*, 2294. http://dx.doi.org/10.1055/s-0033-1338492
73. Alimohammadi, K.; Sarrafi, Y.; Rajabpour, B. *C. R. Chimie* **2014**, *17*, 156. http://dx.doi.org/10.1016/j.crci.2013.06.003
74. Hazra, A.; Bharitkar, Y. P.; Chakraborty, D.; Mondal, S. K.; Singal, N.; Mondal, S.; Maity, A.; Paira, R.; Banerjee, S.; Mondal, N. B. *ACS Comb. Sci.* **2012**, *15*, 41. http://dx.doi.org/10.1021/co3001154
75. Wu, G.; Ouyang, L.; Liu, J.; Zeng, S.; Huang, W.; Han, B.; Wu, F.; He, G.; Xiang, M. *Mol. Divers.* **2013**, *17*, 271. http://dx.doi.org/10.1007/s11030-013-9432-3
76. Taghizadeh, M. J.; Arvinnezhad, H.; Samadi, S.; Jadidi, K.; Javidan, A.; Notash, B. *Tetrahedron Lett.* **2012**, *53*, 5148. http://dx.doi.org/10.1002/chin.201251110
77. Kathirvelan, D.; Haribabu, J.; Reddy, B. S. R.; Balachandran, C.; Duraipandiyan, V. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 389. http://dx.doi.org/10.1016/j.bmcl.2014.10.099
78. Javidan, A.; Taghizadeh, M. J.; Jadidi, K.; Notash, B. *Monatsh. Chem.* **2014**, *145*, 341. http://dx.doi.org/10.1007/s00706-013-1089-1
79. Dandia, A.; Jain, A. K.; Laxkar, A. K.; Bhati, D. S. *Tetrahedron* **2013**, *69*, 2062. http://dx.doi.org/10.1016/j.tet.2012.12.021
80. Naga Siva Rao, J.; Raghunathan, R. *Tetrahedron Lett.* **2012**, *53*, 854. http://dx.doi.org/10.1016/j.tetlet.2011.12.025
81. Kumar, A.; Gupta, G.; Srivastava, S.; Kumar Bishnoi, A.; Saxena, R.; Kant, R.; Khanna, R. S.; Maulik, P. R.; Dwivedi, A. *RSC Adv.* **2013**, *3*, 4731. http://dx.doi.org/10.1039/c3ra21595d
82. Ameta, K. L.; Kumar, B.; Rathore, N. S. *Lett. Org. Chem.* **2013**, *10*, 245.

http://dx.doi.org/10.2174/1570178611310040004
83. Han, Y.; Wu, Q.; Sun, J.; Yan, C.-G. *Tetrahedron* **2012**, *68*, 8539. http://dx.doi.org/10.1016/j.tet.2012.08.030
84. Sarkar, R.; Mukhopadhyay, C. *Tetrahedron Lett.* **2013**, *54*, 3706. http://dx.doi.org/10.1016/j.tetlet.2013.05.017
85. Kiruthika, S. E.; Amritha, R.; Perumal, P. T. *Tetrahedron Lett.* **2012**, *53*, 3268. http://dx.doi.org/10.1016/j.tetlet.2012.04.047
86. Sun, Y.; Sun, J.; Yan, C. *Tetrahedron Lett.* **2012**, *53*, 3647. http://dx.doi.org/10.1016/j.tetlet.2012.05.023
87. Karamthulla, S.; Pal, S.; Nasim Khan, M.; Choudhury, L. H. *RSC Adv.* **2013**, *3*, 15576. http://dx.doi.org/10.1039/c3ra43289k
88. Chen, H.; Shi, D.-Q. *J. Heterocycl. Chem.* **2013**, *50*, 56. http://dx.doi.org/10.1002/jhet.993
89. Wang, J.; Bai, X.; Xu, C.; Wang, Y.; Lin, W.; Zou, Y.; Shi, D. *Molecules* **2012**, *17*, 8674. http://dx.doi.org/10.3390/molecules17078674
90. Rajasekaran, T.; Karthik, G.; Sridhar, B.; Subba Reddy, B. V. *Org. Lett.* **2013**, *15*, 1512. http://dx.doi.org/10.1021/ol400287q
