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Isatin: A key player in multi-component reactions for heterocycle synthesis

Roghayeh Hossein Nia[a*], Manouchehr Mamaghani[a*] and Fatame Tavakoli[a]

[a]*Department of Organic Chemistry, Faculty of Chemistry, University of Guilan, P.O. Box 41335-1914, Rasht, Iran*

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A B S T R A C T

Considering the very important medicinal and biological properties of heterocycles including isatin skeleton, synthesis of isatin-containing compounds has attracted the attention of medicinal and organic chemists, especially researchers involved in the synthesis of heterocycles. The present review focuses on the recent investigation in the synthesis of heterocycles with isatin moiety using isatin derivatives as reaction reactants via multi-component for the period of 2014–2024. The reports were classified according to the conditions of the reactions, which distinguishes this review from similar studies. In some reports, green chemistry has been used, such as the use of green solvent, green and reusable catalyst, solvent-free conditions, microwave irradiations and ultrasonic irradiations. Most reviews of isatin published so far have focused only on spirooxindoles, but this review not only addresses the condition for the synthesis of spirooxindoles, but also the synthesis of other isatin-contaning heterocycles such as pyrroloquinolines, imidazole-indoles and pyrazoloquinoline. The main objective of this review is to present an overview of the latest methodologies involving isatin in the multicomponent synthesis of heterocyclic compounds, specifically for organic and medicinal chemists.

1. Introduction

Heterocyclic compounds play a critical role in producing organic and medicinal compounds and have broad applications in agriculture, polymer, and various industries.[1-7] Chemists involved in the synthesis of heterocycles are constantly searching for the best method to create these valuable compounds. The multicomponent reactions (MCRs) refer to one-pot procedures in which at least three compounds react simultaneously to generate the desired product without the need to separate and purify the intermediates. The main advantages of MCRs, compared to multistep processes, are high efficiency, experimental simplicity, avoidance of large quantities of waste, low cost, reduction of reaction time and labor cost.[8] therefore, using MCRs is an important tool in the synthesis of heterocyclic compounds with medicinal, biological, and industrial applications.

On the other hand, isatin (indoline-2,3-dione or indole-1*H*-2,3-dione) core and its derivatives are probably the most well-known heterocycle used in compounds exhibiting antimicrobial,[9] antiviral,[10] anticancer,[11] anti inflammatory,[12] anticonvulsant,[13] and anti-HIV properties.[14] Isatin, is an organic compound derived from indole. Sandmeyer's method is the oldest and simplest way for the preparation of isatin.[15]

Polycyclic heterocycles are an important category of organic molecules that have wide applications in pharmaceuticals, optical materials, and sensors. The incorporation of two or more distinct heterocyclic structural units within a single molecule frequently leads to significant improvement in its biological properties. Thus, it would be beneficial to design a system that combines a biosensitive core such as isatin with other heterocycles. Because of the high reactivity of the carbonyl group at the 3-position of isatin, this heterocycle has been extensively applied in numerous synthetic reactions to generate a wide variety of indole and particularly spirooxindole derivatives.[16] The spirooxindole compound was first isolated from the Apocynaceae and Rubiaceae plants. This heterocycle has two basic substructural units, namely an oxindole that has a

* Corresponding author
E-mail address hosseinnia.h@gmail.com (R. Hossein Nia) m-chem41@guilan.ac.ir (M. Mamaghani)

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dual character, which can be applied as a donor and acceptor of hydrogen bonds to have interaction with biological targets and the cycloalkyl moiety fuses at the C-3 position of the oxindole.[17–19] The spirooxindole scaffold is widely used in pharmacology and medicinal fields.[20, 21]

Natural compounds are the primary source of inspiration in the design and synthesis of new pharmaceutical molecules, and most of these compounds are composed of heterocyclic cores. Among heterocycles containing isatin, spiroxindole derivatives are abundant in nature. Spirotryprostatine B, a natural alkaloid isolated for Aspergillus Funmigetus, was shown to be inhibitors of the cell cycle in the G2/M phase.[22] Another alkaloides include Horsifiline with analgesic effect,[23] the polycyclic alkaloid Mitrophylline[24] as an anti-inflammatory agent, and Isopterpodine as muscarinic serotonin receptor (**Fig. 1**).[25]

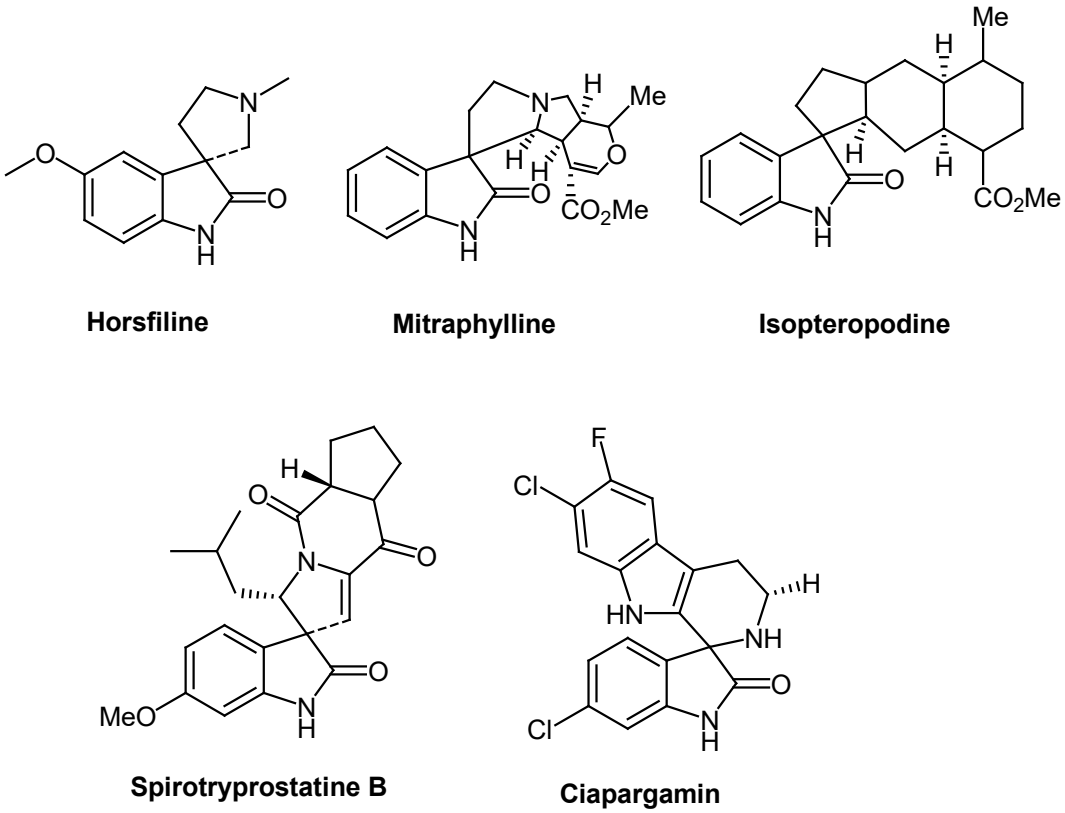


Fig. 1. Natural product samples of spirooxindole.

Due to the importance of isatin-containing heterocycles, especially spirooxindoles, various methods for the synthesis of these heterocycles have been reported. In recent years, several reviews were also published on isatin and spirooxindoles,[26-31] with most of the focus being on spirooxindoles. The search results in the Scopus search system from 2014 to 2024, based on the keywords isatin and isatin derivatives in the field of chemistry and biochemistry, are shown in **Fig. 2**. Most of the research has been on the reactions and properties of isatin and its derivatives. The most reports were published in 2024 (93 articles) and the least in 2016 (53 articles). Among the reported research, in accordance with the purpose of this study, we will discuss the selected reports in this review.

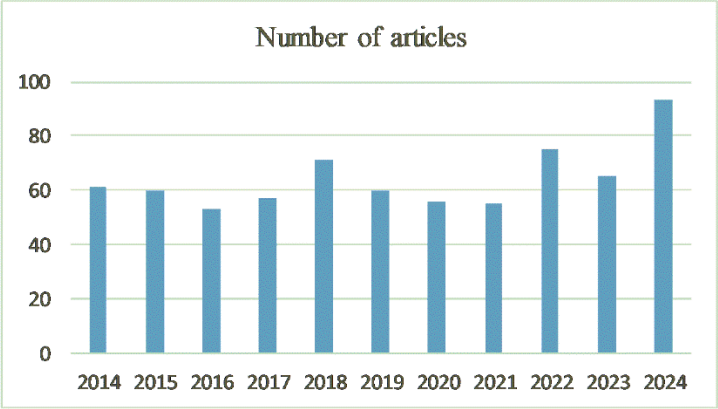


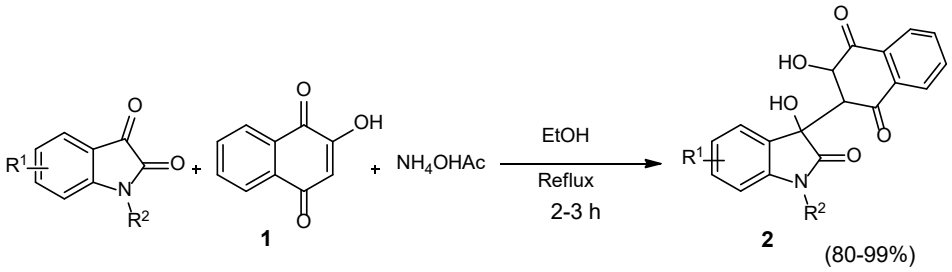
Fig. 2. The research on isatin derivatives from 2014 to 2024.

The present review summarizes some important reports of isatin skeleton used as a reactant for the multi-component synthesis of heterocyclic compounds. Due to the medicinal properties of isatin-containing heterocycles, in some of these reports, the biological properties of the produced heterocycles were also investigated, but in the present paper, only the chemical aspects have been discussed. In this study, we review the reports of recent years (2014-2024) on the multicomponent synthesis of isatin-containing heterocycles. These reports not only include the synthesis of spirooxindoles but also other isatin-contaning heterocycles such as pyrroloquinolines, imidazole-indoles and pyrazoloquinoline. The reports were categorized based on reaction conditions, and green chemistry was utilized in some reports, including the use of green solvent, green and reusable catalyst, solvent-free condition, microwave irradiations and ultrasonic irradiations.

2. Synthesis of isatin-contaning heterocycles

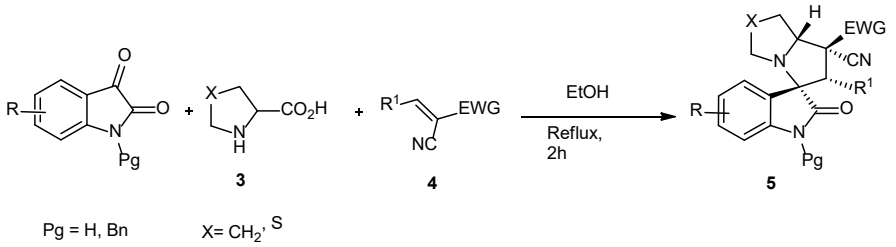
2.1. Using catalyst- free conditions

Che et al.[32] have described the synthesis of 2-(3-amino-2-oxoindolin-3-yl)-3-hydroxynaphthalene-1,4-dione derivatives (**2**) by a one-pot, three-component reaction of isatins, 2-hydroxy-1,4-naphthoquinone (**1**) and ammonium acetate under catalyst-free conditions in ethanol (Scheme 1). The presented mechanism shows that the isatin C=O group is activated by NH_4^+ and then the Michael addition of 2-hydroxy-1,4-naphthoquinone to the formed intermediate occurs.



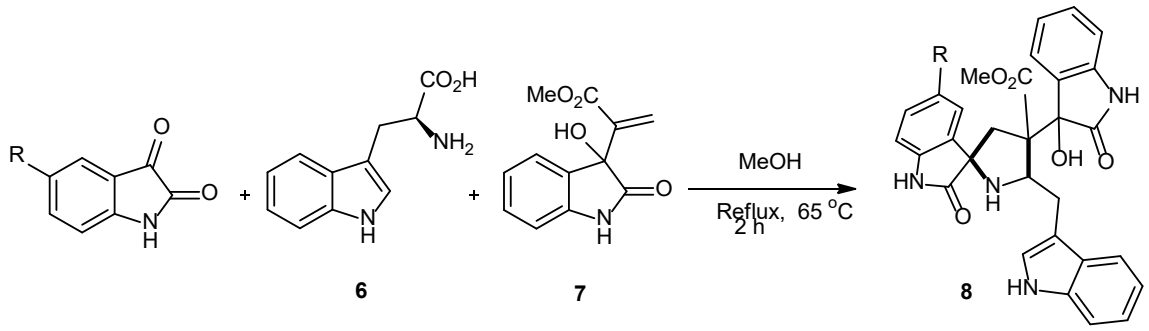
Scheme 1. Preparation of 2-(3-amino-2-oxoindolin-3-yl)-3-hydroxynaphthalene-1,4-dione derivatives.

Wang et al.[33] have reported, the reaction between isatine derivatives, proline or thiproline (**3**) and *α*-cyano-*α,β*-unsaturated compounds (**4**) for the synthesis of a series of 3,3′-pyrrolidinyl-spirooxindoles derivatives (**5**) in high yields (82-92%) and excellent diastereoselectivities (up to >25:1 dr) (Scheme 2). The proposed mechanism proceeds via the 1,3-dipolar cycloaddition reaction of isatin-derived azomethine ylides with α-cyano-*α,β*-unsaturated compounds.



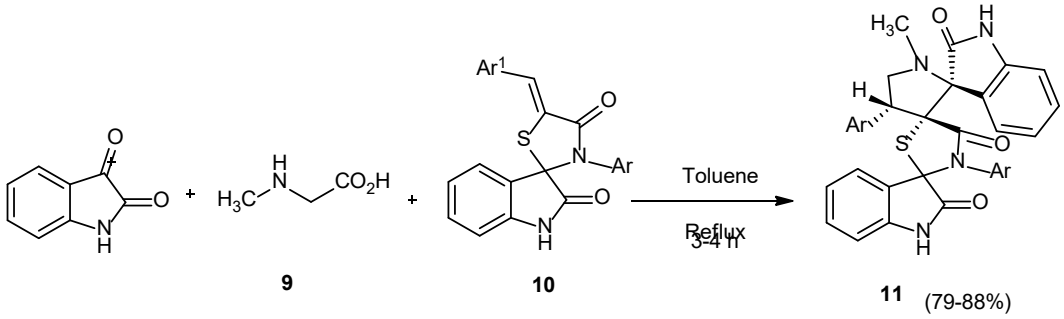
Scheme 2. Preparation of 3,3′-pyrrolidinyl-spirooxindoles derivatives.

In 2024, the synthesis of spirooxindolopyrrolidine engrafted indoles (**8**) has been reported.[34] The presented protocol including the reaction between isatin, L-tryptophan (**6**) and 2-(3-hydroxy-2-oxoindolin-3-yl) acrylate (**7**) (Scheme 3). Methyl 2-(3-hydroxy-2-oxoindolin-3-yl) acrylate (**7**) was also synthesized from Baylis-Hillman reaction between isatin and acrylate, using DABCO as catalyst.[35] In this research, the antimicrobial properties of the products against multidrug resistant ESKAPE clinical pathogens was also evaluated.



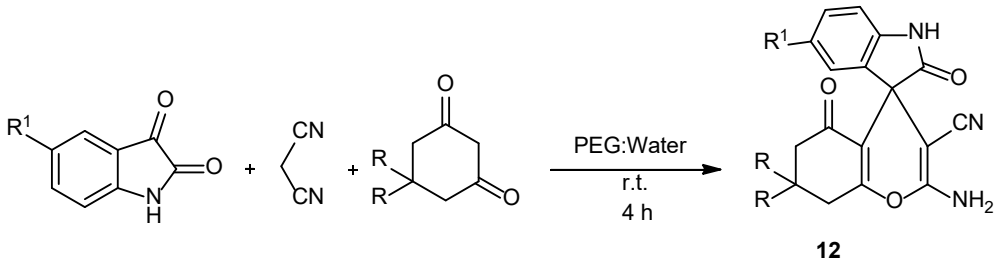
Scheme 3. Synthesis of spirooxindole incorporated indoles.

Preparation of trispiropyrrolidine bisoxindoles (**11**) has been described via a three component 1,3-dipolar cycloaddition reaction of 3-aryl-5-arylmethylenespiro[indole-3′,2- [1,3]thiazolane]-2′(1H),4-dione (**10**), isatin, and sarcosine (**9**) in refluxing toluene (Scheme 4).[36]



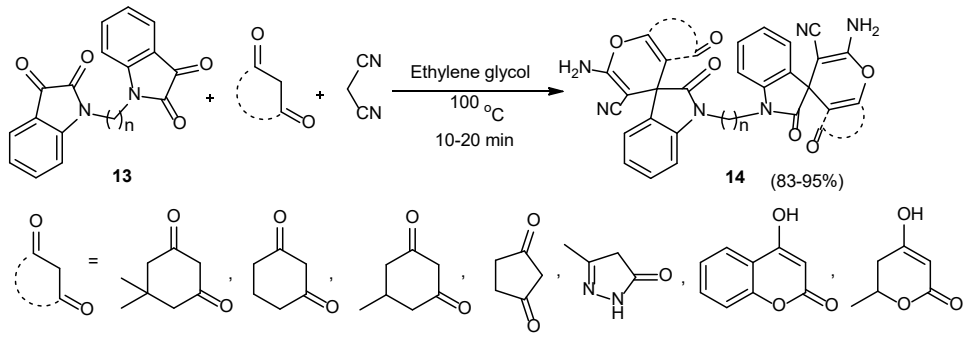
Scheme 4. Formation of trispiropyrrolidine bisoxindoles.

Synthesis of spirochromenes was also studied using PEG-600 (Polyethylene Glycol) as promoting reaction medium in water under catalyst-free conditions.[37] Spirochromene derivatives (**12**) were synthesized by a three-component reaction of isatin, malononitrile and cyclic 1,3-dione at room temperature (**Scheme 5**). The authors used this protocol to prepare other 4*H*-pyran derivatives.

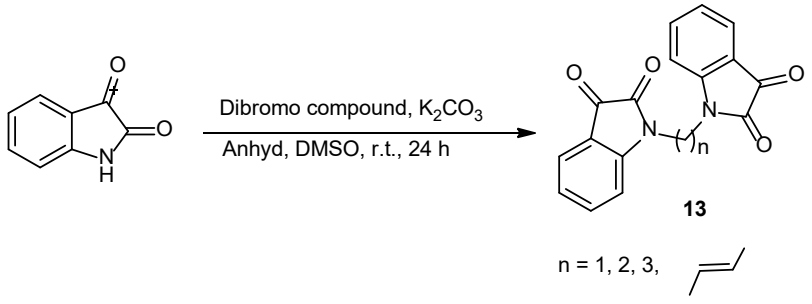


Scheme 5. A catalyst-free synthesis of spirochromenes using PEG-H_2O as green reaction medium.

A catalyst-free synthesis of bis-spirooxindoles (**14**) has been carried out by three-component reaction of bis-isatins (**13**), malononitrile and various cyclic enolizable carbonyl compounds in ethylene glycol at 100°C (**Scheme 6**).[38] Bis-isatins was also prepared by in situ synthesis from reaction of isatin and 1,3-dibromopropane in presence of K_2CO_3 in ethylene glycol at 100°C (5.5 h) (**Scheme 7**). It was mentioned in this report that no chromatographic techniques were used to purify the products.

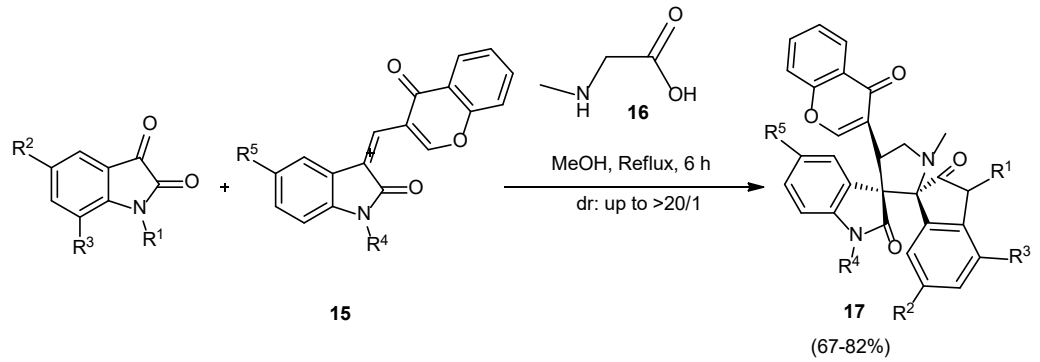


Scheme 6. Synthesis of bis-spirooxindoles.



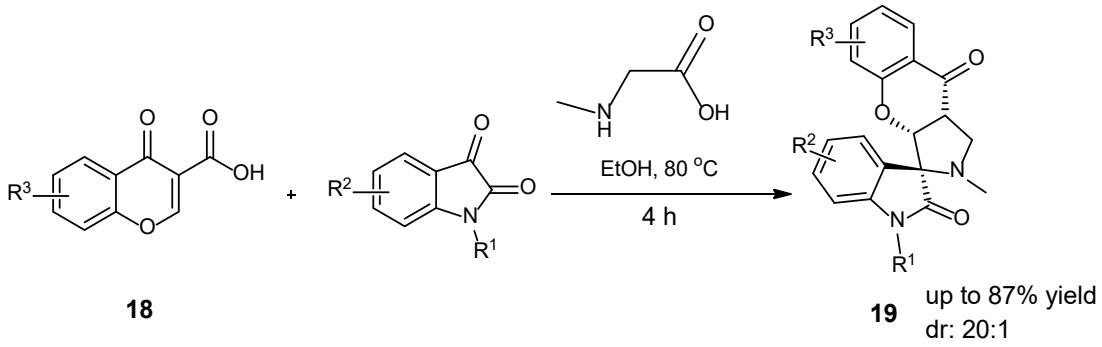
Scheme 7. Formation of bis-isatin.

A method was reported for the synthesis of 3,3′-pyrrolidinyl-dispirooxindoles **(17)** through a 1,3-dipolar cycloaddition reaction of isatylidenyl-chromanones (**15)** with azomethine ylides (thermally generated *in situ* from isatins and sarcosine (**16**) in high yields (67-82% yield)) and good diastereoselectivity (up to >20:1) (**Scheme 8**).[39] The authors also evaluated the biological activity of the products against human leukemia K562 cells and normal L929 cells.



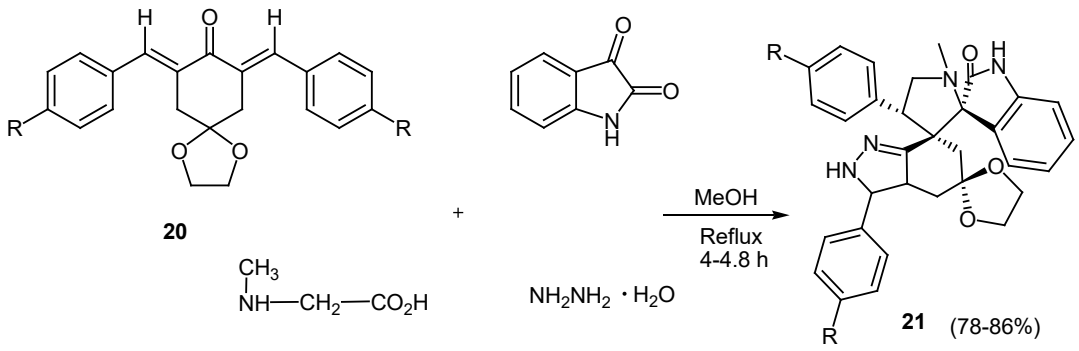
Scheme 8. Synthesis of 3,3′-pyrrolidinyl-dispirooxindoles.

Chen et al.[40] have also used the reaction of carboxylic acid group-activated chromones **(18)** with isatin-derivated azomethine ylides for the synthesis of a series of heterocycle-fused spiro compounds containing chromanone and pyrrolidinyl spirooxindoles **19** (**Scheme 9**). A variety of products with three contiguous stereocenters including a spiro quaternary stereocenter were prepared through a decarboxylative 1,3-dipolar [3 + 2] cycloaddition reaction.



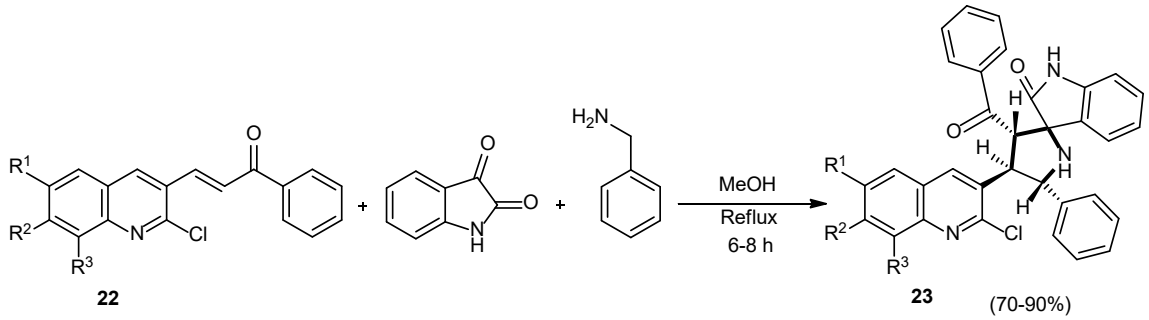
Scheme 9. Synthesis of chromanone-fused pyrrolidinyl spirooxindoles.

Deivasigamani et al.[41] have synthesized a series of hitherto spirooxindolopyrrolidine grafted pyrazolo-1,4-dioxa-spiro[4,5]decanes (**21**) via a one-pot sequential four-component reaction involving [3+2]- cycloaddition reaction of azomethine ylides (in situ synthesis of isatin and sarcosine) to various 7,9-bis[(E)-benzylidene]-1,4-dioxa-spiro[4,5]decane-8-one derivatives **(20)** followed by ring annulation using hydrazine hydrate (**Scheme 10**).



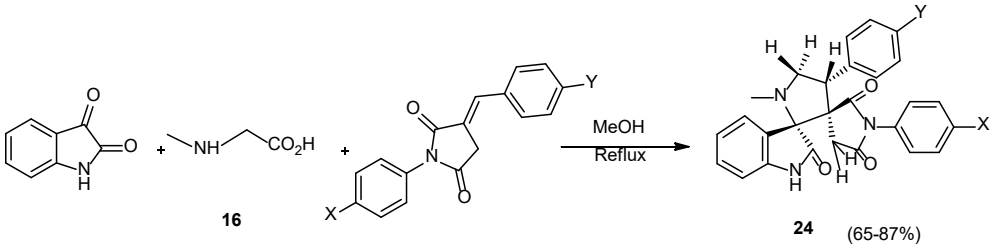
Scheme 9. Synthesis of pyrazolo-1,4-dioxa-spiro[4,5]decane grafted spiro-oxindolopyrrolidines.

