Recent Advances in Green Approaches for Synthesis of Oxindole Derivatives

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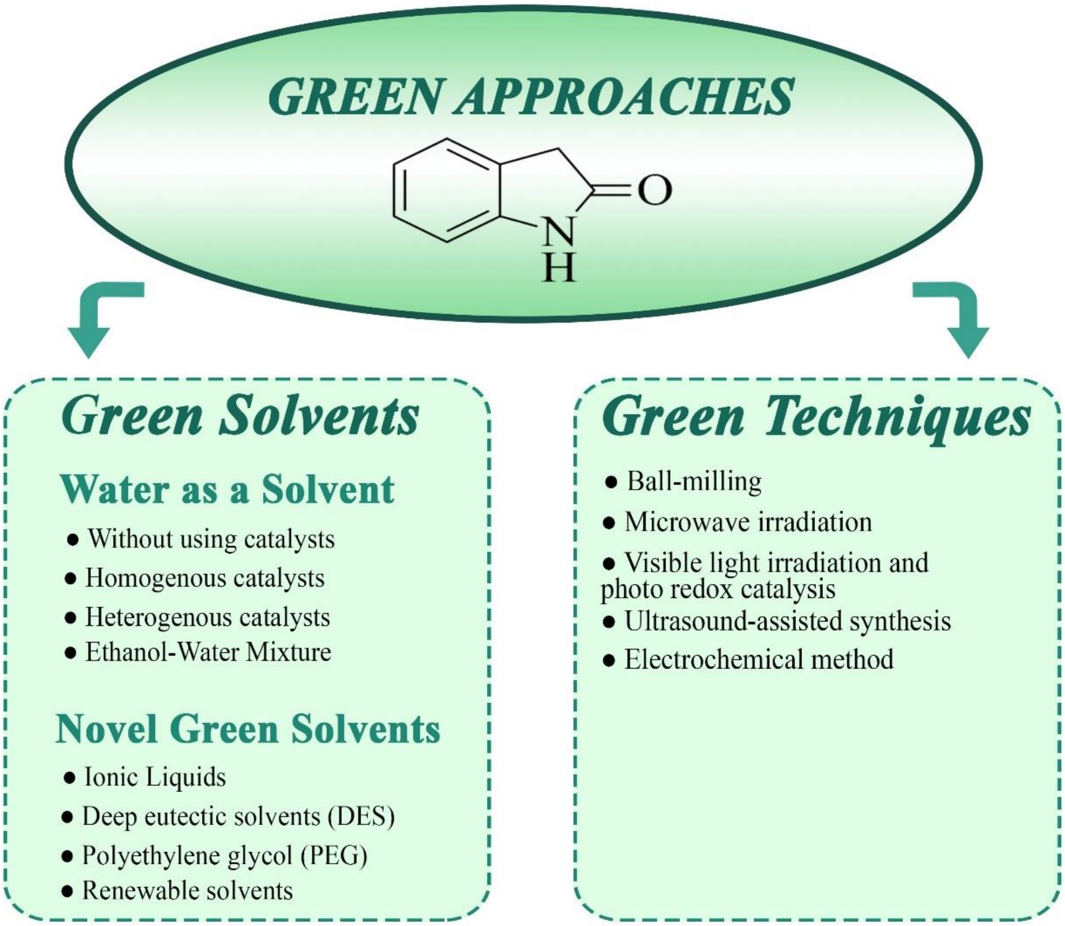
Graphycal Abstract



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Abstract

Oxindole derivatives are nitrogen-containing, five-membered heterocyclic molecules found in both natural and synthetic substances with diverse biological functions. Owing to their pharmaceutical and therapeutic characteristics, oxindoles have received remarkable attention, and various oxindole-containing substances can be synthesized using many different approaches. With the discovery of the importance of oxindole derivatives in medicinal chemistry, mainly in drug synthesis, the demand for finding sustainable protocols has increased, as most classical methods have their limitations and flaws. Hence, it is crucial to establish efficient and sustainable techniques that are safe, cost-effective, have low energy consumption, and cause minimal environmental impact. Nowadays, the use of green solvents in organic synthesis has received much attention because they prevent the formation of waste, are environmentally friendly, and have easy work-up procedures. Green solvents such as water, deep eutectic solvents, ionic liquids, and polyethylene glycol can substitute hazardous solvents. Microwave irradiation, visible-light irradiation, electrochemical methods, and multi-component synthesis are all described under green approaches. Most of these approaches allow the reaction to proceed rapidly while releasing minimal waste into the environment. Recent discoveries in green chemistry applications can be considered a turning point in organic synthesis. This review focuses on promising green approaches, used for the synthesis of oxindole derivatives, carried out in recent years with typical examples in two sections: green solvents and green techniques.

