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Recent applications of ninhydrin in multicomponent reactions

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Ninhydrin (1,2,3-indanetrione hydrate) has a remarkable breadth in different fields, including organic chemistry, biochemistry, analytical chemistry and the forensic sciences. For the past several years, it has been considered an important building block in organic synthesis. Therefore, there is increasing interest in ninhydrin-based multicomponent reactions to rapidly build versatile scaffolds. Most of the works described here are simple reactions with readily available starting materials that result in complex molecular architectures. Some of the synthesized compounds exhibit interesting biological activities and constitute a new hope for anticancer agents. The present review aims to highlight the multicomponent reactions of ninhydrin towards diverse organic molecules during the period from 2014 to 2019.

1. Introduction

The compound ninhydrin **1** was first reported in the literature by English chemist S. Ruhemann more than a century ago.[1] It is a stable, hydrated product of 1,2,3-indanetrione, where two hydroxyl groups at the C-2 position are flanked by two carbonyl groups (Fig. 1). Upon dehydration, the central carbonyl of the resulting indanetrione becomes the most reactive centre towards nucleophiles.[2,3] In fact, ninhydrin is a strong electrophile that reacts with nucleophiles such as ammonia, amines, enamines, ureas, amides and anilines.[2–6] Primary amines and α-amino acids react readily with ninhydrin at the central carbon to produce a highly coloured, condensation product known as Ruhemann's purple. Besides nitrogen-based nucleophiles, its C-2 position is reactive towards various carbon-, oxygen- and sulphur-based nucleophiles, resulting in C–C, C–O and C–S bonds, respectively.[7–14] Due to its unique chemical structure and capability to form a dehydrated triketone analogue, it has the potential to act as a building block in diverse organic synthesis strategies.[15–21]

Furthermore, ninhydrin has special applications in the field of fluorescence. It is most widely applied as a reagent for the determination of latent fingerprints in forensic science.[22–24] The fluorogenic ninhydrin reaction was reported for the assay of primary amines.[25] It has been used as a potential substance for the micromolar determination of human serum albumin based on chemiluminescence.[26] Recently, we employed monoarylated ninhydrin-adducts to develop a new fluorophore system.[27,28] Some indanone-based fluorophores were also explored to act as a receptor for specific metal ions.[29,30]

Ninhydrin is basically an indanone class compound, and indanone core structures have been found in numerous natural products (Fig. 2).[31–40] Indanone derivatives have demonstrated a broad spectrum of biological properties (Fig. 3). Some of the derivatives are well-known for their antimicrobial, anti-inflammatory, antagonistic, anti-allergy, anti-tumor, anti-cancer, and free radical scavenging activities.[41–49] Spirocyclic indanones are prevalent in nature and possess pronounced pharmacological profiles.[50–56] Moreover, heterocycle-fused indanone scaffolds are well recognized for their significant applications in medicinal chemistry.[57–62] Several

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Dr Suven Das was born in West Bengal, India and obtained his BSc and MSc degrees from the University of Calcutta. He completed his PhD in 2007 from the same University under the supervision of Dr Animesh Pramanik. His PhD work primarily focused on the synthesis of heterocycles from ninhydrin. In 2007, he joined as a Lecturer in Chemistry at Rishi Bankim Chandra College for Women, Naihati, India. After his postdoctoral research at the National Tsing Hua University, Taiwan with Professor C. C. Lin (2009), he returned to India and joined the same college as an Assistant Professor to initiate his independent research career. His research interests include the areas of indanone chemistry, organic synthesis and heterocycles.

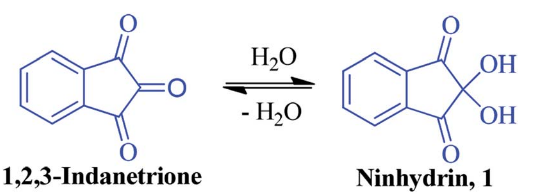


Fig. 1 Structure of ninhydrin.

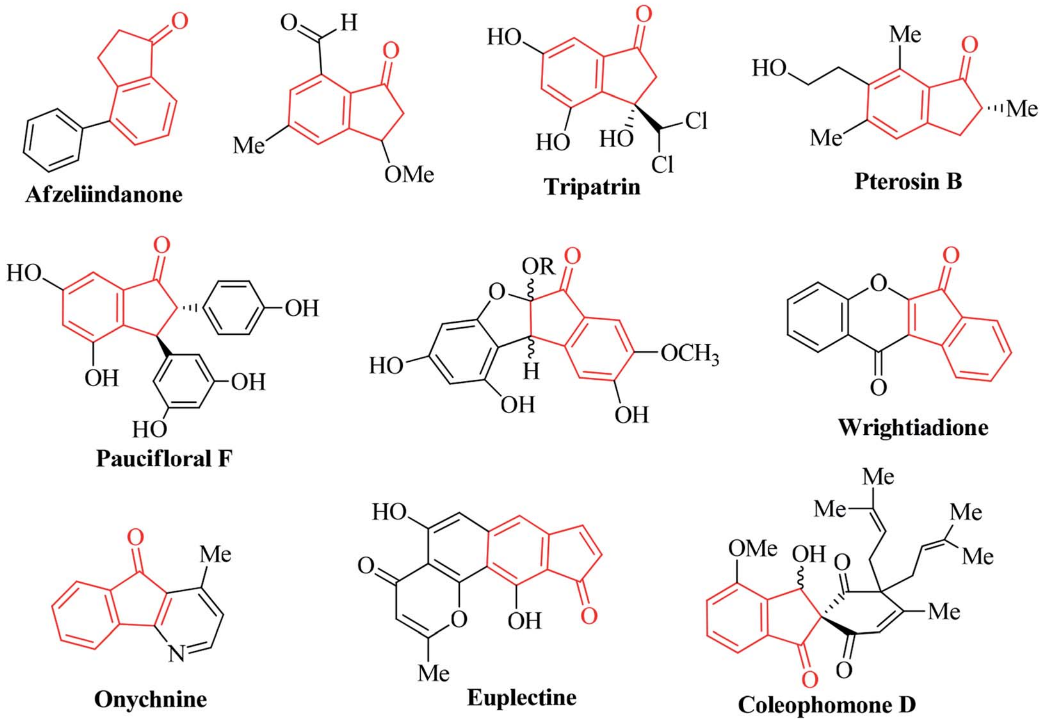


Fig. 2 Some examples of natural products containing the indanone motif.

indenoquinoxaline scaffolds have been reported to function as potential anticancer agents.[61,62]

On the other hand, the multicomponent reaction (MCR) is a powerful synthetic tool for designing and developing a new route towards novel and complex molecular structures.[63–65] In MCRs, three or more starting materials react in a single step to form a product that has substantial portions of all reactants. This strategy provides a high-throughput generation of combinatorial compound libraries in drug discovery research.[66–68] Importantly, MCRs comply with the principles of green chemistry by saving reagents, solvents and time, while including the high atom-economy and selectivity of a reaction. In recent years, ninhydrin has become an unparalleled tricarbonyl compound participating in many MCRs to afford diverse structural scaffolds. It is worth mentioning that vicinal tricarbonyl compounds are rich sources of heterocyclic scaffolds.[69–72] A review article was previously published on ninhydrin by Ziarani *et al.* regarding the synthesis of heterocyclic compounds until 2013.[73] This review aims to highlight important MCRs of ninhydrin reported from 2014 to 2019.

2. Synthesis of indeno-fused heterocycles

In 2014, Perumal and co-workers reported that the reaction of ninhydrin **1** with aniline **2** and (*E*)-3-(dimethylamino)-1-arylprop-2-en-1-one **3** in the presence of a catalytic amount of AcOH led to the formation of dihydroindeno[1,2-*b*]pyrrole **4** in excellent yield (Scheme 1).[74] The facile, solvent-free, three component domino reaction afforded the regio- and stereoselective synthesis of the highly functionalized products at room temperature within 5–8 minutes under grinding condition. This green approach allowed the formation of two C–C and one C–N bonds in a single synthetic operation at ambient temperature. The reaction was initiated *via* Michael addition of aniline **2** to **3**, followed by the elimination of Me_2NH to yield intermediate **A**, which added the central carbonyl of ninhydrin chemoselectively to produce intermediate **B.** Then **B** underwent isomerisation to produce the enaminone pendant indanone intermediate **C.** Finally, annulation afforded the desired product **4.**

Alizadeh described an excellent study *via* a one-pot four-component reaction involving salicylaldehyde **5**, 4-hydroxy-6-methyl-2*H*-pyran-2-one, benzylamine **6** and ninhydrin **1** to access the potentially bioactive coumarin-appended indenopyrrole derivative **7** (Scheme 2).[75] Different salicylaldehydes and benzylamines bearing electron donating and withdrawing substituents were reacted smoothly to deliver the products in good yields. In the presence of an Et_3N catalyst, the Knoevenagel condensation between salicylaldehyde **5** and 4-hydroxy-6-methyl-2*H*-pyran-2-one leads to intermediate **A.** After condensation with benzylamine **6**, this product forms the enamine intermediate **B.** Nucleophilic addition of **B** with ninhydrin **1** provides intermediate **C.** Finally, cyclization furnishes product **7** (Scheme 2).

A new class of ninhydrin-based organic molecular probes, namely, dihydroindenopyrrole **9** was synthesized by Mukhopadhyay *et al.* In non-toxic polyethylene glycol-water (PEG 400-water), the reaction between ninhydrin **1**, aniline **2** and dialkyl acetylenedicarboxylate (DAAD) **8** proceeded smoothly to achieve

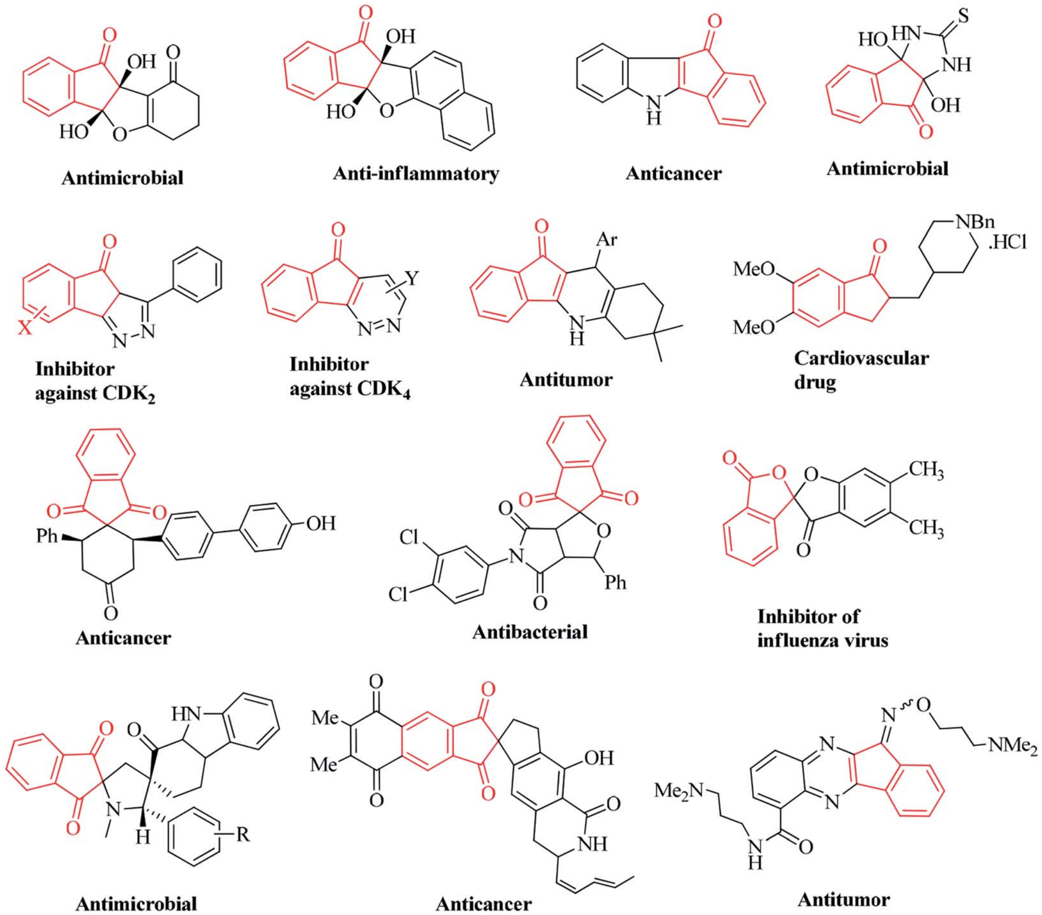


Fig. 3 Representative examples of bioactive compounds containing the indanone skeleton.

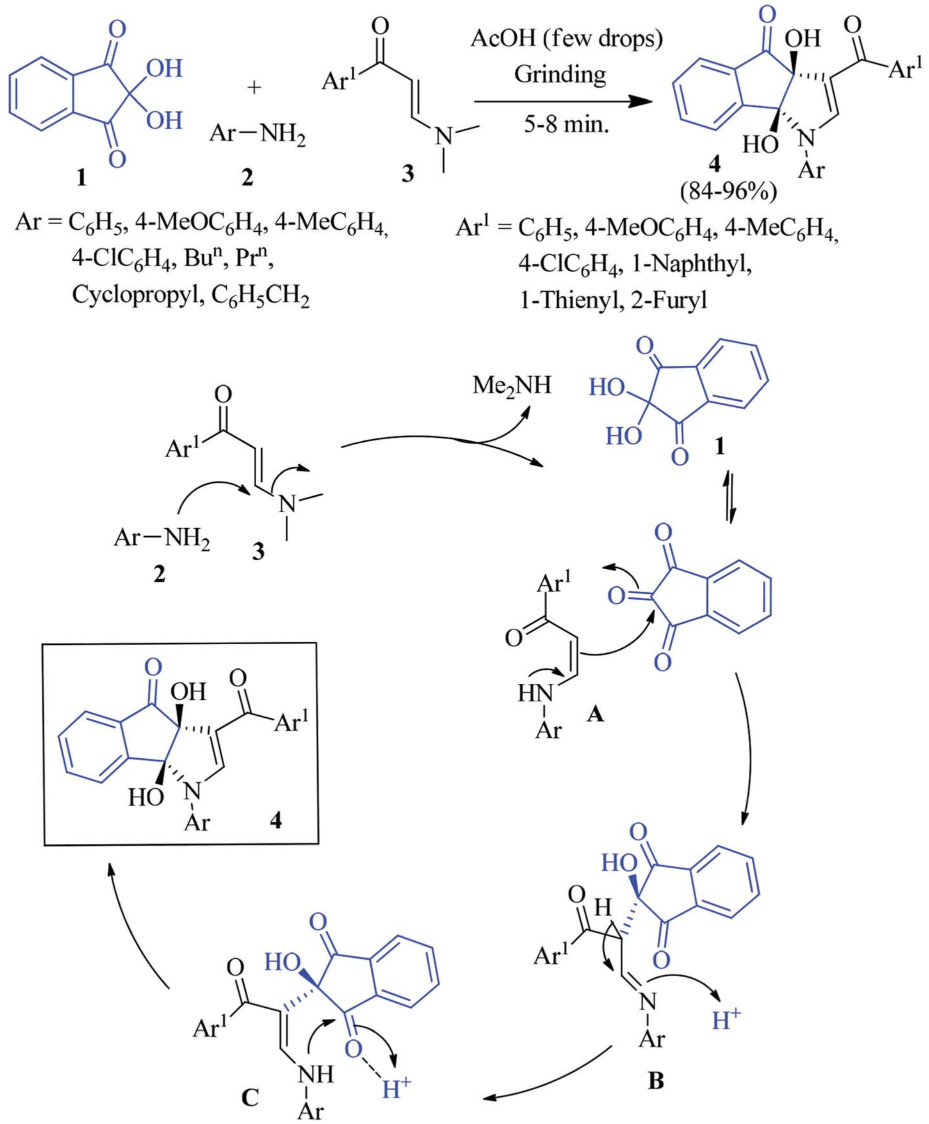
the novel product **9**.[76] A plausible mechanism is shown in Scheme 3, where amine **2** reacts with diester **8** to produce the enaminediester intermediate A. Then, intermediate **A** acts as a nucleophile to attack the central carbonyl of **1** to obtain intermediate **B**, which generates intermediate **C** upon dehydration. Next, the intramolecular cyclization results in the desired heterocyclic product **9**. Interestingly, the synthesized compounds act as a sensor for the selective detection of the Al^{3+} ion through an off–on fluorescence response.

A PPh_3-promoted synthesis of the polysubstituted indenopyrrole **11** was accomplished through a three-component intramolecular Wittig reaction.[77] The construction of the heterocylic skeleton was achieved by an annulation strategy involving ninhydrin **1**, 2-aminopyridine **11** and DAAD **8** under acid or base-free conditions. Initially, zwitterion **A** was produced from the reaction of triphenylphosphene and acetylenic ester **8**. Then, the zwitterion was protonated by the ninhydrin adduct **B** to generate the positively charged phosphonium ion. This ion was subsequently attacked by the intermediate **C**, leading to phosphorane **D**. An intramolecular Wittig reaction followed by dehydration furnished compound **11** (Scheme 4).

A similar version of the one-pot three component reaction was carried out employing **1**, aliphatic amine **12** and 1,3-dicarbonyl compound **13** to access the indenopyrrole derivative **14**.[78] A plausible mechanism is depicted in Scheme 5. Enaminone **A** (produced from the reaction of 1,3-dicarbonyl **13** and amine **12**) attacks ninhydrin **1** to generate intermediate **B**. Adduct **B** after dehydration offers intermediate **C**, which further reacts with triphenyl phosphene to produce zwitterion **D**. Finally, the elimination of triphenyl phosphene oxide affords target compound **14**.

Tin dioxide quantum dot (SnO_2 QD) has been introduced as an efficient catalyst for preparing the indeno[1,2-*b*]indole derivative **16** by a three-component reaction of ninhydrin **1**, amine **2** and cyclic 1,3-dicarbonyl compound **15** in an aqueous medium (Scheme 6).[79] A variety of functional groups were compatible under the sustainable condition where the catalyst was reused for seven cycles with almost unaltered catalytic activity.

Later, a novel ionic liquid coated sulfonated carbon@titania composite (C@TiO_2-SO_3H-IL1) was prepared and applied by the Paul group to access the indeno[1,2-*b*]indolone derivative **17**. They performed the synthesis with ninhydrin **1**, aniline **2** and dimedone in an aqueous medium in the presence of the aforesaid catalyst (Scheme 7).[80] The newly designed catalyst showed remarkable activity and stability in water, resulting in an excellent yield of the product. The environmentally benign



Scheme 1 Synthesis of dihydroindeno[1,2-*b*]pyrrole derivative **4**.

method allows for easy recovery of the catalyst for up to five cycles without a considerable loss of activity.