Spiro[indolin-3,2′-pyrrolidin]-2-ones (**23**) have also been prepared through 1,3-dipolar cycloaddition of azomethine ylides generated *in situ* from the reaction of isatin and benzyl amine with quinoline bearing dipolarophiles (**22**) in refluxing methanol (**Scheme 10**).[42]



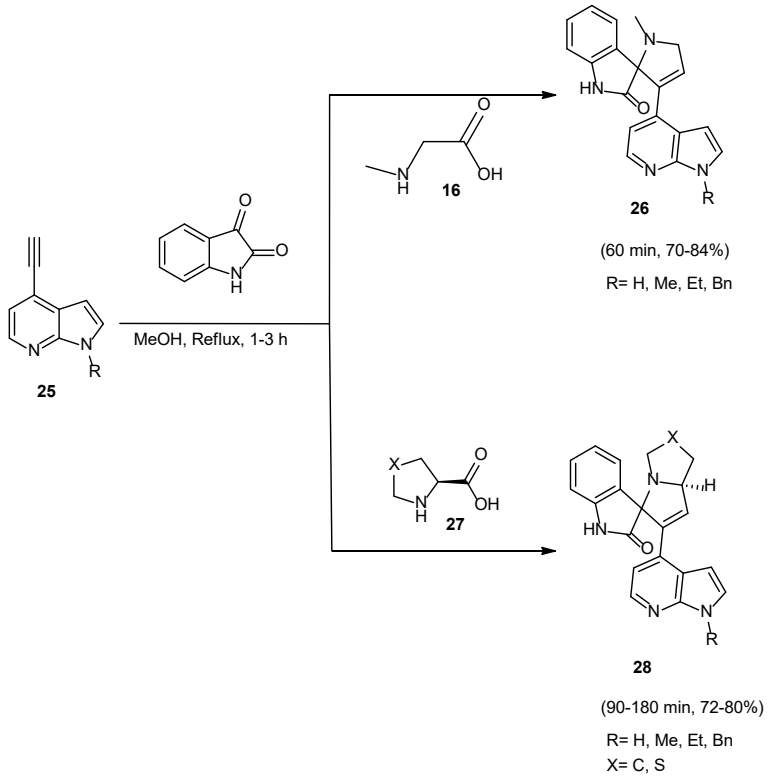
Scheme 10. Synthetic pathway of spiro[indolin-3,2′-pyrrolidin]-2-ones.

Synthesis of dispiro–oxindole–pyrrolidines was also reported[43] through multicomponent 1,3-dipolar cycloaddition reaction of azomethine ylide. 1-*N*-Methyl-spiro[2,3′]oxindole-spiro[3,3″]-1″-*N*-arylpyrrolidine-2″,5″-dione-4-arylpyrrolidines (**24**) has been achieved via a three-component tandem cycloaddition of azomethine ylide generated in situ from isatin and sarcosine (**16**) by decarboxylative condensation with *N*-aryl-3-benzylidene-pyrrolidine-2,5-dione derivatives as dipolarophiles (**Scheme 11**).

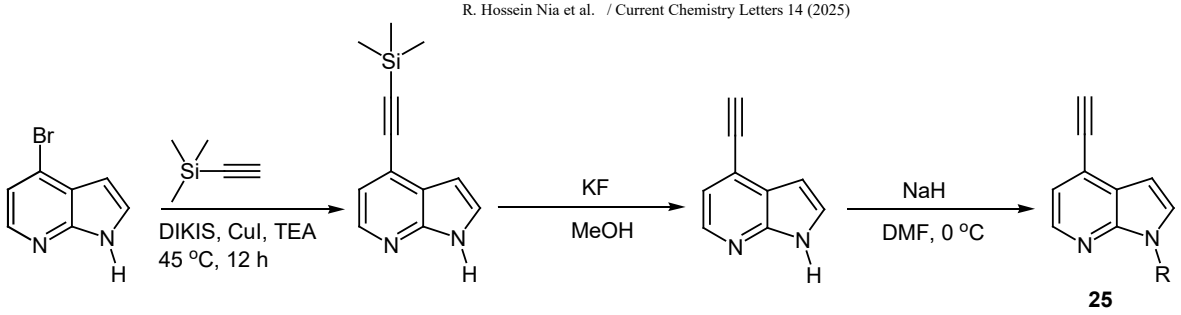


Scheme 11. Formation of dispiro–oxindole–pyrrolidines.

Narayanarao et al.[44] have researched a protocol for the synthesis of spiro-indoline derivatives (**26** and **28**) (**Scheme12**). At first *N*-alkyl ethynyl-7-aza indoles (**25)** was produced according to the Scheme 13,[45-47] then the reaction between indoles **25** with acyclic amino acid (sarcosine) (**16),** isatin in methanol afforded cyclic adduct **26** as a single diastereoisomer, while from the reaction of indoles **25** with isatin and L-proline/ thioproline (**27**), product **28** was formed.

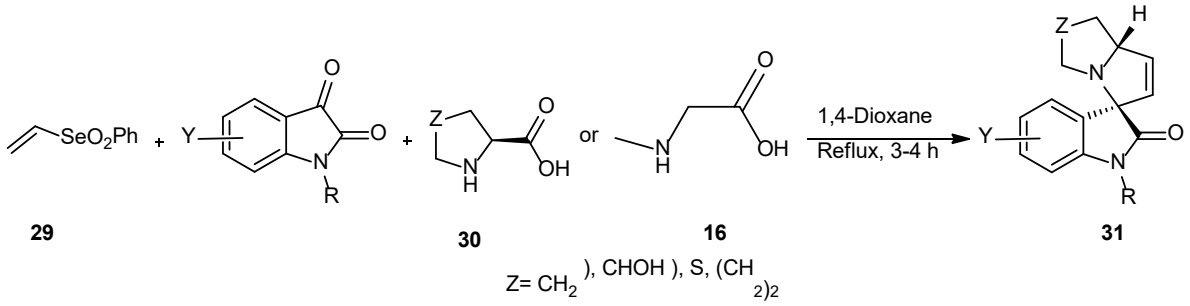


Scheme 12. Synthesis of spiro-indoline derivatives.



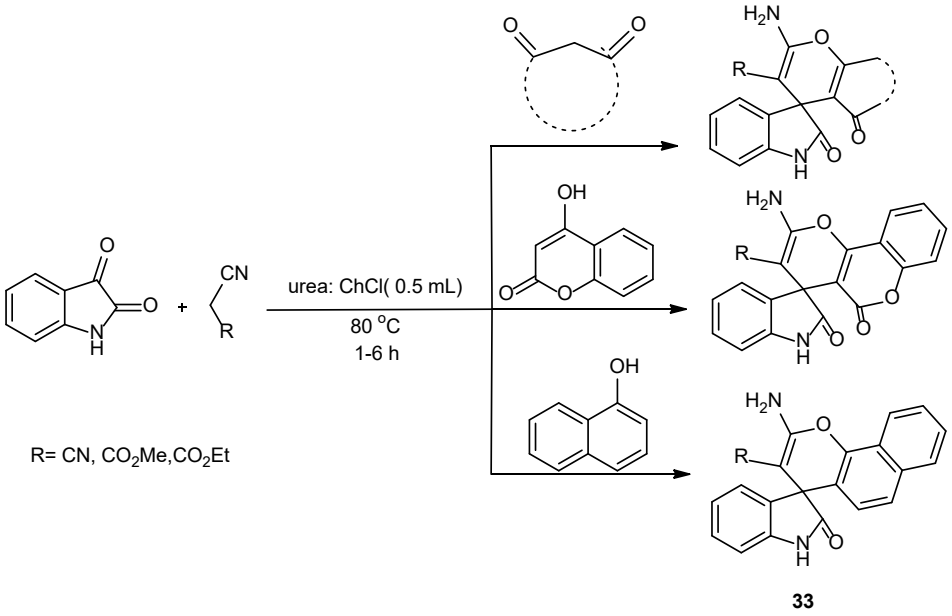
Scheme 13. Preparation of *N*-alkyl ethyl-7-aza indoles.

Spirooxindole-tetrahydropyrrolizines (**31**) was prepared from secondary *α*-aminoacids (**30**), isatins and vinyl selenones (**29**) (**Scheme 14**).[48] Products were formed in 47-96% yields by 1,3-dipolar cycloaddition of in situ generated azomethine ylides followed by spontaneous elimination of benzeneseleninic acid.

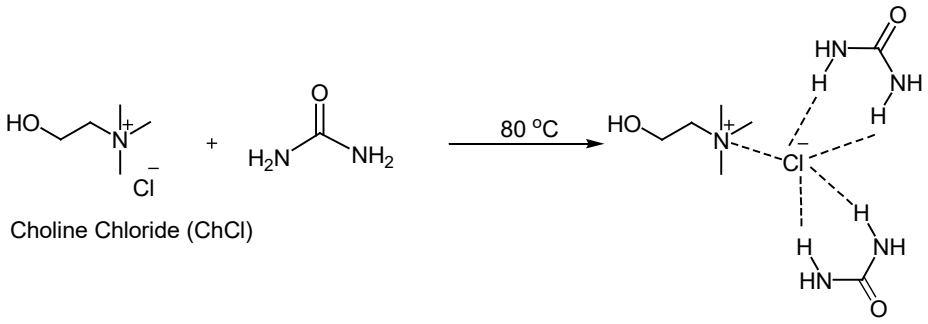


Scheme 14. Formation of spirooxindoles by three-component 1,3-dipolar cycloadditions of the vinyl selenone.

Synthesis of spirooxindole under catalyst-free condition in deep eutectic solvent (DES) was also addressed. A series of biologically important, spirooxindole derivatives (**33**) were synthesized via a multicomponent reaction of isatin, and malononitrile or cyanoacetic ester with 1,3-dicarbonyl compounds, 4-hydroxycumarin and *α*-naphtol in biodegradable choline chloride based deep eutectic solvent in 50-95% yields (**Scheme15**).[49] To prepare desired DES, choline chloride and urea were mixed in a round-bottomed flask and were heated to obtain a clear liquid as DES called urea:ChCl (**Scheme 16**).[50] In the proposed mechanism, it was mentioned that weak acidic nature of choline chloride and hydrogen-bonding donors of urea in DES is the main reason for the high performance of the system.

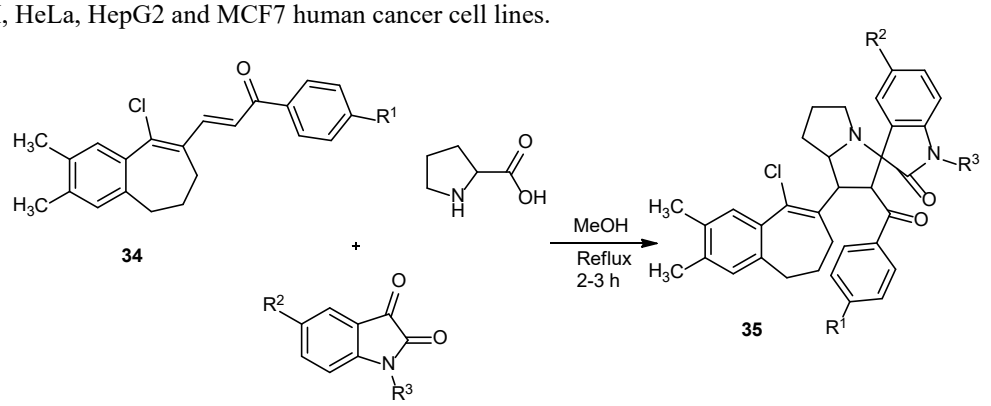


Scheme 15. Formation of spiro-2-oxindoles in DES.

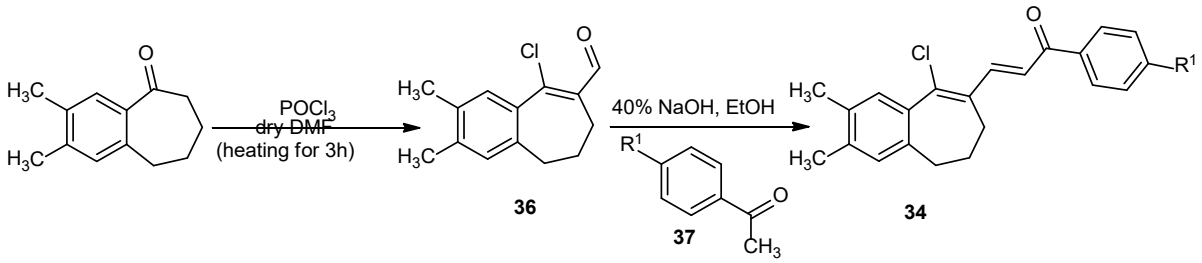


Scheme 16. Preparation of DES from urea and ChCl.

The reaction of (*E*)-3-(9-chloro-2,3-dimethyl-6,7-dihydro-5*H*-benzo[7]annulen-8-yl)-1-phenylprop-2-en-1-ones (**34**) with *N*-substituted isatins and L-proline in methanol has formed a series of novel benzosuberone derivatives bearing hexahydrospiro[indoline-pyrrolizin]-ones (**35**) (**Scheme 17**).[51] (*E*)-3-(9-chloro-2,3-dimethyl-6,7-dihydro-5*H*-benzo[7]annulen-8-yl)-1-phenylprop-2-en-1-one (**34**) was also achieved by the reaction of 9-chloro-2,3-dimethyl-6,7-dihydro-5*H*-benzo [7] annulene-8-carbaldehyde (**36**) with acetophenones (**37**) in the presence of 40% NaOH in ethanol at room temperature (**Scheme 18**). In this research, the products were evaluated for their anti-proliferative activity against A549, SKNSH, HeLa, HepG2 and MCF7 human cancer cell lines.

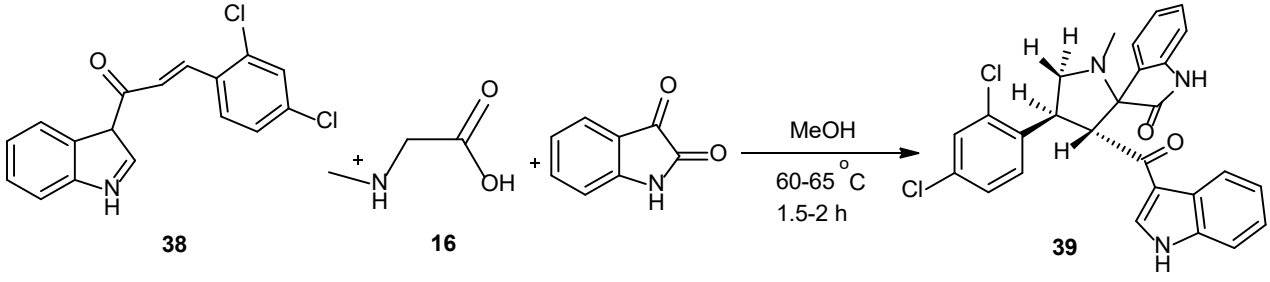


Scheme 17. Synthesis of hexahydrospiro[indoline-pyrrolizin]-one hybrids.



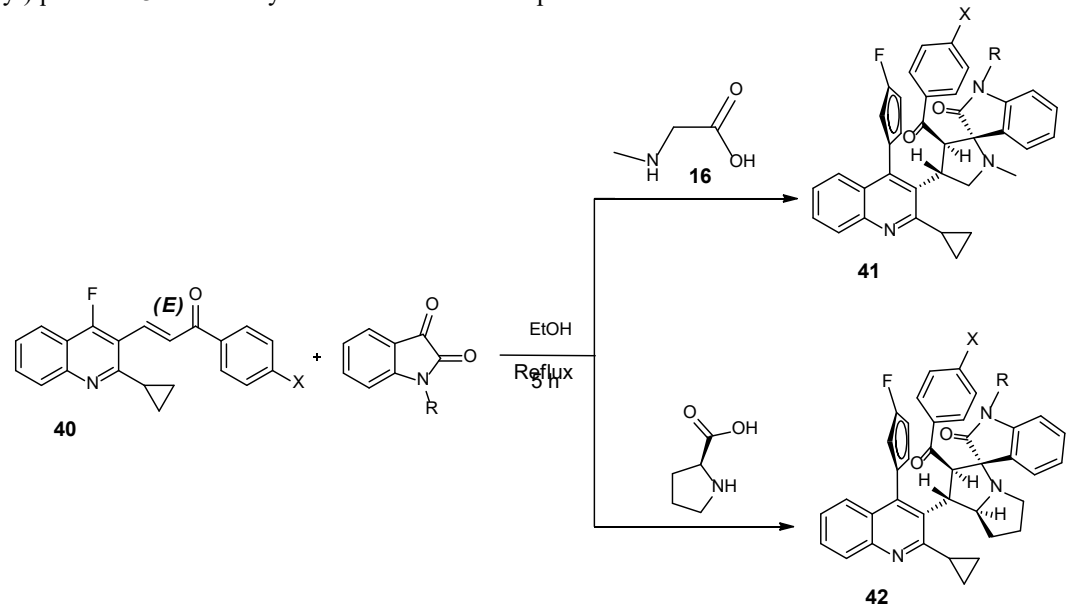
Scheme 18. Synthesis of (*E*)-3-(9-chloro-2,3-dimethyl-6,7-dihydro-5*H*-benzo[7] annulen-8-yl)-1-phenylprop-2-en-1-one derivatives.

[1,3] Dipolar cycloaddition reaction approach of olefin (**38**) [52,53] with amino acid (sarcosine) (**16**), and isatin afforded spiroindolone (**39**) in MeOH at 60-65°C (**Scheme 19**).[54] Authors were also examined product against three different cancer cell lines for liver, breast and colorectal cancer (HepG2, MCF-7 and HCT-116 respectively).



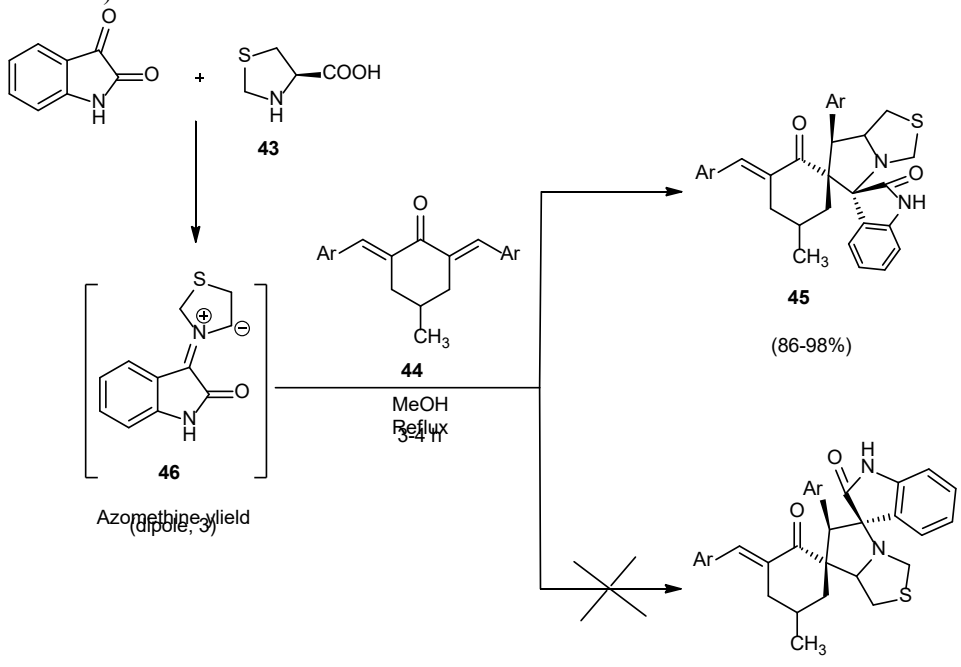
Scheme 19. Formation of spiroindolone from olefin, sarcosine and isatin.

A series of spiro-pyrrolidines (**41** and **42**) have been synthesized through 1,3-dipolar cycloaddition of an azomethine ylide generated from isatin and sarcosine (**16**) or L-proline with the dipolarophile (*E*)-3-(2-cyclopropyl-5-(4-fluorophenyl) quinolin-3-yl)-1-phenylprop-2-en-1-one derivatives (**40**) in refluxing ethanol (Scheme 20).[55] According to this report, (*E*)-3-(2-cyclopropyl-5-(4-fluorophenyl)quinolin-3-yl)-1-phenylprop-2-en-1-one (**40**) was prepared from 2-cyclopropyl-4-(4-fluorophenyl)quinoline-3-carbaldehyde and substituted acetophenone with KOH as a base in methanol under reflux.

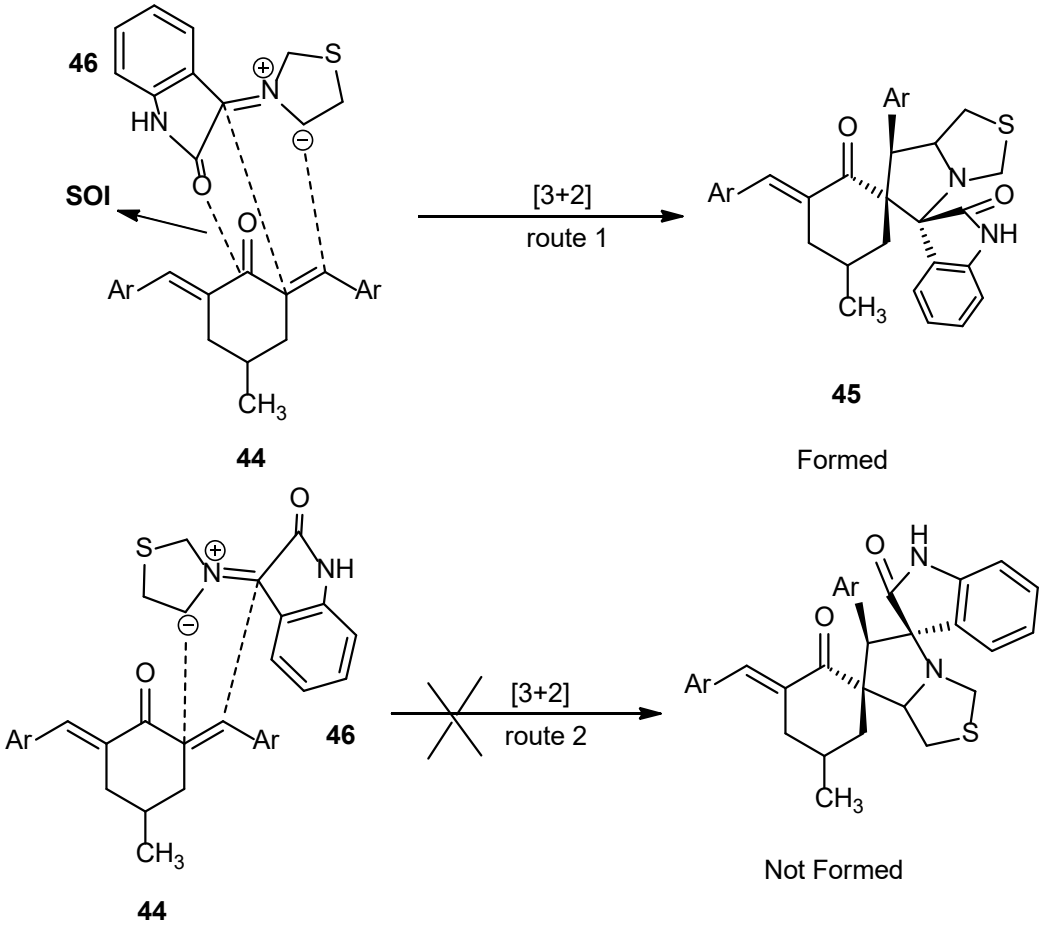


Scheme 20. Formation of spiro-pyrrolidines.

A set of dispirooxindole-pyrrolothiazole derivatives (**45)** has been prepared through 1,3-dipolar cycloaddition reaction of azomethine ylide with dipolarophiles, 2,6-di(arylmethylidene) -4-methylcyclohexanones **(44)** in refluximg MeOH with high degree of stereo-, regio-, and chemoselectivities (Scheme 21).[56] 2,6-Di(arylmethylidene)-4-methylcyclohexanones (**44**) were prepared by Claisen-Schmidt condensation reaction of 4-methylcyclohexanone and various substituted benzaldehydes using NaOH. The synthetic protocol began with 1,3-dipolar cycloaddition reaction of isatin and L-4-thiazolidinecarboxylic acid **(43)** with a class of dipolarophiles **(44)** under reflux which led to the preparation of dispirooxindole-pyrrolothiazole grafted cyclohexanone hetrocyclic hybrids **45**. The proposed mechanism for the regioselectivity of the reaction was disclosed by the addition of the electron rich carbon of the dipole or azomethine ylide **(46)** (decarboxylative condensation of the isatin with L-4-thiazolidinecarboxylic acid) to the electron-deficient *β* carbon of dipolarophile **44** (route-1) which is more encouraging due to the presence of secondary orbital interaction (SOI) which is not in route-2 (**Scheme 22**).

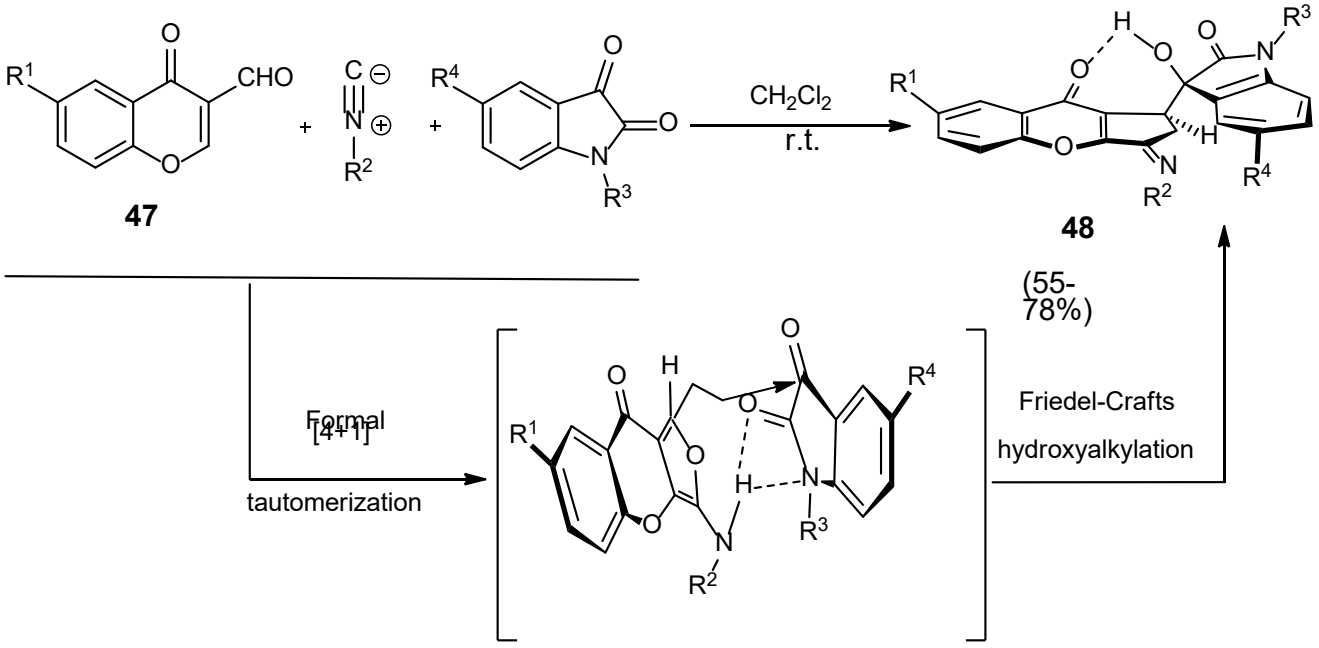


Scheme 21. Synthesis of dispirooxindole-pyrrolothiazoles.