91. Salahi, F.; Taghizadeh, M. J.; Arvinnezhad, H.; Moemeni, M.; Jadidi, K.; Notash, B. *Tetrahedron Lett.* **2014**, *55*, 1515. http://dx.doi.org/10.1016/j.tetlet.2013.11.097
92. Chandam, D. R.; Mulik, A. G.; Patil, P. P.; Jagdale, S. D.; Patil, D. R.; Deshmukh, M. B. *Res. Chem. Intermed.* **2015**, *41*, 761. http://dx.doi.org/10.1007/s11164-013-1226-9
93. Singh, S.; Saquib, M.; Singh, S. B.; Singh, M.; Singh, J. *RSC Adv.* **2015**, *5*, 45152. http://dx.doi.org/10.1039/c5ra02794b
94. Hamama, W. S.; Gouda, M. A.; Badr, M. H.; Zoorob, H. H. *J. Heterocycl. Chem.* **2013**, *50*, 787. http://dx.doi.org/10.1002/jhet.1569
95. Jain, R.; Sharma, K.; Kumar, D. *Helv. Chim. Acta* **2013**, *96*, 414. http://dx.doi.org/10.1002/hlca.201200168
96. Moghaddam, F. M.; Khodabakhshi, M. R.; Ghahremannejad, Z.; Koushki Foroushani, B.; Weng Ng, S. *Tetrahedron Lett.* **2013**, *54*, 2520. http://dx.doi.org/10.1016/j.tetlet.2013.03.023
97. Shi, F.; Xing, G.-J.; Zhu, R.-Y.; Tan, W.; Tu, S. *Org. Lett.* **2012**, *15*, 128. http://dx.doi.org/10.1021/ol303154k
98. Shi, F.; Zhu, R. Y.; Dai, W.; Wang, C. S.; Tu, S. J. *Chem. Eur. J.* **2014**, *20*, 2597. http://dx.doi.org/10.1002/chem.201304187
99. Dai, W.; Lu, H.; Li, X.; Shi, F.; Tu, S.-J. *Chem. Eur. J.* **2014**, *20*, 11382. http://dx.doi.org/10.1002/chem.201402485

100. Shirvan, S. A.; Ghahremanzadeh, R.; Moghaddam, M. M.; Bazgir, A.; Zarnani, A. H.; Akhondi, M. M. *J. Heterocycl. Chem.* **2012**, *49*, 951. http://dx.doi.org/10.1002/jhet.898
101. Kamal, A.; Babu, K. S.; Vardhan, M. V. P. S. V.; Hussaini, S. M. A.; Mahesh, R.; Shaik, S. P.; Alarifi, A. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 2199. http://dx.doi.org/10.1016/j.bmcl.2015.03.054
102. De, K.; Bhaumik, A.; Banerjee, B.; Mukhopadhyay, C. *Tetrahedron Lett.* **2015**, *56*, 1614. http://dx.doi.org/10.1016/j.tetlet.2015.01.163
103. Rahmati, A.; Khalesi, Z. *Tetrahedron* **2012**, *68*, 8472. http://dx.doi.org/10.1016/j.tet.2012.07.073
104. Yuvaraj, P.; Manivannan, K.; Reddy, B. S. R. *Tetrahedron Lett.* **2015**, *56*, 78. http://dx.doi.org/10.1016/j.tetlet.2014.11.001
105. Mohammadi Ziarani, G.; Faramarzi, S.; Lashgari, N.; Badiei, A. R. *J. Iran. Chem. Soc.* **2014**, *11*, 701. http://dx.doi.org/10.1007/s13738-013-0342-1
106. Dandia, A.; Laxkar, A. k.; Singh, R. *Tetrahedron Lett.* **2012**, *53*, 3012. http://dx.doi.org/10.1016/j.tetlet.2012.03.136
107. Rahmati, A.; Kenarkoohi, T.; Khavasi, H. R. *ACS Comb. Sci.* **2012**, *14*, 657. http://dx.doi.org/10.1021/co300047j
108. Esmaeili, A. A.; Amini-Ghalandarabad, S.; Mesbah, F.; Tasmimi, M.; Izadyar, M.; Fakhari, A. R.; Salimi, A. R. *Tetrahedron* **2015**, *71*, 2458. http://dx.doi.org/10.1016/j.tet.2015.01.055