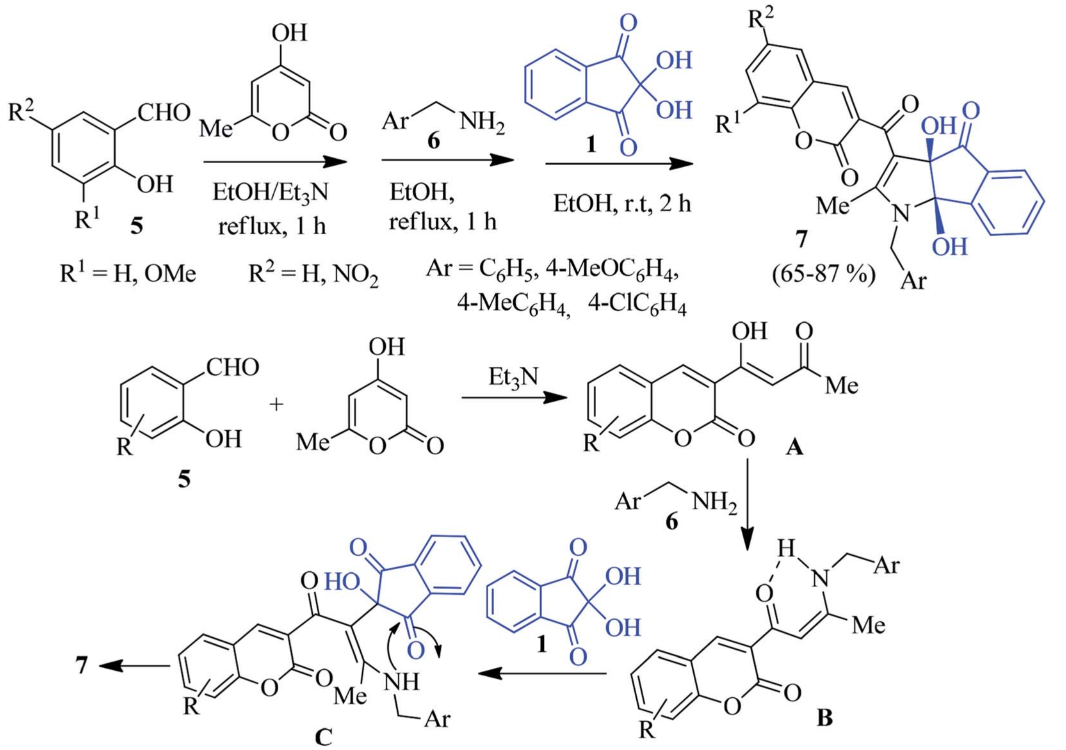
Kapoor *et al.* reported in their study that the reaction of ninhydrin **1** with 2 equivalents of ethyl cyanoacetate resulted in the formation of indenopyran derivative **18** (Scheme 8).[81] The highly reactive C-2 of ninhydrin has been exploited to condense with an active methylene compound, resulting in **18** as the major product. Importantly, the reaction was carried out under an ultrasound condition without using any catalyst.

A facile one-pot four-component reaction of ninhydrin **1**, primary amine **2**, acid chloride **19** and ammonium thiocyanate was disclosed by Moradi to accomplish indenothiazole derivative **20** under solvent-free conditions (Scheme 9).[82] Initially, the reaction of ammonium thiocyanate and acid chloride **19** led to the formation of alkanoyl isothiocyanate **A**. Then, intermediate **A** suffered a nucleophilic attack by amine **2** to form thiourea **B**. Subsequently, it attacked the central carbonyl of ninhydrin to produce intermediate **C**, which furnished compound **20** after annulation.

3. Synthesis of spiro-indanone-bearing N-heterocycles (*via* azomethine ylide)

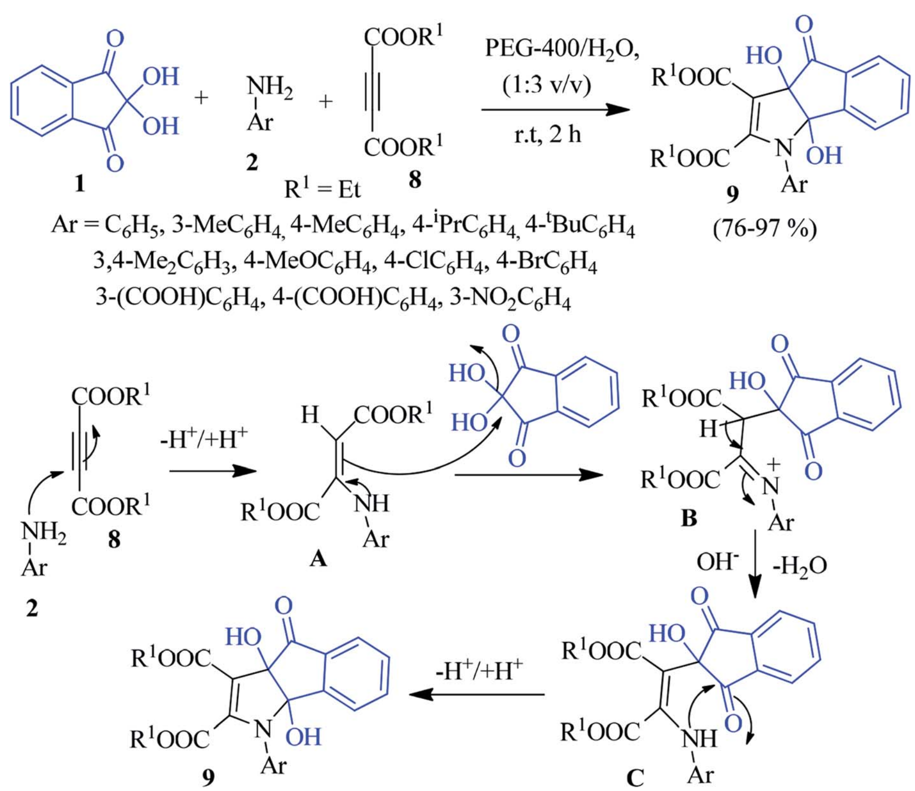
Ninhydrin has been successfully employed for the construction of the spiro indanone framework anchored with various N-heterocyclic scaffolds. It should be mentioned that ninhydrin-derived azomethine ylides have been exploited to react with different dipolarophiles through the [3 + 2] cycloaddition towards the formation of various heterocyclic scaffolds.

Kalluraya's group demonstrated a facile method for the synthesis of nitrofuran-bearing spiroindeno-pyrrolidines **23** *via* a one-pot three component reaction of sarcosine **21**, ninhydrin **1** and chalcone **22**.[83] The reaction proceeded with high

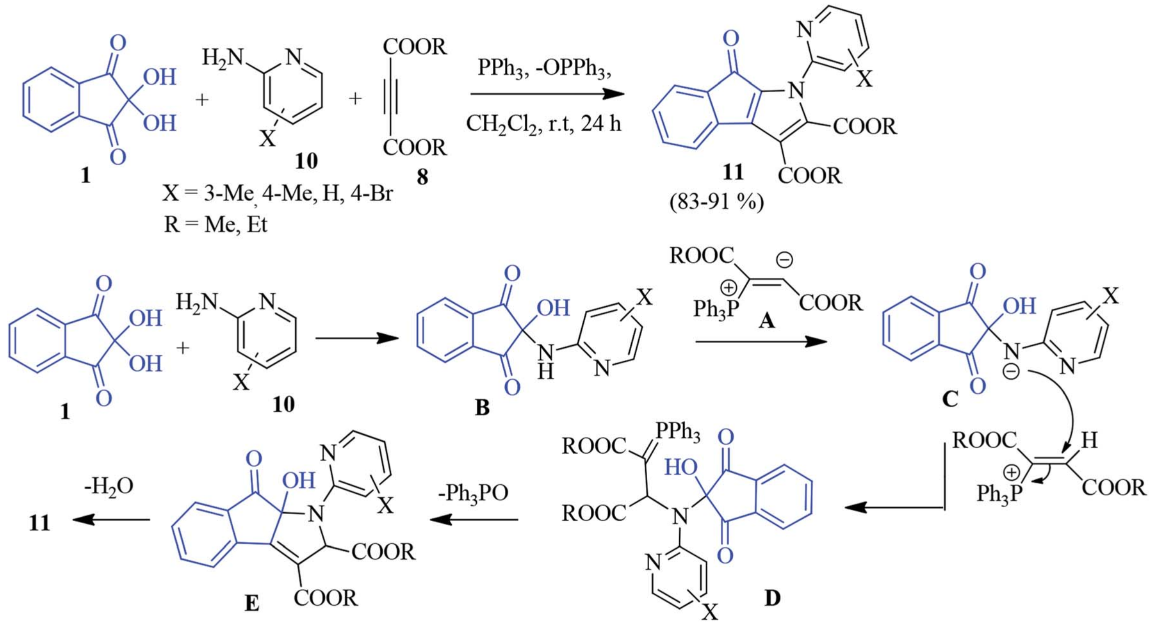


Scheme 2 Synthesis of coumarin-appended indenopyrrole derivative **7**.

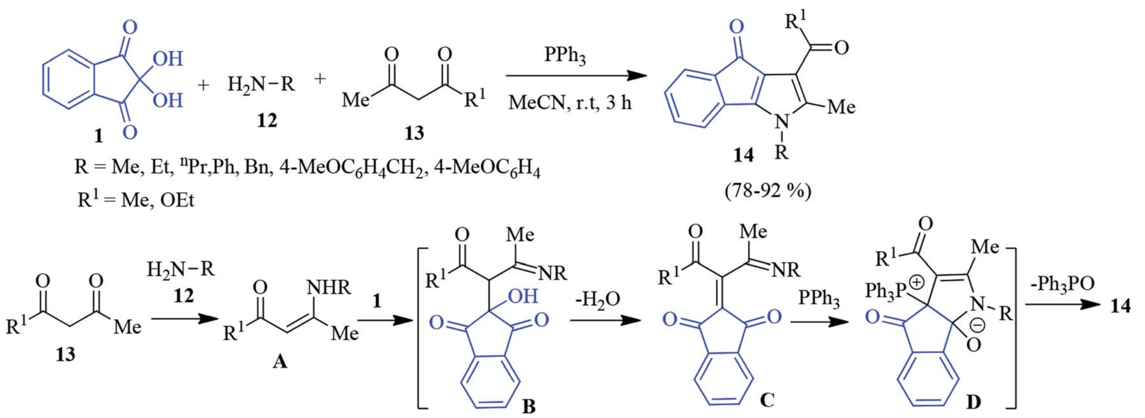
regioselectivity in moderate to excellent yields in refluxing EtOH. Mechanistically, it is conceivable that sarcosine **21** and ninhydrin **1** reacted readily to form intermediate **A**. After decarboxylation, the *in situ* generated azomethine ylide **B** underwent a [3 + 2] cycloaddition with the dipolarophile **22**, resulting in only one regioisomer as the cycloadduct **23** (Scheme 10). Inspired by the



Scheme 3 Green synthesis of dihydroindenopyrrole **9**.



Scheme 4 Synthesis of polysubstituted indenopyrroles **11**.

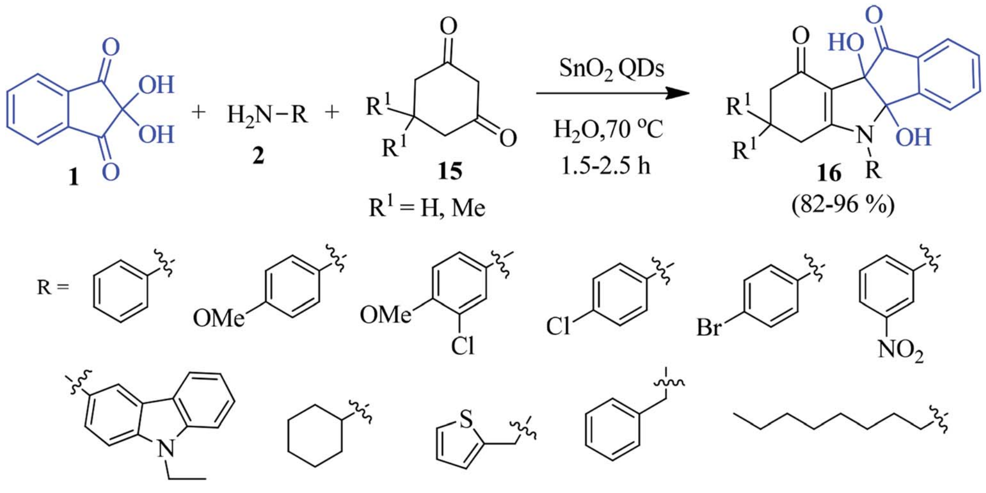


Scheme 5 Synthesis of substituted indenopyrroles **14**.

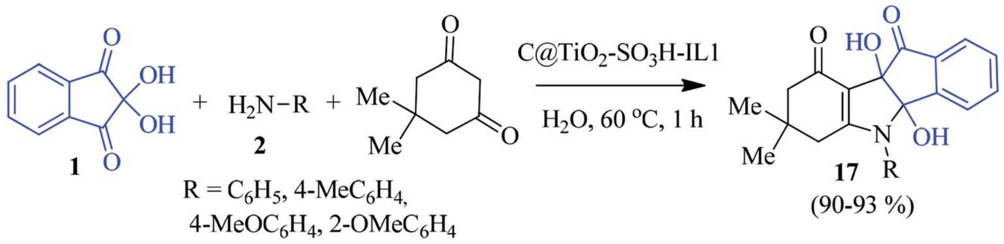
work described above, they developed a microwave-assisted solvent-free synthesis of nitrothiophene containing spiroindeno-pyrrolidines involving **1**, **21** and nitrothiophene bearing chalcone **22**[84] after annulation.

The novel indole/indazole containing spiropyrrolidine compound **26** was prepared by Kamila *et al.* by assembling L-proline **24**, ninhydrin **1** and *N*-alkyl vinyl indole/indazole **25** (Scheme 11).[85] Under similar reaction conditions, sarcosine **21** delivered the corresponding spiropyrrole motif **27** in good yields. The method comprised the 1,3-dipolar cycloaddition reaction between the *in situ* generated azomethine ylide (decarboxylative condensation of ninhydrin and amino acids) and *N*-alkylvinylindole/indazole dipolarophile to obtain the regio- and stereospecific products. Here, a variety of substituted vinyl indoles/indazoles **25** have been engaged to create a library of heterocyclic compounds of biological significance. Later, encouraged by these earlier results, they successfully accessed the azaindole-appended spiro-pyrrolidine skeleton **29**/**30**, employing **1**, proline **24** (or sarcosine **21**) and *N*-alkyl ethynylazaindole as dipolarophiles **28** (Scheme 12).[86]

Alizadeh's group outlined a facile and green protocol for the quinolone-based spiro-pyrrolizidine heterocycle **33** *via* the one-pot four component sequential combination of ninhydrin **1**, L-proline **24**, 2-chloroquinoline-3-carbaldehyde **31** and triphenylphosphanylidene **32**.[87] Utilization of chromene-3-carbaldehyde **34** in place of **31** smoothly afforded the corresponding chromene-linked spiro-pyrrolizidine heterocycle **35**. The reaction took place with excellent diastereoselectivity. Scheme 13 depicts the mechanism of the formation of the product. Initially, the Wittig reactions of **31** and **32** provided quinolinyl chalcone **A**, which acts as a dipolarophile. Azomethine ylide **D** generated from the reaction of ninhydrin **1** and L-proline **24** undergoes a cycloaddition reaction to accomplish the desired product.



Scheme 6 Green synthesis of indeno[1,2-*b*]indole derivatives **16**.

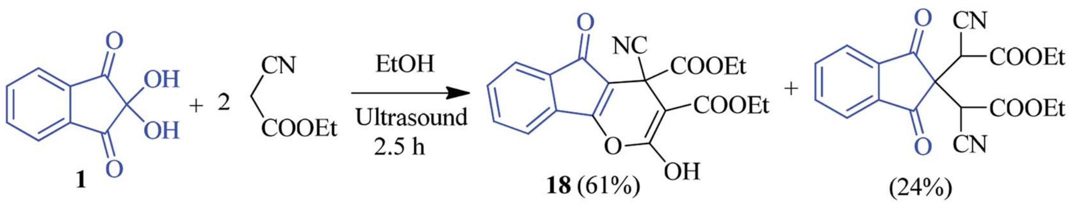


Scheme 7 Green synthesis of indeno[1,2-*b*]indolone derivative **17**.

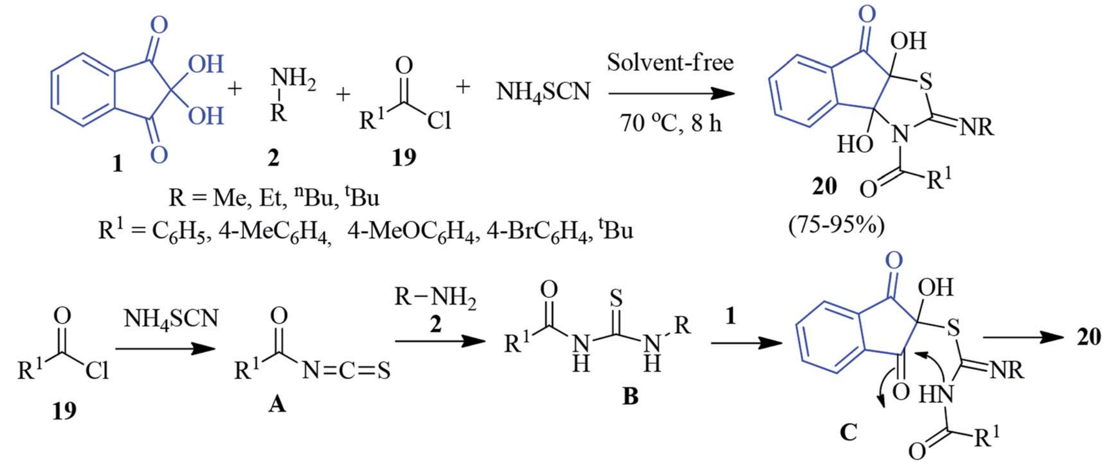
A fascinating approach to access nitrocoumarin-fused spiro-indanone pyrrolidine compounds **37** was revealed by Nayak and co-workers *via* a three component reaction of **1**, L-proline/pipecolic acid **24** and 2-phenyl-nitrochromene dipolarophile **36** (Scheme 14).[88] The simple method registers the formation of the cycloadducts **37** with excellent regio- and stereospecificity under microwave irradiation as well as conventional heating.