Keywords- Oxindole derivatives, Green solvents, Green techniques, Sustainable chemistry, Solvent-free.

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1. Introduction

Over the past few decades, detrimental impacts have been caused to the environment with the increase in the synthesis of various chemical compounds on a very large scale. The world of science is currently working on sustainable development approaches to achieve ecologically friendly protocols which use less hazardous substances, with minimal energy consumption, and less waste, and operate at optimal efficiencies (Anastas and Kirchhoff, 2002, Rios, 2012). Green chemistry is an emerging trend used to develop and design new chemical compounds and techniques which ultimately reduce or prevent the formation of hazardous compounds. Alternative green synthesis methods for conventional organic synthetic approaches are important because they reduce the adverse environmental impact of organic solvents and reagents on plants, animals, and humans (Beach et al., 2009). The principles of green chemistry have been established for over 20 years into a globe-spanning endeavor aimed at sustainability in economic, social, and environmental performance (Elkington, 1994). Reducing the impact of toxic chemical compounds is not the only factor to be considered when designing a green approach. The purification procedure, workup step, reaction yield, and disposal of solvents are other factors that should be considered when designing new sustainable protocols (Poomathi et al., 2018).

Nitrogen-containing heterocyclic compounds are one of the most common classes of bioactive compounds with medicinal properties. Among nitrogen-containing heterocycles, oxindoles are a group of compounds that are mainly used in the field of medicine and organic synthesis, because of their specific chemical properties and biological activities (Millemaggi and Taylor, 2010). It is the fundamental structure of various natural and pharmaceutical substances. Oxindole is a bicyclic compound with a carbonyl group at the C-2 position of the fused pyrrole ring (Ram et al., 2019) and was first reported by Adolf von Baeyer by the reduction of isatin in 1866 (Bergman, 2015).

Oxindoles are valuable naturally occurring compounds found in roots, rhizomes, fungi, bacteria, and many other biological sources. Rhizomes of *Cimicifuga dahurica (*BABA *et al., 1981),* the root bark of *Neolaugeria resinosa* (Weniger et al., 1993), and *Colletotrichum fragariae* (Inoue et al., 1996) are natural sources of oxindoles. As the applications of oxindoles are increasing due to high requirements, industries are highly dependent on synthetic oxindoles, as natural oxindole derivatives are in short supply.

Oxindole derivatives are used in many biological and medicinal applications such as antibacterial, anti-inflammatory, anti-hypertensive, anti-cancer, anti-angiogenic, anti-proliferative, and antiprotozoal compounds (Anastas and Kirchhoff, 2002, Rios, 2012), etc. 3-Alkenyl oxindoles such as sunitinib a powerful compound that can be used to treat advanced renal cell carcinoma and gastrointestinal stromal tumors (Le Tourneau et al., 2007). Furthermore, several oxindole derivatives have the potential to act as aldose reductase inhibitors (ARIs), which are used to prevent and treat diabetic complications from elevated levels of sorbitol (Rajeswaran et al., 1999).

Owing to their wide range of biological applications, various beneficial and powerful strategies for the synthesis of oxindole derivatives have been discovered in recent years. However, many of the classical procedures used to synthesize biologically important compounds are limited by the use of toxic and volatile solvents, high reaction times and energy consumption, the use of expensive and hazardous catalysts, and the disadvantages of the reaction conditions.

In this review, we mainly focus on research articles published from 2015 to 2023 related to the synthesis of oxindole derivatives using green solvents and green techniques.

2. Green solvents

When organic synthetic reactions are carried out on a large scale, large amounts of solvents are used and environmental pollution caused by these hazardous organic solvents is one of the main factors that should be considered. The use of eco-friendly green solvents instead of hazardous organic solvents is the core concept in green chemistry.

2.1. Water as a solvent

Water is one of the most sustainable alternatives that can be used as a green solvent for various organic reactions. Water is the most reachable and eco-friendly solvent on planet Earth that can be used for reactions and in the natural world; it is the most widely used solvent. In recent years, water has been used in many organic reactions because of its eco-friendliness, availability, non-toxicity, natural abundance, inexpensiveness, and high heat capacity (Kitanosono et al., 2018)**.** Therefore, the synthesis of biologically active compounds such as oxindole derivatives in water is important. Using different conditions such as microwave irradiation, ultrasonication, catalysts, different temperatures, and pressure in a water medium has become a promising green protocol with high efficiency.