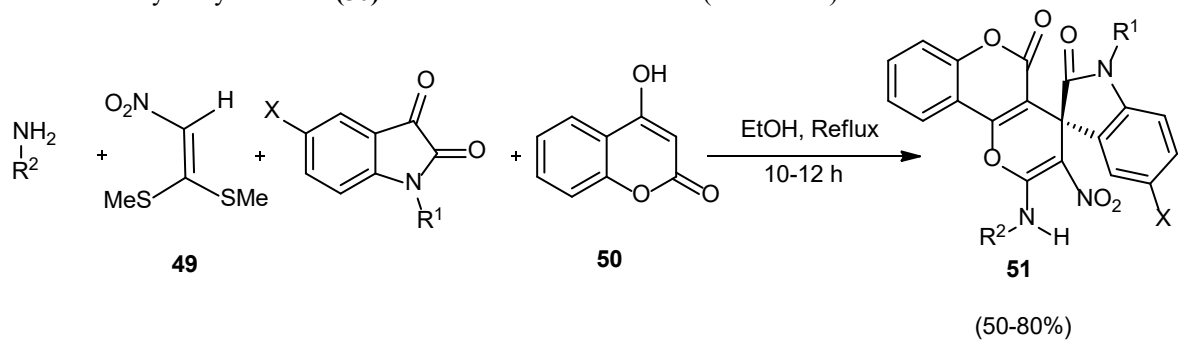
Scheme 22. Proposed mechanism for formation of dispirooxindole-pyrrolothiazoles.

A series of heterocycles containing 3-hydroxyoxindole, and alkyliminofurochromone fused rings (**48**) have been synthesized through the uncatalyzed Friedel-Crafts hydroxyalkylation of 3-(alkylamino)-9*H*-furo[3,4-*b*]chromen-9-ones generated *in situ* by the [4 + 1] cycloaddition/tautomerization of alkyl isocyanides and 3-formylchromones (**47**) with isatin derivatives (**Scheme 23**).[57]



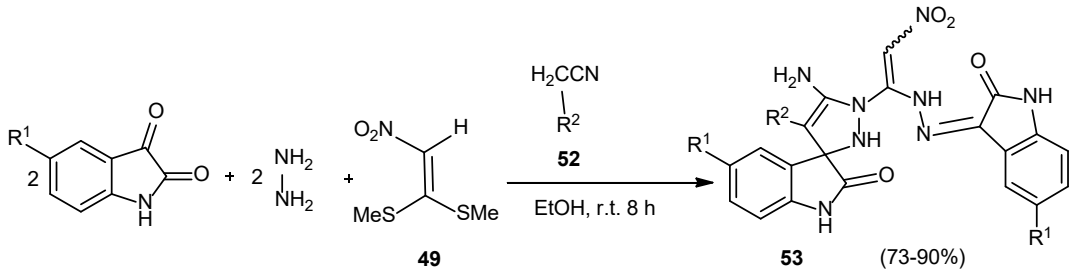
Scheme 23. The reaction of isocyanides and 3-formylchromones in the presence of reactive carbonyl compounds.

Spiro[indoline-3,4′-pyrano[3,2-*c*]chromene]diones (**51**) were prepared, via multicomponent reaction of of *N*-alkyl-1-(methylthio)-2-nitroethenamine derived from the addition of various amines to nitroketene dithioacetal **(49)** with isatin derivatives and 4-hydroxycoumarin **(50)** in ethanol at reflux condition (Scheme 24).[58]

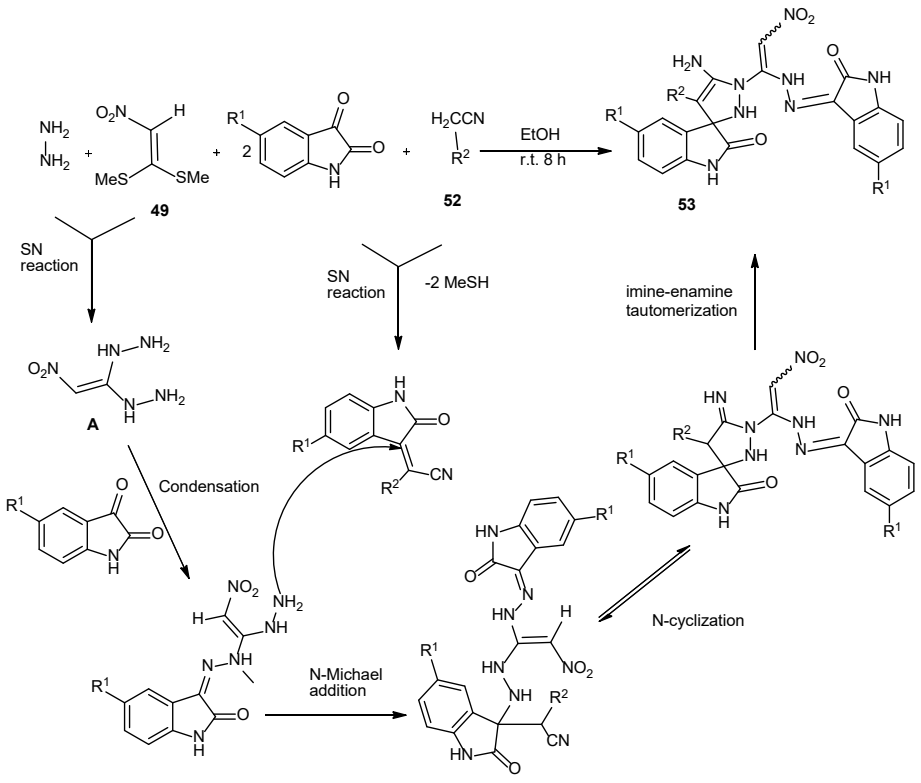


Scheme 24. Formation of spiro[indoline-3,4′-pyrano[3,2-*c*]chromene]diones.

A route for the synthesis of spiropyrazolines (**53**) *via* a pseudo-six component reaction of hydrazine hydrate, nitroketene dithioacetal (**49**), isatin, and active methylene (**52**) at room temperature in ethanol has been studied (**Scheme 25**).[59] The plausible mechanism involves the formation of 1,1-dihydrazino-2-nitroethylene (A) from hydrazine hydrate with nitroketene dithioacetal (**49**) and its reaction with Knoevenagel adduct derived from the corresponding isatin and active methylene (**52**) (**Scheme 26**).

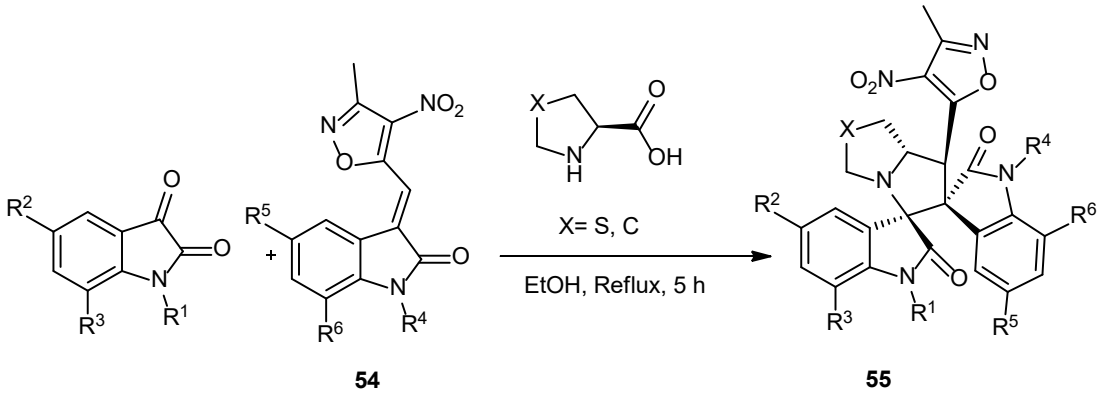


Scheme 25. Preparation of spiropyrazolines via a pseudo-six component reaction.



Scheme 26. Plausible mechanism for synthesis of spiropyrazolines via a pseudo-six component reaction.

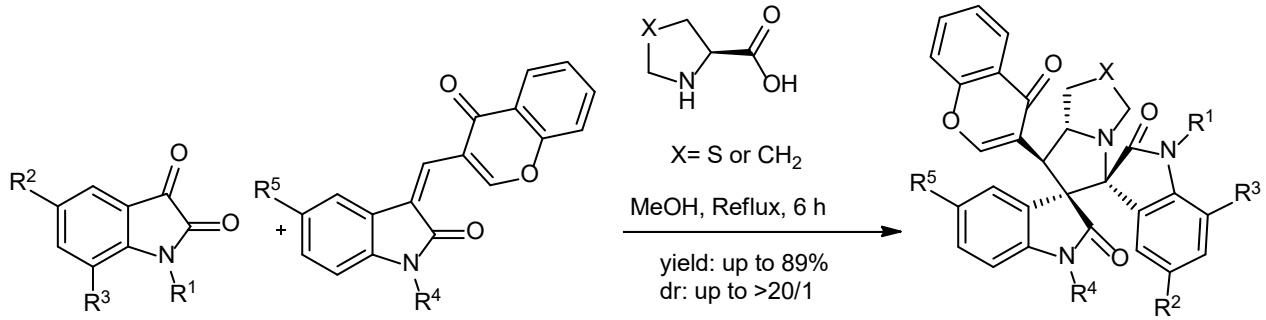
Lin et al.[60] have described the synthesis of polycyclic 3,3'- pyrrolidinyl-dispirooxindoles (**55)** *via* a multicomponent 1,3-dipolar cycloaddition reaction of 3-methyl-4-nitro-5-isatylidenyl-isoxazoles (**54)** with azomethine ylides (thermally generated *in situ* from isatins and proline or thioproline) (**Scheme 27**). 3-Methyl-4-nitro-5-isatylidenyl-isoxazoles (**54**) were prepared by reaction of 3,5-dimethyl-4-nitroisoxazole with isatin.[61] The products **(55)** contain four consecutive stereoesters consisting of two oxindole moieties and a polycyclic pyrrolidinyl core, including adjacent stereoquaternary centers fused into a ring structure.



54 **55**

Scheme 27. Preparation of 3,3'- pyrrolidinyl-dispirooxindoles.

Similarly, polycyclic pyrrolidinyl-dispirooxindoles (**57**) were also prepared via 1,3-dipolar cycloaddition reaction of isatylidenyl-chromanones (**56**) with azomethine ylides (thermally generated in situ from isatins and proline or thioproline) (**Scheme 28**).[62]

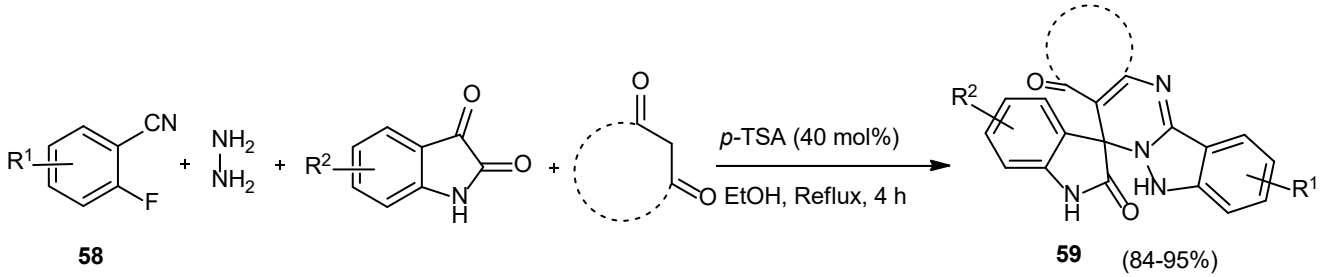


56 **57**

Scheme 28. Synthesis of pyrrolidinyl-dispirooxindoles.

2.2. Using acid catalyst

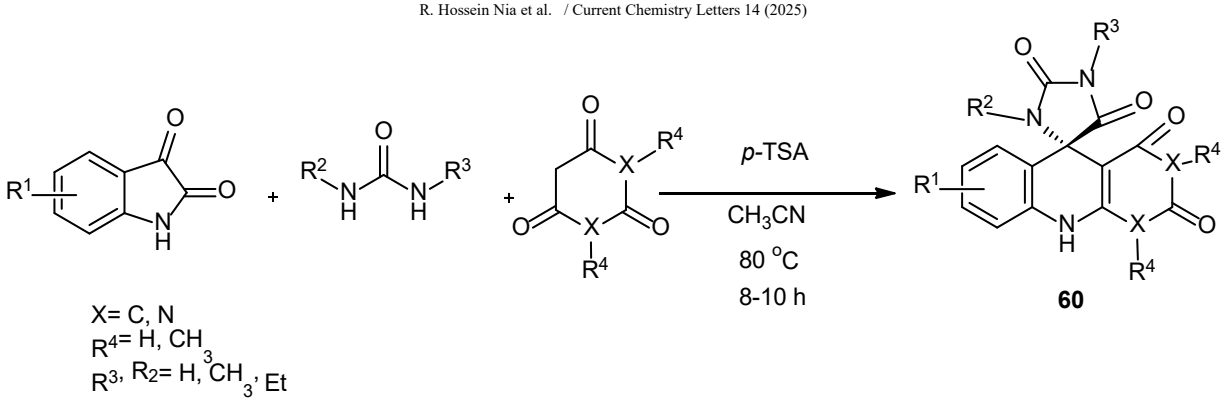
p-Toluenesulfonic acid (*p*-TSA) as catalyst was used in the four-component formation of spiro[indazolo[3,2-*b*]quinazoline-7,3′-indolines (**59**).[63] The reported protocol contains in situ generation of 1*H*-indazol-3-amines (from the reaction of the 2-halobenzonitriles (**58**) with hydrazine) and its reaction with the cyclic 1,3-dicarbonyls and isatin derivatives to furnish complex *N*-fused spiro-polyheterocyclic frameworks (**Scheme 29**).



58 **59** (84-95%)

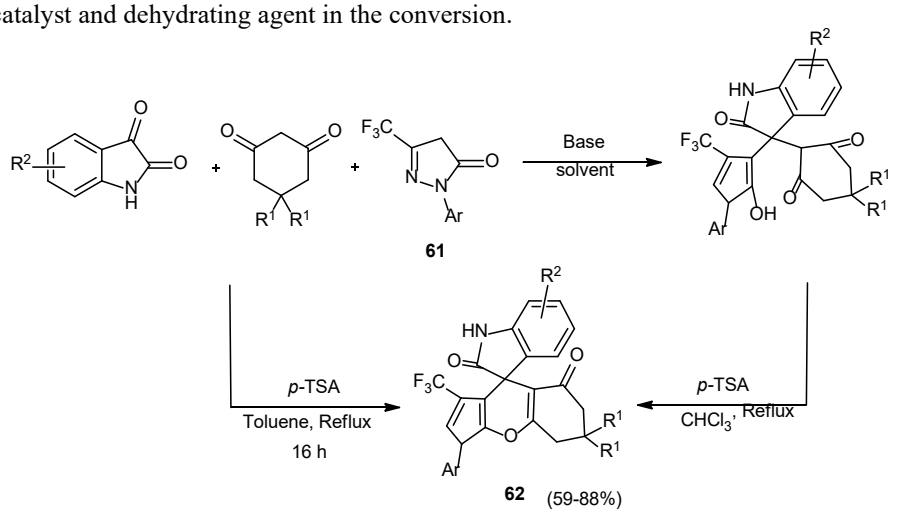
Scheme 29. Four-component synthesis of spiro[indazolo[3,2-*b*]quinazoline-7,3′-indolines.

The annulation reactions of isatins, substituted ureas, and cyclic ketones in the presence of *p*-TSA·H_2O was also reported (**Scheme 30**).[64]



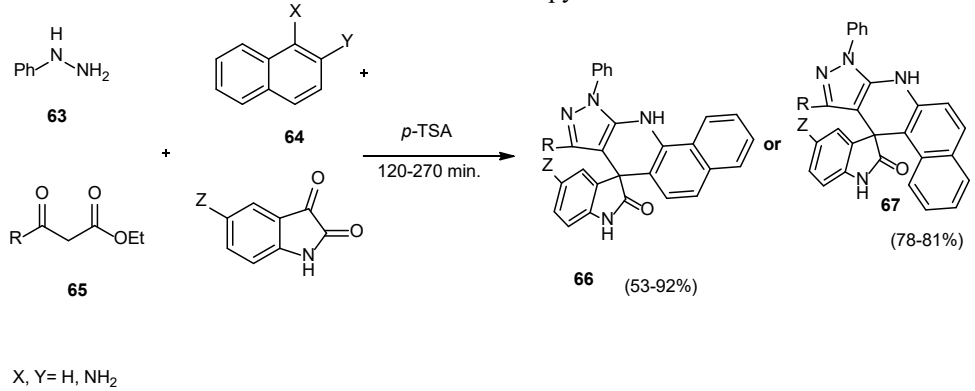
Scheme 30. Formation of spiro-heterocycles in the presence of *p*-TSA.

Synthesis of trifluoromethylated spirochromeno[2,3-*c*]-6*H*-pyrazol-2′,5-dione derivatives (**62**) by the reaction of isatin, cyclohexane-1,3-dione and 1-aryl-3-(trifluoromethyl)-1*H*-pyrazol-5(4H)-one (**61**) in the presence of *p*-toluenesulfonic acid (*p*-TSA) was reported (**Scheme 31**).[65] In the paper, it was cited that compared with the stepwise reactions, the *p*-TSA played dual roles as both catalyst and dehydrating agent in the conversion.



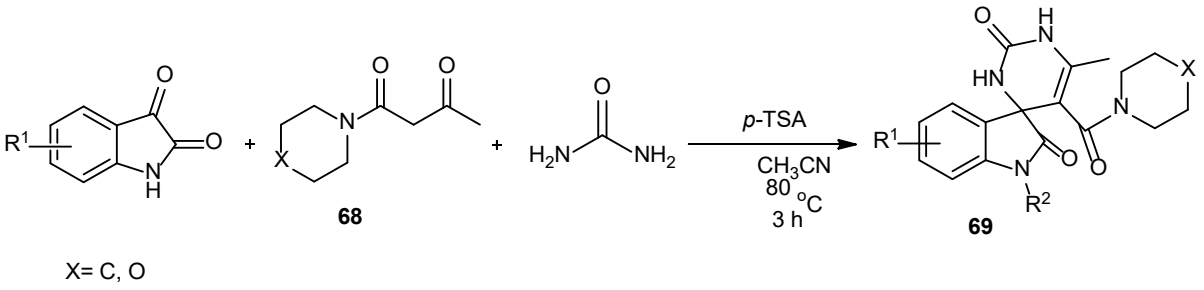
Scheme 31. Formation of trifluoromethylated spirochromeno[2,3-*c*]-6*H*-pyrazol-2′,5-dione derivatives.

p-TSA was also utilized in the preparation of spiro[1*H*-pyrazolo[3,4-*b*]benzo[*h*]dihydroquinolin-4,3-indolin-2-ones] (**66** and **67**) (**Scheme 32**).[66] The four-component reaction was carried out between isatins, phenylhydrazine (**63**), naphthylamines (**64**), and 3-ketoesters (**65**) in presence of *p*-TSA under solvent-free conditions. In the report, it was mentioned that using anilines instead of naphthylamines, under the same conditions, have not led to formation of the expected 4-substituted pyrazolo[3,4-*b*]quinoline derivatives. This difference is due to lower aromatic character of naphthylamines relative to anilines, which enables them to more easily act as enamines in the reaction with the postulated in situ formed intermediates from the condensation of isatines and pyrazolones.



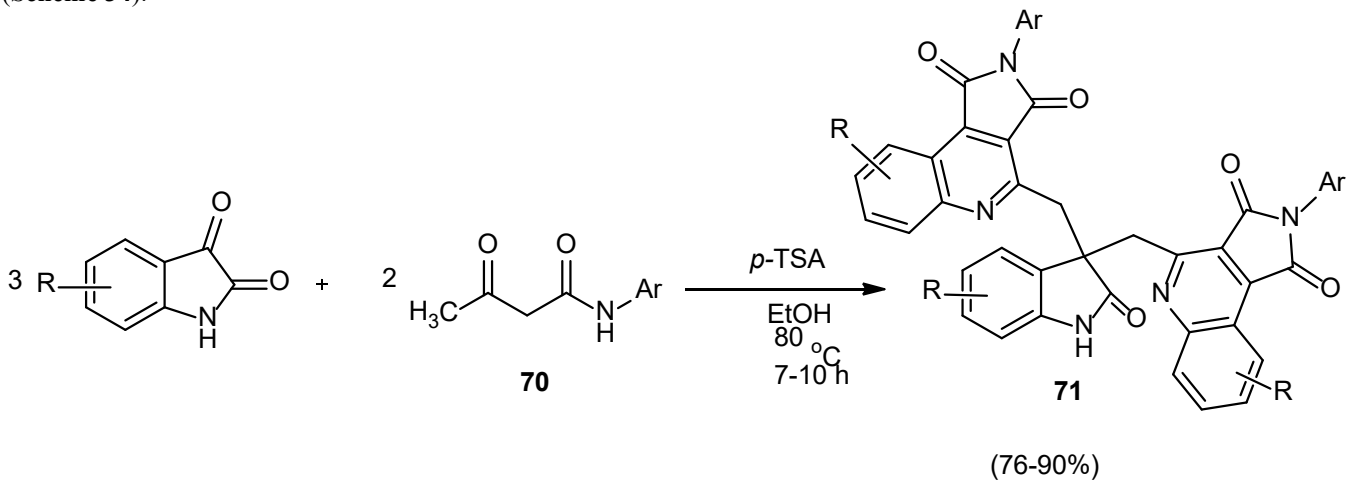
Scheme 32. Preparation of spiro[1*H*-pyrazolo[3,4-*b*]benzo[*h*]dihydroquinolin-4,3-indolin-2-ones].

The reactions of isatins, urea and 1-(piperidin-1-yl)butane-1,3-dione or 1-morpholinobutane-1,3-dione (**68**) using *p*-TSA was applied for the preparation of spiroheterocycles compounds (**69**) (**Scheme 33**).[67]



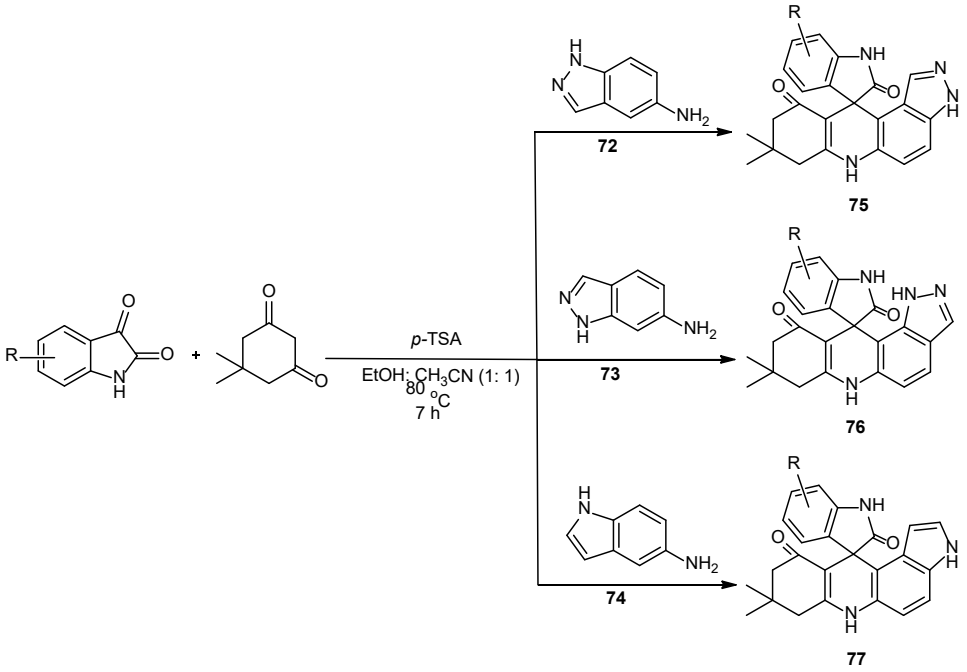
Scheme 33. The reactions of isatins, 1-(piperidin-1-yl)butane-1,3-dione or 1-morpholinobutane-1,3- dione and urea.

P-TSA was also used to catalyze the five-component reaction of isatins and 3-oxo-*N*-arylbutanamide (**70**) for the synthesis of 4,4′-((2-oxoindoline-3,3-diyl)bis(methylene))bis(2-aryl-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione) (**71**) (**Scheme 34**).[68]



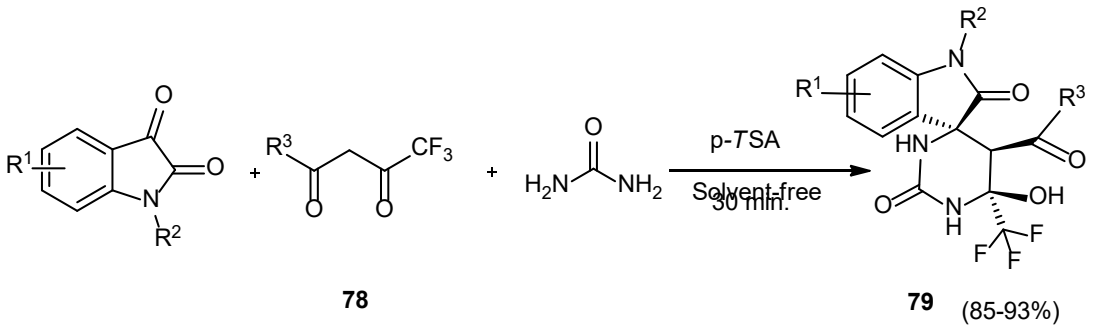
Scheme 34. Five-component synthesis of 4,4′-((2-oxoindoline-3,3-diyl)bis(methylene))bis(2-aryl-1*H*-pyrrolo[3,4-*c*]quinoline-1,3-(2*H*)-dione).

The synthesis of spiroacridinone derivatives (**75-77**) from the reaction of isatins, dimedone, and5-aminoindazole (**72**) (6-aminoindazole (**73**) or 5-aminoindole (**74**)) using *p*-TSA in mixed solvent (EtOH and CH_3CN) was addressed (**Scheme 35**).[69]



Scheme 35. Synthesis of spiroacridinone derivatives.

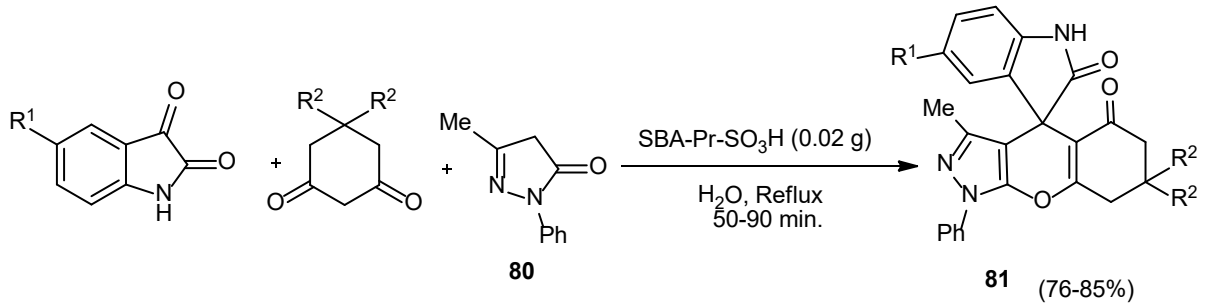
The reactions of isatins, urea, and different diketones under solvent-free conditions using TsOH as catalyst have applied for the synthesis of of 5′,6′-dihydro-6′-hydroxy-6′-(trifluoromethyl)-1′*H*-spiro[indoline-3,4′-pyrimidine]-2,2′(3′*H*)-dione derivatives (**79**) (**Scheme 36**).[70] The spiroheterocyclic compounds with trifluoromethyl group (**79**) were prepared from Biginelli reaction of isatins, 4,4,4-trifluoro-1-(thien-2-yl)butane-1,3-dione (**78**) and urea. Because Biginelli reaction was often performed under acidic condition, TsOH was selected as a preferred catalyst for this reaction.