Likhar *et al.* synthesized a library of potentially bioactive spiro-indanone pyrrole/pyrrolizine derivatives **39** by using the [3 + 2] dipolar cycloaddition reaction of ninhydrin **1**, proline **24** with maleimide **38** (malic anhydride, 2-benzyl-2-methylcyclopent-4-ene-1,3-dione and isothiocyanates also used as dipolarophiles) without any catalyst in CH_3CN (Scheme 15).[89] Different α-amino acids, such as thiazolidine-4-carboxylic acid, leucine, valine, phenyl alanine and methionine were employed for constructing the diverse substituted spiro products in good yields. The scope of the reaction could be further extended utilizing phenacyl bromide **40** leading to *N*-substituted analogue **41.** Interestingly, various functionalized isothiocyanates **42** were utilized to obtain the corresponding spiro-thiazole derivative **43** under ambient conditions (Scheme 15). The stereochemical assignments of the products were made on the basis of a single crystal X-ray diffraction study.

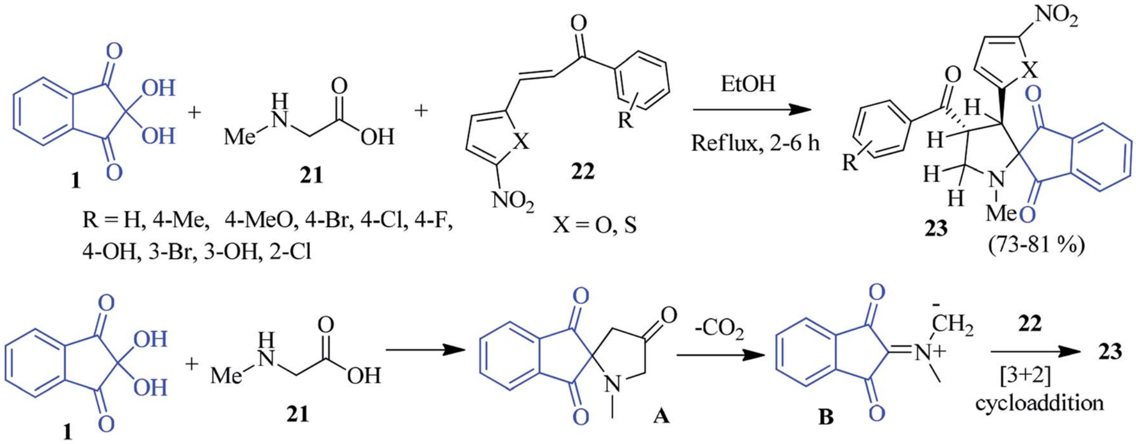
A new class of spiro indeno-pyrrolopyrrole derivatives **45** has been accomplished through the microwave-assisted 1,3-dipolar cycloaddition reaction of maleimides **44**, ninhydrin **1** and sarcosine **21** (Scheme 16).[90] A series of maleimides differing in the aryl part with electron releasing and electron withdrawing substituents were successfully incorporated. Importantly, despite the presence of two stereogenic centres in the cycloadduct **45,** only one diastereomer has been exclusively obtained. The authors successfully grew single crystals suitable for X-ray



Scheme 8 Synthesis of indenopyran derivative **18**.



Scheme 9 Solvent-free synthesis of indenothiazole derivative **20**.



Scheme 10 Regioselective synthesis of spiroindeno-pyrrolidine **23**.

analysis for the complete stereochemical assignments. The synthesized compounds were screened for antimycobacterial properties, and AChE inhibition activity, showing promising results.

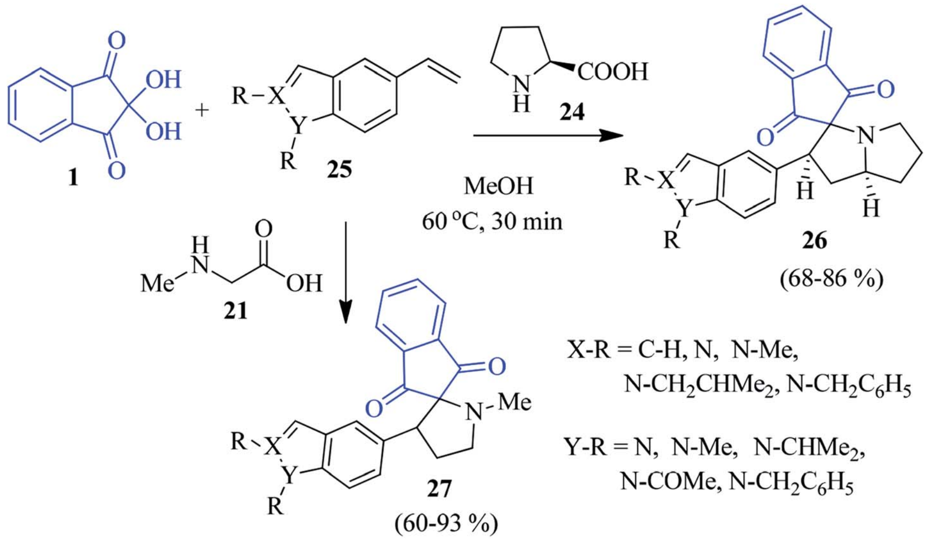
The construction of a biologically relevant spiro-indanone pyrrolizine-fused cyclopropane system **47** with quaternary stereocentres has been demonstrated by the Stepkov group using the 1,3-dipolar cycloaddition of the stable ninhydrin-derived azomethine ylide to cyclopropenes **46** (Scheme 17).[91] The [3 + 2] cycloaddition reaction proceeded smoothly, where the highly reactive and unstable cyclopropene was trapped into the reaction process. A DFT computational study was also performed to reveal factors controlling the regio- and stereoselectivity on the observed reactions.

Cage-like and dispiro compounds

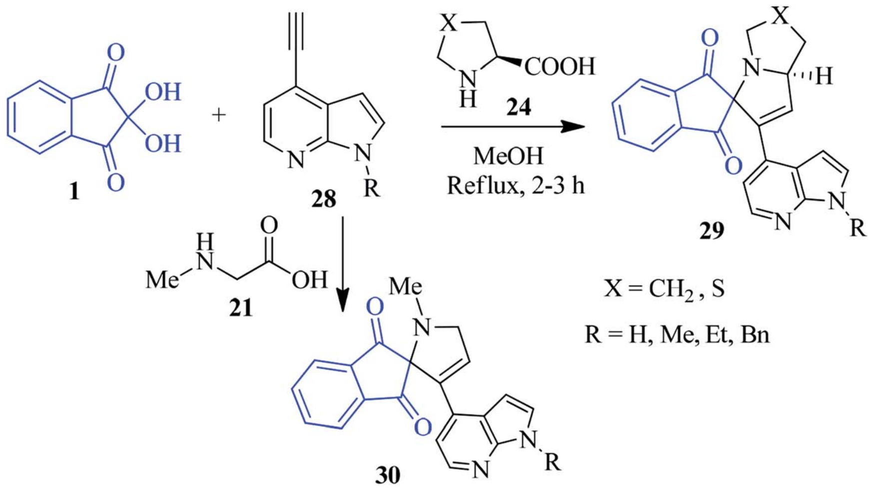
Kumar *et al.* uncovered a significant way in which ninhydrin **1**, proline **24** and (*E*)-3-arylidene-1-methylpiperidin-4-ones **48** were successfully assembled to fabricate the polycyclic spiroindeno cage-like compounds **50** in refluxing MeOH.[92] The three-component tandem [3 + 2] cycloaddition reactions of azomethine ylide and dipolarophile **48** resulted in the exclusive formation of the unexpected hexacyclic product **50** *via* an intramolecular annulation of the expected compound **49**. The formation of a cage-like product was confirmed from single crystal X-ray analysis. Under similar reaction conditions, sarcosine **21** produced dispiro compound **51** (Scheme 18).

Encouraged by the above results, they developed a microwave-assisted solvent-free approach for cage-like compounds and dispiro heterocycles *via* the domino 1,3-dipolar cycloaddition–annulation sequence of reactions.[93] The reaction of ninhydrin **1** and sarcosine **21** with heterocyclic ketone **52** yielded cage-like compounds **53–55**. The heteroatom in the ring might facilitate the annulation of the dispiro compounds initially formed in the reaction, resulting in a cage-like structure. Notably, when the carbocyclic ketones **56** were engaged instead of **52**, a new class of dispiro heterocycles **57** was obtained (Scheme 19).

An interesting access to the *N*-methylmorpholine fused dispiroindanone compound **58** was accomplished by Arumugam and co-workers *via* a sequential pseudo four-component



Scheme 11 Synthesis of indole/indazole-bearing spiroindenopyrrolidine/pyrrole **26** and **27**.



Scheme 12 Synthesis of the azaindole-appended spiroindene derivative **29** and **30**.

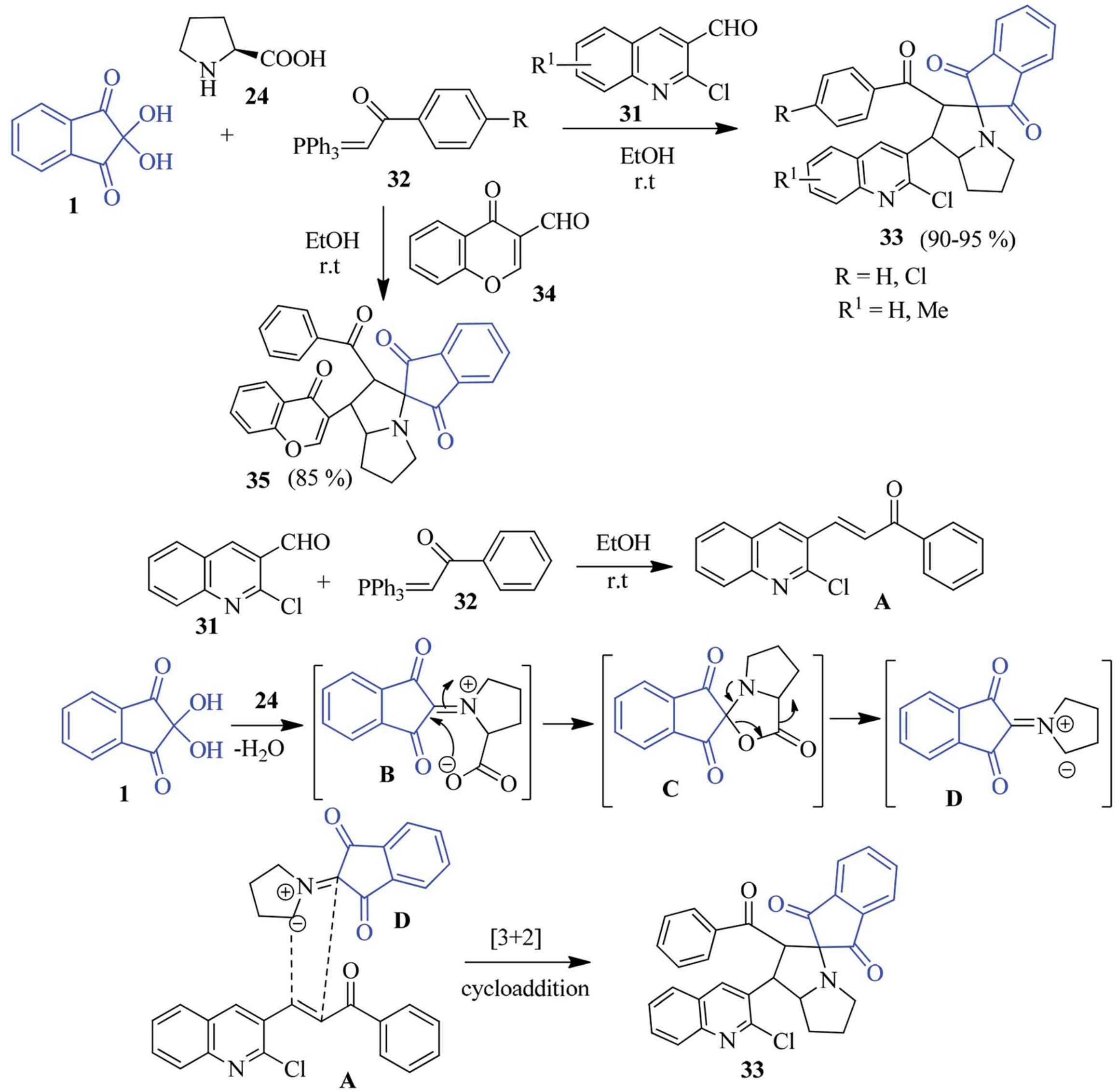
cascade cycloaddition reaction involving ninhydrin **1** and sarcosine **21** in DMF solvent (Scheme 20).[94] The formation of the unusual cycloadduct **58** was supported by DFT calculations, as well as single crystal X-ray diffraction analysis.

Efficient magnesium silicate nanoparticles ($MgSiO_3$ NPs) catalyzed the multicomponent reaction of ninhydrin **1**, sarcosine **21**, *N*,*N*-dimethylbarbituric acid **59** and aromatic aldehyde **60** to achieve dispiropyrrolidine derivatives **61**, and has been outlined by Koodlur and co-workers (Scheme 21).[95] The reaction proceeded rapidly, completing within 1–1.5 h under microwave irradiation. The synthesized products were examined for biological evaluation, showing interesting antibacterial activity and antiproliferative activity against tested cell lines.

4. Synthesis of spiro-indeno pyrans

A convenient and eco-friendly method for the synthesis of spiroindeno-pyran derivatives **64** has been developed by the Siddiqui group *via* a one-pot three component reaction of ninhydrin **1**, active methylene compounds **62** and 1,3-dicarbonyl **63**, employing a compact fluorescent lamp as a source of light.[96] The reaction undergoes a smooth transformation of a variety of 1,3-dicarbonyl compounds, resulting in good yields of the corresponding products. A plausible mechanism is offered in Scheme 22. The reaction is initiated by visible light promoting the homolytic fission of the C–H bond of the active methylene compound **62**. This homolytic fission and fusion of bonds lead to the formation of intermediate **B**, which upon addition of the 1,3-dicarbonyl compound, produces the spiropyran derivative **64**. This protocol allows for the mild, green and sustainable access to desired heterocycles without any additional catalyst.

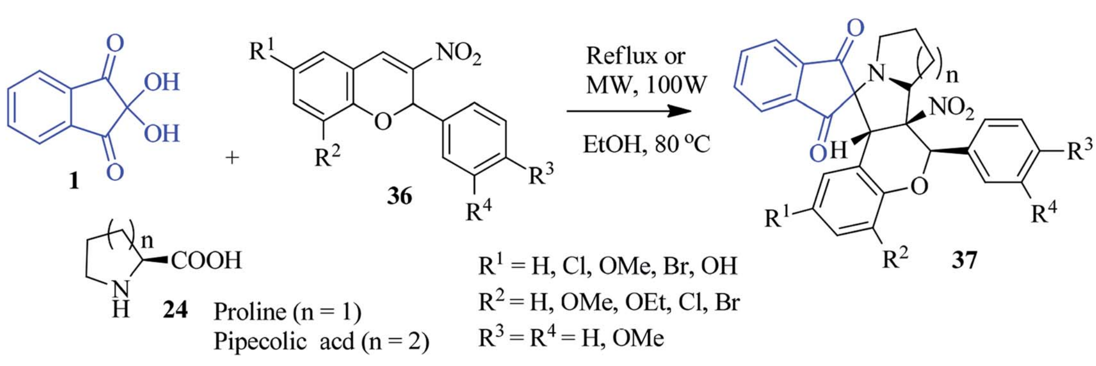
Very recently, Singh *et al.* introduced a glucose–water system as a new eco-friendly organocatalyst for the construction of spiropyran/spirochromene analogue employing the aforementioned starting materials.[97] In another report, the Safari group



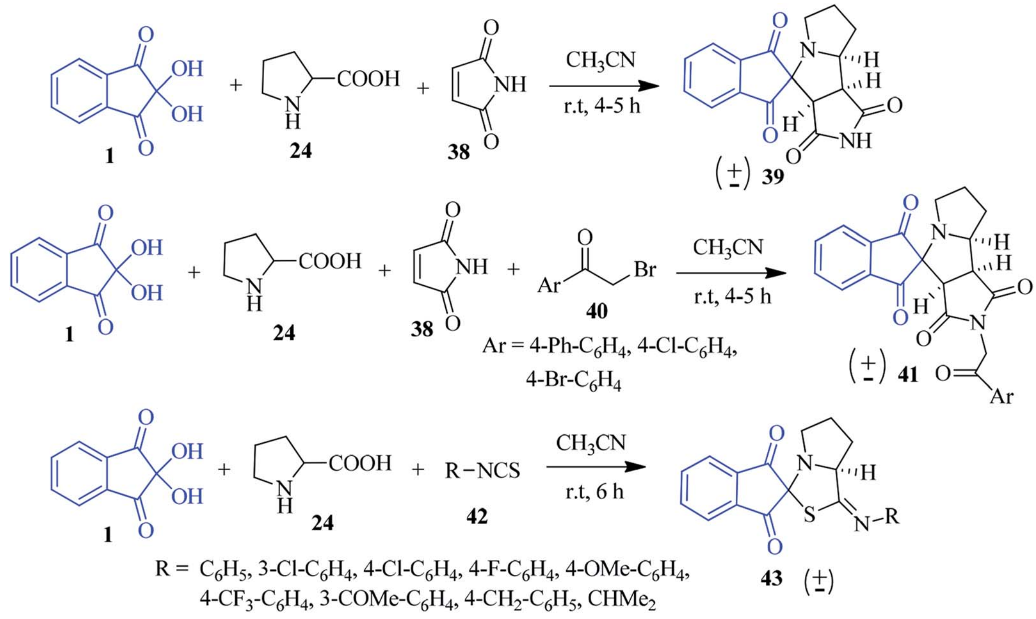
Scheme 13 Synthesis of the quinoline/chromene-linked spiro-pyrrolizidine derivatives 33 and 35.

utilized $NiFe_2O_4$@SiO_2@melamine magnetic nanoparticles[98] as a recyclable catalyst to obtain similar compounds.

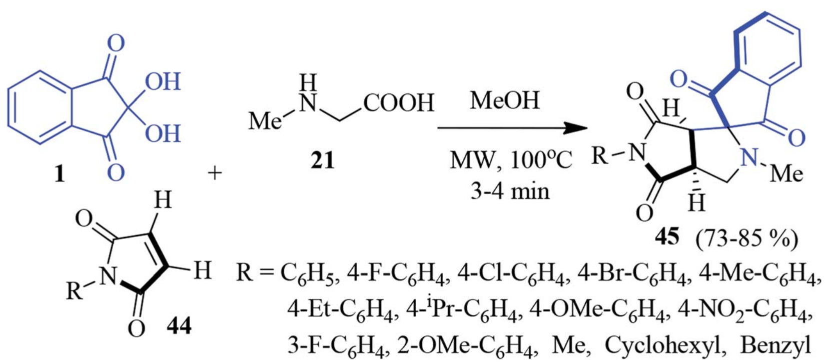
Alizadeh and Bayat elaborated on a one-pot four-component reaction between ninhydrin **1**, malononitrile **62**, hydrazine derivatives **65** and β-ketoesters **13** to afford spiroindeno pyranopyrazole derivatives **66** regioselectively in EtOH medium in the presence of one drop of piperidine catalyst (Scheme 23).[99]



Scheme 14 Formation of nitrocoumarin-fused spiro-indanone pyrrolidine derivatives 37.