Although reactions carried out in the water are cost-effective, eco-friendly, safer, and selective, it has been found that some reactions occur slowly due to the poor substrate solubility. Hence, amphiphilic catalysts or surfactants can be used to create a hydrophobic reaction medium and thereby to increasing substrate solubility. This section discusses recent studies on the synthesis of

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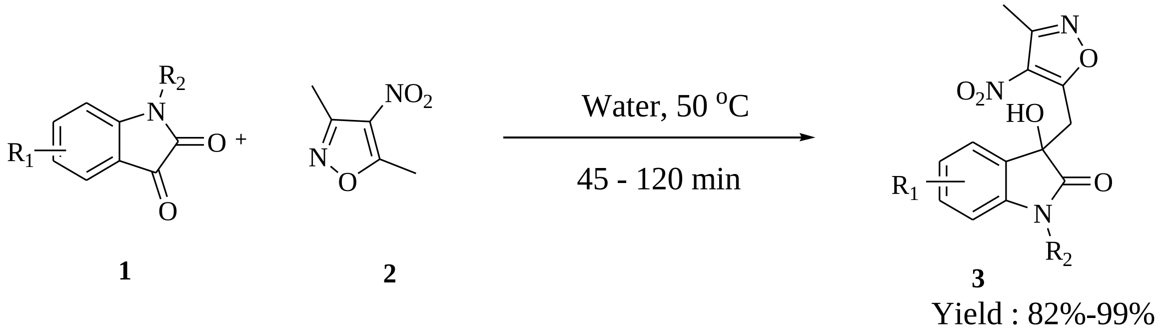
oxindole derivatives in water in the presence and absence of homogeneous or heterogeneous catalysts.

- ***Catalyst-free conditions***

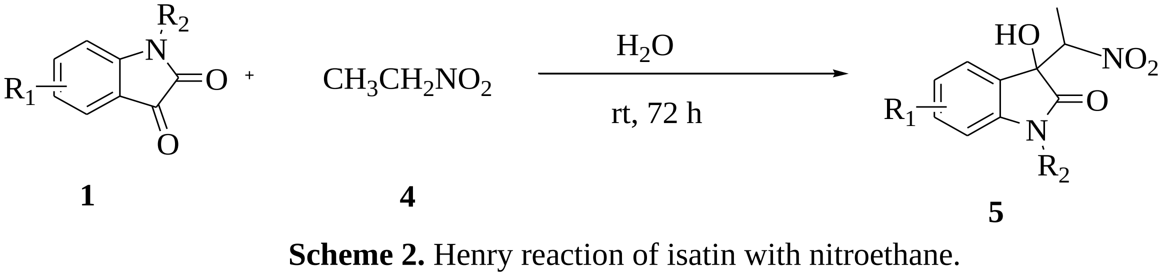
Conventionally, to produce desired products in classic organic reactions, catalysts or reagents are typically used in conjunction with organic solvents, which can be categorized as harmful, toxic, or environmentally friendly solvents. During the past decade, numerous studies have been focused on the development of catalyst-free, solvent-free, and aqueous-mediated processes. In this section, recent catalyst-free approaches to the synthesis of oxindole derivatives are discussed.

Dhurke Kashinath and co-workers developed an efficient protocol for the synthesis of 3-substituted-3-hydroxy isoxazole-oxindole hybrids **3** under catalyst-free conditions, using water as the reaction medium. The synthesis was performed via Vinylogous Henry reaction at 50 ˚C using isatin **1 and** 3, 5- dimethyl-4-nitroisoxazole **2** as starting materials (**Scheme 1)**. The avoidance of a catalyst, use of a green solvent, excellent yield of approximately 82%-99%, and low reaction time (45-120 min) are the key advantages of the developed approach (Nagaraju et al., 2015).



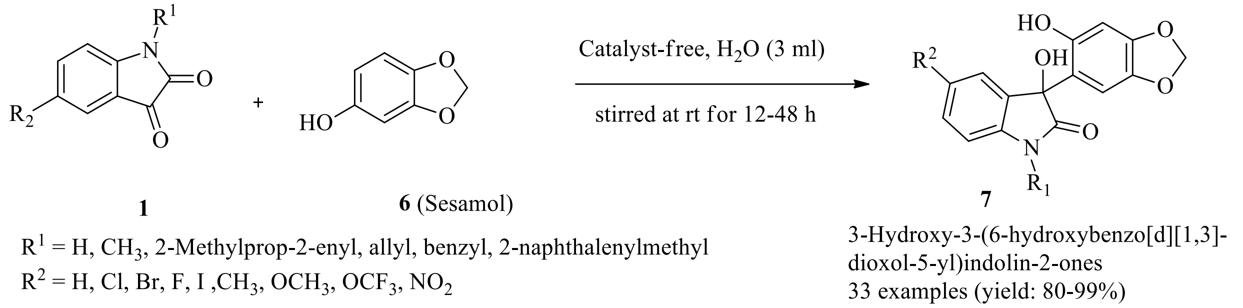
Scheme 1. Catalyst-free Henry reaction using water as the reaction medium.