78 **79** (85-93%)

Scheme 36. Synthesis of 5′,6′-dihydro-6′-hydroxy-6′-(trifluoromethyl)-1′*H*-spiro[indoline-3,4′-pyrimidine]-2,2′(3′*H*)-diones.

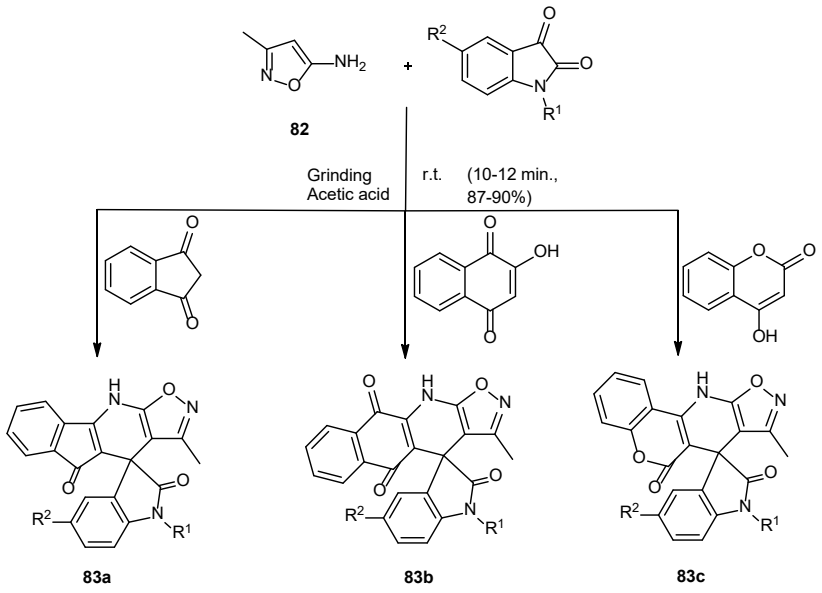
SBA-PrSO_3H (sulfonic acid-functionalized mesoporous silica) as an efficient heterogeneous solid acid catalyst was utilized for the synthesis of spiro[chromeno[2,3-*c*]pyrazole-4,3′-indoline]-2′,5(6*H*)-diones **(81**) via cyclocondensation reaction of isatins, 1,3-cyclohexadiones and pyrazolone (**80**) in aqueous media (**Scheme 37**).[71] The antimicrobial activities of the synthesized compounds were also tested.



80 **81** (76-85%)

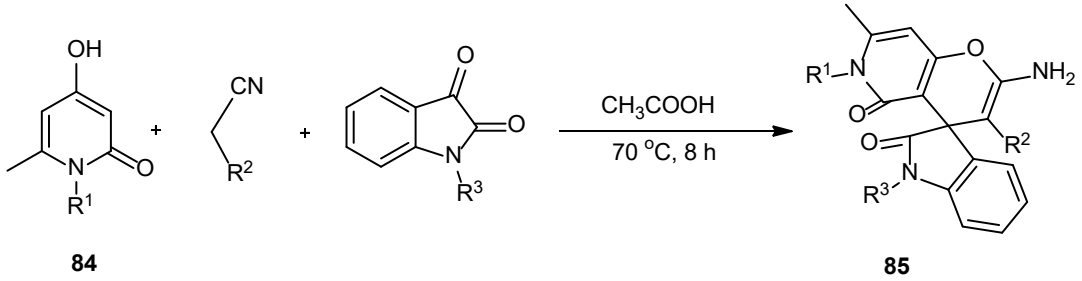
Scheme 37. Formation of spiro[chromeno[2,3-*c*]pyrazole-4,3′-indoline]-2′,5(6*H*)-diones in the presence of SBA-PrSO_3H.

Jinal et al.[72] have applied grinding condition for the synthesis of spiro-isoxazolo[5,4- *b*]pyridines/ quinolines (**83a-c**) by one pot condensation of isatins, 3-methylisoxazol-5-amine (**82**) and enolizable cyclic carbonyl compounds under solvent-free condition in presence of catalytic CH_3COOH at room temperature (**Scheme 38**).



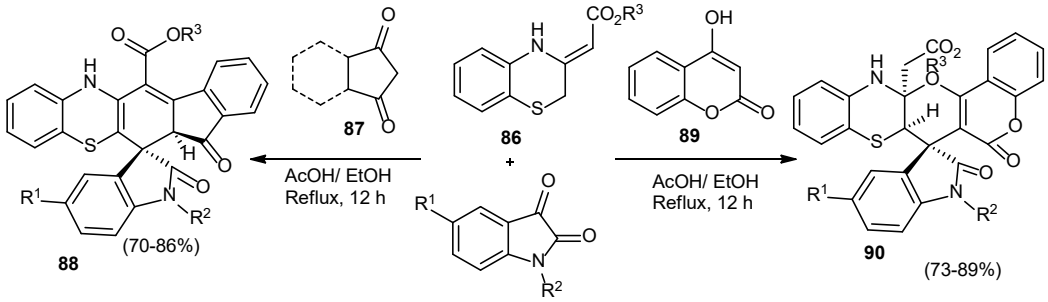
Scheme 38. Formation of spiro-isoxazolo[5,4- *b*]pyridines/ quinolines under grinding conditions.

In 2023,[73] synthesis of 4-hydroxy-2-pyridone-fused spiropyran derivatives (**85**) through the reaction of 4-hydroxy-6-methylpyridine-2-ones alkaloids (**84**), malononitrile or ethyl cyanoacetate, and isatin derivatives in ethanol and in the presence of acetic acid at 70 °C, was reported (**Scheme 39**). In the study, instead of isatin, ninhydrin was also used at ambient temperature.



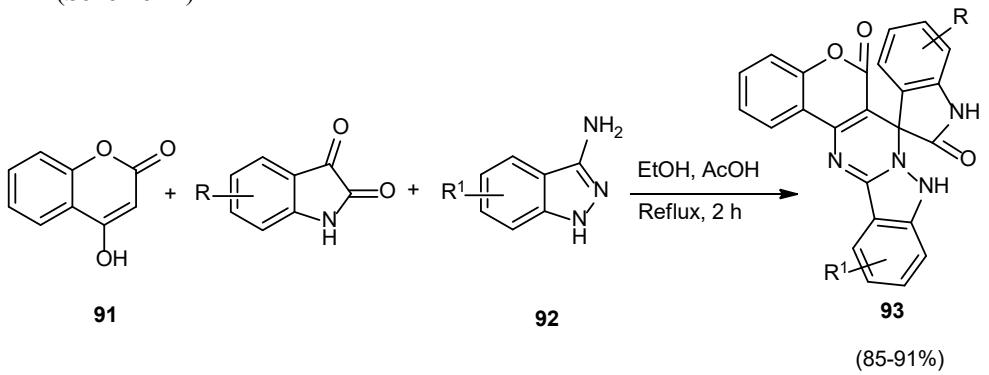
Scheme 39. Synthesis of 4-hydroxy-2-pyridone-fused spiropyran derivatives.

The reaction of alkyl 2-(benzo[*b*][1,4]thiazin-3-ylidene)acetates (**86**), isatins, and 1,3-indanedione or 1,3-cyclopentanedione (**87**) in ethanol in the presence of acetic acid afforded spiro[indeno[1,2-*b*]phenothiazine-6,3'-indolines] or spiro[cyclopenta[*b*]phenothiazine-4,3'-indolines] (**88**) with high diastereoselectivity (**Scheme 40**).[74] The similar three-component reaction with 4-hydroxychromen-2-one (**89**), was used for the preparation of spiro[benzo[*b*]chromeno-[3',4':5,6]pyrano[2,3-*e*][1,4]thiazine-7,3'-indolines] (**90**).



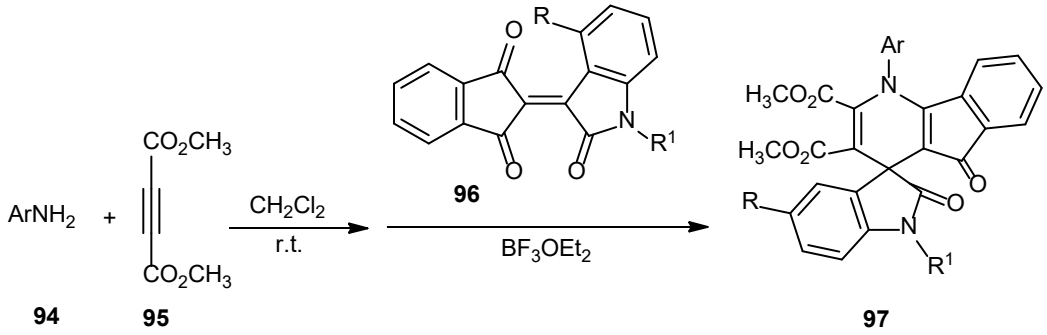
Scheme 40. Synthesis of spirooxindoles fused cyclic mercaptosubstituted enamino esters in the presence of acetic acid.

The formation of spiro[chromeno[4′,3′:4,5]pyrimido[1,2-*b*]indazole-7,3′-indoline]-2′,6(9*H*)-dione derivatives (**93**) was studied by condensation of 4-hydroxy-2*H*-chromen-2-one (**91**), isatin, and 1*H*-indazole-3-amine (**92**), in the presence of acetic acid in EtOH (**Scheme 41**).[75]



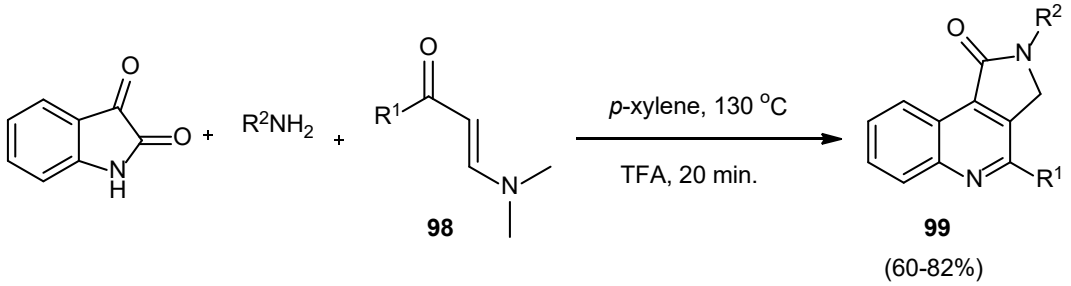
Scheme 41. Preparation of spiro[chromeno[4′,3′:4,5] pyrimido[1,2-*b*]indazole-7,3′-indoline]-2′,6(9*H*)-dione derivatives in the presence of acetic acid.

Formation of spiro[indeno[1,2-*b*]pyridine-4,3'-indolines] (**97**) was reported using Lewis acid $BF_3 \cdot OEt_2$ via cycloaddition reaction of 2-isatylidene-1,3-indanedione (**96**), which were prepared by the base catalyzed condensation of isatins with 1,3-indanedione, with *β*-enamino esters generated from addition of arylamines (**94**) to dimethyl acetylenedicarboxylate (**95**) (**Scheme 42**).[76] It was mentioned in the report, that isatins without *N*-alkyl group did not give the desired spiro compounds because the NH group in isatin would destroy the Lewis acid $BF_3 \cdot OEt_2$ in the reaction.



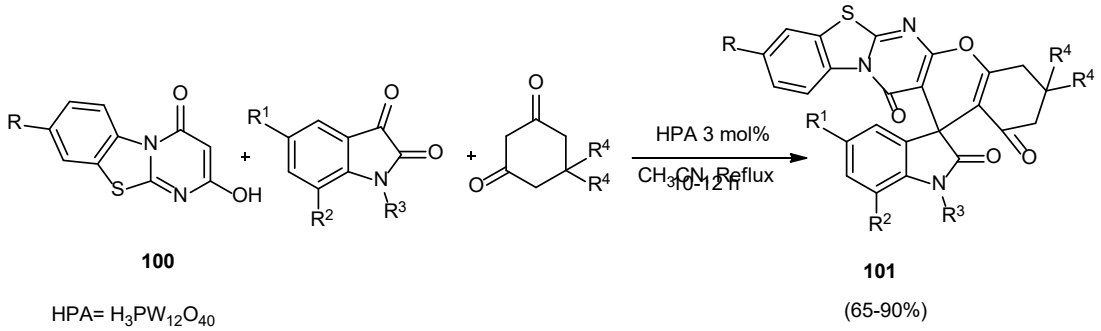
Scheme 42. Synthesis of spiro[indeno[1,2-*b*]pyridine-4,3'-indolines] using $BF_3{\cdot}OEt_2$

Trifluoroacetic acid (TFA) was utilized for synthesis of pyrrolo[3,4-*c*]quinoline-1-one derivatives **(99**) via a three-component cascade reaction of enaminones (**98**), amines, and isatin in *p*-xylene at 130 °C (**Scheme 43**).[77]



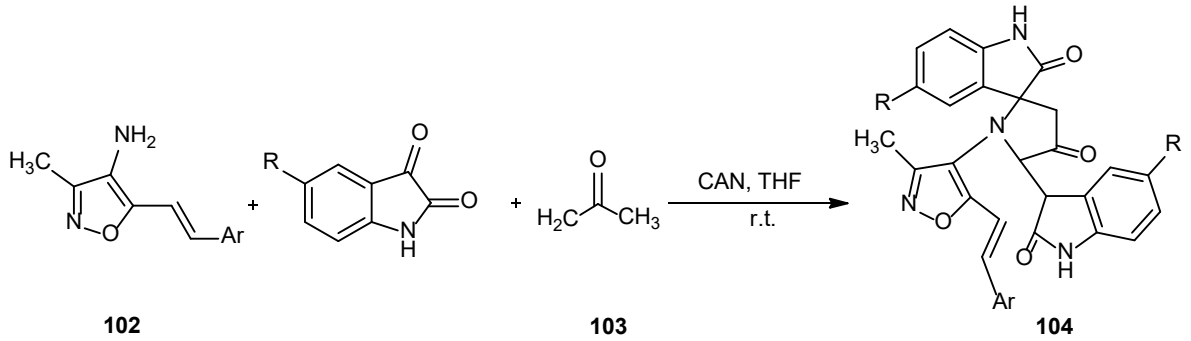
Scheme 43. Formation of pyrrolo[3,4-c]quinoline-1-one derivatives using TFA.

12-tungstophosphoric acid ($H_3PW_{12}O_{40}$) as an effective catalyst was used for the synthesis of spiro[benzo[4,5]thiazolo[3,2-*a*]chromeno[2,3-*d*]pyrimidine-14,3'-indoline]-1,2',13(2*H*)-triones (**101**) *via* the domino Knoevenagel condensation–Michael addition–intermolecular cyclization sequences of isatin derivatives, cyclohexane-1,3-diones, and 2-hydroxy-4*H*-benzo[4,5]thiazolo[3,2-*a*]pyrimidin-4-ones (**100**) in refluxing CH_3CN (**Scheme 44**).[78] Authors have tested various acid including acetic acid, *p*-toluenesulfonic acid, and L-proline, and the among of selected acids, tungstophosphoric acid ($H_3PW_{12}O_{40}$) provided the best result. Heteropolyacids (HPAs) as strong Brønsted acids, particularly tungstophosphoric acid ($H_3PW_{12}O_{40}$), are stronger acid catalysts than conventional acid catalysts.



Scheme 44. Synthesis of novel spiro[benzo[4,5]thiazolo[3,2-*a*]chromeno[2,3-*d*]pyrimidine-14,3′-indoline]-1,2′,13(2*H*)-triones using $H_3PW_{12}O_{40}$.

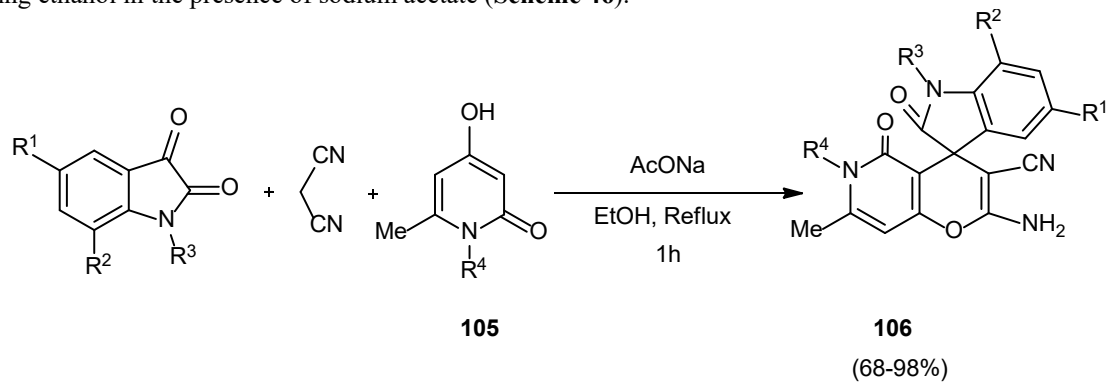
CAN is a suitable reagent for synthesis of heterocyclic compounds because of its solubility in organic solvents, low toxicity, and high reactivity. A CAN-catalyzed synthesis of isoxazolyl spiro[indoline-3,2′-pyrrolidine]-2,4′-diones (**104**) has addressed via reaction of isoxazole amine (**102**), differently substituted isatins, and acetone (**103**) at room temperature (**Scheme 45**).[79] Several catalysts and solvents have been tested in the model reaction by the authors and the optimum results were obtained with CAN in THF.



Scheme 45. CAN-catalyzed synthesis of isoxazolyl spiro[indoline-3,2′-pyrrolidine]-2,4′-diones.

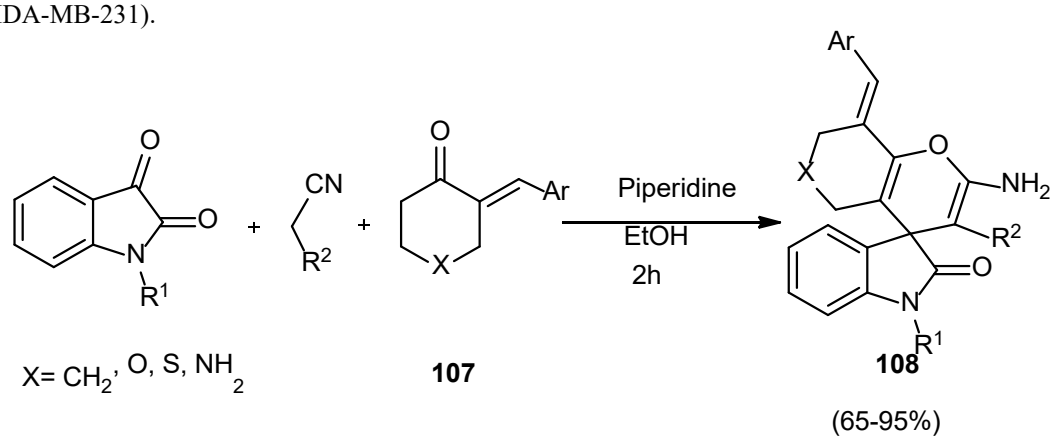
2.3. Using base catalyst

The multicomponent reaction of isatins, malononitrile and 4-hydroxy-6-methylpyridin-2(1*H*)-ones (**105**) was carried out to produce 2'-amino-7'-methyl-2,5'-dioxo-5',6'-dihydrospiro[indoline-3,4'-pyrano[3,2-*c*]pyridine]-3'-carbonitriles (**106**) in refluxing ethanol in the presence of sodium acetate (**Scheme 46**).[80]



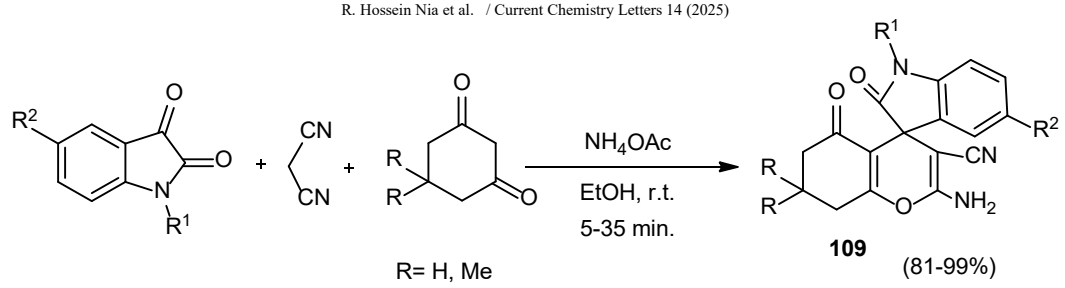
Scheme 46. Preparation of 2'-amino-7'-methyl-2,5'-dioxo-5',6'-dihydrospiro[indoline-3,4'-pyrano[3,2-*c*]pyridine]-3'-carbonitriles in the presence of sodium acetate.

A cyclization procedure for the synthesis of (E)-8′-arylidene-5′,6′,7′,8′-tetrahydrospiro[oxindole-3,4′-pyrano[3,2-*c*]pyridin] derivatives (**108**) was achieved via condensation of isatins, malononitrile and (E)-3-arylidene-1-methylpiperidin-4-ones (**107**) using piperidine as a base catalyst in ethanol (**Scheme 47**).[81] The authors examined various bases, such as piperidine, pyrrolidine, DIEA, DBU and triethylamine, and found that the highest yield for desired product was obtained when piperidine was selected as the catalyst. The authors also evaluated the antitumor activity of the products in human cervical carcinoma cell line (Hela), human liver hepatocellular carcinoma cell line (HepG2), and human breast carcinoma cell line (MDA-MB-231).



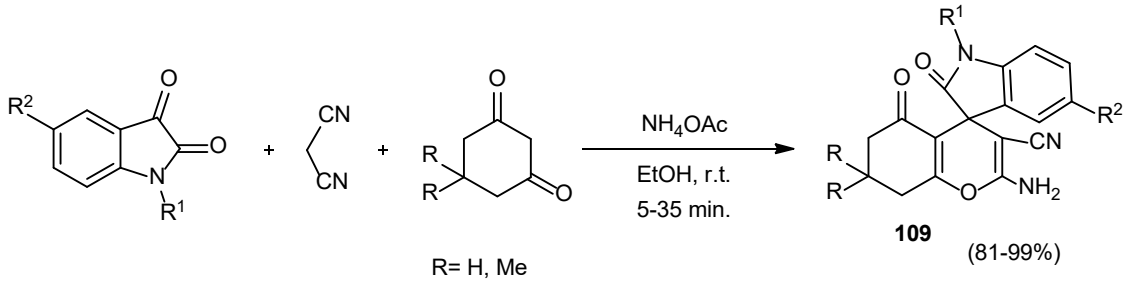
Scheme 47. Formation of (E)-8′-arylidene-5′,6′,7′,8′-tetrahydrospiro[oxindole-3,4′-pyrano[3,2-*c*]pyridin] derivatives in the presence of piperidine.

In 2023,[82] syntheses of spirooxindole derivatives **(109)** has achieved by combining Knoevenagel condensation and Michael addition between isatin, malononitrile, and dimedone or cyclohexan-1,3-dione in presence of ammonium acetate (NH_4OAc) by simple stirring in ethanol at room temperature (**Scheme 48**).



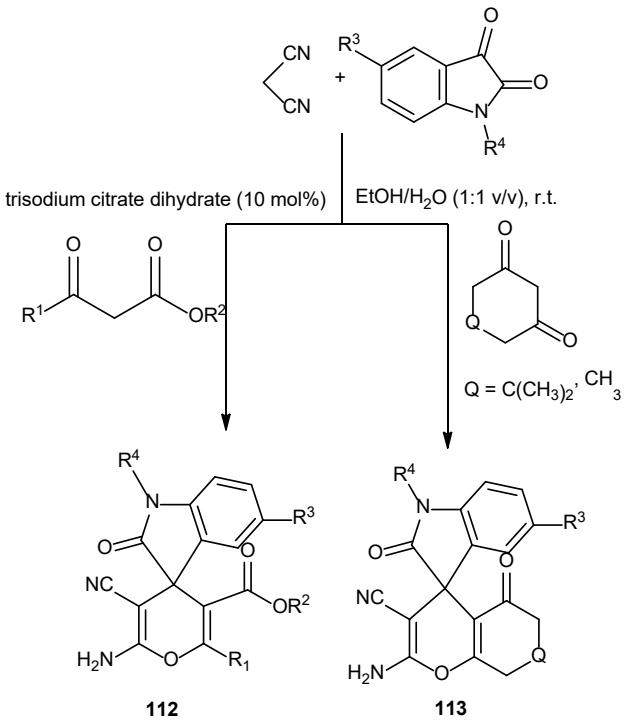
Scheme 48. Synthesis of spirooxindoles in the presence of ammonium acetate.

Synthesis of thiopyran fused spirooxindoles (**111**) was achieved by a multicomponent reaction of *N*-methyl isatin, malononitrile/ethyl cyanoacetate and *β*-oxodithioester (**110**) using *N,N′*-dimethylaminopyridine (DMAP) as the catalyst in CH_2Cl_2 (**Scheme 49**).[83]

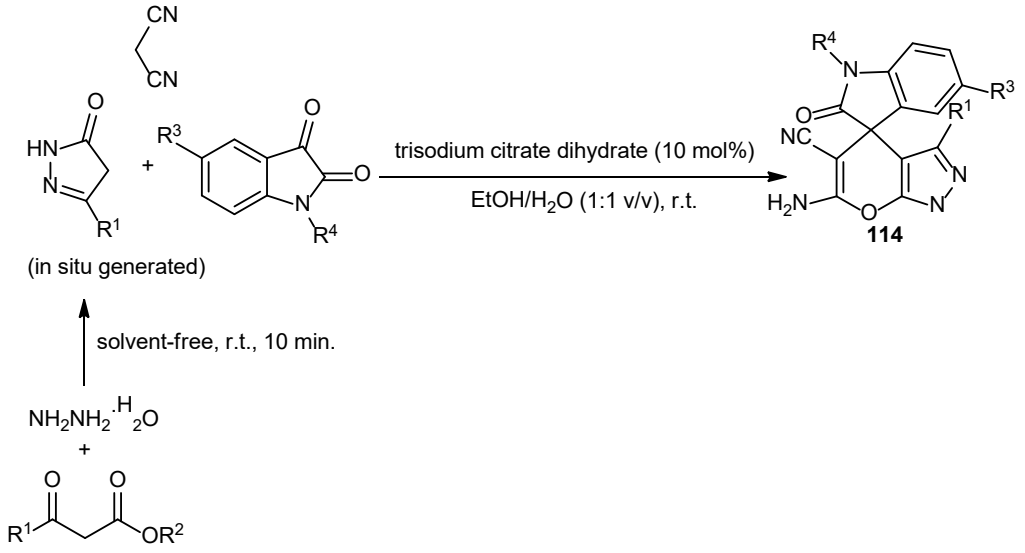


Scheme 49. Synthesis of thiopyran fused spirooxindoles in the presence of DMAP.

Synthesis of fused *O*- and *N*-heterocycles, such as spiro[indoline-3,4′-pyrans] (**112/113**) (**Scheme 50**) and spiro[indolin-2-one-3,4′-pyrano[2,3-c]pyrazoles (**114**) (**Scheme 51**), catalyzed by trisodium citrate dihydrate under ambient conditions was reported.[84] The synthetic protocol contains tandem Knoevenagel–cyclocondensation of isatin, malononitrile and various C-H activated acids in aqueous ethanol at room temperature. In this study, the production of other heterocycles was also reported by this protocol.