Scheme 15 Synthesis of the spiro-indanone pyrrole/pyrrolizine/thiazole derivatives 39, 41 and 43.

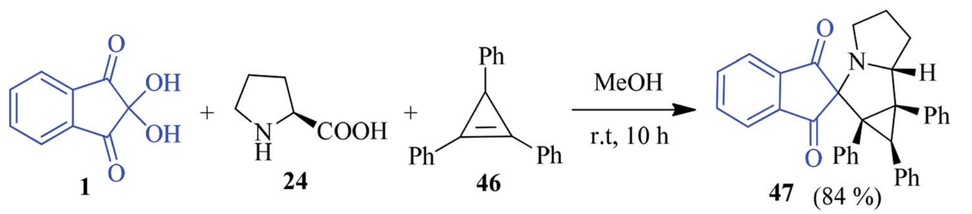


Scheme 16 Synthesis of bioactive spiro indeno-pyrrolopyrrole derivatives 45.

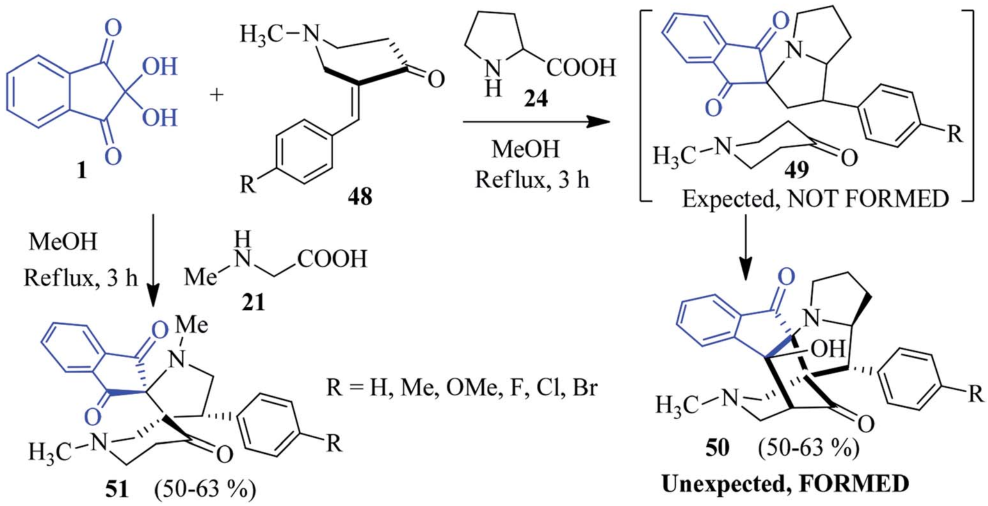
Employment of dimethylacetylenedicarboxylate (DMAD) **8** in place of **13** resulted in a spiro compound **67**.

Later, Das *et al.* introduced an appealing approach to access the spiro pyranopyrazoles **70**, involving dodecylbenzenesulphonic acid (DBSA) as a Brønsted acid–surfactant-combined catalyst in aqueous medium.[100] The sequential reaction comprises the tandem Knoevenagel/Michael addition reaction followed by the dehydrative cyclisation of pyrazolone derivatives **69** (prepared from ethylacetoacetate **13** and hydrazines **65**), cyclic 1,3-diketones **63**, and ninhydrin **1** (Scheme 24). The synthetic strategy is operationally simple, economical, and environmentally benign, delivering target compounds in good yields (78–96%).

Recently, Bayat and Hosseini published an efficient one-pot protocol for the synthesis of spiro indeno pyranopyridazine derivatives **72** involving cyanoacetohydrazide **71**, ninhydrin **1**,



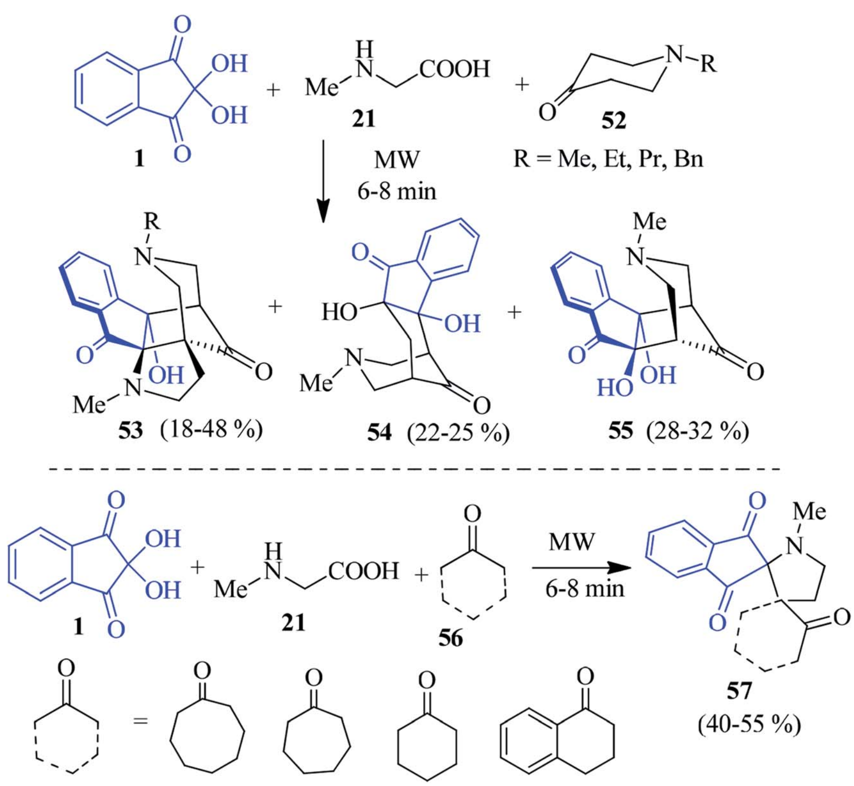
Scheme 17 Synthesis of spiro-indanone pyrrolizine-fused cyclopropane system 47.



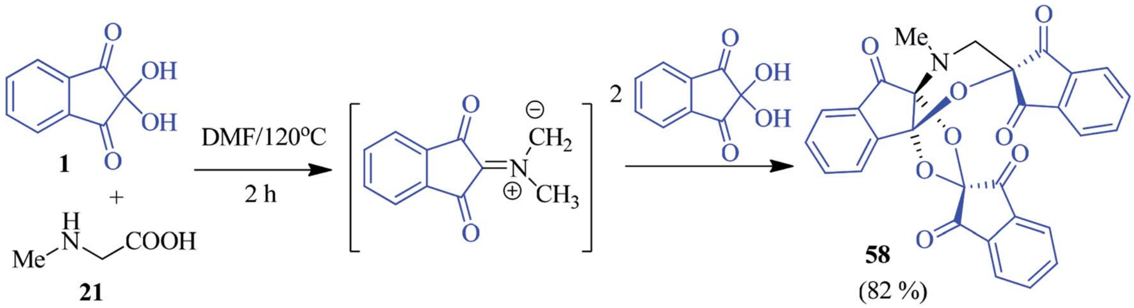
Scheme 18 Synthesis of spiro indeno cage-like compounds **50** and dispiro compounds **51**.

malononitrile **62** and different cyclic CH-acids **63** in refluxing EtOH.[101] According to the mechanism, ninhydrin **1** and cyanoacetohydrazide **71** condenses to form azomethine intermediate **A.** Subsequently, the intramolecular cyclisation of **A** generates indeno-pyridazine intermediate **B.** The Knoevenagel condensation of malononitrile **62** produces **C.** Then, the Michael addition of cyclic CH-acids **63** affords intermediate **D.** Finally, cyclisation followed by imine–enamine tautomerization results stable product **72** (Scheme 25). The products are examined for biological activity.[102] It has been found that some of the compounds exhibit pronounced antimicrobial (*E. coli* and *S. aureus*), cytotoxic activity (on lung cancer cells, prostate cancer cells, breast cancer cell line *etc.*) and pro-apoptotic effects.

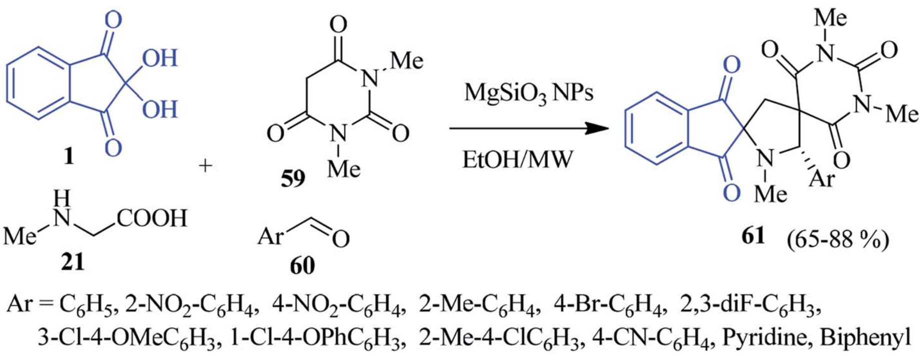
A new spiro thiopyrano pyran derivative **74** has been prepared by Palchykov and co-workers with the help of dihydro-2*H*-thiopyran-3(4*H*)-one-1,1-dioxide **73**, ninhydrin **1** and malononitrile **62** (Scheme 26).[103] The high reactivity of ketosulfone **73**



Scheme 19 Formation of the cage-like compounds **53** and dispiro heterocycles **57**.



Scheme 20 Synthesis of the *N*-methylmorpholine fused dispiroindanone compound **58**.



Scheme 21 Construction of dispiropyrrolidine scaffold **61**.

was exploited to afford the desired product within a short reaction time.

Azizian *et al.* pioneered a concise green method for the synthesis of spiroindeno oxathiazine derivatives **76** by the one-pot three component condensation of tetramethyl guanidine **74**, ninhydrin **1** and isothiocyanates **75**.[104] The reaction was fruitful in water at room temperature, where simple filtration afforded novel spiro heterocycle containing oxygen, sulphur and nitrogen. A plausible mechanism is offered in Scheme 27. The nucleophilic attack of tetramethyl guanidine **74** to isothiocyanate **75** produces intermediate **A**. Subsequently **A** attacks through its sulphur atom to the central carbonyl of ninhydrin **1** to furnish intermediate **B** (route a) or **C** (route b). Finally cyclisation followed by removal of $NHMe_2$ leads to the formation of product **76**.

5. Synthesis of indenoquinoxalines

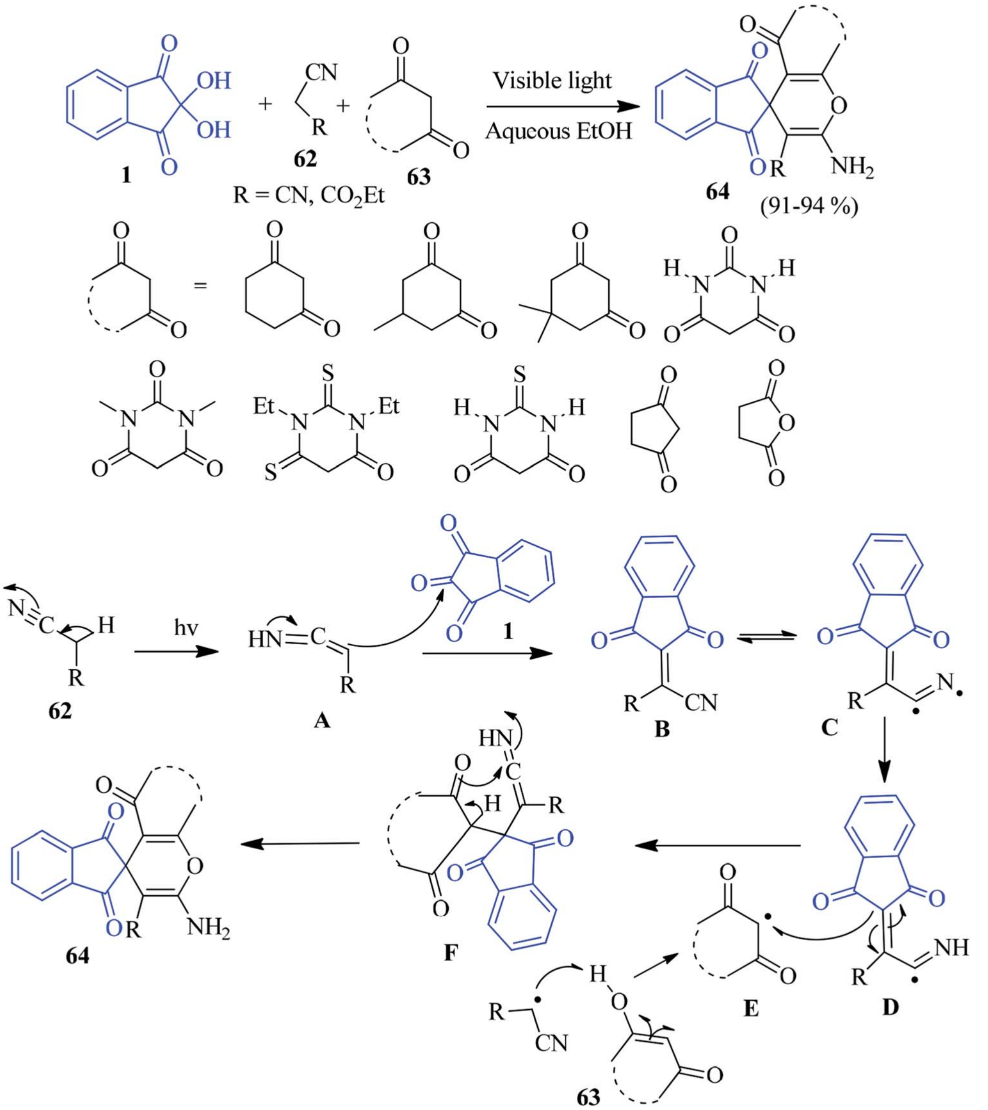
In 2015, the Ghahremanzadeh group published a highly efficient protocol for the novel α-aminophosphonate-anchored indenoquinoxaline moiety **81** based on the Kabachnik–Fields reaction involving ninhydrin **1**, *o*-phenylenediamine (PDA) **77** and dialkyl or diaryl phosphites **78** (Scheme 28).[105] The reaction proceeded successfully under solvent-free conditions sequentially with the formation of **79** and **80** without any catalyst, resulting in the desired compound **81** in high yields. It should be mentioned that anilines with an electron donating group reacted smoothly. However, anilines with electron withdrawing groups failed.

A green regioselective approach to accomplish the production of new indenoquinoxaline compounds containing pyrrolopyrimidine scaffolds **86** was presented by Alizadeh and co-workers (Scheme 29).[106] The indenoquinoxaline **79** (generated from ninhydrin **1** and PDA **77**) was reacted sequentially with 1-aryl-2-(1,1,1-triphenyl-λ^5-phosphanylidene)ethan-1-one **82** to obtain (*E*)-indenoquinoxaline arylethanone derivatives **83**, which were further allowed to react with diamine **84** and 1,1-bis(methylthio)-2-nitromethylene **85** under ultrasound irradiation towards the final compound **86** (which remains in equilibrium with **86′**).

6. Synthesis of spiro-indenoquinoxaline containing heterocycles

In 2015, Jadidi *et al.* demonstrated a one-pot four component reaction of ninhydrin **1**, PDAs **77**, optically active cinnamoyl-crotonyl oxazolidinone **87** and sarcosine **21**/proline **24** to afford the novel chiral spiro-indenoquinoxaline pyrrolidines/pyrrolizidines **88–89** (Scheme 30).[107] The protocol offers the formation of a complex product (with four contiguous stereogenic centres) from simple starting materials with high regio-, diastereo- (up to 96% dr) and enantioselectivity (up to 99% ee), which proceeded through a 1,3-dipolar cycloaddition reaction of the azomethine ylide in refluxing ethanol.

In the same year, an efficient strategy was introduced by Hamzehloueian for the synthesis of spiro-indenoquinoxaline



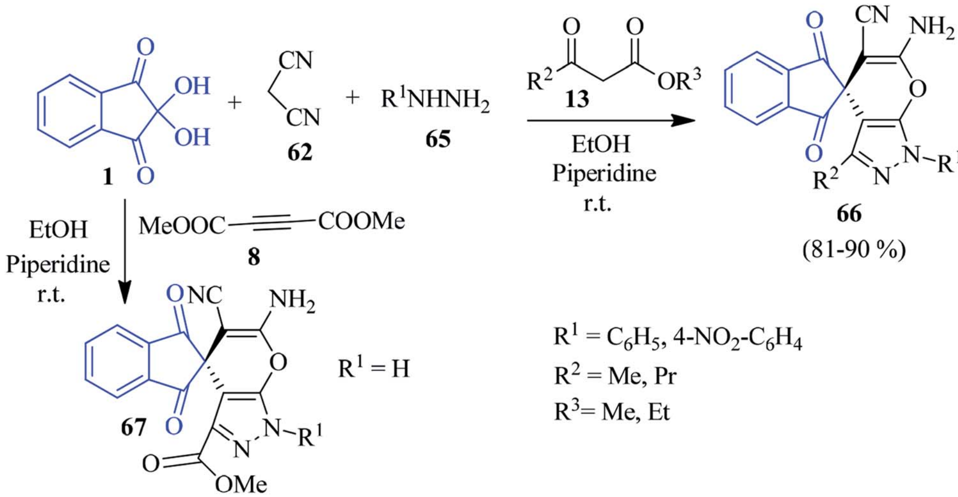
Scheme 22 Green synthesis of spiroindeno-pyran derivatives **64**.

pyrrolothiazoles **91** involving 1,3-thiazolane-4-carboxylic acid **24**, ninhydrin **1**, PDA **77** and *trans*-β-nitrostyrene derivatives **90** in refluxing EtOH (Scheme 30).[108] The reaction proceeded *via* the cycloaddition of *trans*-β-nitrostyrene dipolarophile and *in situ* azomethine ylide generated from **1**, **24** and **77**. They successfully analysed the mechanism and regioselectivity of the formation of the *endo* product **91** by DFT.