109. Yang, H. B.; Guan, X.-Y.; Wei, Y.; Shi, M. *Eur. J. Org. Chem.* **2012**, *2012*, 2792. http://dx.doi.org/10.1002/ejoc.201200185
110. Liang, Y. R.; Chen, X. Y.; Wu, Q.; Lin, X. F. *Tetrahedron* **2015**, *71*, 616. http://dx.doi.org/10.1016/j.tet.2014.12.027
111. Yu, F.; Huang, R.; Ni, H.; Fan, J.; Yan, S.; Lin, J. *Green Chem.* **2013**, *15*, 453. http://dx.doi.org/10.1039/c2gc36552a
112. Alizadeh, A.; Moafi, L. *Helv. Chim. Acta* **2015**, *98*, 546. http://dx.doi.org/10.1002/hlca.201400263
113. Safaei, S.; Mohammadpoor-Baltork, I.; Khosropour, A. R.; Moghadam, M.; Tangestaninejad, S.; Mirkhani, V.; Khavasi, H. R. *ACS Comb. Sci.* **2013**, *15*, 141. http://dx.doi.org/10.1021/co3001204
114. Iarosnko, V. O.; Dudkin, S.; Sosnovskikh, V. Y.; Villinger, A.; Langer, P. *Synthesis* **2013**, *45*, 971. http://dx.doi.org/10.1055/s-0032-1318273
115. Vilches-Herrera, M.; Spannenberg, A.; Langer, P.; Iaroshenko, V. O. *Tetrahedron* **2013**, *69*, 5955. http://dx.doi.org/10.1016/j.tet.2013.04.115
116. Naeimi, H.; Rashid, Z.; Zarnani, A. H.; Ghahremanzadeh, R. *New J. Chem.* **2014**, *38*, 348.

http://dx.doi.org/10.1039/C3NJ00940H
117. Rad-Moghadam, K.; Youseftabar-Miri, L. *J. Fluorine Chem.* **2012**, *135*, 213. http://dx.doi.org/10.1016/j.jfluchem.2011.11.007
118. Rahmati, A.; Eskandari-Vashareh, M. *J. Chem. Sci.* **2014**, *126*, 169. http://dx.doi.org/10.1007/s12039-013-0552-1
119. Heravi, M. M.; Zakeri, M.; Moharami, A. *J. Chem. Sci.* **2012**, *124*, 865. http://dx.doi.org/10.1007/s12039-012-0284-7
120. Mondal, A.; Mukhopadhyay, C. *J. Am. Chem. Soc.* **2015**, *17*, 404. http://dx.doi.org/10.1021/acscombsci.5b00038
121. Karmakar, R.; Kayal, U.; Bhattacharya, B.; Maiti, G. *Tetrahedron Lett.* **2014**, *55*, 1370. http://dx.doi.org/10.1016/j.tetlet.2014.01.028
122. Dabiri, M.; Noroozi Tisseh, Z.; Bazgir, A. *Monatsh. Chem.* **2012**, *143*, 139. http://dx.doi.org/10.1007/s00706-011-0571-x
123. Zhao, H. W.; Li, B.; Tian, T.; Meng, W.; Yang, Z.; Song, X. Q.; Chen, X. Q.; Pang, H. L. *Eur. J. Org. Chem.* **2015**, 3320. http://dx.doi.org/10.1002/ejoc.201500152
124. Ghahremanzadeh, R.; Rashid, Z.; Zarnani, A. H.; Naeimi, H. *Appl. Catal., A* **2013**, *467*, 270. http://dx.doi.org/10.1016/j.apcata.2013.07.029
125. Ghahremanzadeh, R.; Rashid, Z.; Zarnani, A. H.; Naeimi, H. *Ultrason. Sonochem.* **2014**, *21*, 1451. http://dx.doi.org/10.1016/j.ultsonch.2014.02.014
126. Periyaraja, S.; Shanmugam, P.; Mandal, A. B.; Senthil Kumar, T.; Ramamurthy, P. *Tetrahedron* **2013**, *69*, 2891. http://dx.doi.org/10.1016/j.tet.2013.02.037
127. Gao, H.; Sun, J.; Yan, C. G. *Synthesis* **2014**, *46*, 489. http://dx.doi.org/10.1055/s-0033-1340459