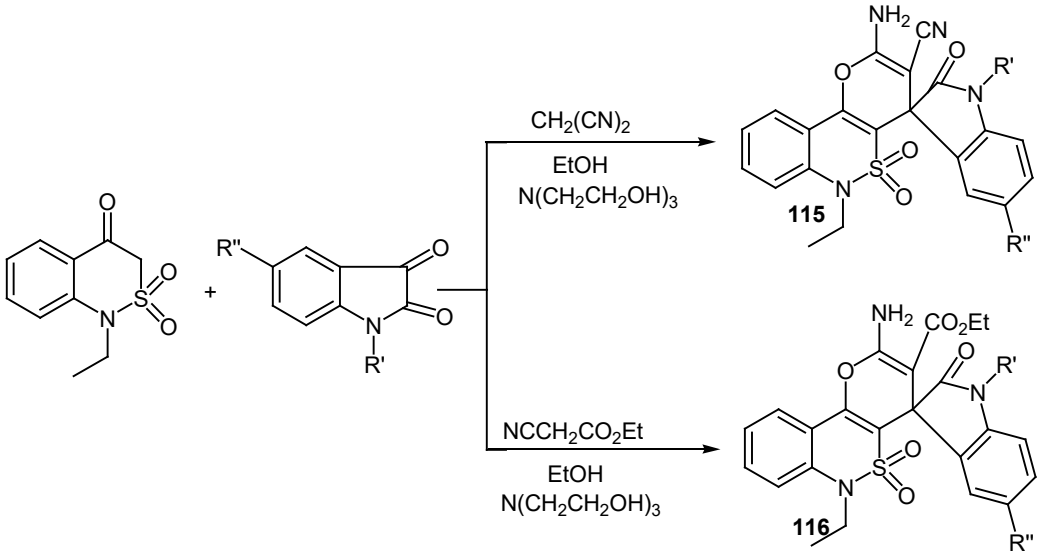


Scheme 50. Formation of spiroindolines using trisodium citrate dihydrate.



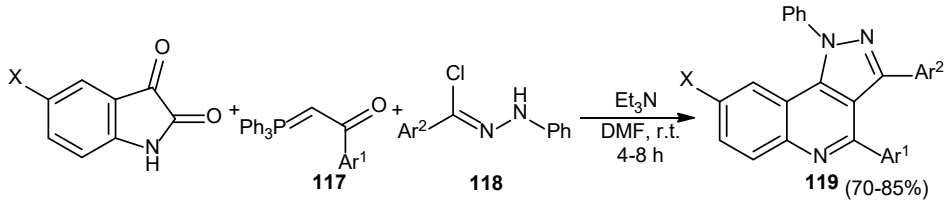
Scheme 51. Synthesis of synthesis of spiro[indolin-2-one-3,4′-pyrano[2,3-c]pyrazoles.

The derivatives of 2-amino-3-r-6-ethyl-4,6-dihydropyrano[3,2-*c*][2,1]benzothiazine-5,5-dioxide spirocombined with a 2-oxindole nucleus (**115** and **116**) were synthesized using triethanolamine under reflux for 30 min in ethanol (**Scheme 52**).[85]



Scheme 52. Synthesis of heterocycles with a 2-oxindole nucleus in the presence of triethanolamine.

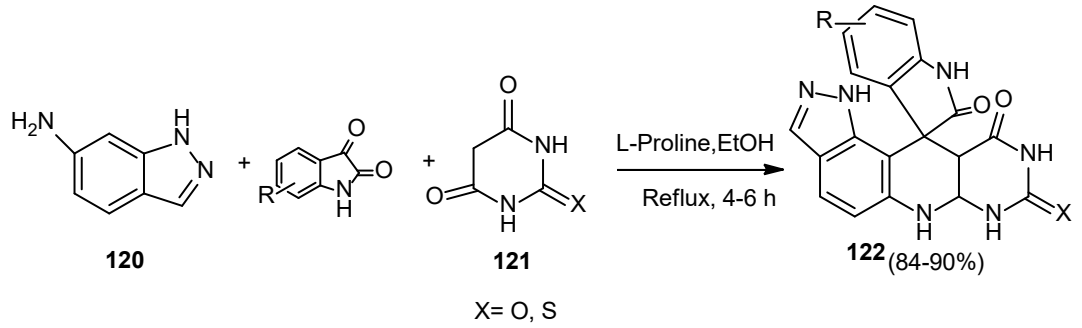
A series of pyrazolo[4,3-*c*]quinoline **(119)** was also prepared using Et_3N as catalyst (**Scheme 53**).[86] A multicomponent reaction was designed using isatins, 1-aryl-2-(1,1,1-triphenyl-λ^5-phosphanylidene)-1-ethanone **(117)** and hydrazonoyl chlorides **(118)** in the presence of Et_3N in DMF.



Scheme 53. Synthetic strategy for the formation of pyrazolo[4,3-*c*]quinolines.

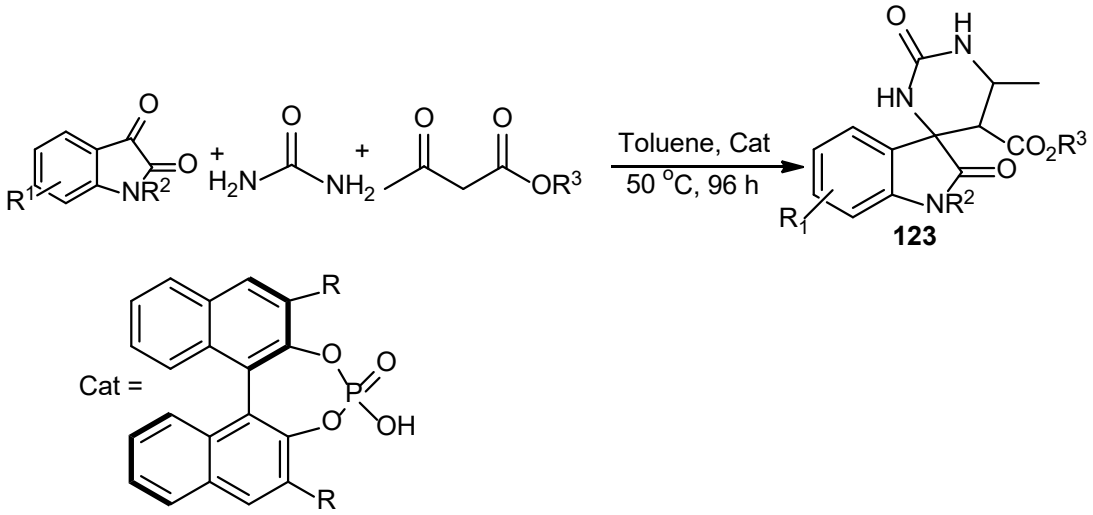
2.4. Using organic catalyst

Synthesis of spiro[indoline-3,11′-pyrazolo[3,4-*f*]pyrimido[4,5-*β*]quinoline] derivatives (**122**) was studied by one-pot condensation of 1*H*-indazol-6-amine (**120**), isatin and barbituric acid or 2-thiobarbituric acid (**121**), in refluxing EtOH in the presence of L-proline as organic catalyst (**Scheme 54**).[87]



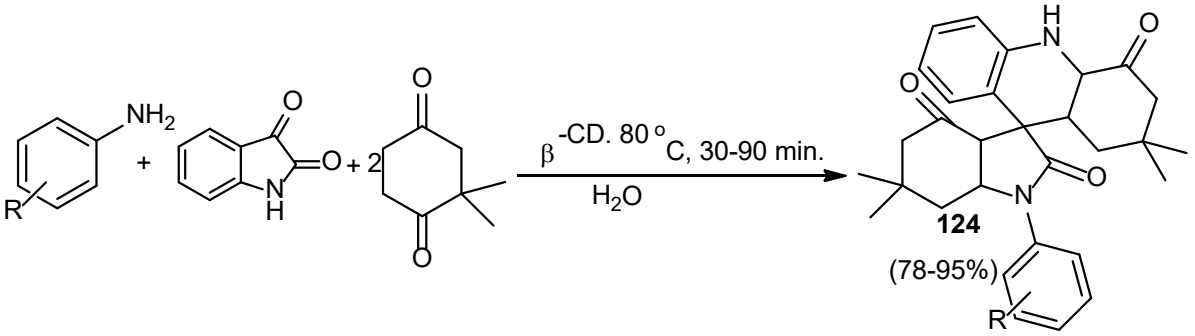
Scheme 54. Preparation of spiro[indoline-3,11′-pyrazolo[3,4-*f*]pyrimido[4,5-*β*]quinoline] derivatives using L-Proline.

Organocatalytic asymmetric Biginelli-like reaction involving isatin was reported.[88] The Brønsted acid-catalyzed Biginelli-like reaction carried out by employing *N*-substituted isatins as carbonyl substrates, urea and alkyl acetoacetates in the presence of (R)-BINOL-derived phosphoric acid for synthesis of spiro(indoline-pyrimidine)-diones derivatives (**123)** (**Scheme 55**).



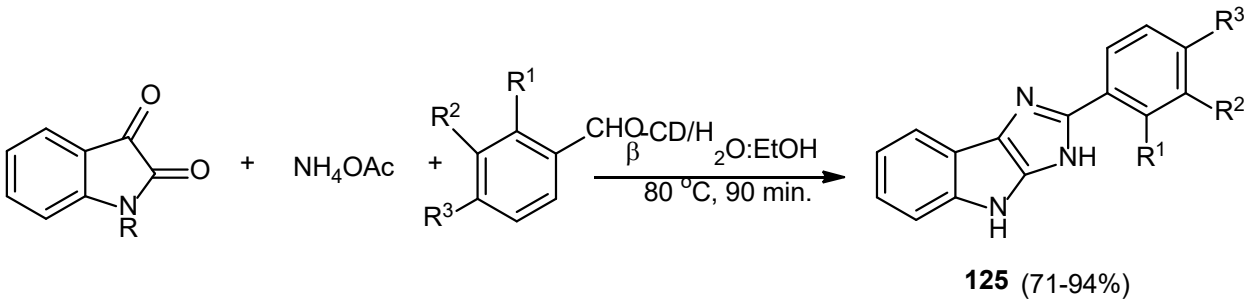
Scheme 55. Strategy used for the asymmetric construction of the spiro(indoline-pyrimidine)-dione scaffold.

An approach for the synthesis of spiro[acridine-9,3′-indole]-2′,4,4′(1′*H*,5′*H*,1′*H*)-trione derivatives (**124**) was addressed by one-pot four component condensation involving two equivalent of dimedone, substituted anilines, and isatin catalyzed by *β*-cyclodextrin (*β*-CD) in water at 80 °C (**Scheme 56**).[89] Synthesized compounds were also evaluated for their antimicrobial activities.



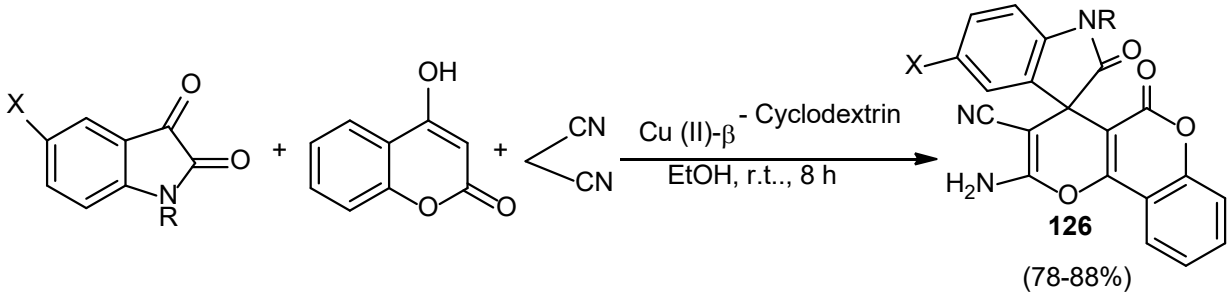
Scheme 56. The pathway for synthesis of spiro[acridine-9,3′-indole]-2′,4,4′(1′H,5′H,1′H)-trione derivatives using *β*-CD.

β-Cyclodextrin (*β*-CD) as a supramolecule, biodegradable, and recyclable catalyst was also used for the synthesis of 1,8-dihydroimidazo[2,3-*b*]indoles (**125**) via a three-component reaction of aldehyde, isatin, and ammonium acetate in H_2O–EtOH at 80°C (**Scheme 57**).[90]



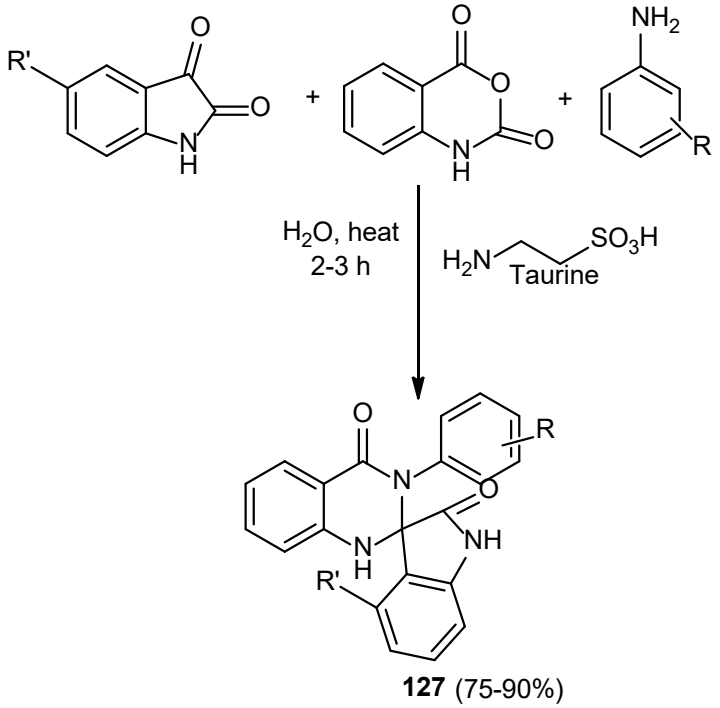
Scheme 57. Formation of 1,8-dihydroimidazo of 3,4- dihydroimidazo[4,5-*b*]indoles using *β*-Cyclodextrin.

Cu(II)-*β*-cyclodextrin catalyzed synthesis of spiro[indoline-3,4'-pyrano[3,2-*c*]chromene]-3'-carbonitriles (**126**) was investigated through the reaction of isatin derivatives, 4-hydroxycoumarin, and malononitrile in ethanol at room temperature (**Scheme 58**).[91]



Scheme 58. Cu(II)-*β*-cyclodextrin catalyzed synthesis of spiro[indoline-3,4'-pyrano[3,2-*c*]chromene]-3'-carbonitriles.

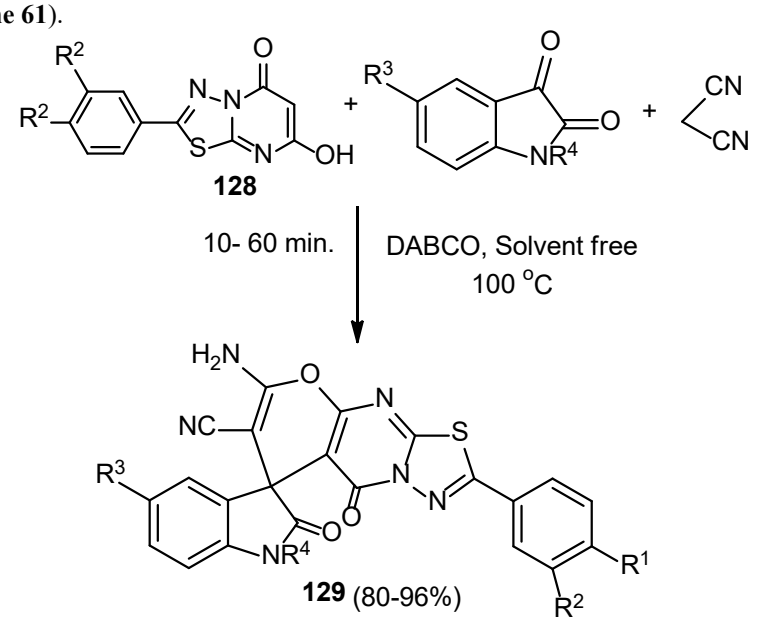
2-Aminoethanesulfonic acid (taurine) as organocatalyst was utilized for synthesis of spirooxindole dihydroquinazolinones (**127**) in water.[92] The reaction between isatoic anhydride, aniline and substituted isatines carried out (**Scheme 59**). In the report, it was mentioned, that taurine could be easily recovered and reused for at least three runs without any significant impact on the yield of the products. This protocol was also applied for the synthesis of 1,2-(dihydroquinazolin-3(4*H*)isonicotinamides.



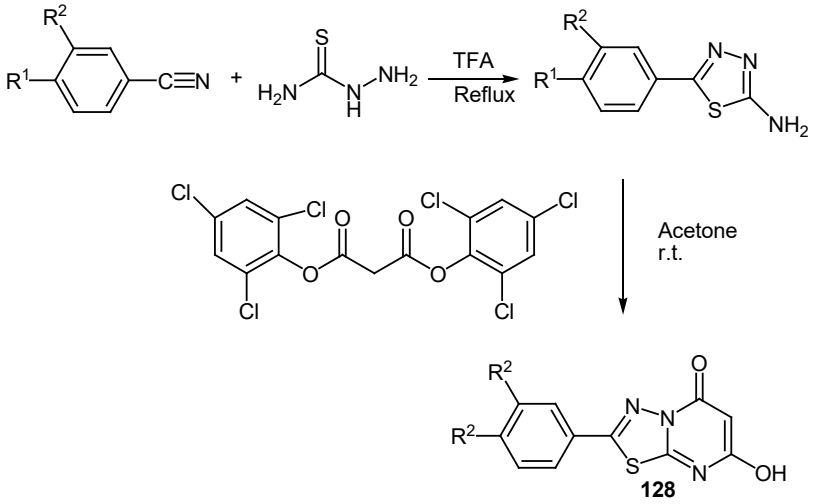
Scheme 59. The synthesis of 3′-phenyl-1′*H*-spiro[indoline-3,2′-quinazoline]-2,4′(3′*H*)-diones.

DABCO as organobase-catalyst was used for preparation of a family of spiro-pyrano-thiadiazolo-pyrimidine derivatives (**129**) via a one-pot three-component condensation reaction of 7-hydroxy-2-phenyl-5*H*-[1,3,4]thiadiazolo[3,2-a]pyrimidin-5-one derivatives (**128**), malononitrile and isatin compounds under solvent-free conditions (**Scheme 60**).[93] In this study,

derivatives of [1,3,4]thiadiazolo[3,2-*a*]pyrimidin-5-one (1**28**) were first prepared and then employed for the production of 6′-amino-2,9′-dioxo-2′-phenyl-9′*H*-spiro[indoline-3,8′-pyrano[2,3-*d*][1,3,4]thiadiazolo[3,2-a]pyrimidine]-7′-carbonitrile derivatives (**129**) (**Scheme 61**).

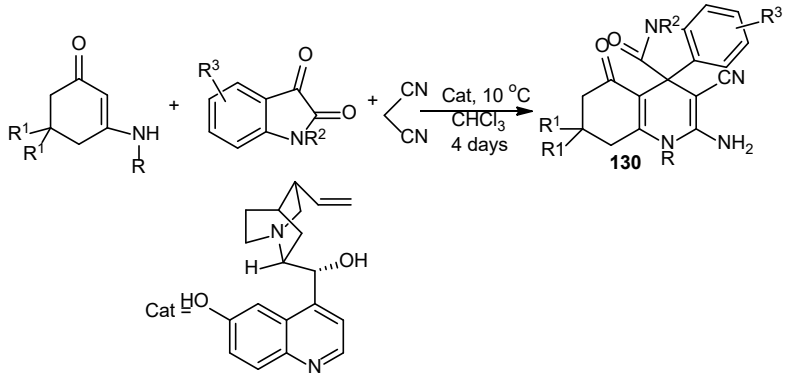


Scheme 60. Synthesis of 6′-amino-2,9′-dioxo-2′-phenyl-9′H-spiro[indoline-3,8′-pyrano[2,3-*d*][1,3,4]thiadiazolo[3,2-*a*]pyrimidine]-7′-carbonitriles.



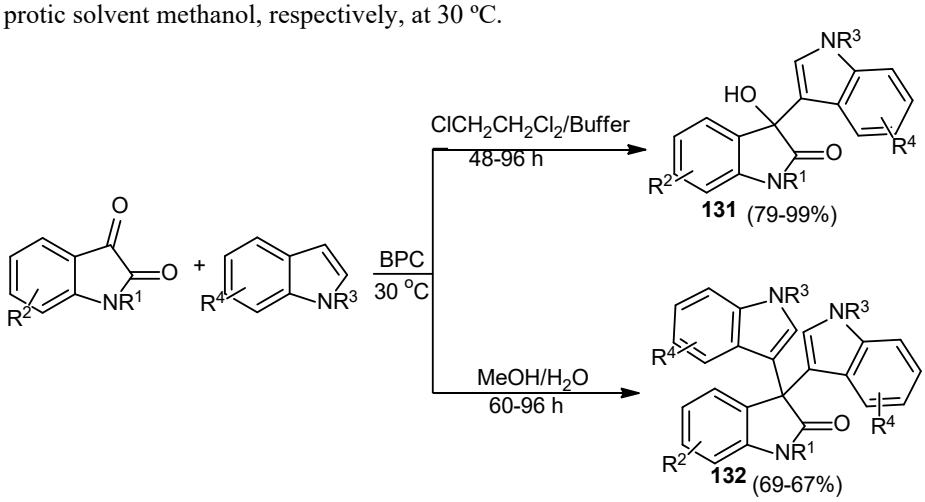
Scheme 61. Formation of [1,3,4]thiadiazolo[3,2-*a*]pyrimidin-5-one derivatives.

The asymmetric multicomponent [3+3] cyclization of cyclic enaminone, isatin, and malononitrile was catalyzed by a tertiary amine-based bifunctional organocatalyst for the synthesis of tetrahydroquinolin-5-one-based spirooxindoles (**130**) (**Scheme 62**).[94]



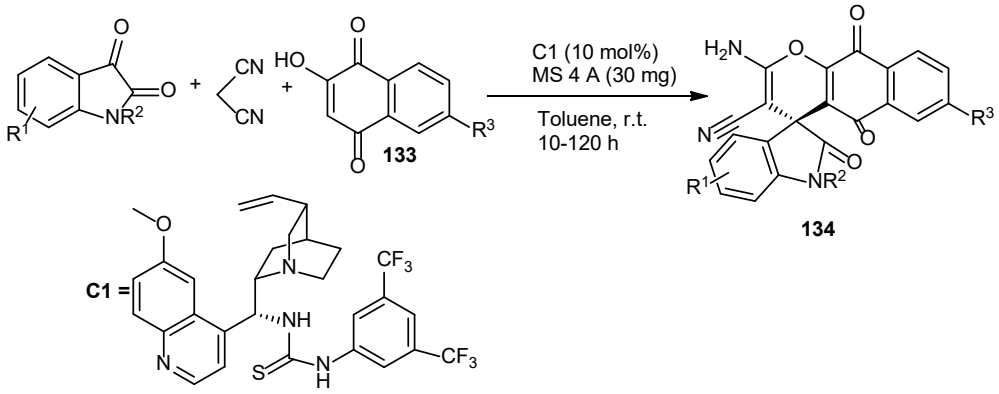
Scheme 62. Asymmetric cyclization of cyclic enaminone, isatin, and malononitrile.

Friedel-Crafts reactions between isatins and indoles catalyzed by *α*-chymotrypsin from bovine pancreas (BPC) was reported (**Scheme 63**).[95] The results of this research showed that the reaction can be controlled by the property of solvents, so that 3-hydroxy-oxindole (**131**) and 3,3-bis(indol-3-yl)indolin-2-one (**132**) derivatives were obtained in aprotic solvent $ClCH_2CH_2Cl$ and protic solvent methanol, respectively, at 30 ºC.



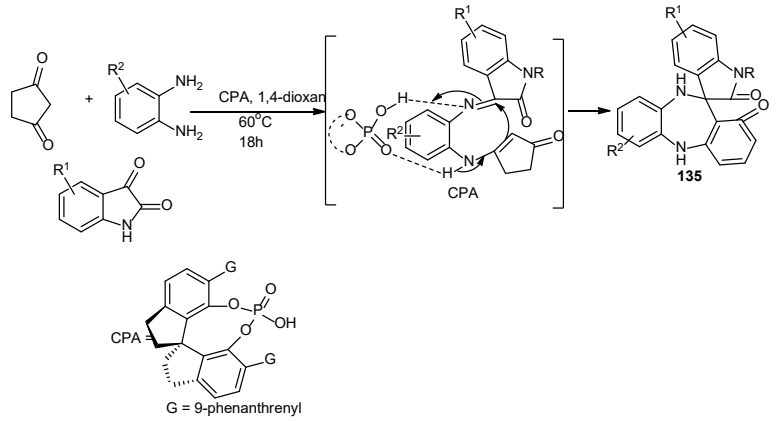
Scheme 63. reactions between isatins and indoles catalyzed by BPC.

Cinchona-thiourea organocatalyst **C1**, was used for three-component cascade reaction of isatins, malononitrile, and 2-hydroxynaphthalene-1,4-diones **(133)** to furnish chiral pyranonaphthoquinone-fused spirooxindoles **(134)** (**Scheme 64**).[96]



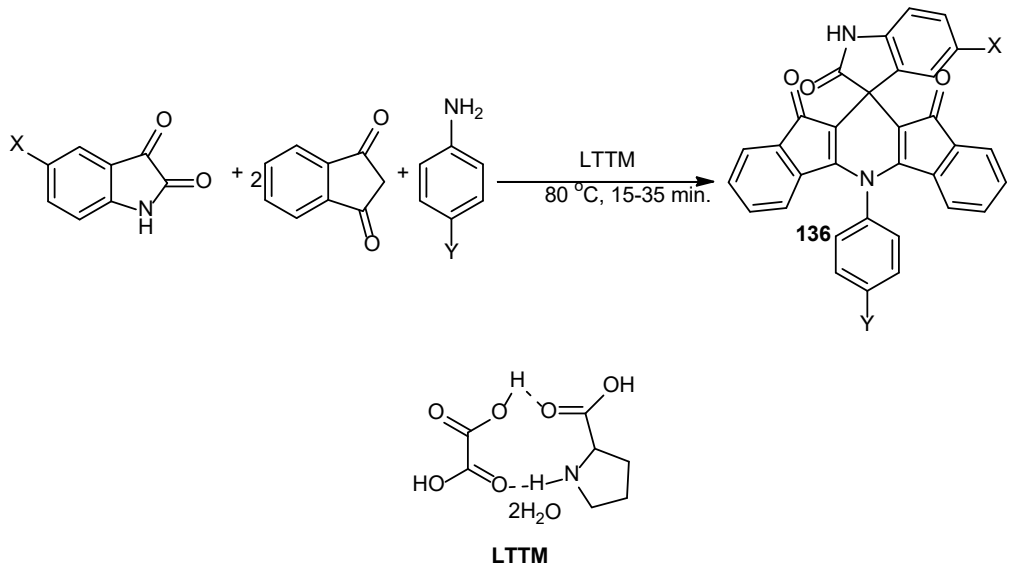
Scheme 64. Synthesis of chiral pyranonaphthoquinone-fused spirooxindoles using cinchona-thiourea organocatalyst.

A chiral spiro-phosphoric-acid-catalyzed asymmetric approach for synthesis of cyclopenta[1,4]diazepine scaffold (**135**) has been investigated through reaction between cyclopentane-1,3-dione, 1,2- phenylenediamine, and isatins in 1,4-dioxan at 60ºC (**Scheme 65**).[97] In the research, among a series of chiral phosphoric acids that were examined to prepare desired product, chiral spiro-phosphoric acid (CPA) exhibited the highest catalytic activity on controlling the enantioselectivity of the three-component tandem reaction.