Parvathaneni et al. reported an eco-friendly and efficient methodology for the synthesis of 3-hydroxy-3-nitromethylindolin-2-ones **5** by the reaction of isatin **1** with nitroethane **4**. The reaction was performed at room temperature using water as the reaction medium under catalyst-free conditions **(Scheme 2)**. Excellent yields, applicability in large-scale production, and reduction of waste generation due to toxic solvents are some of the attractive features of the developed method (Rao, 2015).



Scheme 2. Henry reaction of isatin with nitroethane.

Kumar and co-workers discovered a green, efficient catalyst-free Friedel-Crafts reaction in water, using phenol derivatives **6** and substituted isatins **1** for the synthesis of 3-aryl-3-hydroxy-2-oxindoles **7** with an excellent yield of 98% **(Scheme 3)**. Density functional theory studies have confirmed that water acts as a catalyst by activating the reactants through hydrogen bonding interactions (Kumar et al., 2016).



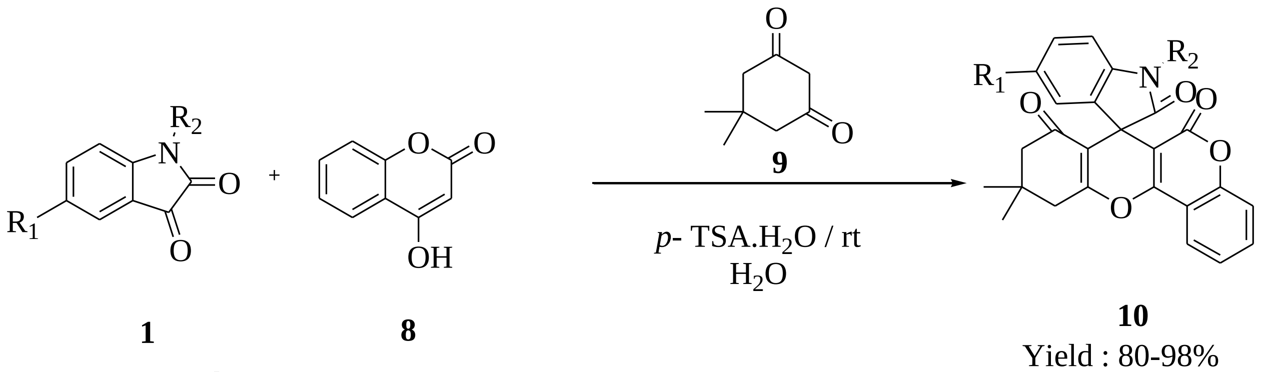
R^1 = H, CH_3, 2-Methylprop-2-enyl, allyl, benzyl, 2-naphthalenylmethyl
R^2 = H, Cl, Br, F, I ,CH_3, OCH_3, OCF_3, NO_2

3-Hydroxy-3-(6-hydroxybenzo[d][1,3]-dioxol-5-yl)indolin-2-ones
33 examples (yield: 80-99%)

Scheme 3. Synthesis of 3-aryl-3-hydroxy-2-oxindoles **3** using Friedel-Crafts reaction.

- ***In the presence of a homogeneous catalyst***

In 2018, Dhayabaran and co-workers successfully developed a methodology for the one-pot synthesis of a new spiro[chromeno[4,3-b]chromene-7,3′-indoline]- 2′,6,8-triones **10** using water as the reaction medium in the presence of *p*-toluenesulfonic acid (*p*-TSA·H_2O) as the catalyst. The reaction was carried out at room temperature for 3-5 hours, using isatin **1**, 4-hydroxycoumarin **8**, and cyclic diketone **9** as the starting materials **(Scheme 4)**. Using an optimized amount of catalyst, shortened reaction time, high yield (80%-98%), and column chromatography-free conditions are some of the attractive features of this procedure (Kumar et al., 2018).



Yield : 80-98%

R_1 = H, Br, Cl, NO_2
R = 4-Chlorobenzyl, Ethyl, H

Scheme 4. Synthesis of spiro[chromeno[4,3-b]chromene-7,3′-indoline]-2′,6,8-triones in water using *p*-TSA·H_2O as catalyst.