Inspired by the above works, Lakshmi Kantam and Trivedi developed a microwave-assisted protocol towards spiro-indenoquinoxaline pyrrolizine derivatives **92** involving proline **24** (Scheme 30). They successfully evaluated their AChE inhibitory activity.[109] Rajendran *et al.* disclosed the formation of the quinoline pendant spiro-indenoquinoxaline pyrrolizines **94** involving ninhydrin **1**, substituted PDA **77**, proline **24** and dipolarophile various quinoline substituted chalcones **93** (Scheme 30).[110] Immediately after, they synthesized pyrrolothiazole derivatives **95** using thiazolidine-2-carboxylic acid instead of proline. The compounds were screened for *in vitro* antioxidant activities and *in vivo* cytotoxic activity against breast cancer cell line MCF-7 and adenocarcinomic cancer cell line A-549.[111]

Novel indole appended spiro-indenoquinoxaline pyrrolidines/pyrrolizidines **98**/**99** were isolated by Zhu *et al.* through a five-component reaction using ninhydrin **1**, PDA **77**, amino acids **21**/**24**, 3-cyanoacetyl indoles **96** and aryl aldehydes **60** in EtOH.[112] The Knoevenagel product **97** generated from the 3-cyanoacetyl indoles **96** and aryl aldehydes **60** acts as dipolarophile (Scheme 31). Notably, the utilization of primary amino acids such as glycine or phenylalanine in this reaction did not afford the target product.

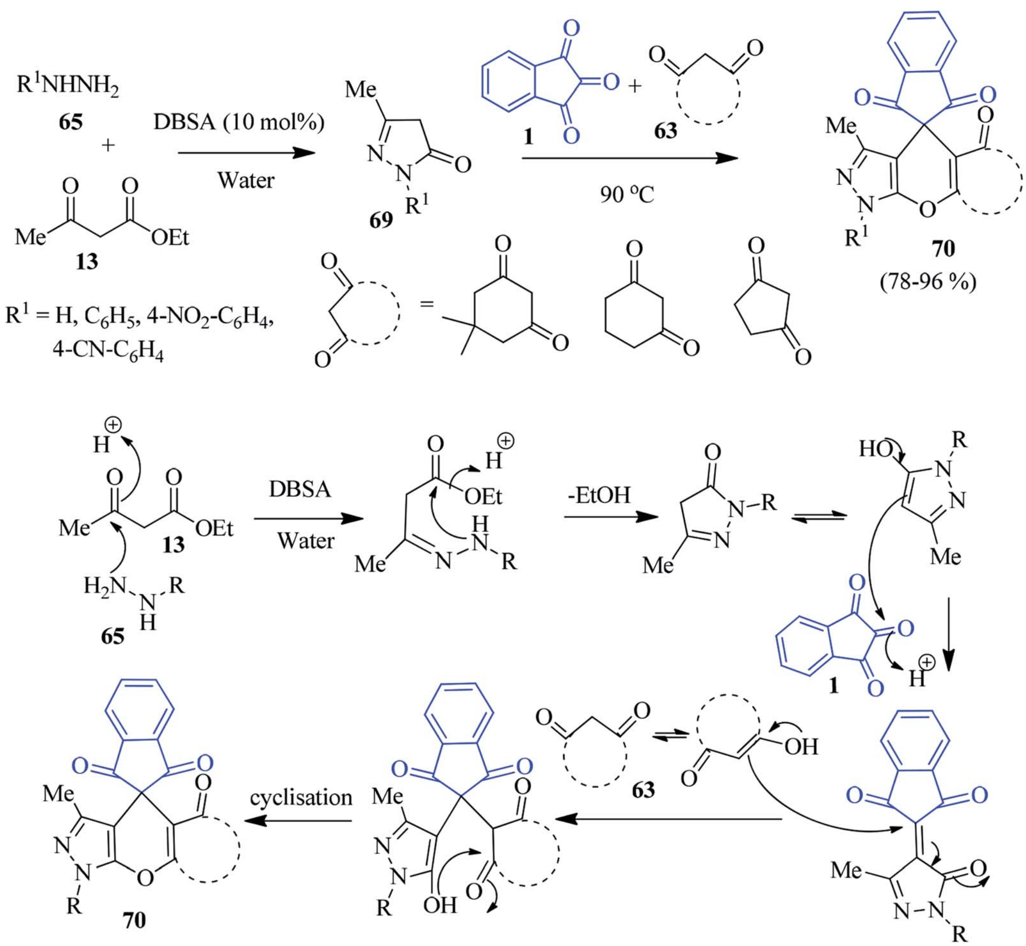
As a part of their synthetic plan, Khurana and Gupta developed a convenient four-component approach to access isoxazole-linked spiro-indenoquinoxaline pyrrolizines **101** involving ninhydrin **1**, substituted PDA **77**, L-proline/thioproline **24** and 3-methyl-4-nitro-5-styrylisoxazoles **100** in MeOH



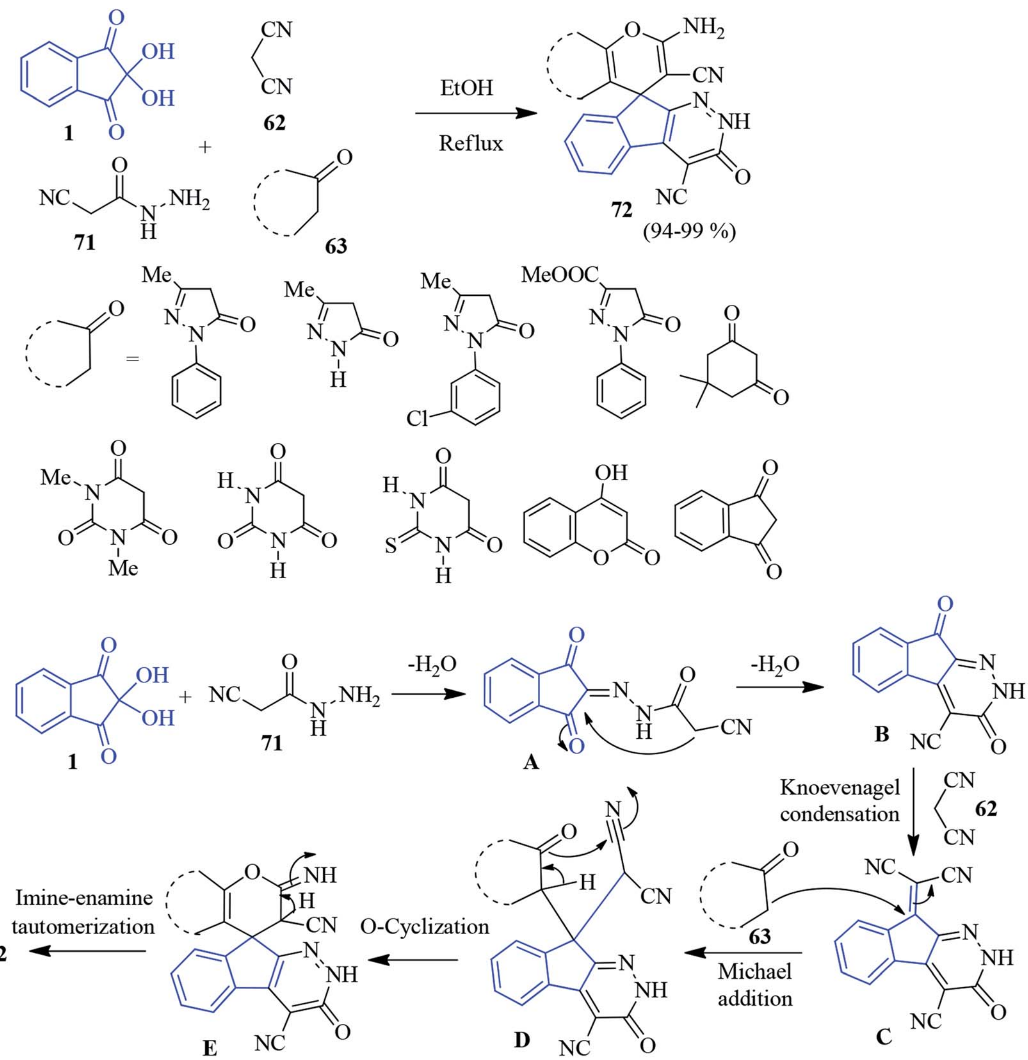
Scheme 23 Regioselective synthesis of spiroindeno pyranopyrazole derivatives 66 and 67.

(Scheme 31).[113] The catalyst-free simple protocol provides high regioselectivity in a short time frame.

Chowhan and co-workers accomplished a similar type of isoxazole pendant compound **102** through a four-component reaction with high regio- and diastereoselectivity.[114] They incorporated benzylamine **6**, ninhydrin **1**, PDA **77** and isoxazole derivatives **100** to achieve the desired product **102** *via* the 1,3-dipolar [3 + 2] cycloaddition reaction. In particular, the nature of the substitution and their position on the aromatic rings of styrene (dipolarophile), benzylamines and PDA control the



Scheme 24 Water-mediated synthesis of the spiroindeno-pyranopyrazole derivatives 70.



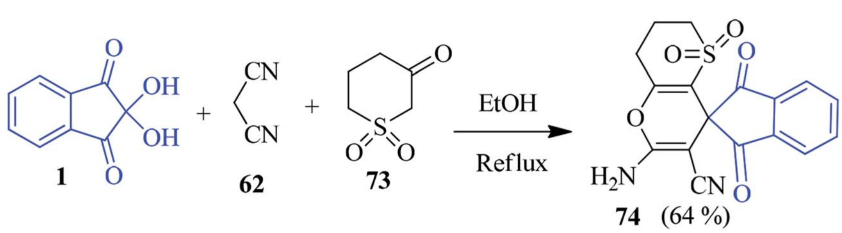
Scheme 25 Synthesis of spiroindeno pyranopyridazine derivatives 72.

diastereoselectivity of the reaction (Scheme 31). The method is simple, efficient, mild, catalyst-free, column chromatography-free, and does not require any workup procedure.

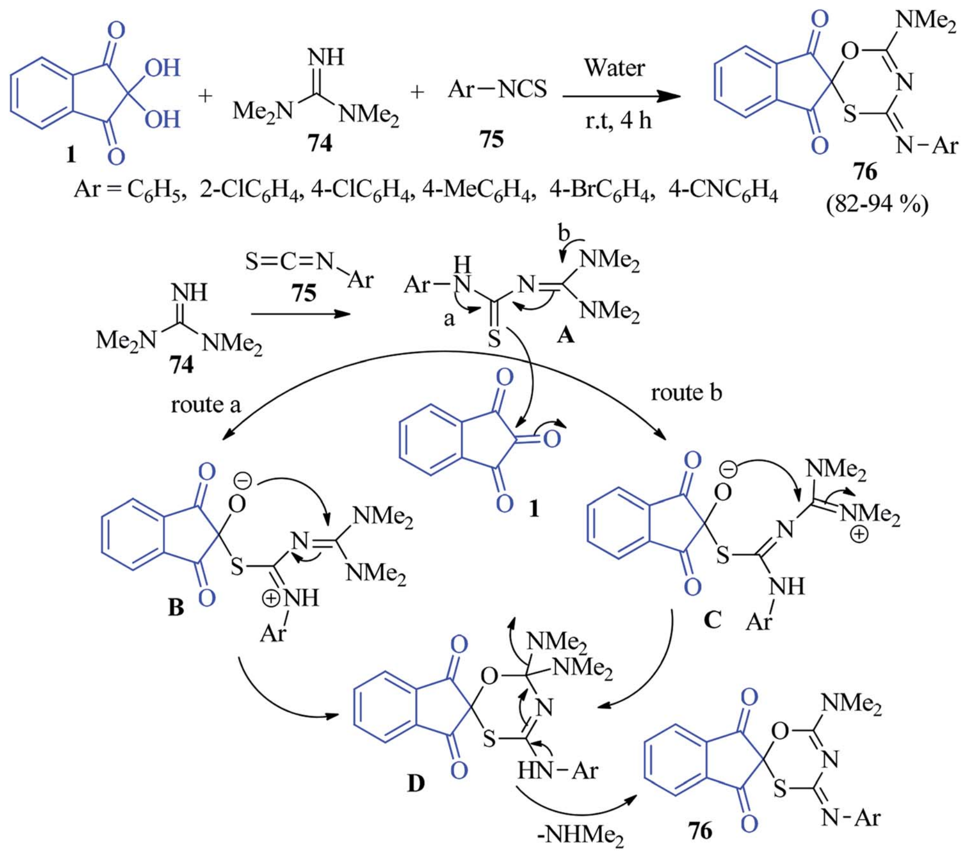
A simple cost-effective method was pioneered by Mahdavinia for the combinatorial synthesis of furan-appended spiro-indenoquinoxaline derivatives **104** *via* a one-pot four-component reaction of ninhydrin **1**, PDAs 77, DAAD **8** and isocyanides **103** (Scheme 32).[115] Various substituted benzene-1,2-diamine, methyl and ethyl acetylenedicarboxylates and isocyanides were applied to form the corresponding spiro derivatives in excellent yields. Notably, the reaction did not proceed in protic solvents like EtOH, MeOH, water. However, an excellent yield was obtained in aprotic CH_2Cl_2.

Indenoquinoxaline anchored dispiro scaffolds

In 2014, Raghunathan and co-workers established a concise route to construct pyrazolo cycloalkane-grafted spiro-indenoquinoxaline pyrrolidines **106** by a sequential five-



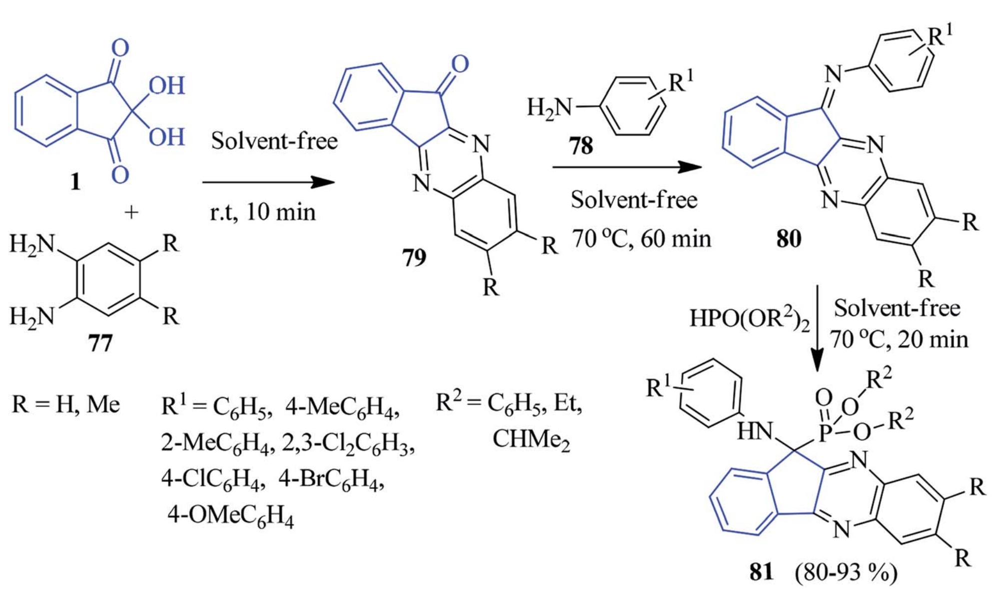
Scheme 26 Synthesis of spiroindeno thiopyrano pyran derivative 74.



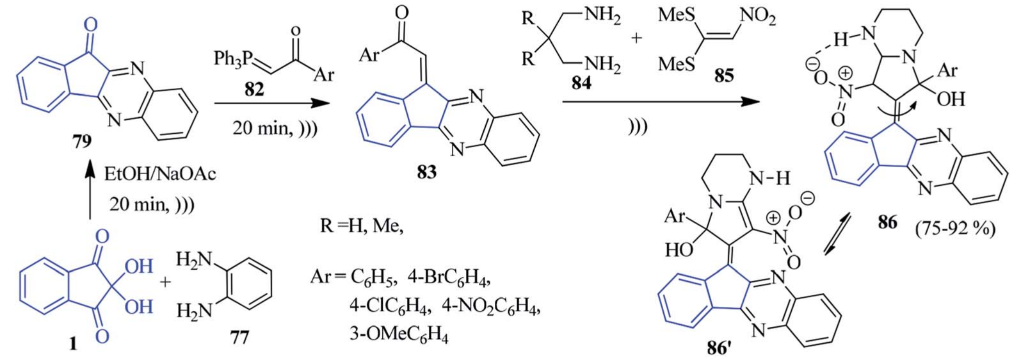
Scheme 27 Formation of spiroindeno oxathiazine derivatives 76.

component reaction involving ninhydrin **1**, PDAs **77**, sarcosine **21**, 2,5-bis-(arylmethylidene)-cycloalkanone **105** and hydrazine hydrate **65** *via* the [3 + 2] cycloaddition strategy.[116] This reaction is applicable to a variety of bis-(arylmethylidene)-cyclopentanone/cyclohexanone systems **105** for the regioselective construction of complex structural entities **106** (Scheme 33).

Later, the Kumar group expanded the scope of the reaction by employing sulphur-containing dipolarophiles, *viz.*, (2*Z*,4*Z*)-2,4-bis-(arylidene)dihydrothiophen-3(2*H*)-ones **105** to build



Scheme 28 Synthesis of α-aminophosphonate-anchored indenoquinoxalines 81.



Scheme 29 Green synthesis of indenoquinoxalines bearing pyrrolopyrimidine scaffolds **86**.

potentially bioactive dihydrothiophenone engrafted spiro-indenoquinoxalines **107** and **108** (Scheme 33).[117] The reactions are associated with the generation of up to four new contiguous stereocentres, and the formation of two C–C bonds and one C–N bond in a single transformation.

A facile five-component cascade reaction to fabricate novel dispiro-indenoquinoxaline pyrrolidine derivatives **110** was investigated by Li and co-workers utilizing ninhydrin **1**, PDA **77**, sarcosine **21**, 1,3-indanedione **109** and various aldehydes **60**.[118] The reaction took place in high chemo-, regio-, and stereo-selective mode. The strategy comprises the cycloaddition of the 1,3-dipole azomethine ylide and dipolarophile simultaneously generated *in situ*, which is complementary to the classical Huisgen synthesis towards the formation of dispiro heterocyclic compounds (Scheme 33).

As part of their studies, the Kumar group exploited ninhydrin **1** and PDA **77** to fabricate dispiro-*N*-methyl-4-piperidone-indenoquinoxaline-pyrrolothiazole/pyrrolidine hybrid heterocycles **111** and **112** by the multicomponent [3 + 2] cycloaddition strategy involving (*E*)-3-arylidene-1-methylpiperidin-4-ones **48** as the dipolarophile (Scheme 34).[92] These reactions occurred with controlled stereoselectivity, delivering only single isomer.