128. Meshram, G.; Wagh, P.; Deshpande, S.; Amratlal, V. *Lett. Org. Chem.* **2013**, *10*, 445. http://dx.doi.org/10.2174/1570178611310060006
129. Baghernejad, B.; Khorshidi, M. *Bull. Chem. Soc. Ethiop.* **2013**, *27*, 309. http://dx.doi.org/10.4314/bcse.v27i2.17
130. Xie, X.; Peng, C.; He, G.; Leng, H.-J.; Wang, B.; Huang, W.; Han, B. *Chem. Commun.* **2012**, *48*, 10487. http://dx.doi.org/10.1039/c2cc36011j
131. Yang, H.-B.; Zhao, Y.-Z.; Sang, R.; Tang, X.-Y.; Shi, M. *Tetrahedron* **2013**, *69*, 9205. http://dx.doi.org/10.1016/j.tet.2013.08.071
132. Yang, H.; Takrouri, K.; Chorev, M. *Curr. Org. Chem.* **2012**, *16*, 1581. http://dx.doi.org/10.2174/138527212800840937
133. Mohammadi Ziarani, G.; Lashgari, N.; Badiei, A. *Sci. Iran. C* **2013**, *20*, 580. http://dx.doi.org/10.1016/j.scient.2012.11.018

134. Rahmati, A.; Rezayan, A.; Alizadeh, M.; Nikbakht, A. *J. Iran. Chem. Soc.* **2013**, *10*, 521. http://dx.doi.org/10.1007/s13738-012-0187-z
135. Deng, J.; Mo, L. P.; Zhao, F. Y.; Zhang, Z. H.; Liu, S. X. *ACS Comb. Sci.* **2012**, *14*, 335. http://dx.doi.org/10.1021/co3000264
136. Mirhosseini Moghaddam, M.; Bazgir, A.; Akhondi, M. M.; Ghahremanzadeh, R. *Chin. J. Chem.* **2012**, *30*, 709. http://dx.doi.org/10.1002/cjoc.201280014
137. Guo, R. Y.; Wang, P.; Wang, G. D.; Mo, L. P.; Zhang, Z. H. *Tetrahedron* **2013**, *69*, 2056. http://dx.doi.org/10.1016/j.tet.2012.12.081
138. Mohammadi Ziarani, G.; Lashgari, N.; Faramarzi, S.; Badiei, A. *Acta Chim. Slov.* **2014**, *61*, 574.
139. Asadi, S.; Mohammadi Ziarani, G.; Rahimifard, M.; Abolhassani Soorki, A. *Res. Chem. Intermed.* **2015**, *41*, 6219. http://dx.doi.org/10.1007/s11164-014-1734-2
140. Paul, S.; Das, A. R. *Tetrahedron Lett.* **2013**, *54*, 1149. http://dx.doi.org/10.1016/j.tetlet.2012.12.079
141. Poomathi, N.; Mayakrishnan, S.; Muralidharan, D.; Srinivasan, R.; Perumal, P. T. *Green Chem.* **2015**, *17*, 3362. http://dx.doi.org/10.1039/c5gc00006h
142. Kidwai, M.; Jahan, A.; Kumar Mishra, N. *Appl. Catal., A* **2012**, *425- 426*, 35. http://dx.doi.org/10.1016/j.apcata.2012.02.043
143. Hasaninejad, A.; Golzar, N.; Beyrati, M.; Zare, A.; Doroodmand, M. *J. Mol. Catal. A: Chem.* **2013**, *372*, 137. http://dx.doi.org/10.1016/j.molcata.2013.02.022
144. Saluja, P.; Aggarwal, K.; Khurana, J. M. *Synth. Commun.* **2013**, *43*, 3239. http://dx.doi.org/10.1080/00397911.2012.760130
145. Wu, C.; Shen, R.; Chen, J.; Hu, C. *Bull. Korean Chem. Soc.* **2013**, *34*, 2431. http://dx.doi.org/10.5012/bkcs.2013.34.8.2431
146. Mobinkhaledi, A.; Jabbarpour, M. *J. Chem. Soc. Pak.* **2013**, *35*, 1211.
147. Jalili-Baleh, L.; Mohammadi, N.; Khoobi, M.; Ma'mani, L.; Foroumadi, A.; Shafiee, A. *Helv. Chim. Acta* **2013**, *96*, 1601. http://dx.doi.org/10.1002/hlca.201200516