An efficient one-pot procedure was developed for the synthesis of spirooxindole dihydroquinazolinone derivatives **13** using water as the solvent. Chate and co-workers in 2019. Isatoic anhydride **11**, aniline **12**, and isatin **1** were used as the starting materials for the reaction, and 2-aminoethanesulfonic acid (taurine) was used as the homogeneous catalyst **(Scheme 5)**. The avoidance of toxic catalysts, use of water as the solvent, column chromatography-free conditions, simple workup procedure, and eco-friendliness make the procedure more efficient and beneficial (Chate et al., 2020).

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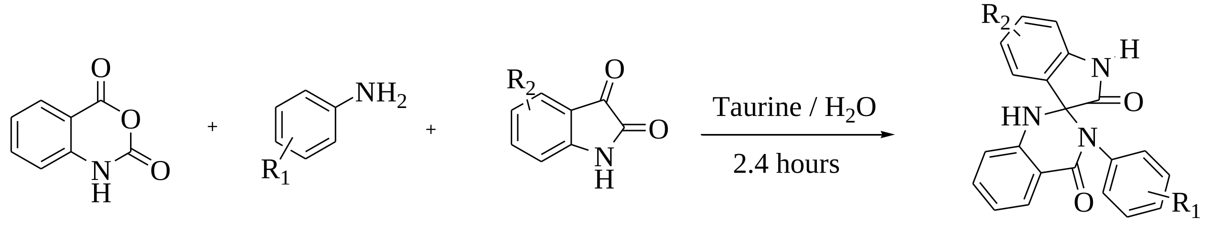
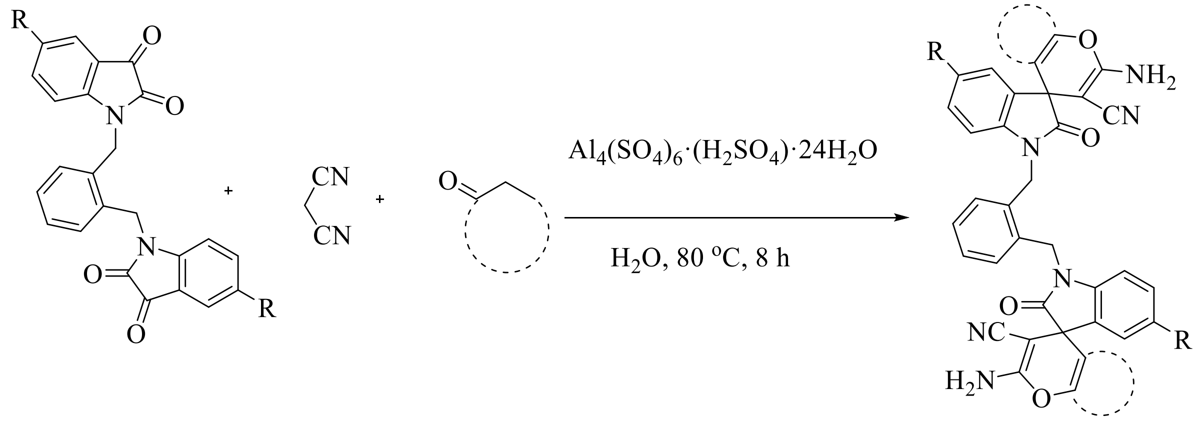


11 **12** **1** **13**

R_1 = H, 4-Br, 4-Cl, 4-F, 4-NO_2, 3-NO_2, 4-OCH_3, 4-CH_3, pyridine
R = H, 4-Br, 4-NO_2

Scheme 5. Synthesis of spirooxindole dihydroquinazolinone derivatives using water as solvent.

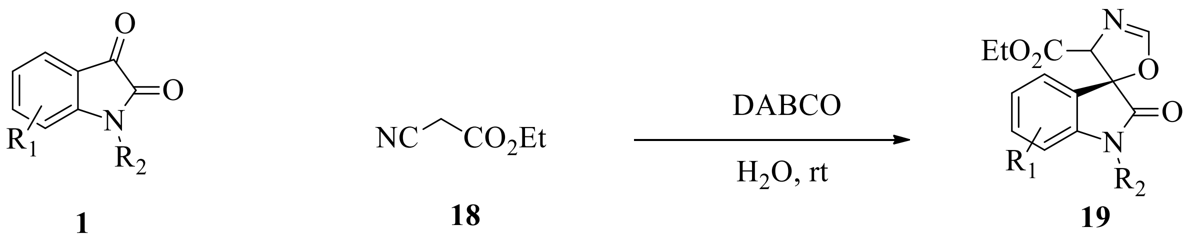
In 2021, Bashkar et al. reported a one-pot, multicomponent procedure using a double salt, $Al_4(SO_4)_6{\cdot}(H_2SO_4){\cdot}24H_2O$, as a water-soluble and recyclable catalyst for the synthesis of novel spirooxindole derivatives **17** using water as the reaction medium. The reaction was conducted using bis (isatin) **14**, malononitrile **15**, and 1,3-dicarbonyl compound **16** as starting materials for 8 h at 80° C **(Scheme 6)**. Simple workup procedures, high yields, short reaction times, and eco-friendly reaction conditions make this approach an efficient alternative (Bashkar et al., 2021).