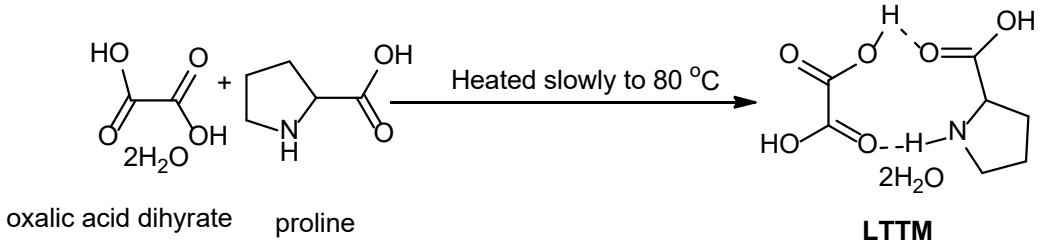


Scheme 65. CPA-catalyzed asymmetric reaction for synthesis of chiral cyclopenta[1,4]diazepine framework.

The green and resultant mixture of oxalic acid: proline (LTTM) as dual solvent/catalyst has been applied for synthesis of spiro[diindenopyridine-indoline] triones derivatives (**136**) through reaction between isatin, 1,3-indanedione and aniline at 80 °C (**Scheme 66**).[98] Firstly, The LTTM has been prepared by heating a mixture of proline and oxalic acid dihydrate (**Scheme 67**).[99] The hydrogen bonding nature of LTTM causes electrophilic activation of carbonyl group.

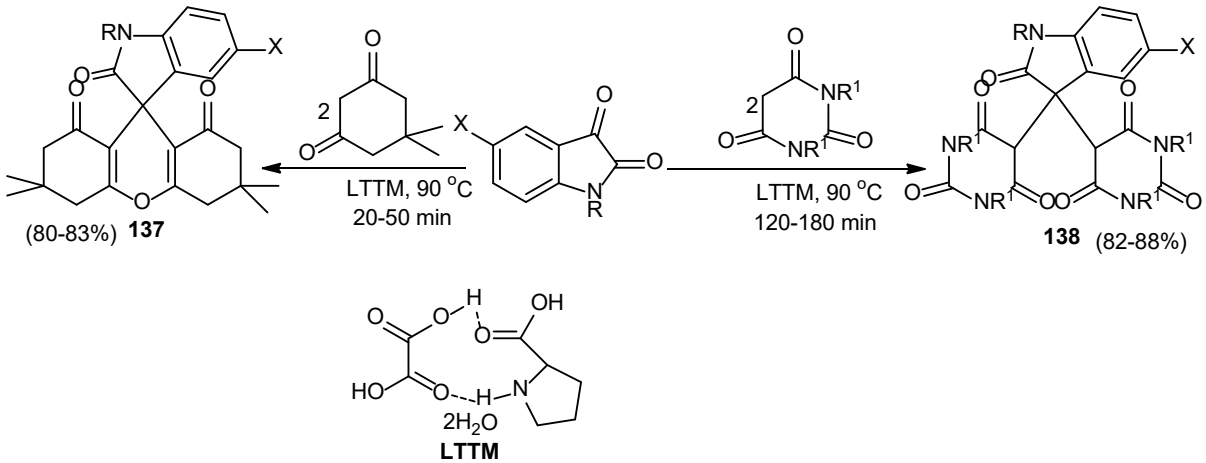


Scheme 66. Oxalic acid dihydrate: proline LTTM assisted synthesis of spiro[diindeno[1,2-b:2′,1′-*e*]pyridine-11,3′-indoline]-triones.



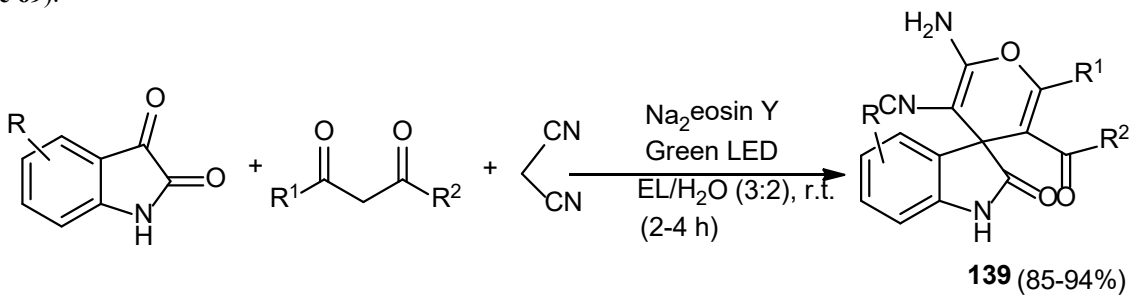
Scheme 67. Preparation of oxalic acid dihydrate: proline LTTM.

The mixture of oxalic acid: proline (LTTM) was also utilized for the synthesis of spiroxanthene (**137**) and dibarbiturate (**138**) derivatives (**Scheme 68**).[100] In the research, In the reaction of isatin with barbituric acid or dimethyl barbituric acid in the mixture of oxalic acid: proline (LTTM), conditions, instead of cyclized products, dibarbiturate derivatives of oxindole (**138**) were obtained.



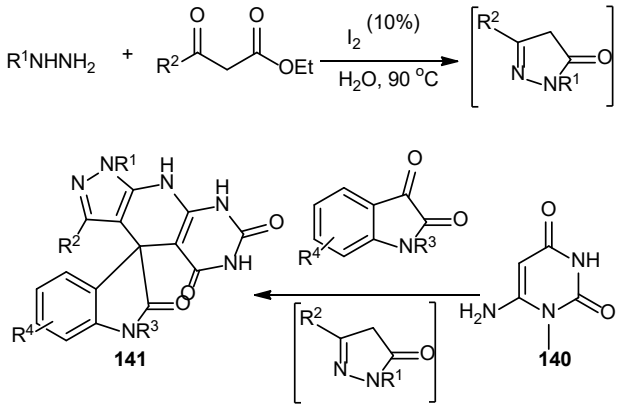
Scheme 68. LTTM promoted synthesis of spiro[indoline-3,9′- xanthene]trione and dibarbiturate derivatives.

The use of light as a rich, available and almost inexhaustible source of clean energy in green organic synthesis has attracted significant attention. visible light-mediated was used for synthesis of spiro[oxindole- 3,4'-(4'*H*-pyran)] derivatives (**139**) via reaction of isatins, 1,3-dicarbonyl compounds and malononitrile by using an inexpensive organic dye, Na_2eosin Y, as the photocatalyst in aqueous ethyl lactate under green LED irradiation and an air atmosphere at room temperature (**Scheme 69**).[101]



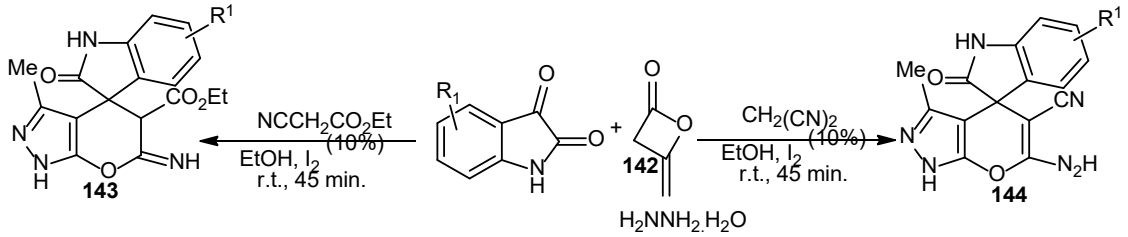
Scheme 69. Eosin Y-catalyzed synthesis of spiro[4*H*-pyran-oxindole] under visible light irradiation.

A green protocol for the synthesis of diversely substituted spiro pyrazolo-pyridopyrimidines (**141**) has been addressed via a four-component reaction of hydrazine, ethyl acetoacetate, 6-amino-1-methyluracil (**140**), and isatin catalyzed by iodine in water (**Scheme 70**).[102] In the investigation using aldehyde instead of isatin, pyrazolo-pyridopyrimidines was obtained.



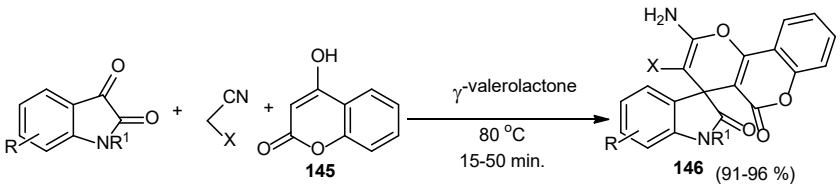
Scheme 70. Iodine catalyzed synthesis spiopyrazolo-pyrido-pyrimidines.

Iodine as an efficient catalyst was also used for production of spiro[indoline-3,4′- pyrano-pyrazole] carbonitrile derivatives (**143** and **144**) through a four-component reaction involving hydrazine hydrate, diketene (**142**), isatins, and malononitrile or ethyl cyanoacetate in ethanol at room temperature (**Scheme 71**).[103]



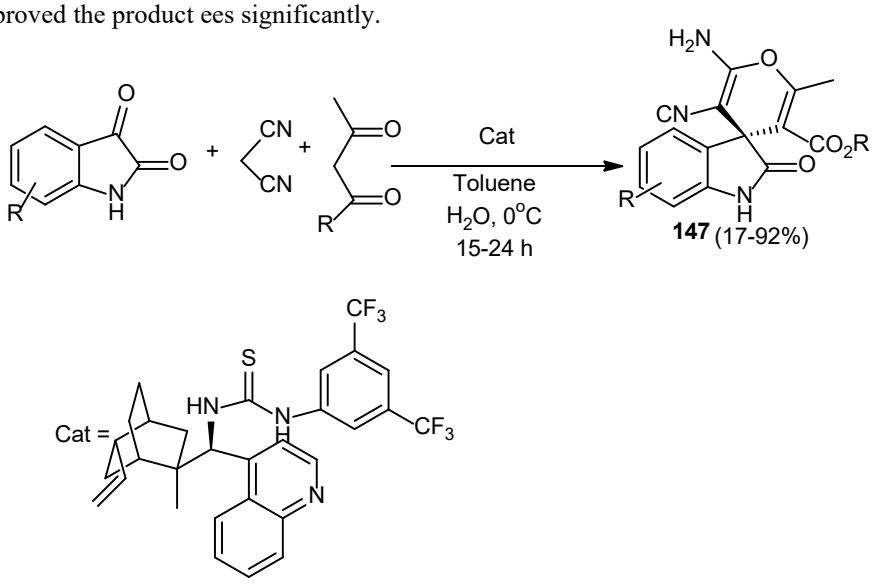
Scheme 71. Iodine-catalyzed synthesis of spiro[indoline-3,4′-pyrano-pyrazole] derivatives.

A green protocol using of γ- valerolactone as a green reaction media for the synthesis of spiro[indoline- 3,4′-pyrano[3,2-c]chromene derivatives (**146**) was reported (**Scheme 72**).[104] This approach involves reaction between substituted isatin, active methylene group, and 4-hydroxy coumarin (**145**) in γ-valerolactone at 80°C. The report states that the reaction medium can be recycled and reused several times without significant loss of its efficiency.



Scheme 72. Formation of spiro[indoline-3,4′-pyrano[3,2-*c*]chromene] derivatives in γ-valerolactone.

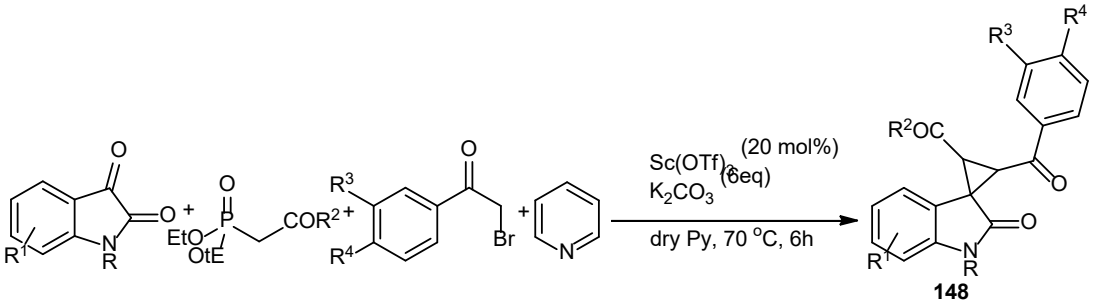
In 2019, a stereoselective reaction for the synthesis of spiro[4*H*-pyran-3,3′-oxindole] derivatives **(147**) was studied through an organocatalyzed domino Knoevenagel/Michael/ cyclization reaction using a cinchonidine-derived thiourea as the catalyst and water as the additive in toluene at 0 °C (**Scheme 73**).[105] In the report, it was stated that the use of water as the additive was improved the product ees significantly.



Scheme 73. Stereoselective reaction for the synthesis of spiro[4*H*-pyran-3,3′-oxindole] derivatives.

2.5. Using inorganic catalyst

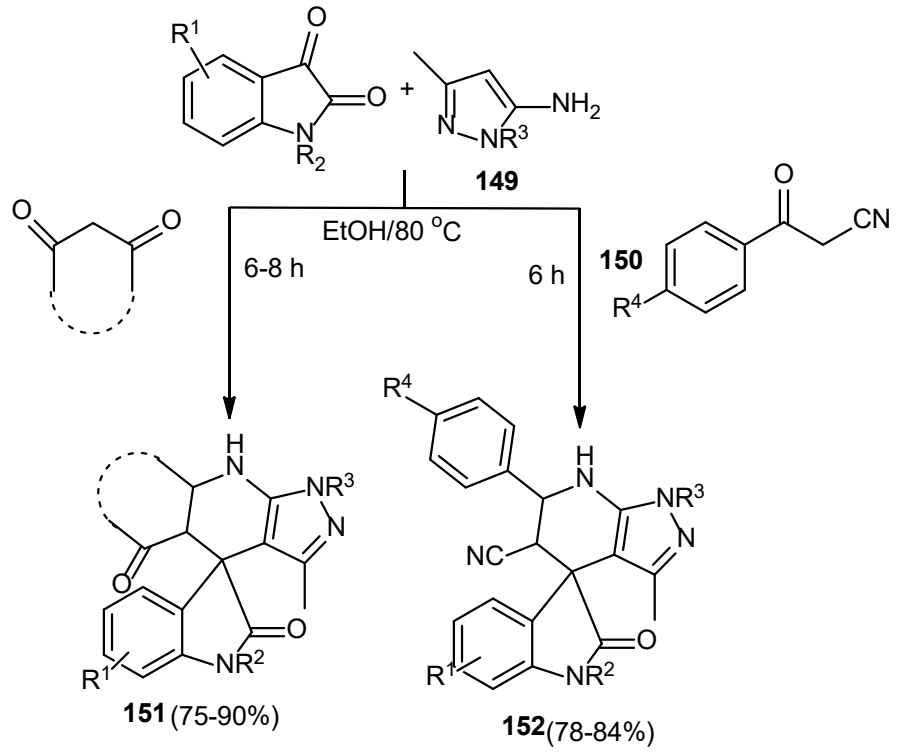
Inorganic catalysis has been utilized for the synthesis of isatin-containing heterocycles. Rare-earth heavy metals (REM), include a large family of heavy metals including 17 lanthanoid elements, yttrium, and scandium. As Lewis acid, they have been mostly used, as halogen or triflate salts, in organic synthesis. The synthesis of polysubstituted spirocyclopropyl oxindoles (**148**) using a series of rare-earth metal (REM) salts is reported (**Scheme 74**).[106] REMs, in particular $Sc(OTf)_3$, allowed access to the target compounds by a multicomponent reaction with high diastereoselectivity (≤94:6:0:0). Density functional theory calculations on the model reaction are consistent with the observed selectivity and revealed that the special coordinating capabilities and the oxophilicity of the metal are key factors in inducing the formation of one main diastereoisomer.



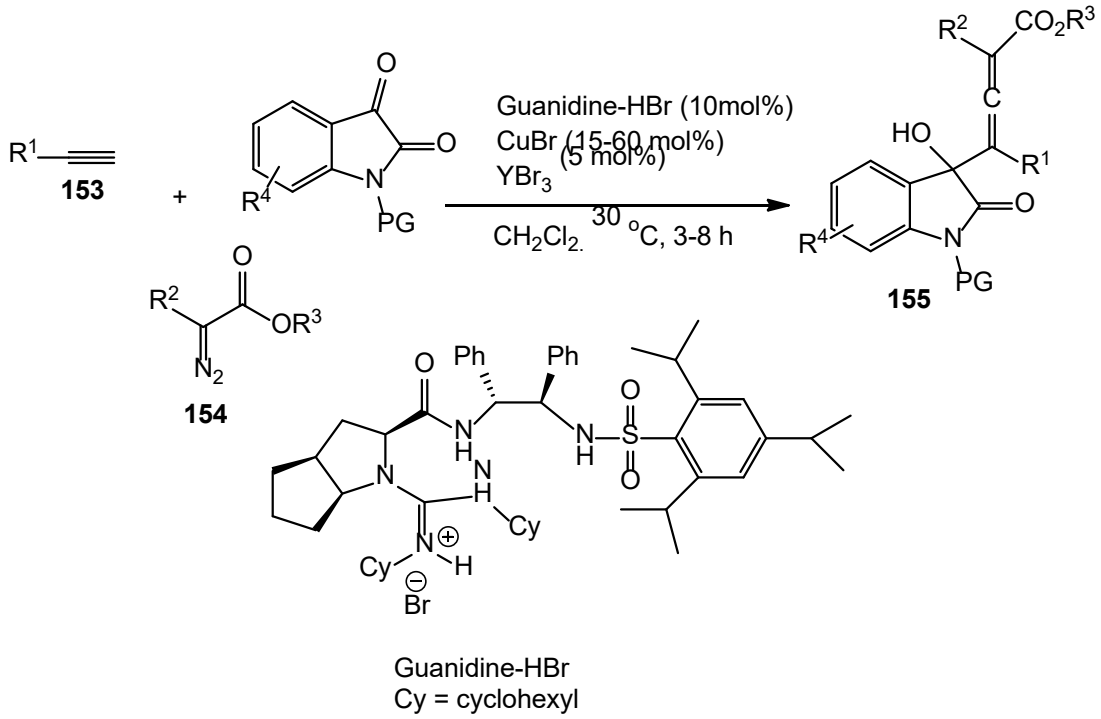
Scheme 74. Synthesis of spirocyclopropyl oxindoles using $Sc(OTf)_3$.

Synthesis of spirooxindole derivatives **(151** and **152**) catalyzed by copper triflate has studied through the reaction of isatin, 5-aminopyrazole (**149**), and 1,3-dicarbonylcompounds (or *β*-oxo-benzenepropanenitrile (**150**)) in ethanol (**Scheme 75**).[107]

The chiral guanidinium salt/CuBr/YBr_3 catalytic system has utilized for the synthesis of tetrasubstituted allenes (**155**) via asymmetric multicomponent reaction α-diazoesters (**154**), terminal alkynes (**153**), and isatins (**Scheme 76**).[108] In the research, the successful Cu(I)-involved asymmetric reaction of diazo compounds was achieved through the utilization of a multifunctional chiral guanidinium salt ligand. The unique multi-nitrogen structure of guanidine as organocatalyst provides variable opportunities for formation of designed acid catalysts.

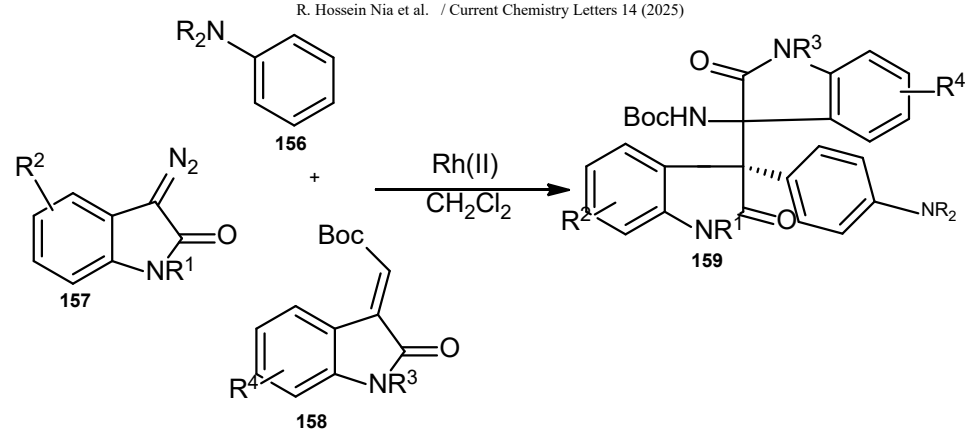


Scheme 75. $Cu(OTf)_2$-catalyzed synthesis of spirooxindoles.



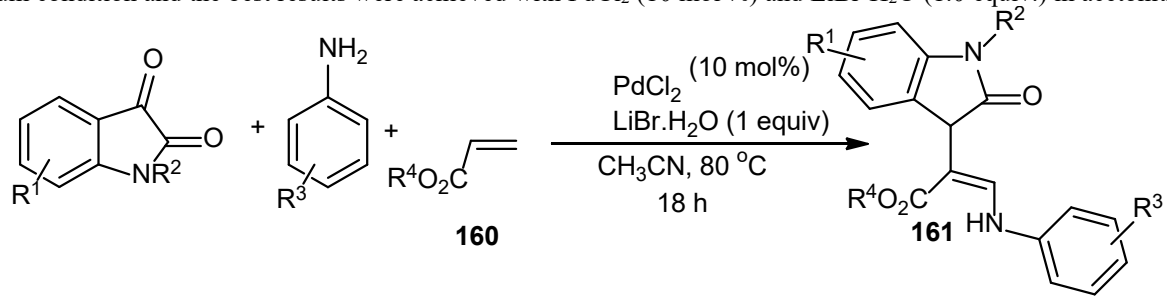
Scheme 76. Asymmetric formation of tetrasubstituted allenes by the combined-acid system.

Rhodium (II) was used for preparation of 3-amino-3'-aryl-bioxindole compounds (**161**) containing continuous quaternary carbons (**Scheme 77**).[109] A rhodium (II) catalyzed reaction of *N*,*N*-disubstituted anilines (**156**), 3-diazooxindoles (**157**) and isatin ketimines (**158**) to deliver the 3-amino-3'-aryl-bioxindoles (**159**). The proposed transformation involves the Mannich type trapping of a zwitterion intermediate that is initiated through the functionalization of an aromatic C-H bond.



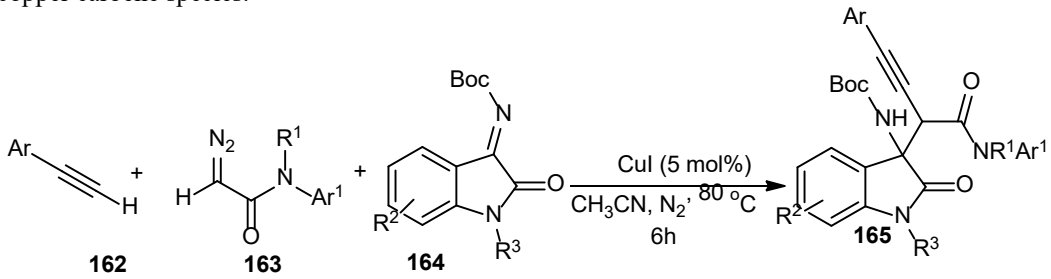
Scheme 77. Formation of bioxindole containing continuous quaternary carbons.

Pratap et al. have addressed the intermolecular dehydrogenative carboamination of alkenes (**160**) with aromatic amines and *N*-substituted isatin using palladium as a catalyst (**Scheme 78**).[110] The Authors examined different conditions to achieve optimum condition and the best results were achieved with $PdCl_2$ (10 mol %) and $LiBr{\cdot}H_2O$ (1.0 equiv.) in acetonitrile.



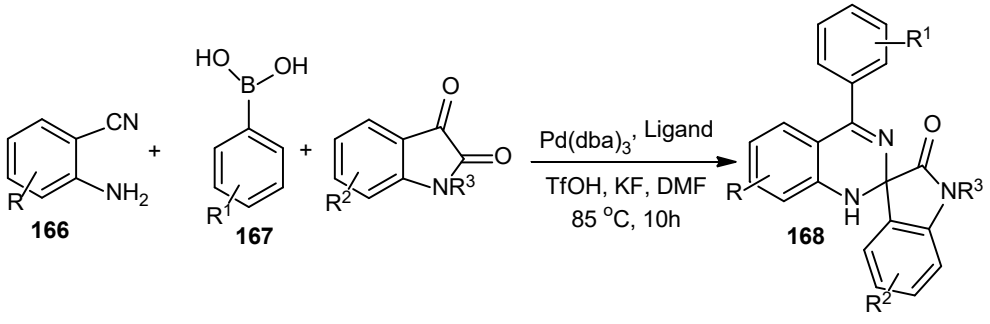
Scheme 78. Intermolecular dehydrogenative carboamination of alkenes.

Copper has utilized as catalyst in the reaction between terminal alkyne (**162**), *α*-diazo amide (**163**), and isatin ketimine (**164**) for synthesis of a series of alkynyl-containing 3,3-disubstituted oxindoles (**165**) (**Scheme 79**).[111] The proposed process involves the transformation proceeding via a Mannich-type trapping of an alkynoate copper intermediate from a terminal alkyne and copper carbene species.



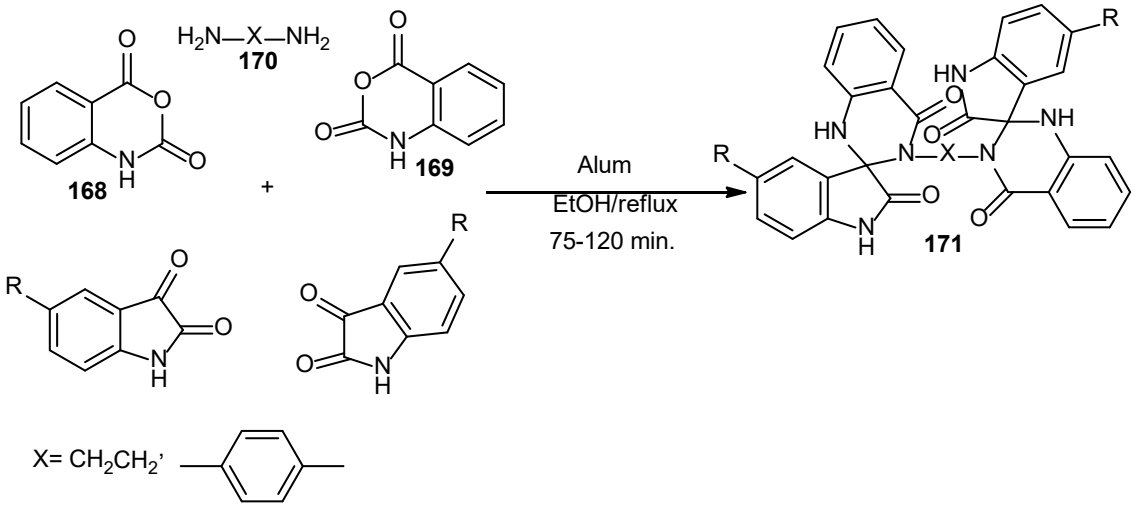
Scheme 79. Cu(I)-Catalyzed Reaction for the synthesis of a series of alkynyl-containing 3,3-disubstituted oxindoles.