148. Mohammadi Ziarani, G.; Lashgari, N.; Badiei, A.; Shakiba, M. *Chemija* **2013**, *24*, 142.
149. Lashgari, N.; Mohammadi Ziarani, G.; Badiei, A.; Zarezadeh-Mehrizi, M. *J. Heterocycl. Chem.* **2014**, *51*, 1628. http://dx.doi.org/10.1002/jhet.1746
150. Mohammadi Ziarani, G.; Badiei, A.; Mousavi, S.; Lashgari, N.; Shahbazi, A. *Chin. J. Catal.* **2012**, *33*, 1832. http://dx.doi.org/10.1016/S1872-2067(11)60456-7

151. Mohammadi Ziarani, G.; Hosseini Mohtasham, N.; Lashgari, N.; Badiei, A.; Amanlou, M.; Bazl, R. *J. NanoStruct.* **2013**, *2*, 489.
152. Baharfar, R.; Azimi, R. *Synth. Commun.* **2014**, *44*, 89. http://dx.doi.org/10.1080/00397911.2013.789527
153. Safaei, H. R.; Shekouhy, M.; Shirinfeshan, A.; Rahmanpur, S. *Mol. Divers.* **2012**, *16*, 669. http://dx.doi.org/10.1007/s11030-012-9392-z
154. Khurana, J. M.; Yadav, S. *Aust. J. Chem.* **2012**, *65*, 314. http://dx.doi.org/10.1071/CH11444
155. Riyaz, S.; Naidu, A.; Dubey, P. K. *Lett. Org. Chem.* **2012**, *9*, 101. http://dx.doi.org/10.2174/157017812800221771
156. Sarrafi, Y.; Mehrasbi, E.; Vahid, A.; Tajbakhsh, M. *Chin. J. Catal.* **2012**, *33*, 1486. http://dx.doi.org/10.1016/S1872-2067(11)60423-3
157. Karmakar, B.; Nayak, A.; Banerji, J. *Tetrahedron Lett.* **2012**, *53*, 5004. http://dx.doi.org/10.1016/j.tetlet.2012.07.030
158. Rao, B. M.; Reddy, G. N.; Reddy, T. V.; Prabhavathi Devi, B. L. A.; Prasad, R. B. N.; Yadav, J. S.; Subba Reddy, B. V. *Tetrahedron Lett.* **2013**, *54*, 2466. http://dx.doi.org/10.1016/j.tetlet.2013.02.089
159. He, T.; Zeng, Q. Q.; Yang, D. C.; He, Y. H.; Guan, Z. *RSC Adv.* **2015**, *5*, 37843. http://dx.doi.org/10.1039/c4ra16825a
160. Wang, G.-D.; Zhang, X.-N.; Zhang, Z.-H. *J. Heterocycl. Chem.* **2013**, *50*, 61. http://dx.doi.org/10.1002/jhet.994
161. Kidwai, M.; Jain, A.; Nemaysh, V.; Kumar, R.; Luthra, P. *Med. Chem. Res.* **2013**, *22*, 2717. http://dx.doi.org/10.1007/s00044-012-0249-x
162. Wu, Q.; Feng, H.; Guo, D.-D.; Yi, M.-S.; Wang, X.-H.; Jiang, B.; Tu, S.-J. *J. Heterocycl. Chem.* **2013**, *50*, 599. http://dx.doi.org/10.1002/jhet.1537
163. Safaei, H. R.; Shekouhy, M.; Rahmanpur, S.; Shirinfeshan, A. *Green Chem.* **2012**, *14*, 1696. http://dx.doi.org/10.1039/c2gc35135h
164. Azizi, N.; Dezfooli, S.; Mahmoudi Hashemi, M. *J. Mol. Liq.* **2014**, *194*, 62. http://dx.doi.org/10.1016/j.molliq.2014.01.009
165. Ponpandian, T.; Muthusubramanian, S. *Synth. Commun.* **2014**, *44*, 868. http://dx.doi.org/10.1080/00397911.2013.837488
166. Elinson, M. N.; Ilovaisky, A. I.; Merkulova, V. M.; Zaimovskaya, T. A.; Nikishin, G. I. *Mendeleev Commun.* **2012**, *22*, 143. http://dx.doi.org/10.1016/j.mencom.2012.05.010
167. Zakeri, M.; Nasef, M. M.; Abouzari-Lotf, E.; Moharami, A.; Heravi, M. M. *J. Ind. Eng. Chem.* **2015**, *29*, 273. http://dx.doi.org/10.1016/j.jiec.2015.03.035