14 **15** **16** **17**

Scheme 6. Synthesis of bid-spirooxindole derivatives using $Al_4(SO_4)_6{\cdot}(H_2SO_4){\cdot}24H_2O$ in an aqueous medium.

Chandran Rankan and co-workers reported a rapid, regioselective approach to synthesize spirooxindoleoxazoline **19** in water by using isatin **1** and isocyanate **18** in water at room temperature with 1 eq. of 1,4-diazabicyclo[2.2.2]octane (DABCO) as the base catalyst **(Scheme 7)**. Mild reaction conditions, operational simplicity, easy purification procedure, broad substrate scope, high yield (up to 70%), and high atom economy are the major advantages of this green protocol (Rankan et al., 2020).



R_1 = H, 5-Cl, 5-I, 5-F, 5-OCH_3, 5-NO_2, 5-CH_3, 7-Br, 7-Cl, 7-F, 5,7-Br

R_2 = H,CH_3, Ph

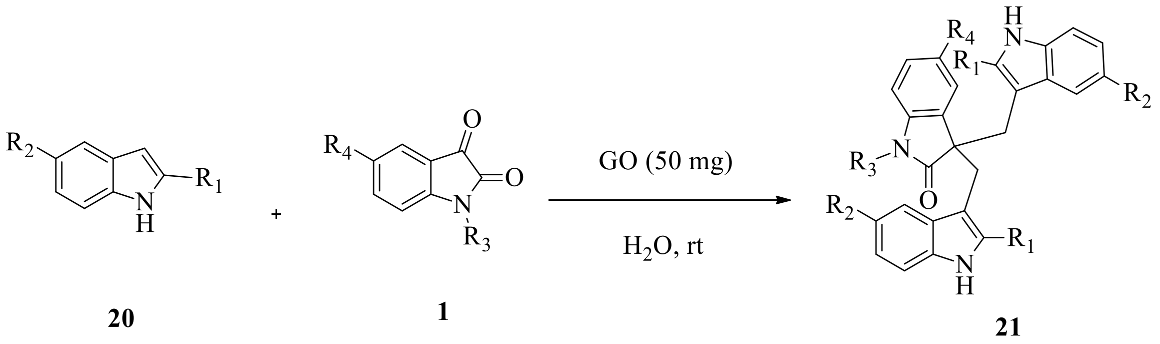
Yield : up to 70%

Scheme 7. Synthesis of spirooxindoleoxazoline using DABCO as the catalyst.

2.1.1. Synthesis using heterogeneous catalysts

Despite the benefits of homogenous catalysts, some of them still have limitations, such as non-reusability, low thermal stability, and inability to be recycled. Heterogeneous catalysts can overcome these drawbacks. Recently, nanocomposite-mediated organic transformations have been used in both material science and synthetic organic chemistry. However, toxic and volatile organic solvents are required for some reactions that use nanocomposites (Ebrahimiasl et al., 2019; Wang et al., 2019). Therefore, considerable attention has been paid to finding a green and sustainable approach to overcome this problem. The use of water as a solvent allows the synthesis of oxindole derivatives using heterogeneous catalysts with low toxicity, high activity, high selectivity, and reusability (Allahresani et al., 2018b).

Ali Allahresani and co-workers discovered a proficient and green approach to synthesize 3, 3-diheteroaromatic oxindole derivatives **21** with isatins **1** and indole derivatives **20** via Friedel–Crafts 3-indolylation reaction in aqueous media by using Graphene oxide (GO) based solid acid as the heterogeneous nano-catalyst, which is efficient and reusable **(Scheme 8)**. This green protocol has benefits, such as the ability to perform the reaction at room temperature, simplicity, mild reaction conditions, recyclability of the catalyst, short reaction time, and economic viability. etc (Allahresani et al., 2015).



Yield : up to 73%

Scheme 8. Synthesis of diindolyl-oxindole derivatives using graphene oxide as catalyst.