A palladium-catalyzed strategy has been studied for synthesis of spiro(indoline-3,2'-quinazolin)-2-one derivatives (**168**) from 2-aminobenzonitriles (**166**), arylboronic acids (**167**) and isatins (**Scheme 80**).[112]



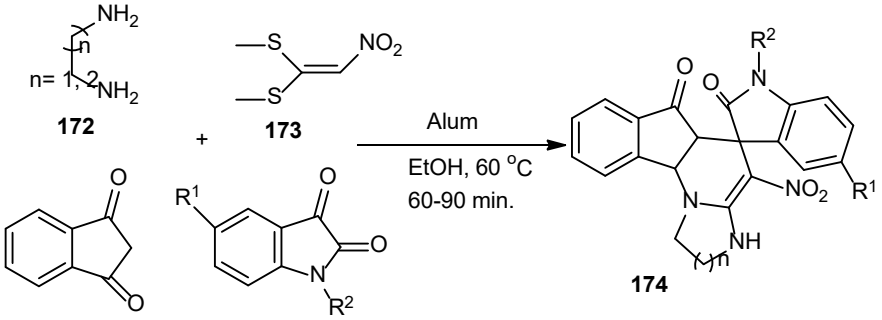
Scheme 80. A palladium-catalyzed strategy for synthesis of spiro(indoline-3,2'-quinazolin)-2-one derivatives.

A protocol for the synthesis of bis[spiro(quinazoline-oxindole)] derivatives (**170**) by one-pot pseudo five-component condensation of two molecules of isatoic anhydride (**169**), two molecules of isatins, and diamines (**170**) was catalyzed by Alum ($KAl(SO_4)_2.12H_2O$) as a non-toxic, reusable reagent (**Scheme 81**).[113] In the report, it was mentioned that in the reaction two diastereomers may be formed but ^{1}H-NMR spectra exhibited one diastereomer. Therefore, the reaction is diasteroselective. The stereochemistry of products cannot be established by the spectroscopic data. Though authors tried hardly, unfortunately, none of the compounds were crystalized properly for the X-ray crystallography.



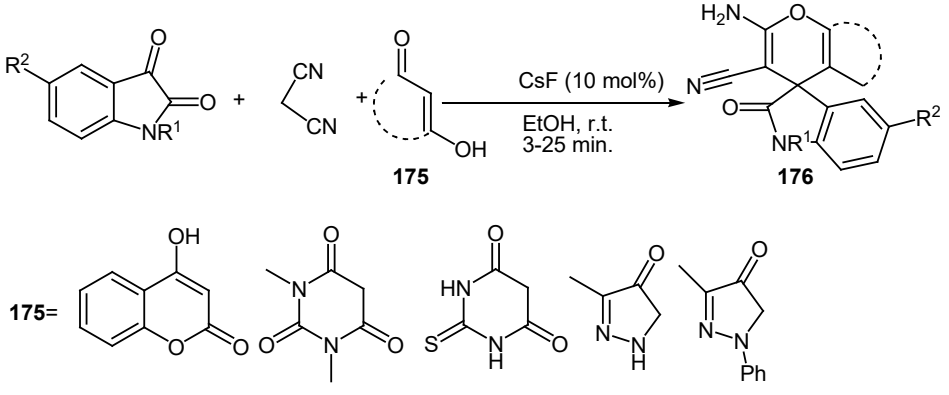
Scheme 81. Synthesis of bis[spiro(quinazoline-oxindole)] derivatives.

Alum ($KAl(SO_4)_2.12H_2O$) was also utilized for the condensation of isatin, 1,3-indandione, diamine (**172**), and nitro ketene dithioacetal (**173**) to prepare 4-nitro-2,3-dihydrospiro[imidazo [1,2-*α*]indeno[2,1-*e*] pyridine-5,3′-indoline]-2′,6(1*H*)-dione compounds (**174**) (**Scheme 82**).[114]



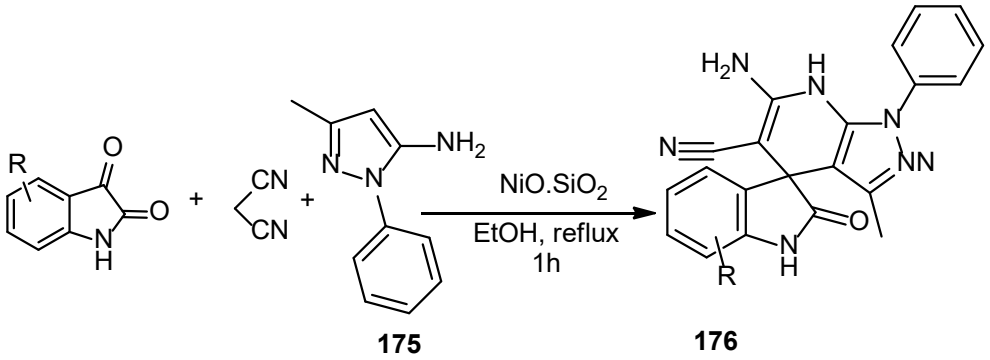
Scheme 82. Formation of 4-nitro-2,3-dihydrospiro[imidazo [1,2-*α*]indeno[2,1-e] pyridine-5,3′-indoline]-2′,6(1*H*)-dione in the presence of Alum.

In 2020, the use of CsF for the synthesis of spirooxindole-pyran annulated heterocycles **(176)** at room temperature in ethanol was reported (**Scheme 83**).[115] The procedure was based on CsF-promoted tandem Knoevenagel-Michael cyclocondensation reaction of isatin, malononitrile, and 4-hydroxycoumarin/ barbituric acids/pyrazolone (**175**), at room temperature in ethanol. In the proposed mechanism, CsF has a dual role as a base and carbonyl activator.



Scheme 83. CsF-promoted synthesis of spirooxindole-pyran annulated heterocycles.

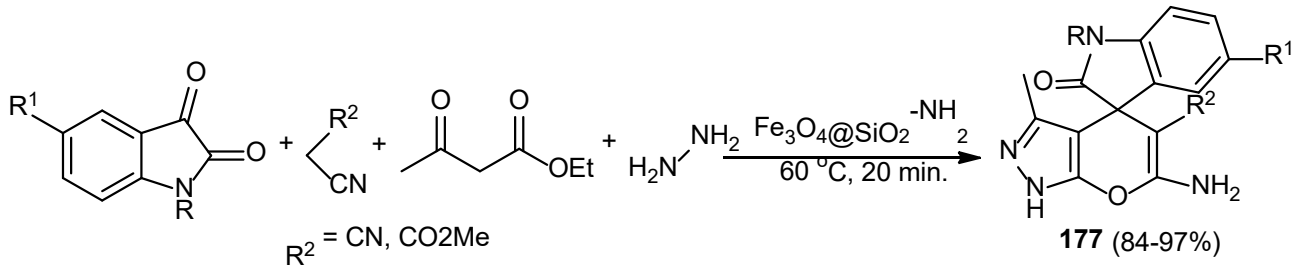
$NiO–SiO_2$ as reusable solid acid heterogeneous catalyst was used for the synthesis of spirooxindole-fused pyrazolo pyridine derivatives (**178**) via three-component reaction of isatin, 5-amino-3-methylpyrazole (**179**), and malononitrile in EtOH (**Scheme 84**).[116] The new compounds were also examined for *in-vitro* anti-microbial activity.



Scheme 84. Preparation of spirooxindole-fused pyrazolo pyridine derivativesin the presence of $NiO–SiO_2$ catalyst.

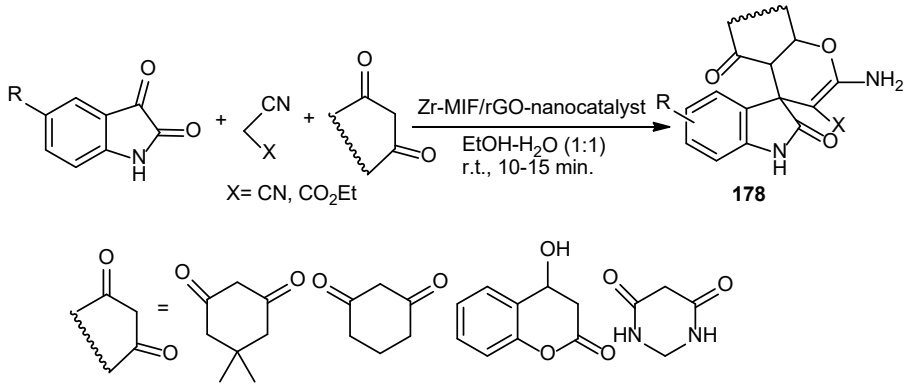
2.6. Using nano catalyst

(3-Aminopropyl)-triethoxysilane attached to $Fe_3O_4@SiO_2$ nanoparticles has been employed as a heterogeneous catalyst in the synthesis of spirooxindoles (**177**) in four-component reactions of isatin, methyl cyanoacetate or malononitrile, hydrazine hydrate, and ethyl acetoacetate (**Scheme 85**).[117] According to presented mechanism in the paper, the catalytic active site in $Fe_3O_4@SiO_2$ NPs is Fe^{+3} and Fe^{+2}, which behaves as a Lewis acid and attaches to carbonyl groups of ethyl acetoacetate, isatin, and nitriles to accelerate the conjugate and direct additions of nucleophiles to corresponding substrates. Another rule of the catalyst is related to basic ($-NH_2$) properties of functionalized Fe_3O_4, which plays a crucial catalytic role in the transformation.



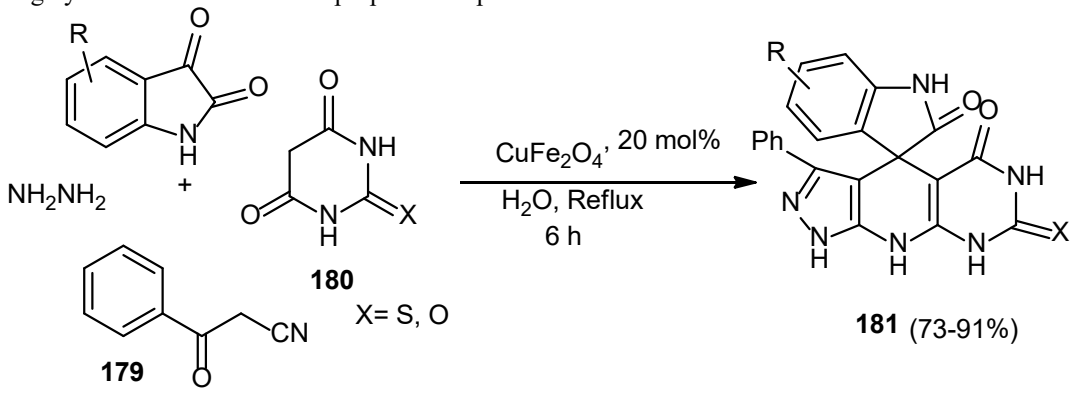
Scheme 85. Preparation of spirooxindoles in the presence of $Fe_3O_4@SiO_2$-NH_2 nanoparticles.

The coordination of metal ions and organic components results in the creation of well-ordered materials with a crystal-like structure, known as Metal-Organic Frameworks (MOFs). One of the tactics to increase the catalytic efficiency of MOFs is the introduction of graphene. Reduction of GO (rGO), graphene oxide (GO) to MOFs can lead to surprising improvements in conductivity, stability and selectivity.[118] Kumar and his research group,[119] have reported the synthesis and characterization of a Zr-based metal-organic framework fabricated on the surface of the rGO sheet (Zr-MOF/rGO) nanocomposites as a heterogeneous catalyst for the synthesis of spirooxindole derivatives (**178**) in aqueous ethanol environments. (**Scheme 86**). The reported protocol involves a reaction consists of satin, malononitrile, or ethyl cyanoacetate as well as several 1,3-dicarbonyl compounds at room temperature.



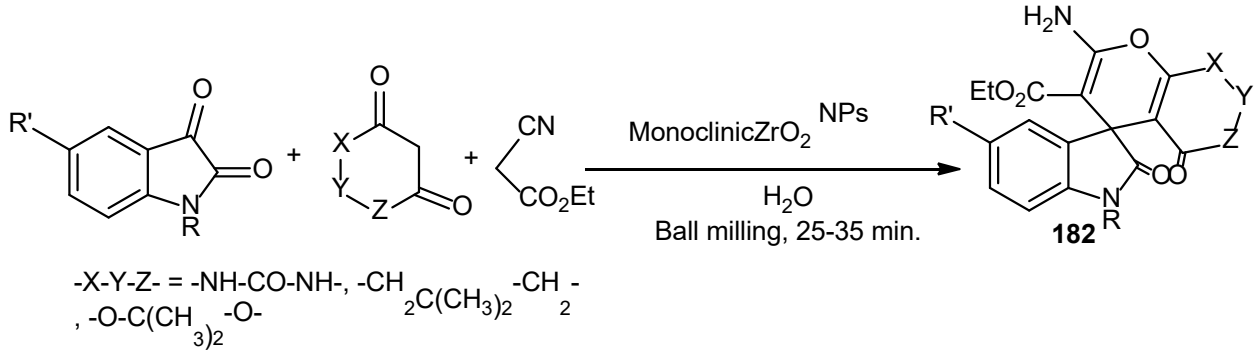
Scheme 86. Preparation of spirooxindoles using Zr-MOF/rGO nanocatalyst.

Kumar Ganta et al.[120] have developed the synthesis of spiro pyrazolo-pyrimidine derivatives (**181**) by four-component one-pot reaction of pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**180**) 3-oxo-3-phenylpropanenitrile (**179**) hydrazine and isatins by using nano copper ferrite ($CuFe_2O_4$) in water (**Scheme 87**). It was stated that isatin with electron withdrawing groups gave products in high yields. The antibacterial properties of products were also evaluated.



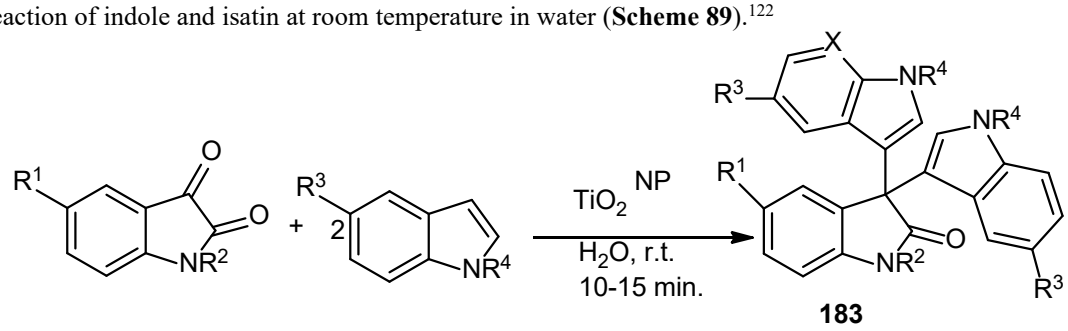
Scheme 87. Synthetic strategy of spiro pyrazolo-pyrimidines by using nano copper ferrite.

Monoclinic zirconia nanoparticle was used for regioselective and green synthesis of spirooxindoles (**182**) (**Scheme 88**).[121] In the report *m*-ZrO_2 NPs catalyzed reaction of isatin with ethyl cyanoacetate and 1,3-dicarbonyl compounds in a ball mill.



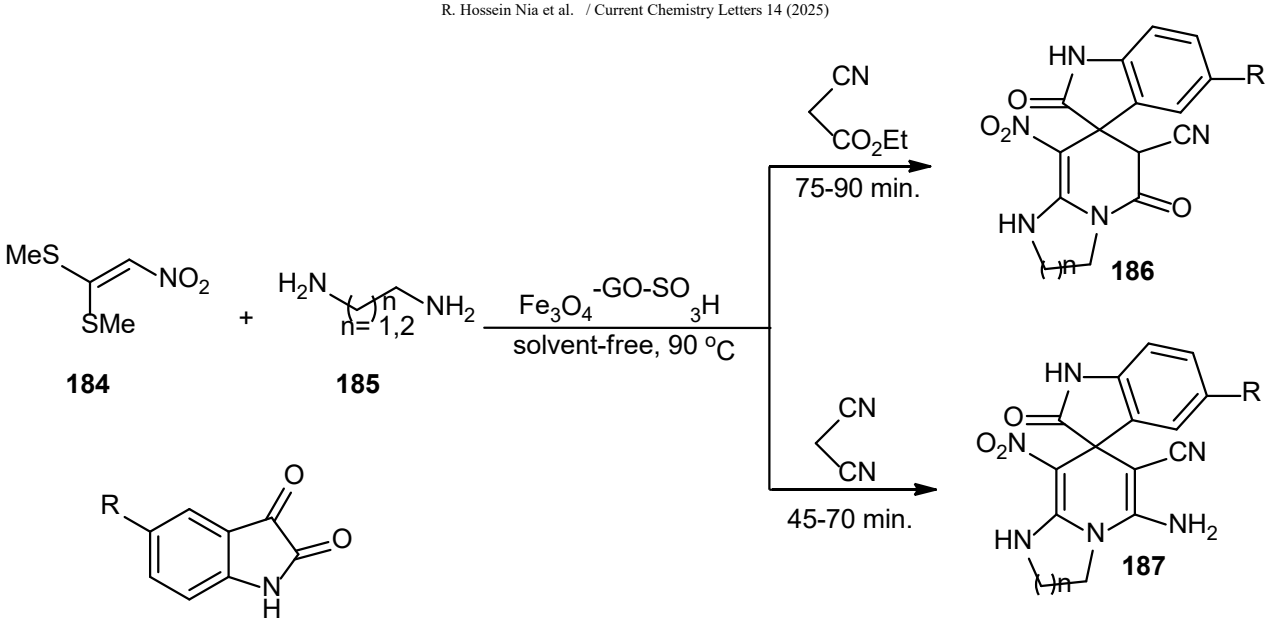
Scheme 88. Green synthesis of spirooxindoles in a ball mill in the presence of m-ZrO_2 NPs.

The heterogenous titanium dioxide nanoparticles (TiO_2 NPs) was used for the synthesis of 3,3-di(indolyl)indolin-2-ones (**183**) by reaction of indole and isatin at room temperature in water (**Scheme 89**).[122]



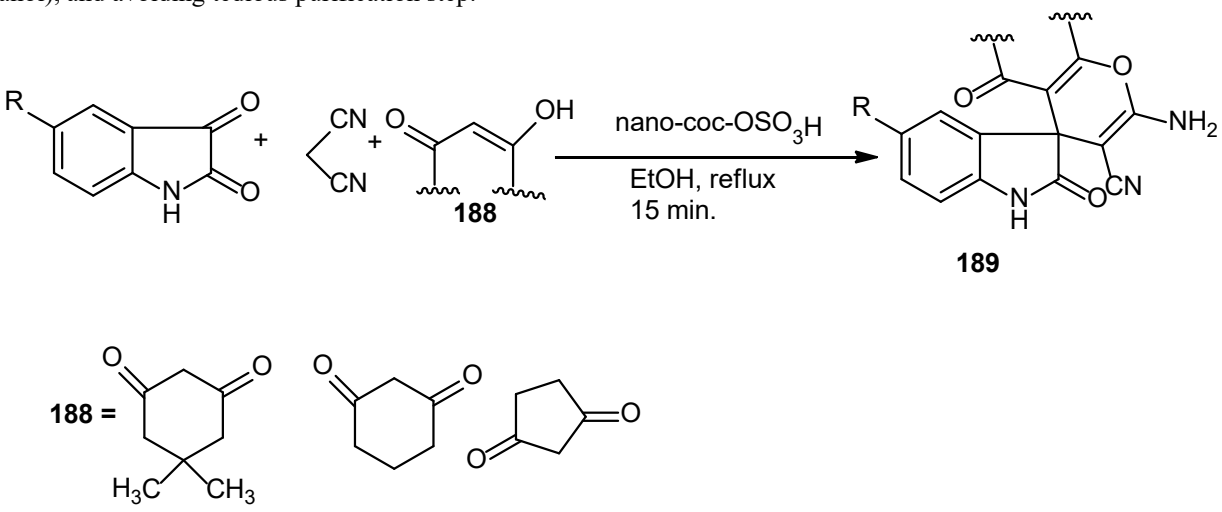
Scheme 89. Formation of synthesis of 3,3-di(indolyl)indolin-2-ones using TiO_2 NPs.

Recently, there has been a growing interest in the utilization of solid-supported reagents because of their convenient filtration and the straightforward recycling of catalysts such as graphene oxide (GO) and its functionalized versions. These catalysts have been increasingly employed in various chemical reactions. [123,124] Graphene oxide, due to its oxygen-containing functionalities (C–O, –OH, COOH) offers a wide range of routes to synthesize divers functionalized catalysts. On the other hand, having a large particular surface, creates a suitable situation for metal nanoparticles such as Fe_3O_4 to spread on its surface.[125-128] In 2021,[129] nano-Fe_3O_4-$GOSO_3H$ as a solid acidic catalyst was used for synthesis of spiro-oxindole derivatives (**186** and **187**) from 1,1-bis(methylthio)-2-nitroethylene (**184**), diamine (**185**), malononitriles (or ethylcyanoacetate), and isatins under solvent-free conditions (**Scheme 90**). Authors have also prepared aryl-substituted imidazo[1,2-*a*]pyridines and pyrido[1,2-*a*]pyrimidines by this protocol.



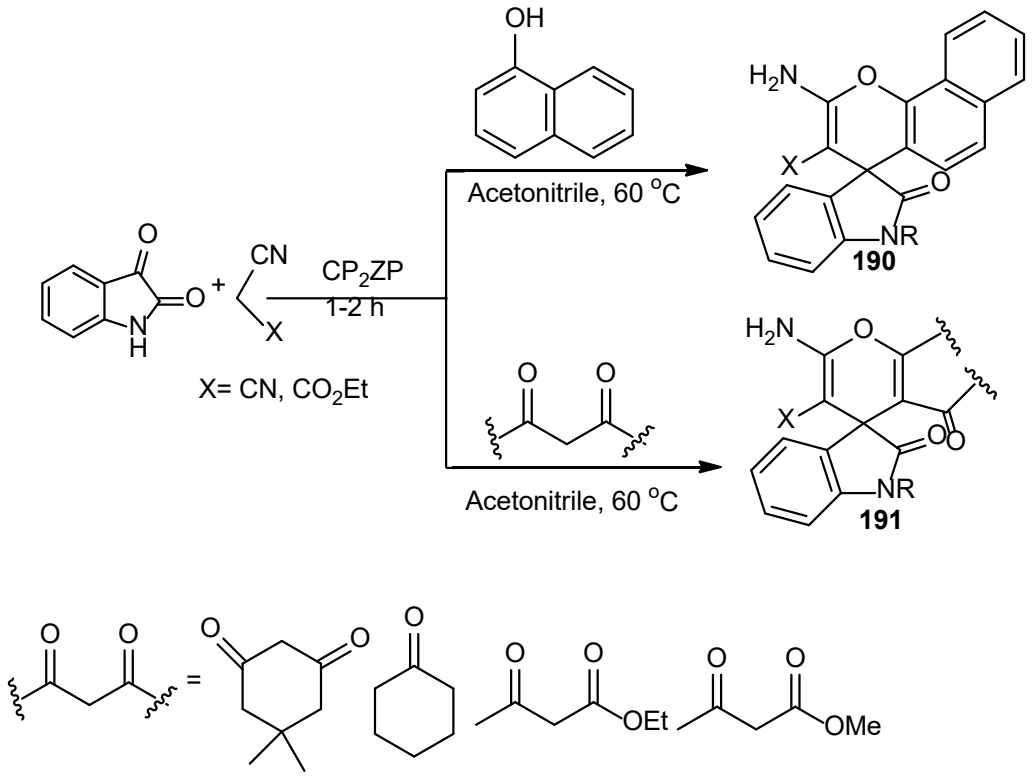
Scheme 90. Synthesis of spiro-oxindolo-imidazo[1,2-*a*]pyridines and -pyrido[1,2-*a*] pyrimidines using nano-Fe_3O_4-$GOSO_3H$.

Chlorosulfonic acid supported on coconut shell (nano-coc-OSO_3H) as nano catalyst was applied for synthesis of spirooxindoles (**189**) via three-component condensation of isatin derivatives, enolizable systems (dimedone, cyclohexadione, cyclopantadione) (**188**) and malononitrile in EtOH (**Scheme 91**).[130] The significant features of this methodology are nontoxic catalyst, short reaction time (15 min.), recyclability, low catalyst loading, green organic solvent (ethanol), and avoiding tedious purification step.



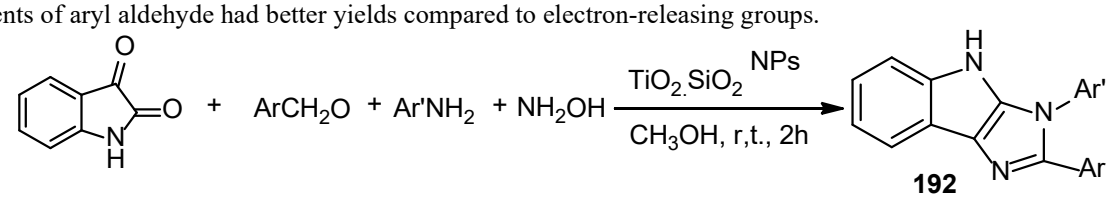
Scheme 91. Preparation of spirooxindoles in the presence of nano-coc-OSO_3H.

Pradhan and Mishra,[131] have prepared a composite catalytic system by dispersing cesium exchanged phosphotungstic acid ($Cs_xH_{3-x}PW_{12}O_{40}$) nanoparticles in the micropores of Zr-pillared α-zirconium phosphate (ZZP) and applied as catalyst for synthesis of spirooxinole derivatives containing chromene (**190** and **191**) via multicomponent condensation of isatin, malononitrile and naphthol/1,3-dicarbonyl compounds (**Scheme 92**).



Scheme 92. CP_2ZZP catalyzed synthesis of spriooxindoles fused chromens.

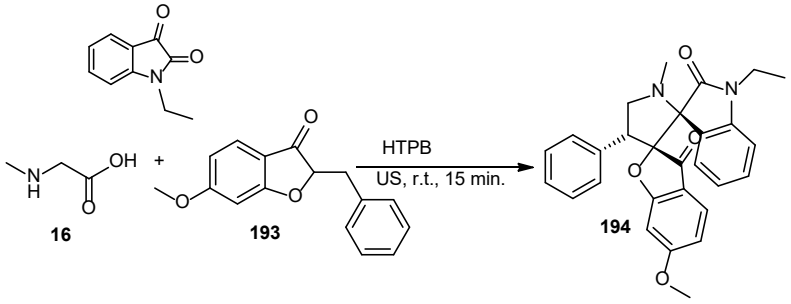
Titania nanoparticles hosted on silica ($TiO_2.SiO_2$ NPs) as nano heterogeneous catalyst were used to synthesize a series 2,3-diaryl- 3,4-dihydroimidazo[4,5-*b*]indole derivatives (**192**) via four-component reaction of aryl aldehydes, anilines, ammonium acetate and isatin in MeOH at room temperature (**Scheme 93**).[132] $TiO_2.SiO_2$ nanoparticles activate the carbonyl aldehyde and isatin group and the reaction is promoted. The result of this report showed that the electron-withdrawing substituents of aryl aldehyde had better yields compared to electron-releasing groups.