Very recently, Arumugam and co-workers introduced the ionic liquid [bmim]Br-mediated synthesis of novel dispiropyrrolidinyl-piperidone tethered indenoquinoxaline derivatives **115**.[119] The azomethine ylide generated *in situ* from indenoquinoxalinone and L-tryptophan **113** (*via* decarboxylative condensation) undergoes a 1,3-dipolar cycloaddition reaction with bis-arylidenepiperidone **114**, regioselectively furnishing the hybrid heterocycle **115** (Scheme 35). The authors performed tests for biological activity, as well as a docking study. The synthesized compounds were found to exhibit cholinesterase inhibitory activity (AChE and BChE activity).

7. Synthesis of propellanes

In 2014, Alizadeh and co-workers disclosed a sequential four-component approach to accomplish oxa-aza[3,3,3]propellanes **116** by the reaction of the aryl isothiocyanates **75**, malonate compounds **13**, ninhydrin **1** and malononitrile in the presence of NaH in DMF (Scheme 36).[120] This methodology offers remarkable chemo- and regioselectivity associated with the formation of five new bonds. The purification of the compounds was carried out without column chromatography. The mechanism of the formation of propellanes **116** is depicted in Scheme 36. The strategy was extended by the authors for the synthesis of a similar type of heterocyclic propellane **117** involving malononitrile, ninhydrin **1**, β-ketoesters **13** and hydrazine derivatives **65** in the presence of a piperidine catalyst (Scheme 37).[101]

An interesting three-component domino reaction of ninhydrin **1**, enaminones **3** and malononitrile was reported by Huang *et al.* to access propellanes **118** (Scheme 38).[121] The reaction was most effective in EtOH in the presence of L-proline as a catalyst (10 mol%) at room temperature. *n*-Butyl, naphthalene-1-yl, and phenyl rings with electron-withdrawing or donating groups on the enaminone ring were well tolerated under the reaction conditions. This reaction comprises the formation of two rings and four bonds by a one-pot procedure.

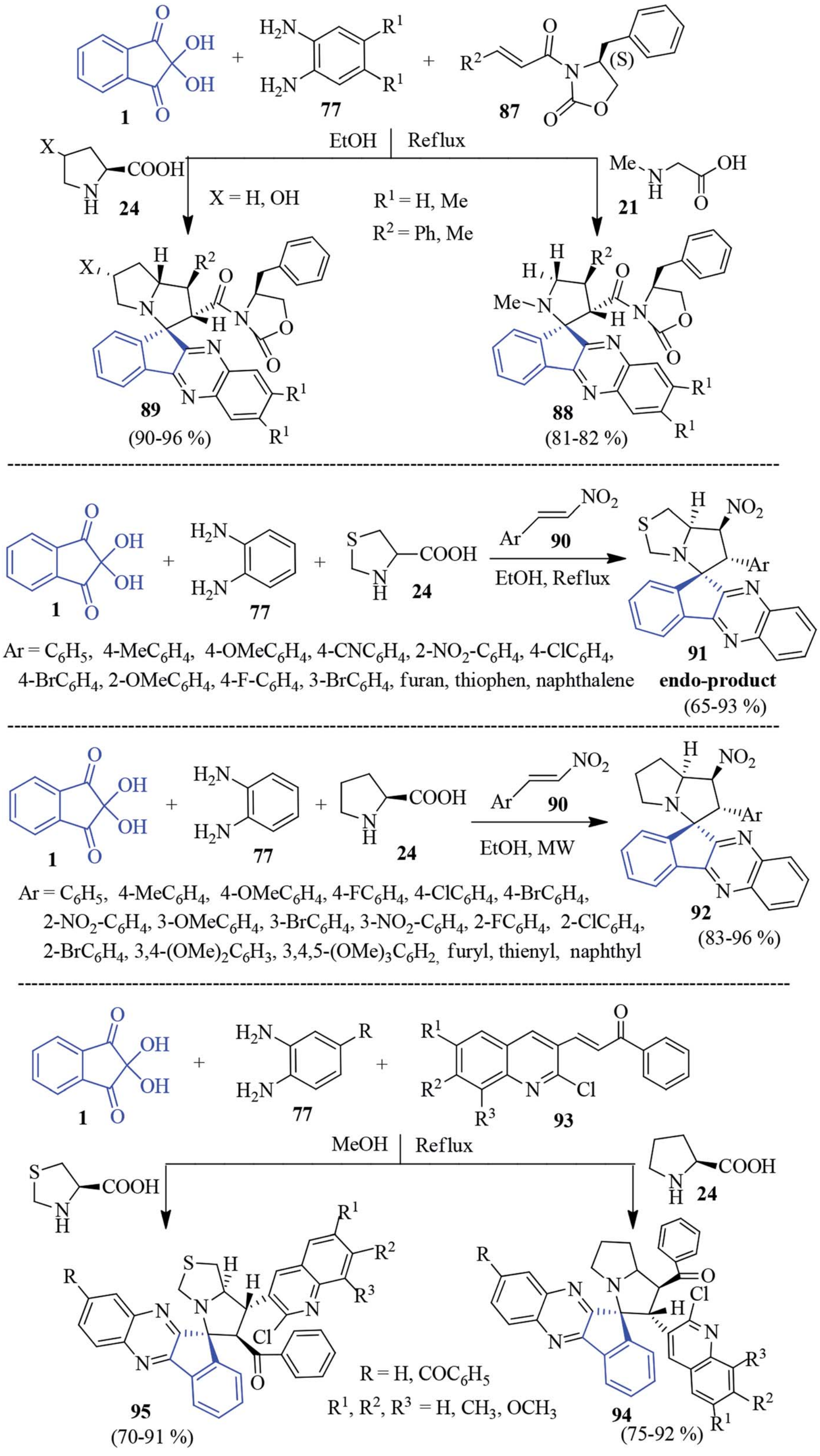
Yavari and co-workers found that a tandem reaction of trichloroacetonitrile, substituted benzylamines **6**, ninhydrin **1** and malononitrile led to the formation of trichloromethylated [3,3,3]propellanes **120** (Scheme 39). The trichloroacetamidine intermediate **119**, generated *in situ* by the addition of trichloroacetonitrile and benzylamines **6** reacted with the Knoevenagel condensation product of ninhydrin **1** and malononitrile to accomplish the desired compound **120**.[122]

8. Development of diverse molecular scaffolds

In this section, the construction of different ninhydrin-derived skeletons through various rearrangements will be discussed.

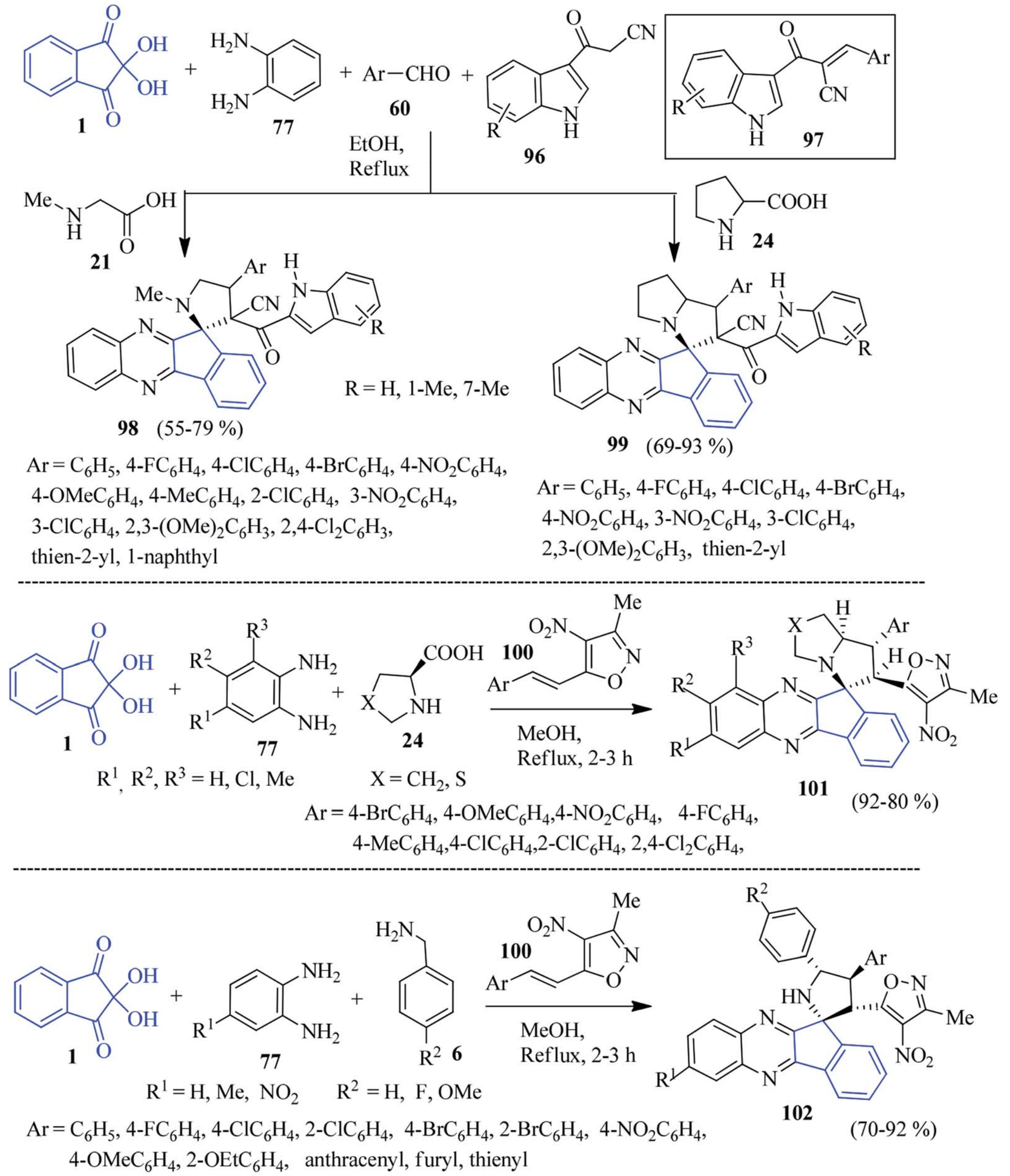
α-Amino acids

Naeimi and co-workers have developed a facile method to access structurally interesting α-amino acids **121** from ninhydrin **1** and anilines **2** in the presence of $CHCl_3$ and NaOH based on the Bargellini reaction in THF medium (Scheme 40).[123] In this reaction, the ninhydrin core has been exploited as an active carbonyl compound in the Bargellini reaction. Various anilines containing electron donating and withdrawing groups successfully responded under mild conditions. Mechanistically, the NaOH-promoted reaction might proceed *via* deprotonation of $CHCl_3$,



Scheme 30 Regioselective synthesis of spiro-indenoquinoxaline derivatives 88, 89, 91, 92, 94, and 95.

followed by a nucleophilic attack on ninhydrin and resulting in the dichloro epoxide **B**. Then, the opening of the epoxide ring by a nucleophilic attack of amine **2** led to the formation of acid chloride **C**, which after hydrolysis, afforded the desired amino acid **121**. Diarylamine compounds also responded well in this transformation. It should be mentioned that other activated

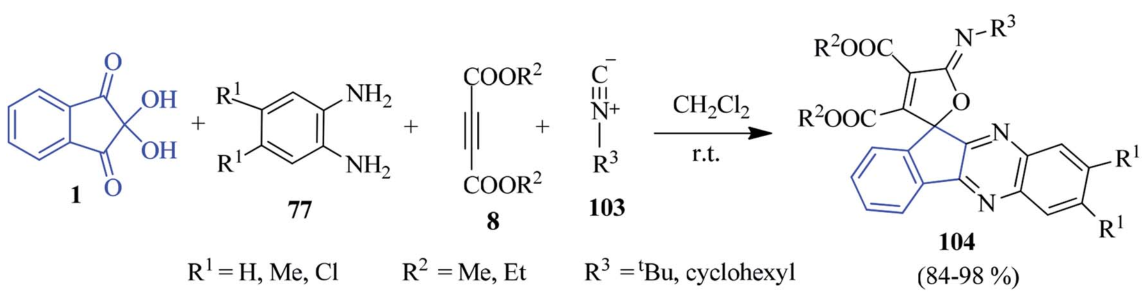


Scheme 31 Synthesis of spiro-indenoquinoxaline derivatives 98, 99, 101 and 102.

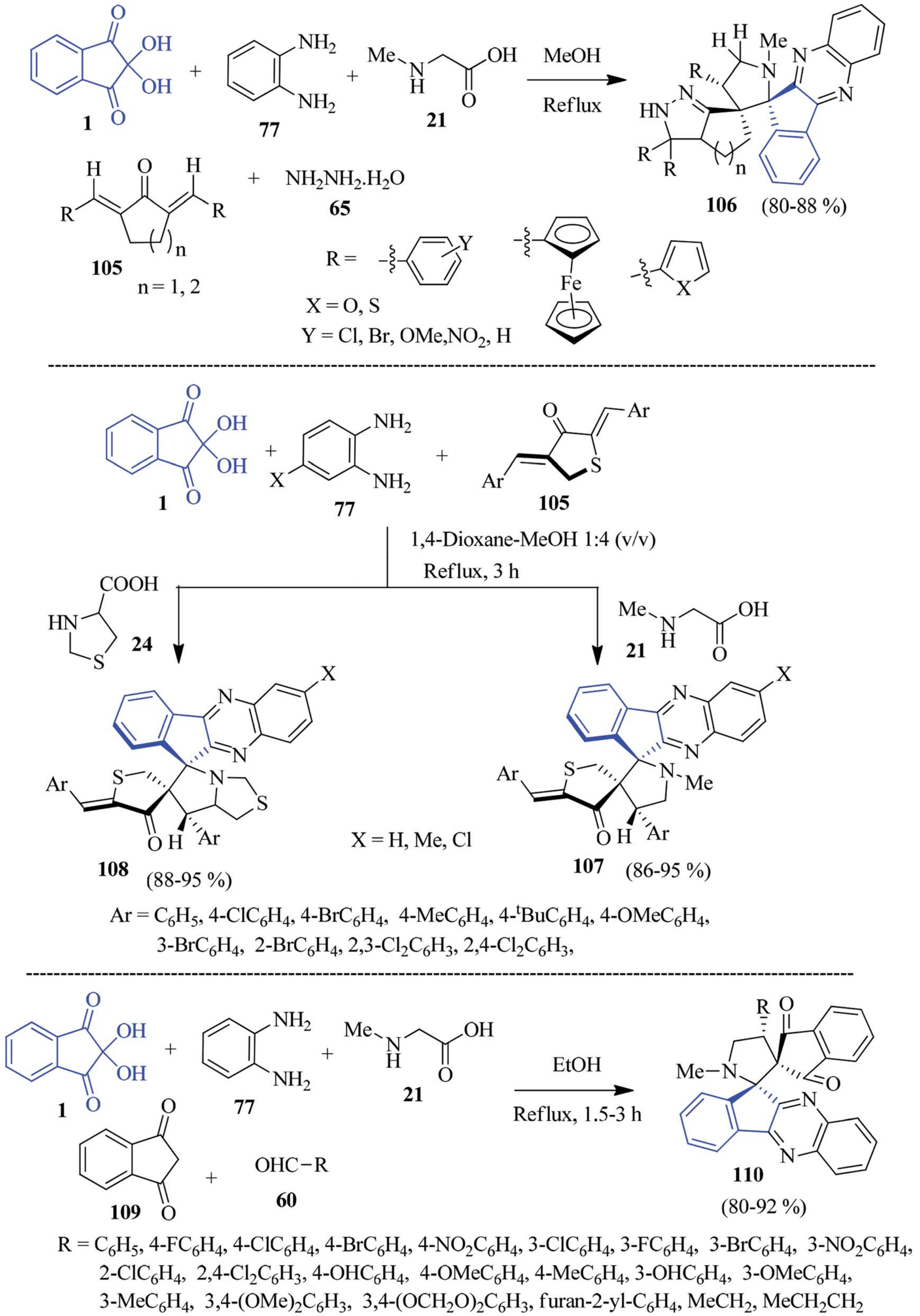
carbonyl compounds, such as isatin, acenaphthaquinone and 9,10-phenanthraneraquinone (instead of ninhydrin), did not yield the desired product.

Pyrrolizines/pyrroles

A convenient multicomponent methanolysis protocol has been demonstrated by the Meshram group to afford pyrrolizine and

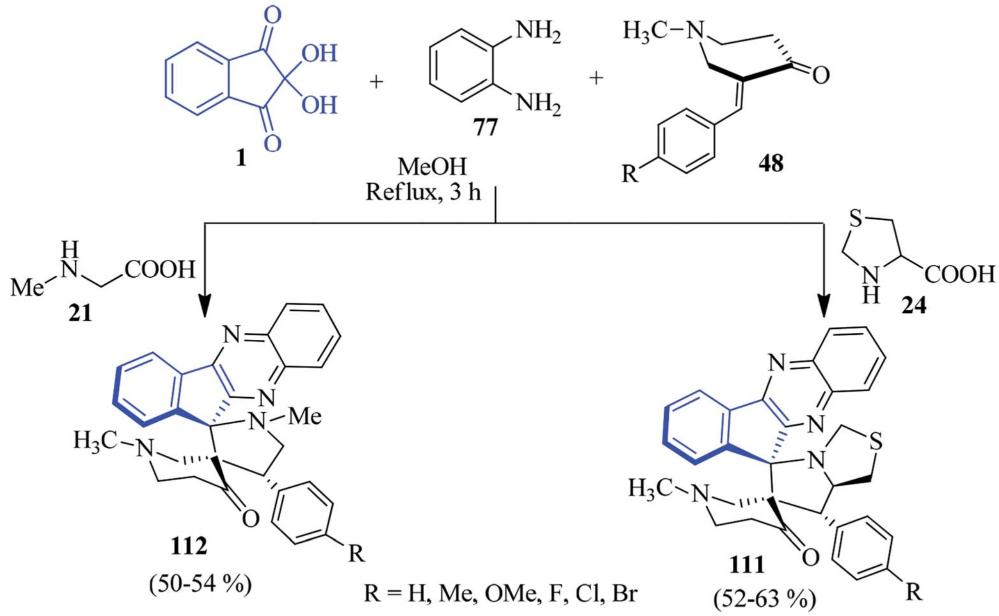


Scheme 32 Construction of furan-appended spiro-indenoquinoxaline derivatives 104.