Mohammad Ali Nasseri and co-workers successfully developed a methodology for the synthesis of a class of bioactive compounds, diindolyl oxindoles **23** using nano-NiO particles as

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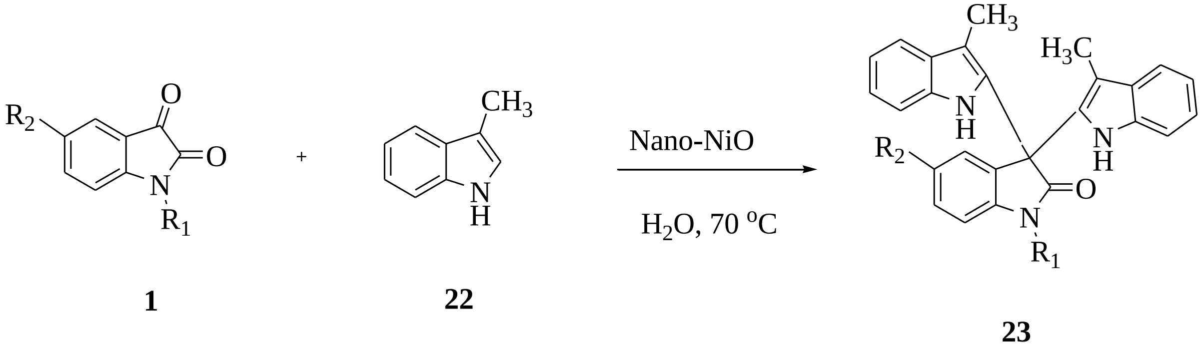
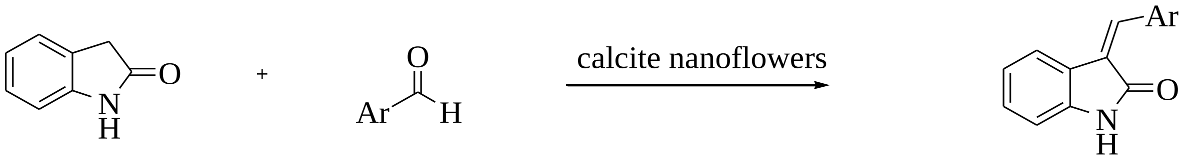
the catalyst, via condensation reaction between indole **22** and isatin **1** compounds. The reaction was carried out using water as the reaction medium at 70 °C **(Scheme 9)**. The developed approach facilitated the synthesis of 3,3-diindolyloxindole and 2,2-diindolyloxindole derivatives. Good to excellent yields using an environmentally friendly solvent and an efficient and inexpensive catalyst are some attractive features of this methodology (Nasseri et al., 2015).



23

Scheme 9. Synthesis of 2,2-diindolyloxindole derivatives.

In 2023, Dnyaneshwar Sanap, and co-workers synthesized C3-arylidene-oxindole derivatives **26**, which is used in the field of medicine, using calcite nanoflowers ($CaCO_3$ NFs) as heterogeneous catalyst for the first time. Knoevenagel condensation between 2-oxindoles **24** and aromatic aldehydes **25** produced an excellent yield of up to 99% **(Scheme 10)**. Lower environmental toxicity impact, cost-effectiveness, reusability of the catalyst, and higher catalytic activity of the catalyst are some attractive features of the developed approach (Sanap et al., 2023).



24 **25** **26**

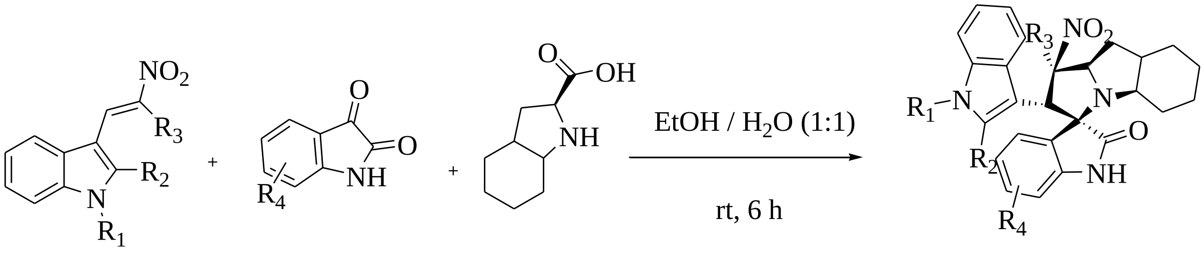
Yield : up to 99%

Scheme 10. Synthesis of C3-arylidene-oxindole derivatives.