Scheme 93. Formation of 2,3-diaryl-3,4-dihydroimidazo[4,5-b] indole derivatives (5a-o) via using $TiO_2.SiO_2$ NPs

2.7. Using ionic liquid

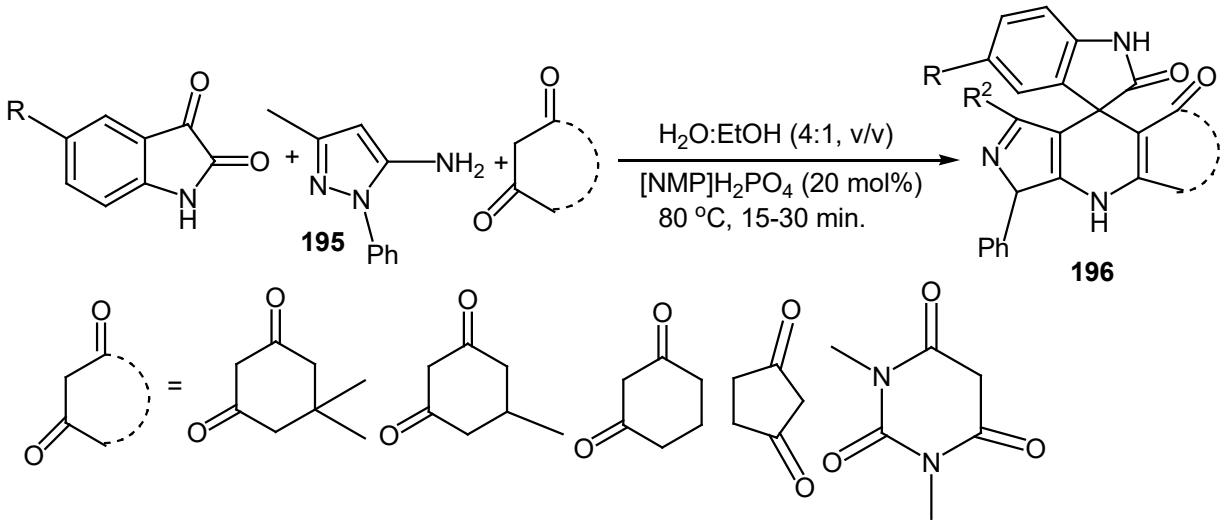
Over the past few years, there has been a growing interest with ionic liquids (ILs), which have proven to be effective in numerous reactions as eco-friendly catalysts and solvents. This is mainly due to their low vapor pressure, low viscosity, high thermal and chemical stability.[133-136] Currently, there is a significant emphasis on organic reactions utilizing ILs as solvents or catalysts, leading to successful synthetic reactions being conducted in ILs with exceptional results. The reactions for the production of isatin-containing heterocycles using ionic liquid are given in the following reports.



Scheme 94. The regioselective synthesis of dispiropyrrolidineoxindoles in the presence of hexyltriphenylphosphonium bromide (HTPB) under ultrasonic irradiation.

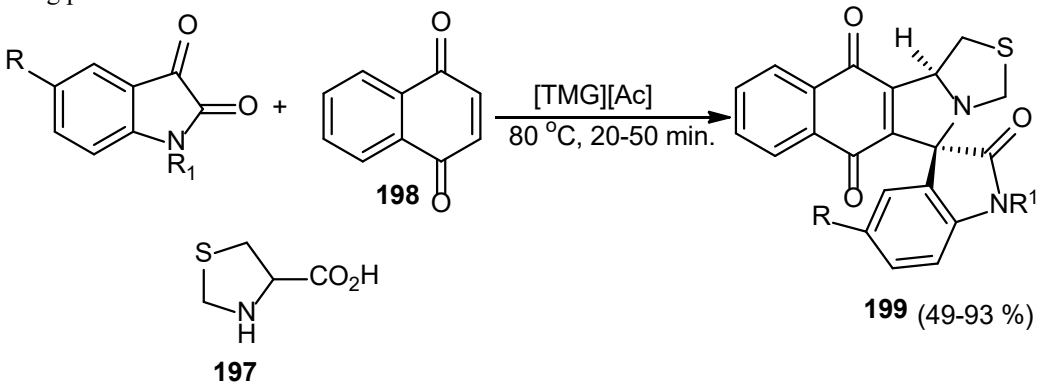
In 2023,[137] hexyltriphenylphosphonium bromide (HTPB) as an ionic liquid and recyclable solvent was applied for the regioselective synthesis of dispiropyrrolidineoxindole derivatives (**194**) through the one-pot 1,3-dipolar cycloaddition reaction of isatins, sarcosine (**16**), and 2-benzylidenebenzofuran-3(2*H*)-one derivatives (**193**) at room temperature under ultrasonic conditions (**Scheme 94**). The phosphorus in HTPB has a strong tendency to react with oxygen, thus helping to activate the carbonyl group. The authors also investigated the anticancer activity of the new products.

Acidic ionic liquid ([NMP]H_2PO_4 (*N*-methyl-2-pyrrolidonium dihydrogen phosphate) as a recyclable catalyst was utilized for the synthesis of spiro[indoline-3,4′-pyrazolo[3,4- *b*]quinoline]diones (**196**) *via* a three-component condensation of isatins, 1,3- dicarbonyls and 5-amino-1-phenyl-3-methylpyrazole (**195**) in EtOH: H_2O at 80 ºC (**Scheme 95**).[138] The authors have examined the photophysical properties of the products. The paper noted that the products exhibited intramolecular charge transfer and are potential fluorescent materials. The effect of pH on absorbance and fluorescence of products has also been examined.



Scheme 95. Formation of spiro[indoline-3,4′-pyrazolo[3,4- *b*]quinoline]diones in presence of [NMP]H_2PO_4.

Guanidine-based task-specific ionic liquid 1,1,3,3-tetramethylguanidine acetate [TMG][Ac] was applied for the synthesis of spiro[benzo[*f*]thiazolo[4,3-*α*]isoindole-5,3′-indoline]-2′,6,11-triones (**199**) through multicomponent reaction of substituted isatin, thiazolidine-4-carboxylic acid (**197**) and naphthoquinone (**198**) (**Scheme 96**).[139] The authors also investigated the reaction of ninhydrin or acenaphthenequinone instead of isatin under optimal reaction conditions to prepare the corresponding products.



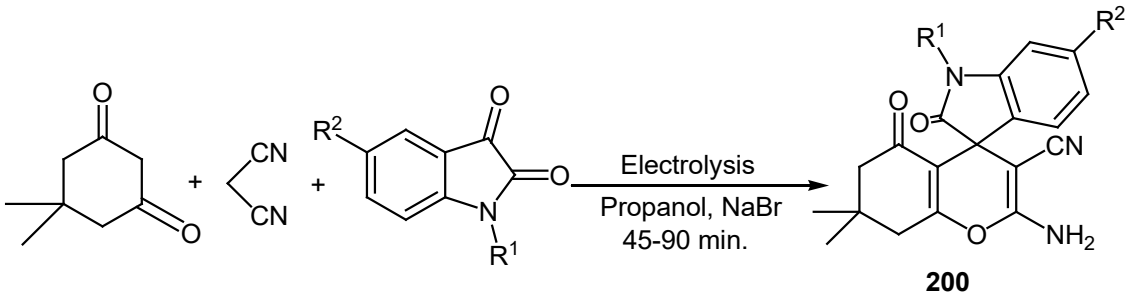
Scheme 96. Synthesis of spiro[benzo[*f*]thiazolo[4,3-*α*]isoindole-5,3′-indoline]-2′,6,11-triones in the presence of [TMG][Ac].

2.8. Using electrochemistry

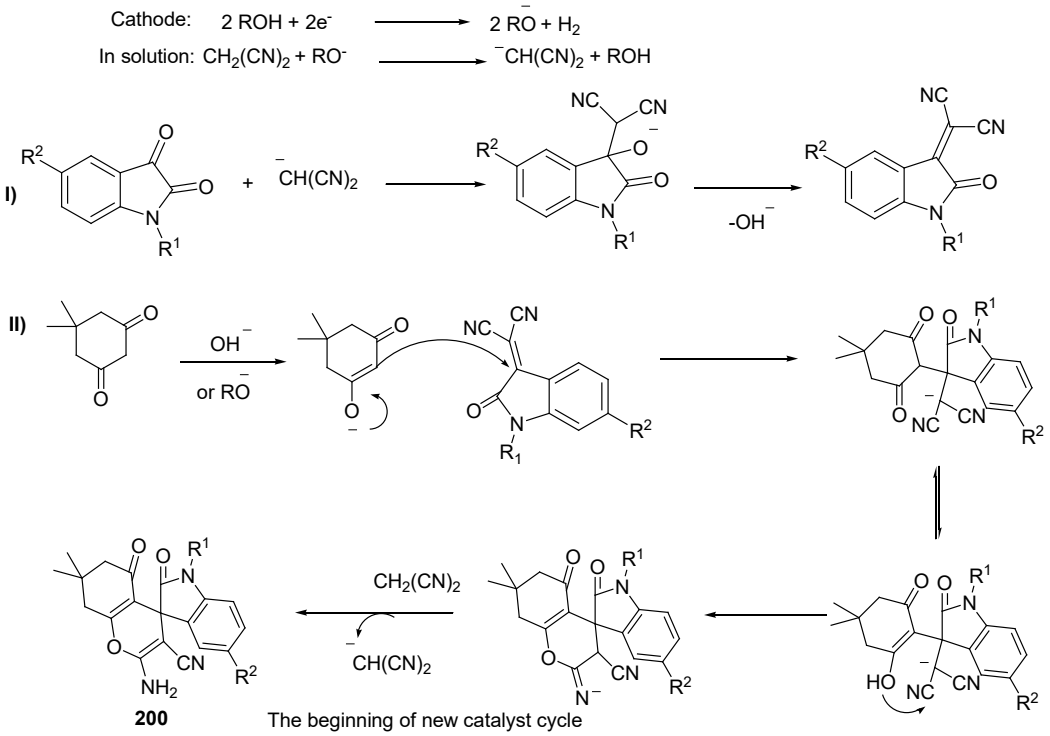
Because of extensive research on the electrochemistry of organic compounds, electro-synthesis has become a beneficial technique.[140] In addition, electrochemical approaches are of interest from an environmental perspective because the clean generated electricity acts as an oxidative and reductive agent in organic synthesis.

An electrocatalytic synthesis of nanoparticles of spirooxindole derivatives (**200**) was reported, using an electrogenerated base of the anion of propanol in three-component condensations of isatins, dimedone, and malononitrile in an undivided

cell in the presence of sodium bromide as an electrolyte at 50 °C (**Scheme 97**).[141] The electrocatalytic mechanism for preparation of spirooxindole derivatives **(200)** was outlined in the **Scheme 98**.

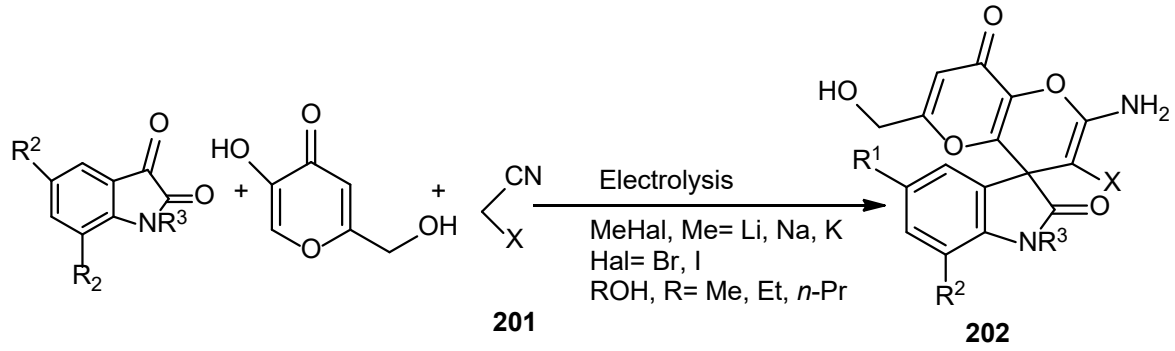


Scheme 97. Electrocatalytic synthesis of spirooxindole derivatives.



Scheme 98. Electrocatalytic mechanism for the synthesis of spirooxindole derivatives.

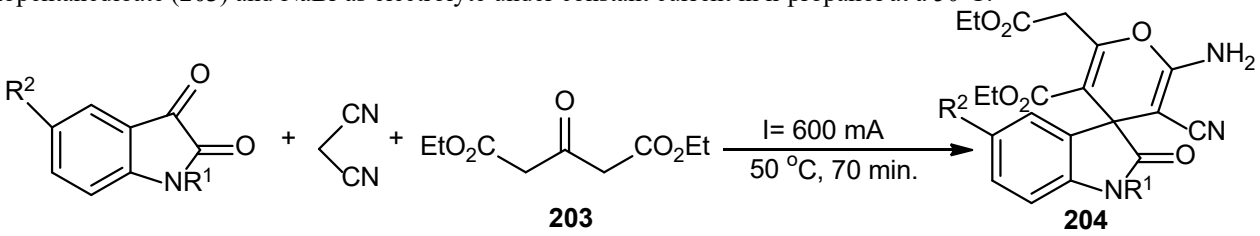
In another report,[142] electrochemically induced multicomponent assembling of isatins, kojic acid (**201**), and malonic acid derivatives in *n*-propanol in the presence of sodium iodide as an electrolyte in an undivided cell led to the formation of unsymmetrical spiro(indole-3,4′-pyrano[3,2-*β*]pyranes) derivatives (**202**) in 86–98% yields (**Scheme 99**).



X= CN, CO_2Me, CO_2Et

Scheme 99. Electrosynthesis of spiro(indole-3,4′-pyrano[3,2-*β*]pyranes) derivatives.

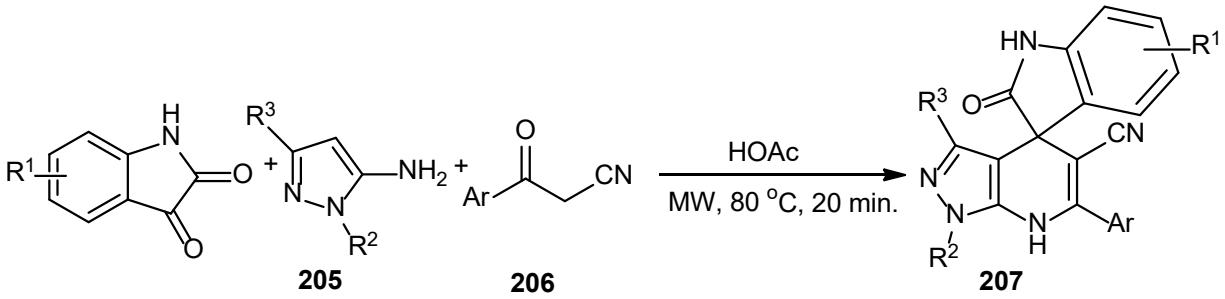
Electrosynthesis of spirooxindole-pyran derivatives (**204)** was also reported (**Scheme 100**).[143] The reaction was carried out through a three-component reaction of isatins, malononitrile, and an enolizable C-H-activated compound of diethyl 3-oxopentanedioate (**203**) and NaBr as electrolyte under constant current in n-propanol at a 50°C.



Scheme 100. Electrosynthesis of spirooxindole-pyran derivatives.

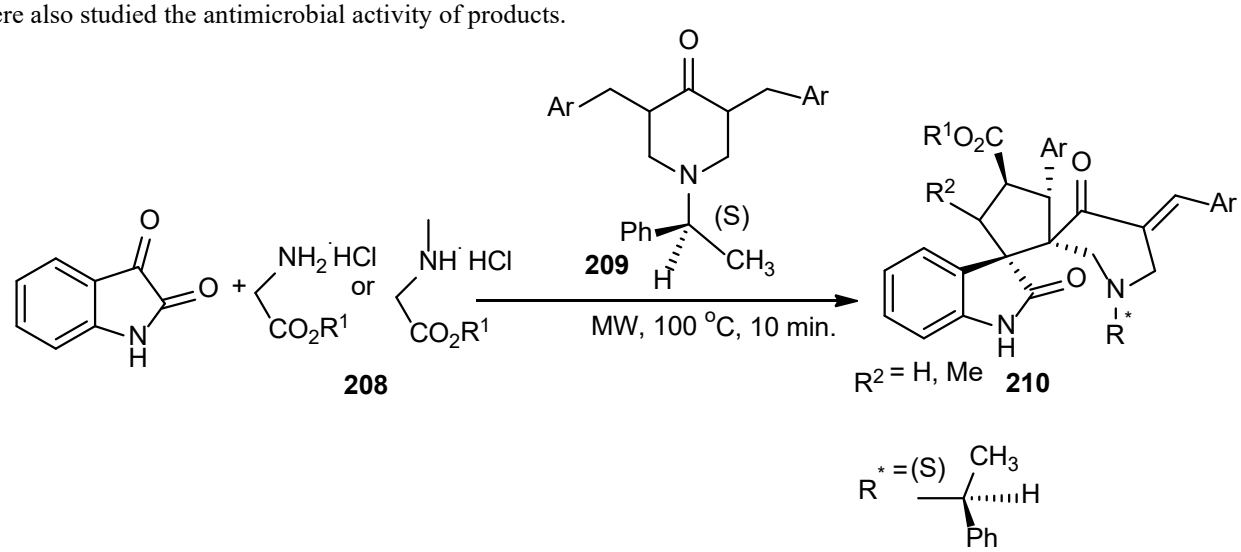
2.9. Using microwave irradiations

Gao et al.[144] have described the strategic synthesis of spiro[indoline-3,4′- pyrazolo[3,4-*b*]pyridines] derivatives (**207)** from isatins, pyrazol-5-amines (**205)** and *β*-ketonitriles (**206**) under microwave conditions in HOAc. HOAc plays a dual role in this reaction, both as a reaction medium and as a Brønsted acid-promoter (**Scheme 101**).



Scheme 101. Preparation of spiro[indoline-3,4′- pyrazolo[3,4-*b*]pyridines]derivatives under MW conditions.

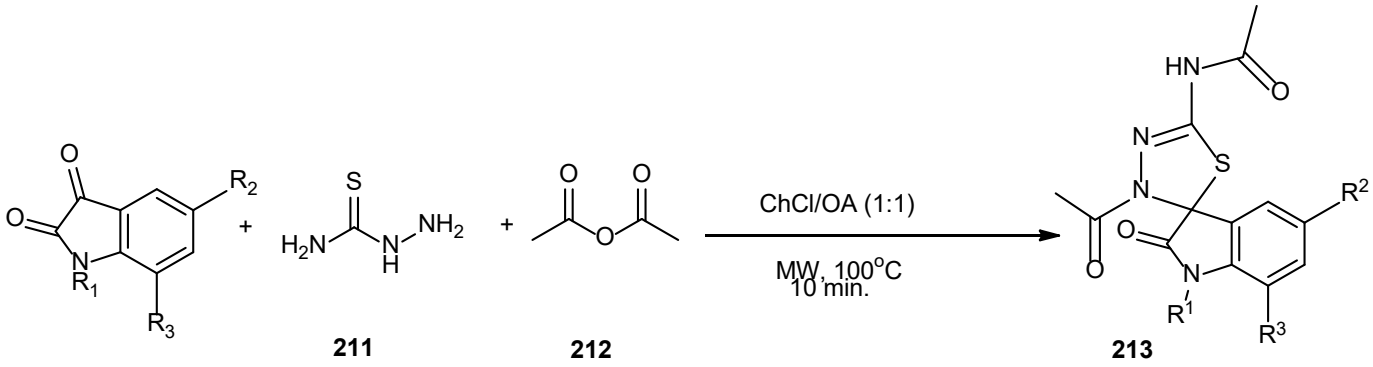
In 2024,[145] microwave-assisted multicomponent reaction of enantiopure *(E,E)*-3,5-bisarylidene-*N*-[(*S*)-(-)-methylbenzyl]-4-piperidones (**209**), isatin and *α*-amino esters (**208**) in methanol in the presence of Et_3N has addressed for the synthesis of a series of optically active tetracyclic dispirooxindolopyrrolidine-piperidones (**210**) (**Scheme 102**). Authors were also studied the antimicrobial activity of products.



Scheme 102. Formation of tetracyclic dispirooxindolopyrrolidine-piperidones under MW irradiation.

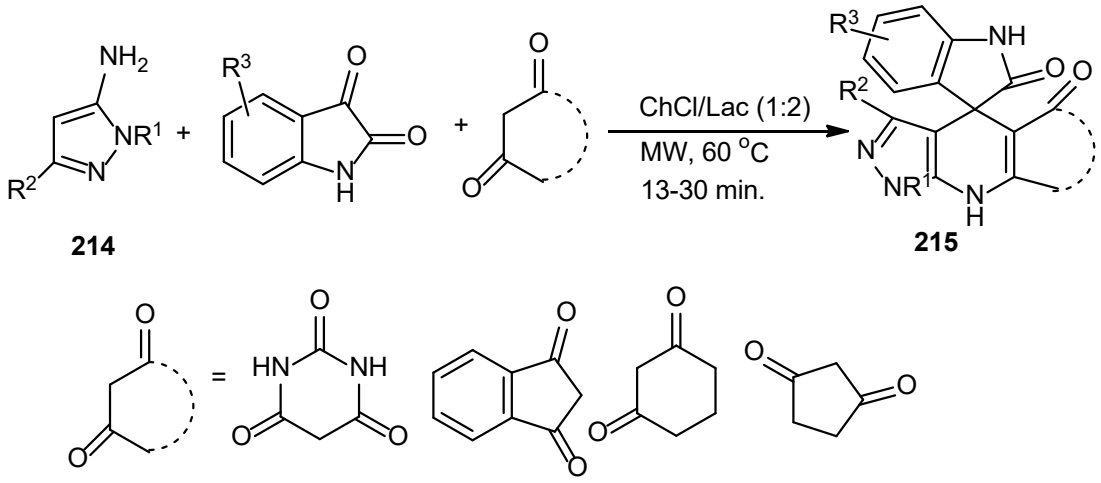
Castro et al.[146] have utilized the combination of deep eutectic solvents (DES) with microwave irradiation to prepare 1,3,4-thiadialzolinic spirocompounds (**213**) in a three-component reaction including isatin derivatives (monomeric and dimeric), thiosemicarbazide (**211**), and acetic anhydride (**212**) (**Scheme 103**). In the research, a series of DES based on

different acids was explored as a solvent for the synthesis of the desired product and choline chloride and oxalic acid (ChCl/OA) (1:1) showed better results than other evaluated solvents.



Scheme 103. preparation 1,3,4-thiadialzolinic spirocompounds using deep eutectic solvents (DES) with microwave irradiation.

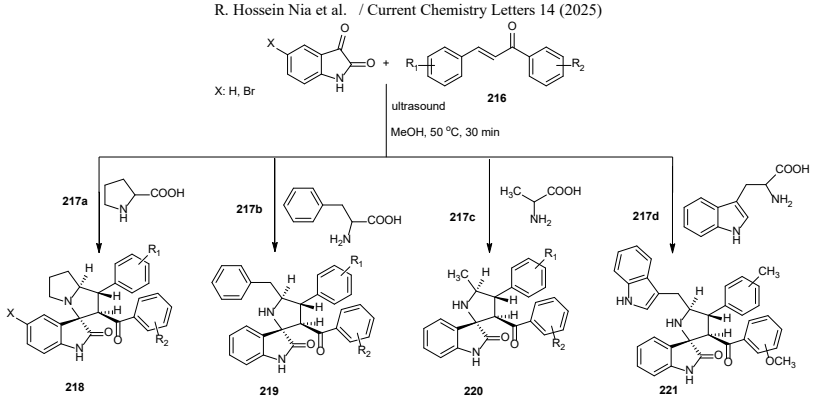
Zhang et al. [147] have also applied the combination of microwave irradiation with choline chloride and lactic acid based natural eutectic solvent (NDDES) for the synthesis of spiro[indoline-3,4'-pyrazolo[3,4-*b*]pyridines] derivatives (**215**) via three-component reactions of 1*H*-pyrazol-5-amin (**214**), isatin and enolizable C-H activated compound (**Scheme 104**). Using choline chloride and lactic acid as a degradable, recyclable and reusable media are the advantages of this protocol as a sustainable and safe process for the environment.



Scheme 104. Formation of pyrazolo[3,4-*b*]quinoline spirooxindoles in ChCl/Lac.

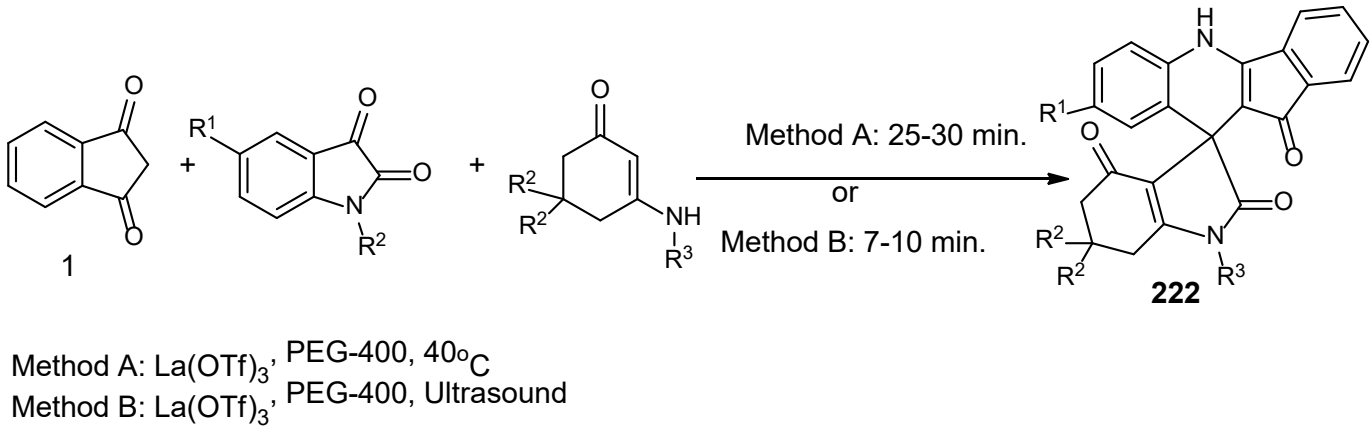
2.10. Using ultrasound irradiations

In 2024,[148] ultrasonic irradiation was applied fo the synthesis of a series of the pharmacologically privileged substructures, i.e., chalcone-isatin based spirooxindole compounds **(218-221)** which were derived by the reaction of various substituted amino acids, substituted chalcone (**216**) and isatins *via* three-component [3+2] cycloaddition reaction in MeOH at 50 °C (**Scheme 105**). The chalcones were prepared using Claisen–Schmidt reactions. The paper also included reports on the antimicrobial and antitubercular activities, SAR studies of the products.



Scheme 105. Preparation of spirooxindole compounds using ultrasonic irradiation.

La(OTf)$_3$ catalyzed three-component reaction has been addressed for the synthesis of spiro[indolo-3,10′-indeno[1,2-*b*]quinolin]-2,4,11′-triones (**222**) in PEG-400 at 40°C under conventional heating and ultrasonic irradiation (**Scheme 106**).[149] In the proposed mechanism, the ring opening takes place by nucleophilic attack of nitrogen to amidic carbonyl carbon of isatin.



Scheme 106. Formation of spiro[indolo-3,10′-indeno[1,2-*b*]quinolin]-2,4,11′-triones.

3. Conclusions

This study explored recent developments in isatin-based MCRs for heterocycle synthesis between 2014 and 2024. The reported synthetic protocols that were studied include the synthesis of spirooxindoles and other heterocycles containing isatin such as pyrroloquinolines, imidazole-indoles and pyrazoloquinolines. In the review, the reports were classified based on the reaction conditions. These methods were carried out under both classical and non-classical conditions, incorporating principles of green chemistry, including the utilization of environmentally friendly solvents, green and reusable catalysts, and solvent-free processes. The main objective of this review is to provide a summary of recently reported strategies in the use of isatin in the multicomponent synthesis of heterocycles for organic and medicinal chemists, especially researchers who are interested in the synthesis of heterocycles containing isatin or synthesis of compounds with more than one heterocyclic nucleus.

Acknowledgements

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