168. Park, J. H.; Lee, Y. R.; Kim, S. H. *Tetrahedron* **2013**, *69*, 9682.

http://dx.doi.org/10.1016/j.tet.2013.09.021
169. Pal, S.; Nasim Khan, M.; Karamthulla, S.; Choudhury, L. H. *Tetrahedron Lett.* **2015**, *56*, 359. http://dx.doi.org/10.1016/j.tetlet.2014.11.095
170. Parthasarathy, K.; Praveen, C.; Balachandran, C.; Kumar, P. S.; Ignacimuthu, S.; Perumal, P. T. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 2708. http://dx.doi.org/10.1016/j.bmcl.2013.02.086
171. Rahmati, A.; Khalesi, Z.; Kenarkoohi, T. *Comb. Chem. High Throughput Screen.* **2014**, *17*, 132. http://dx.doi.org/10.2174/13862073113166660067
172. Kamalraja, J.; Murugasan, P.; Perumal, P. T. *RSC Adv.* **2014**, *4*, 19422. http://dx.doi.org/10.1039/c4ra01524j
173. Jin, S.-S.; Wang, H.; Guo, H.-Y. *Tetrahedron Lett.* **2013**, *54*, 2353. http://dx.doi.org/10.1016/j.tetlet.2013.02.073
174. Noroozi Tisseh, Z.; Ahmadi, F.; Dabiri, M.; Khavasi, H. R.; Bazgir, A. *Tetrahedron Lett.* **2012**, *53*, 3603. http://dx.doi.org/10.1016/j.tetlet.2012.05.019
175. Majumdar, K. C.; Ponra, S.; Nandi, R. K. *Tetrahedron Lett.* **2012**, *53*, 1732. http://dx.doi.org/10.1016/j.tetlet.2012.01.099
176. Liu, R.; Wu, M.; Li, G. *Heteroat. Chem.* **2014**, *25*, 140. http://dx.doi.org/10.1002/hc.21146
177. Sindhu, J.; Singh, H.; Khurana, J. M. *Mol. Divers.* **2014**, *18*, 345. http://dx.doi.org/10.1007/s11030-014-9505-y
178. Li, X.; Liu, H.; Zheng, A.; Li, Z.; Yu, X.; Yi, P. *Synth. Commun.* **2014**, *44*, 1414. http://dx.doi.org/10.1080/00397911.2011.557850
179. Ghahremanzadeh, R.; Moghaddam, M. M.; Bazgir, A.; Akhondi, M. M. *Chin. J. Chem.* **2012**, *30*, 321. http://dx.doi.org/10.1002/cjoc.201180471
180. Arya, A. K.; Gupta, S. K.; Kumar, M. *Tetrahedron Lett.* **2012**, *53*, 6035. http://dx.doi.org/10.1016/j.tetlet.2012.08.099
181. Kumar, M.; Sharma, K.; Arya, A. K. *Tetrahedron Lett.* **2012**, *53*, 4604. http://dx.doi.org/10.1016/j.tetlet.2012.06.085
182. Sun, J.; Wu, Q.; Zhang, L.; Yan, C. *Chin. J. Chem.* **2012**, *30*, 1548. http://dx.doi.org/10.1002/cjoc.201100657
183. Zhang, L.-J.; Wu, Q.; Sun, J.; Yan, C.-G. *Beilstein J. Org. Chem.* **2013**, *9*, 846. http://dx.doi.org/10.3762/bjoc.9.97
184. Gao, H.; Sun, J.; Yan, C. G. *J. Org. Chem.* **2014**, *79*, 4131. http://dx.doi.org/10.1021/jo500144z
185. Gao, H.; Sun, J.; Yan, C. G. *Mol. Divers.* **2014**, *18*, 511. http://dx.doi.org/10.1007/s11030-014-9512-z

186. Sun, J.; Sun, Y.; Gao, H.; Yan, C.-G. *Eur. J. Org. Chem.* **2012**, 1976. http://dx.doi.org/10.1002/ejoc.201101737
187. Debnath, K.; Pramanik, A. *Tetrahedron Lett.* **2015**, *56*, 1654. http://dx.doi.org/10.1016/j.tetlet.2015.02.030
188. Sun, Y.; Sun, J.; Yan, C.-G. *Beilstein J. Org. Chem.* **2013**, *9*, 8. http://dx.doi.org/10.3762/bjoc.9.2