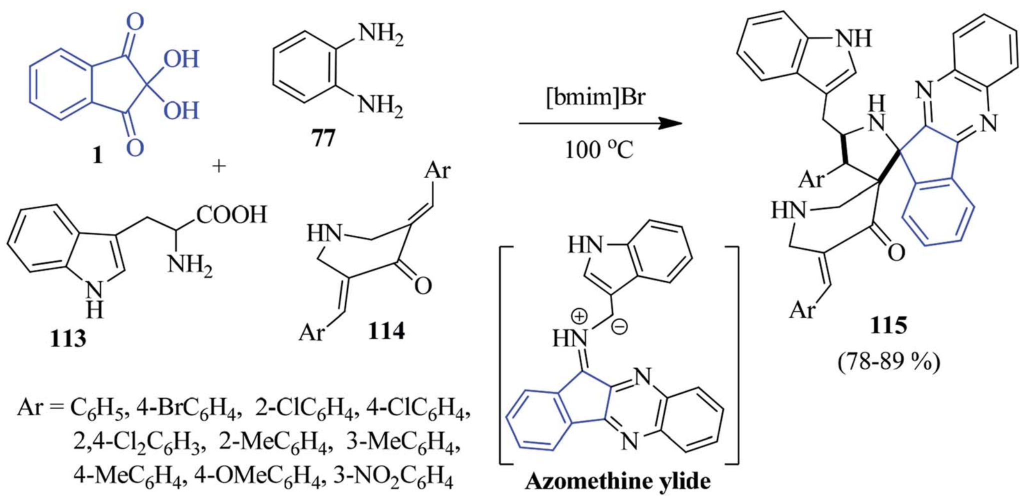


Scheme 33 Synthesis of indenoquinoxaline-anchored dispiro scaffolds **106**, **107**, **108** and **110**.

pyrrole derivatives **122–123** from ninhydrin **1**, alkyne **8** and amines **6**/**24** (Scheme 41).[124] The reaction was proposed to go through a [3 + 2] cycloaddition reaction between azomethine ylide and dipolarophile **8**. First, ninhydrin **1** transforms into 1,2,3-indanetrione, which reacts with benzyl amine **8** (or amino acids) to obtain the C–N–C dipole intermediate **A**. Subsequently,



Scheme 34 Synthesis of dispiro-indenoquinoxaline hybrid heterocycles 111 and 112.



Scheme 35 Formation of dispiropyrrolidinyl-piperidone tethered indenoquinoxalines 115.

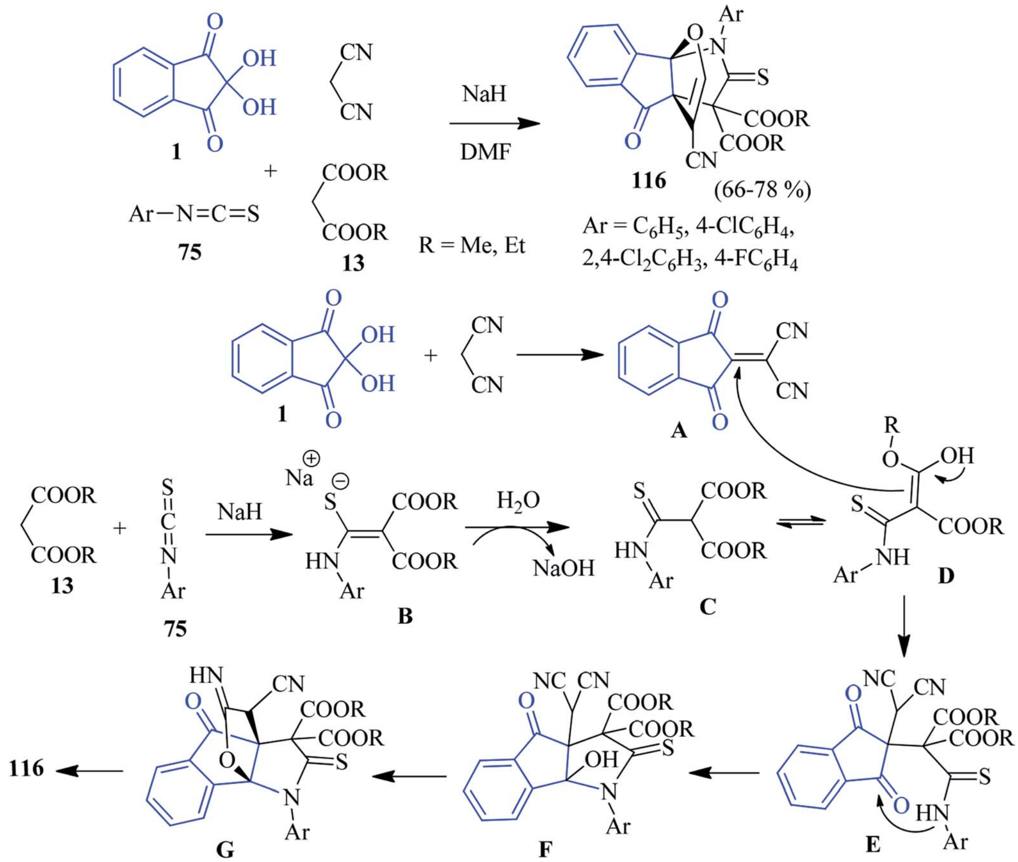
the addition of intermediate **A** to dipolarophile **8** offers spirocycloadduct **B**, which upon methanolysis, leads to the formation of intermediate **C**. Finally, oxidation affords the desired product **123** (or **122**). Notably, the C–C bond of the ninhydrin core is broken here to develop a new skeleton.

Indolizino-indoles

In 2019, Kumbhare *et al.* developed a fascinating four-component approach towards the production of dihydroindolizino[8,7-*b*]indoles **126**, engaging ninhydrin **1**, substituted tryptamine **124**, acetylenic ester **8** and different aliphatic alcohols **125** (Scheme 42).[125] The reaction proceeded *via* Pictet–Spengler, Michael addition and the nucleophilic addition reaction, leading to the formation of C–C and C–N bonds in the MeCN medium. Notably, the heterocyclic motif was achieved through a double tandem cyclisation in the presence of a CF_3COOH catalyst.

Isoquinolinones

In the same year, they invented a base-promoted three-component diastereoselective reaction of ninhydrin **1**, anilines **2** and acetylenic esters **8** to accomplish *N*-aryl-substituted dihydroisoquinolin-2-(1*H*)-ones **127** in MeOH (Scheme 43).[126] Initially, the addition of amine **2** and acetylenic esters **8** gives intermediate **A**, which is subsequently reacted with ninhydrin **1** to form intermediate **B**. The intramolecular cyclization of **B** affords intermediate **C**, which then undergoes a pinacol–pinacolone rearrangement to afford intermediate **D**. Finally,



Scheme 36 Synthesis of oxa-aza[3,3,3]propellanes **116**.

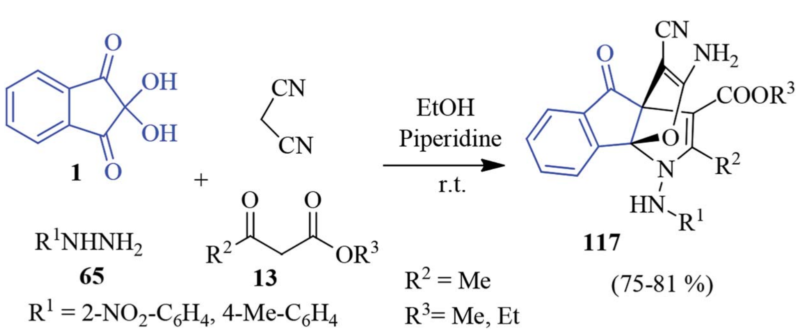
methanolysis (intramolecular cyclization) offers the desired product **127** with excellent diastereoselectivity. In this reaction, the insertion of nitrogen occurs to form an isoquinolinone scaffold. The relative stereochemistry of the product was confirmed by single crystal X-ray diffraction studies.

Pyrido-isoquinolinones

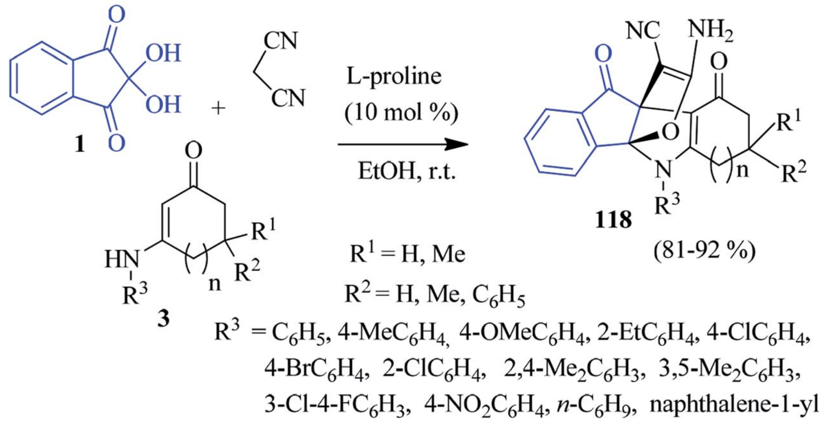
Likhar and co-workers devised a convenient one-pot tandem approach to obtain a library of pyrido[1,2-*b*] isoquinoline derivatives **128**, employing readily available ninhydrin **1**, proline **24** and alkynes **8** under ambient condition (Scheme 44).[127] A wide range of aromatic alkynes bearing electron donating and electron withdrawing groups at different positions on the aromatic ring smoothly underwent the reaction to furnish the desired product. This method comprises a [3 + 2] cycloaddition reaction between alkynes and isoquinolium ylide (1,3 dipole) generated *in situ* from ninhydrin and proline. Importantly, two new C–N bonds, three C–C bonds and three new rings are formed in a single step.

Isoquinolino-quinazoline

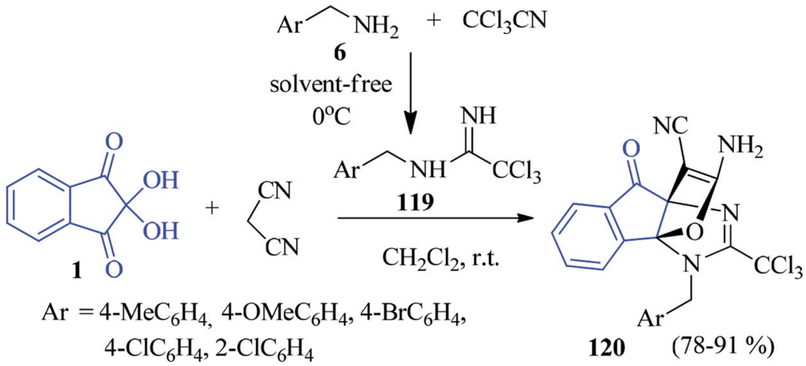
A simple and efficient approach for the construction of substituted isoquinolino-quinazoline derivatives **130** has been introduced by the Raghunadh group through a multicomponent reaction employing ninhydrin **1**, aliphatic/aromatic



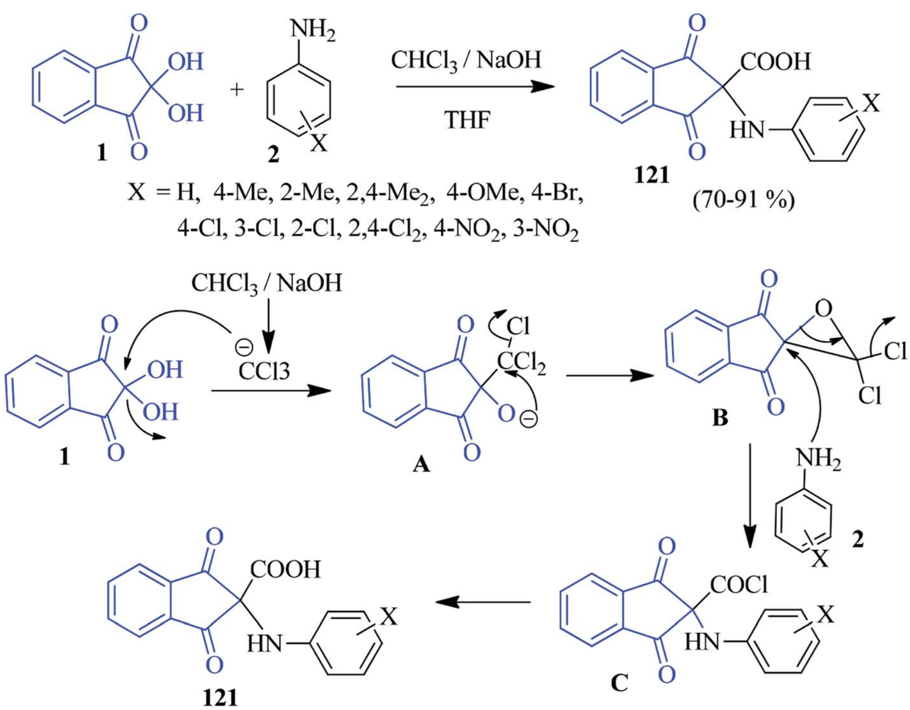
Scheme 37 Synthesis of heterocyclic propellanes **117**.



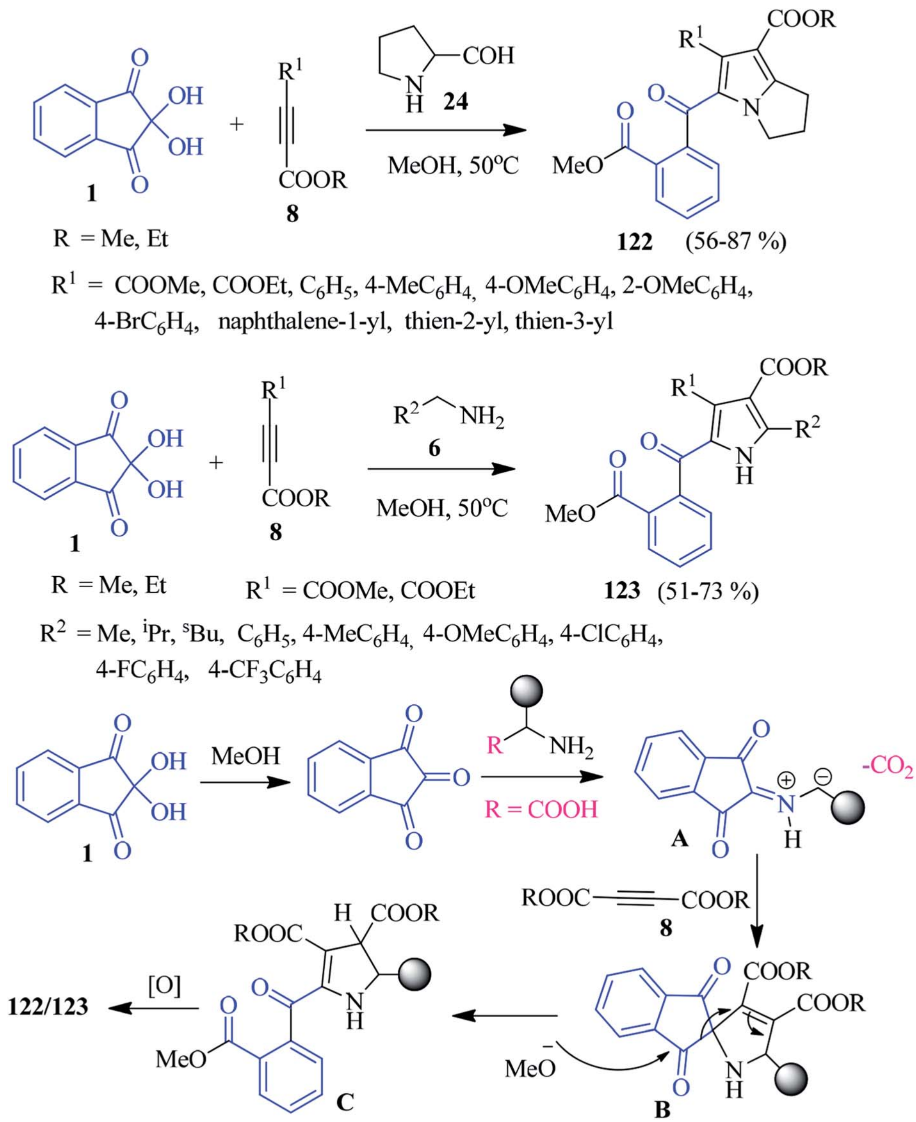
Scheme 38 Synthesis of propellanes **118**.



Scheme 39 Formation of trichloromethylated [3,3,3]propellanes **120**.

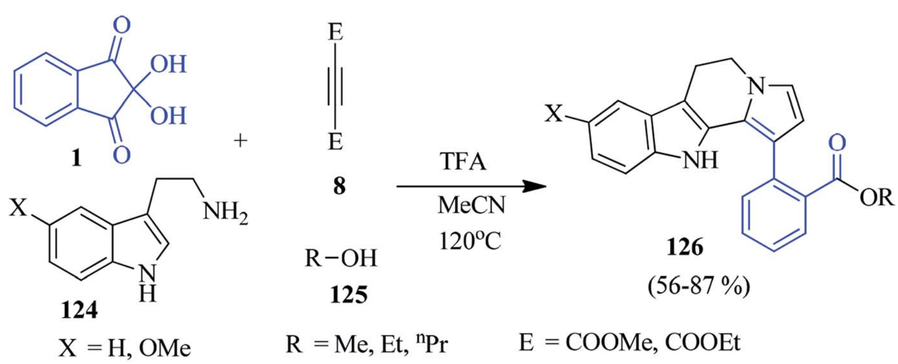


Scheme 40 Synthesis of indanone-based α-amino acids **121**.