189. Elinson, M. N.; Vereshchagin, A. N.; Nasybullin, R. F.; Bobrovsky, S. I.; Ilovaisky, A. I.; Merkulova, V. M.; Bushmarinov, I. S.; Egorov, M. P. *RSC Adv.* **2015**, *5*, 50421. http://dx.doi.org/10.1039/c5ra03452c
190. Mahdavinia, G. H.; Mirzazadeh, M.; Notash, B. *Tetrahedron Lett.* **2013**, *54*, 3487. http://dx.doi.org/10.1016/j.tetlet.2013.04.082
191. Shen, T.; Fu, Z.; Che, F.; Dang, H.; Lin, Y.; Song, Q. *Tetrahedron Lett.* **2015**, *56*, 1072. http://dx.doi.org/10.1016/j.tetlet.2015.01.062
192. Liu, X.; Xu, X.; Wang, X.; Yang, W.; Qian, Q.; Zhang, M.; Song, L.; Deng, H.; Shao, M. *Tetrahedron Lett.* **2013**, *54*, 4451. http://dx.doi.org/10.1016/j.tetlet.2013.06.038
193. Yu, J.; Zhou, Y.; Shen, T.; Mao, W.; Chen, K.; Song, Q. *J. Chem. Res.* **2013**, 365. http://dx.doi.org/10.3184/174751913X13687116634925
194. Zou, Y.; Hu, Y.; Liu, H.; Shi, D. *ACS Comb. Sci.* **2012**, *14*, 38. http://dx.doi.org/10.1021/co200128k
195. Mohammadi Ziarani, G.; Rahimifard, M.; Nouri, F.; Badiei, A. *J. Serb. Chem. Soc.* In Press, **2015**. http://dx.doi.org/10.2298/JSC140930045M
196. Pore, D. M.; Hegade, P. G.; Gaikwad, D. S.; Patil, P. B.; Patil, J. D. *Lett. Org. Chem.* **2014**, *11*, 131. http://dx.doi.org/10.2174/15701786113106660069
197. Feng, J.; Ablajan, K.; Sali, A. *Tetrahedron* **2014**, *70*, 484. http://dx.doi.org/10.1016/j.tet.2013.11.019
198. Paul, S.; Pradhan, K.; Ghosh, S.; De, S. K.; Das, A. R. *Tetrahedron* **2014**, *70*, 6088. http://dx.doi.org/10.1016/j.tet.2014.02.077
199. Hosseinjani-Pirdehi, H.; Rad-Moghadam, K.; Youseftabar-Miri, L. *Tetrahedron* **2014**, *70*, 1780. http://dx.doi.org/10.1016/j.tet.2014.01.025
200. Pore, D. M.; Patil, P. B.; Gaikwad, D. S.; Hegade, P. G.; Patil, J. D.; Undale, K. A. *Tetrahedron Lett.* **2013**, *54*, 5876. http://dx.doi.org/10.1016/j.tetlet.2013.08.084
201. Pal, S.; Nasim Khan, M.; Karamthulla, S.; Abbas, S. J.; Choudhury, L. H. *Tetrahedron Lett.* **2013**, *54*, 5434. http://dx.doi.org/10.1016/j.tetlet.2013.07.117
202. Wang, C.; Jiang, Y. H.; Yan, C. G. *Chin. Chem. Lett.* **2015**, *26*, 889.

http://dx.doi.org/10.1016/j.cclet.2015.05.018
203. Alizadeh, A.; Firuzyar, T.; Mikaeili, A. *Synthesis* **2010**, 3913. http://dx.doi.org/10.1055/s-0030-1258249
204. Ghahremanzadeh, R.; Hosseini, G.; Akbarzadeh, R.; Bazgir, A. *J. Heterocycl. Chem.* **2013**, *50*, 272. http://dx.doi.org/10.1002/jhet.1010
205. Alizadeh , A.; Mikaeili, A.; Firuzyar, T. *Synthesis* **2012**, *44*, 1380. http://dx.doi.org/10.1055/s-0031-1290884
206. Zohreh, N.; Alizadeh, A. *ACS Comb. Sci.* **2013**, *15*, 278. http://dx.doi.org/10.1021/co400005y
207. Alizadeh, A.; Zohreh, N. *Synlett* **2012**, *23*, 428. http://dx.doi.org/10.1055/s-0031-1290322

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