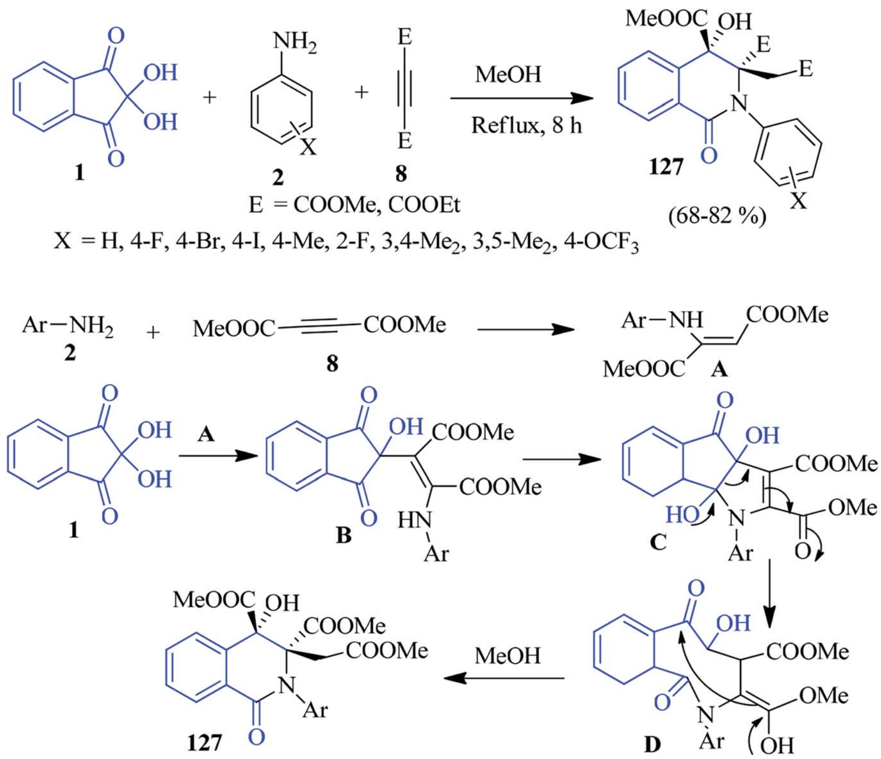


Scheme 41 Synthesis of pyrrolizine and pyrrole derivatives **122–123**.

amines **2** and isatoic anhydride **129**.[128] The reaction was most effective in 10% HCl in 1,4-dioxane. A plausible mechanism of the tandem cyclization is offered in Scheme 45. Initially, a nucleophilic attack by the primary amine on the carbonyl group of isatoic anhydride followed by decarboxylation leads to compound **A**, which condenses with the central carbonyl of ninhydrin to give intermediate **B**. Next, the intramolecular cyclization produces spiro intermediate **C**, and the nucleophilic



Scheme 42 Acid-catalyzed formation of dihydroindolizino[8,7-*b*]indoles **126**.



Scheme 43 Base-prompted synthesis of dihydroisoquinolin-2-(1*H*)-ones **127**.

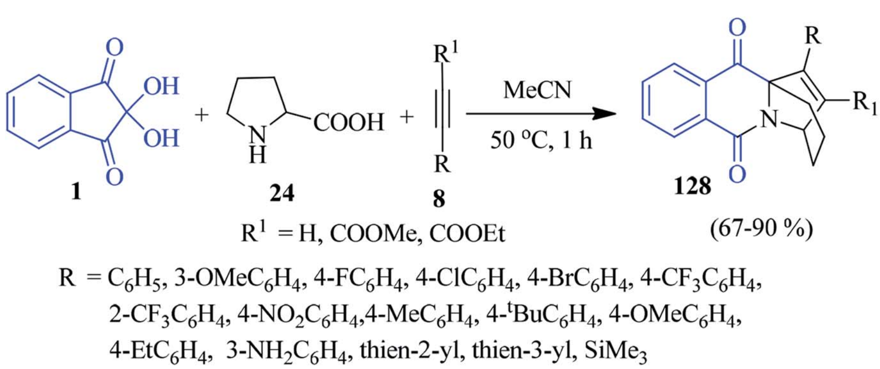
attack of the amine on the keto group generates the aziridine intermediate **D**. Finally, a rearrangement furnishes the tetracyclic quinazolinone derivatives **130**.

Isochromeno-pyrrole

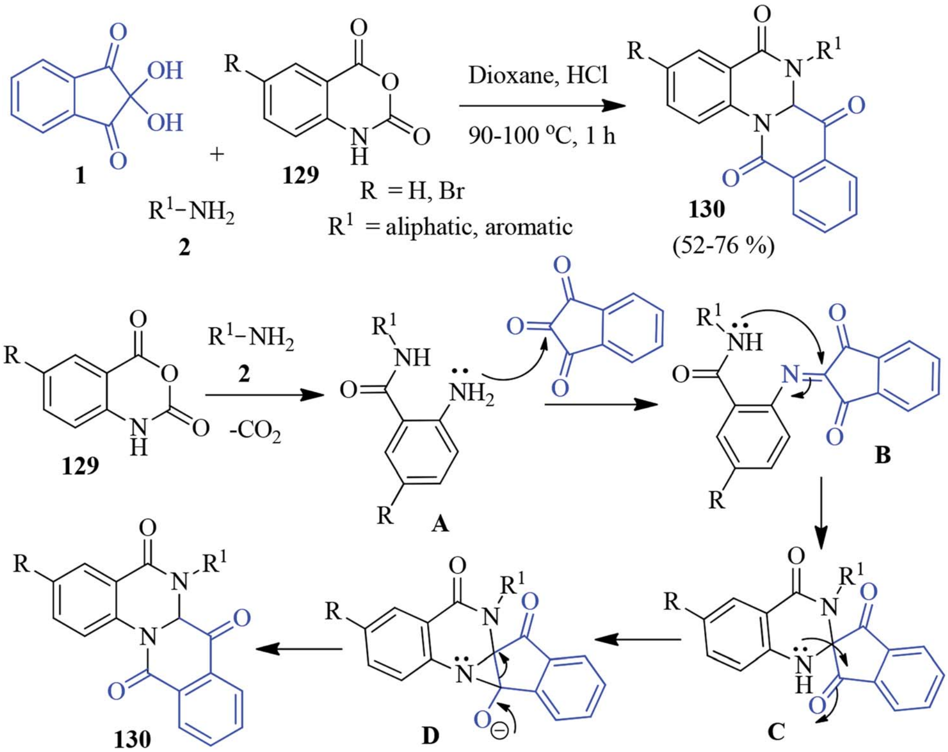
A highly convergent one-pot domino protocol was developed by Alizadeh to afford isochromeno-pyrroles containing a disulfide linkage **131** (Scheme 46).[129] The sequential reaction involves the assembly of enamines (generated from a β-keto ester **13** and propylamine) with aryl isothiocyanates **75**, producing an intermediate that is trapped by ninhydrin **1** to deliver the desired compound. The formation of the isochromeno-pyrrole skeleton was confirmed by X-ray crystal structure. A plausible pathway for the formation of the product is depicted in Scheme 46. The nucleophilic addition of enamine **A** (produced from propylamine and β-ketoester **13**) to the electrophilic centre of the aryl isothiocyanate **75** takes place to generate intermediate **B**. Then, intermediate **B** attacks the central carbonyl of ninhydrin (**B** to **C**) followed by an intramolecular azaene reaction to furnish intermediate **D**. The eight-membered lactam intermediate **E** (produced *via* ring opening) then undergoes tautomerisation, resulting in the keto form **F**. Nucleophilic attack by hydroxyl group affords intermediate **G**, which after ring closing, gives intermediate **H**. Dehydration (**H** to **I**) followed by aromatisation produces the isochromeno-pyrrole skeleton **K**. Finally, air oxidation leads to the formation of the desired product **131**.

Benzofuran

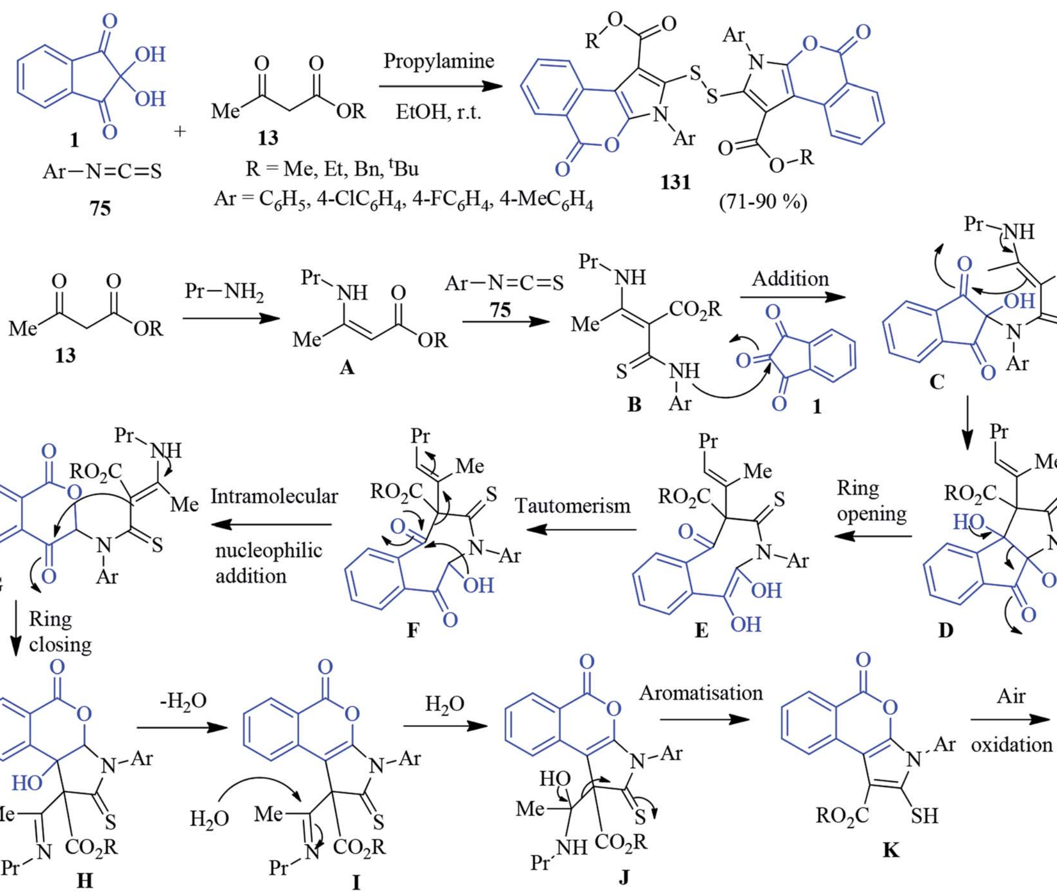
Pramanik and Kundu described an efficient method for the construction of biologically relevant multi-functionalized



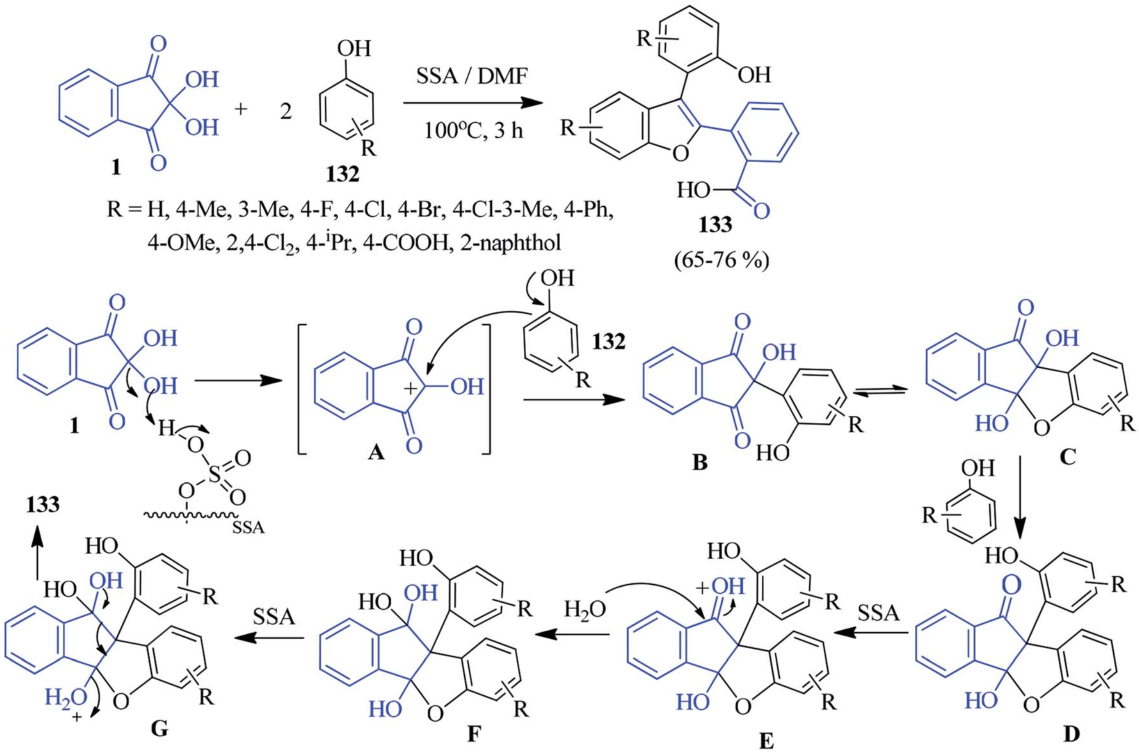
Scheme 44 Synthesis of pyrido[1,2-*b*] isoquinoline derivatives **128**.



Scheme 45 Construction of substituted isoquinolino-quinazolines 130.



Scheme 46 Synthesis of disulfide-linked isochromeno-pyrrole derivatives 131.



Scheme 47 Acid-catalyzed formation of multi-functionalized benzofuran derivatives **133**.

benzofurans **133** involving ninhydrin **1** and substituted phenols **132** in a 1 : 2 molar ratio. In this reaction, the environmentally benign silica sulphuric acid (SSA) was used as a heterogeneous acid catalyst to carry out the rearrangement in DMF medium.[130] The salient features of this work are its operational simplicity, cost-effectiveness, metal-free property, good yield and use of recyclable SSA. A possible reaction mechanism has been proposed in Scheme 47. The X-ray data unambiguously supports the formation of substituted benzofuran derivatives **133**.

Chromeno-isoindolo-pyrrole

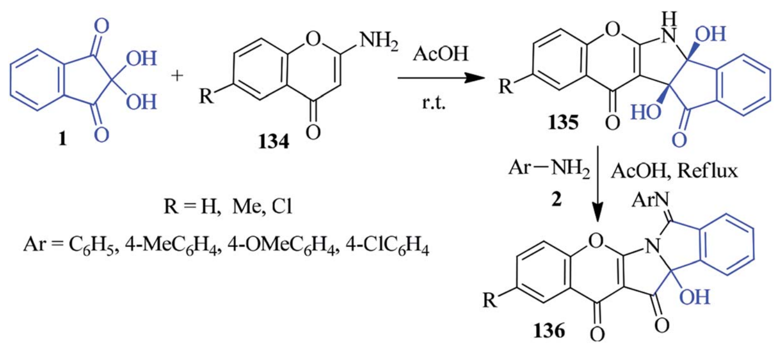
Bandyopadhyay *et al.* described a sequential one-pot protocol to access the chromeno[2,3-*b*]isoindolo[1,2-*e*]pyrrole scaffold **136** *via* acid-catalyzed rearrangement.[131] At room temperature, the stirring of ninhydrin **1** and 2-aminochromen-4-ones **134** in AcOH furnished chromeno-indeno-pyrrole derivatives **135**, which upon reflux with aromatic amines **2** in AcOH, delivered the final product **136** (Scheme 48).

Isochroman-1,4-diones

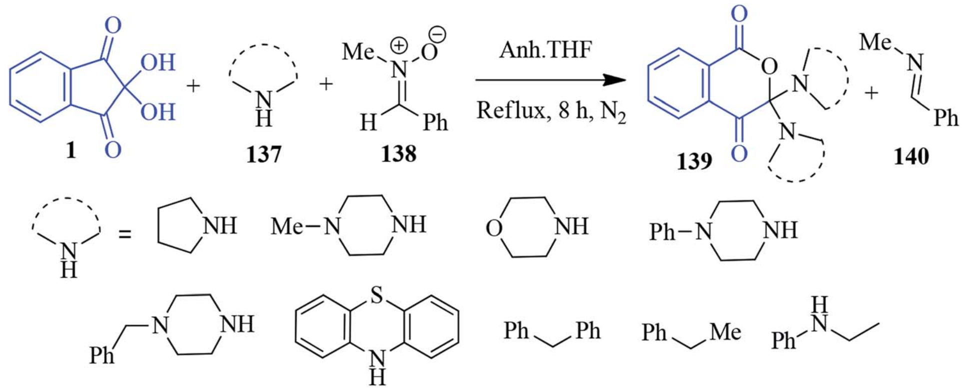
The synthesis of 3,3-disubstituted isochroman-1,4-dione **139** was reported by Deepthi *et al.* involving ninhydrin **1**, secondary amines **137** and *N*-methyl-*C*-phenyl nitrone **138** (Scheme 49).[132] In fact, nitrone acts as an oxygen atom donor to afford desired product **139** and imine **140** as side product. Interestingly, most of the isochroman-1,4-dione derivatives were found to be fluorescent in solution with high quantum yields.

Spirofuran-isoindole

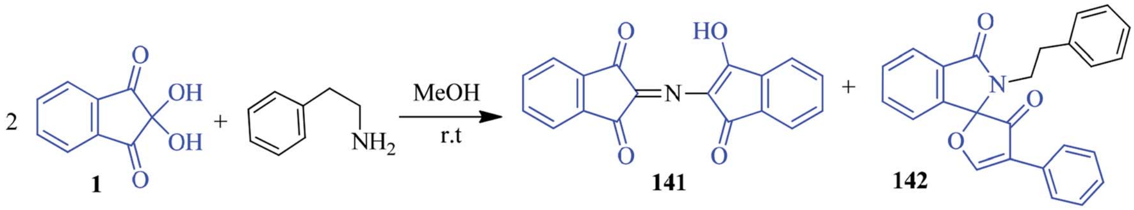
We complete our discussion by considering an interesting example of a ninhydrin reaction with amine. The reaction of



Scheme 48 Acid-catalyzed synthesis of chromeno[2,3-*b*]isoindolo[1,2-*e*]pyrroles **136**.



Scheme 49 Synthesis of 3,3-disubstituted isochroman-1,4-diones **139**.



Scheme 50 Formation of benzo-fused spiroheterocyclic compound **142**.

ninhydrin with amines usually leads to a single product known as Ruhemann's purple. However, the Quevedo group disclosed that the reaction between ninhydrin **1** and phenylethylamine (2 : 1 ratio) generated Ruhemann's purple **141**, along with the formation of the new benzo-fused spiroheterocyclic system **142** (Scheme 50).[133] The spiro compound **142** was formed through the rearrangement of the ninhydrin ring structure. The structure of the newly formed compound was established using correlation spectroscopy and single crystal X-ray diffraction study.

9. Conclusions

Being a unique tricarbonyl compound, ninhydrin has already left its imprint in organic chemistry, biochemistry, analytical chemistry and the forensic sciences. It has been successfully employed as a potential synthon by exploiting its most electrophilic C-2 position to react with various nucleophiles. In this review, we surveyed progress from the last six years on the development of diverse molecular scaffolds employing ninhydrin in multicomponent reactions. These reactions led to the construction of complex molecular systems, such as indeno-fused heterocycles, spiro-indeno heterocycles, quinoxalines, propellanes, cage-like compounds and dispiro heterocycles. In addition, the formation of several novel molecular architectures *via* different rearrangement was highlighted. Some of the rearrangements involved the breaking of the ninhydrin core to achieve various heterocyclic skeletons. Interesting examples of the regio- and stereoselective synthesis of biologically relevant compounds have also been disclosed. We believe that this review will attract the attention of researchers in the field of chemistry and biology.

Conflicts of interest

The author declares no conflicts of interest.

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