- ***Ethanol – water mixture***

Ethanol-water mixture can be regarded as an inexpensive and non-toxic solvent system. One of the major problems of using water as the solvent in the organic reaction is the limited solubility of organic compounds in the water medium. This problem can be avoided by using this mixed solvent of water and ethanol, as the solubility of organic compounds is high. Also, it facilitates the crystallization of the product. For drug design and advances in green chemistry, it is important to discover new multicomponent reactions in mixtures of water and alcohol solutions (Wang et al., 2018).

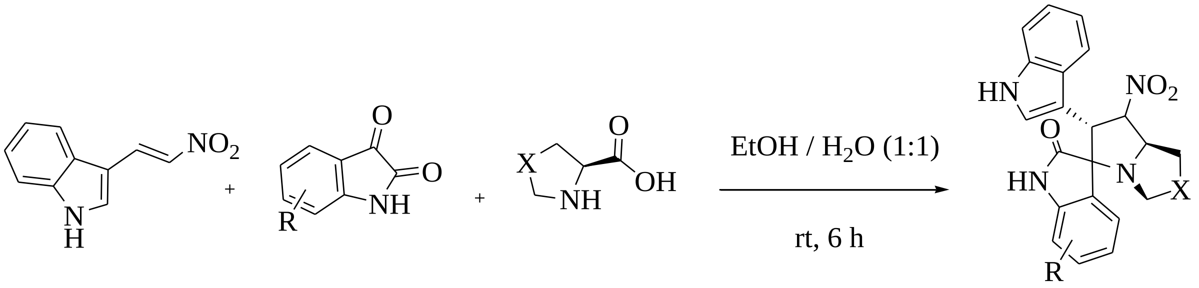
In 2018, Yong-Chao Wang and co-workers successfully developed a sustainable and green approach to form new multiple C-C bonds and C-N bonds for the synthesis of polycyclic pyrrolidine-fused spirooxindole compounds **30** and **31** via one-pot, three-component reaction using isatins **1**, (E)-3-(2-nitrovinyl)-indoles **27**, and chiral polycyclic a-amino acids **28** and **29** as starting materials. The reaction has been performed at room temperature without using any catalysts in the ethanol-water mixture **(Schemes 11 and 12).** Excellent yields, environmental friendliness, and column chromatography-free conditions are some of the prominent advantages of this technique (Wang et al., 2018).



27 **1** **28** **30**

R1 =H, CH_3
R2 = H, Ph
R3 = H, CH_3
R4 = H, 5-CH_3, 5-Cl, 5-Br, 5-F, 5-OCH_3, 6-Cl, 6-Br,7 -Cl

Scheme 11. Synthetic approach for polycyclic pyrrolidine-fused spirooxindole derivatives.

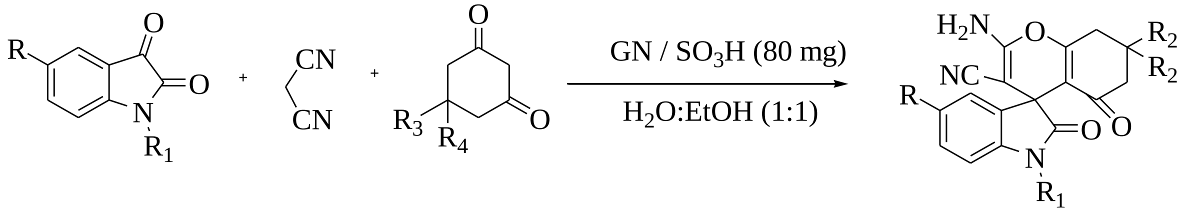


27 **1** **29** **31**

X = CH_2 , S
R = H, 5-CH_3, 5-F, 5-OCH_3,6-Cl, 6-Br, 7-Cl, 7-Br, 5,6-diF

Scheme 12. Synthesis of polycyclic pyrrolidine-fused spirooxindole derivatives.

A one-pot multicomponent reaction has described by Ali Allahresani and co-workers for the synthesis of spirooxindole derivatives **33** using malononitrile **15**, isatins **1**, and 1,3-dicarbonyl compounds **32**, using ethanol/water mixture as green solvent **(Scheme 13)**, catalyzed by GN/SO_3H nanocomposite, as heterogeneous solid acid which could be efficiently recovered and reused several times with minimal reduction of its catalytic efficiency. The reaction was performed at 80 ° C under refluxed conditions. Additionally, excellent yields, short reaction times, and eco-friendliness are other benefits of this developed approach (Allahresani et al., 2018a).



1 **15** **32** **33**

Scheme 13. Synthesis of spirooxindole derivatives catalyzed by GN/SO_3H nanocomposite.

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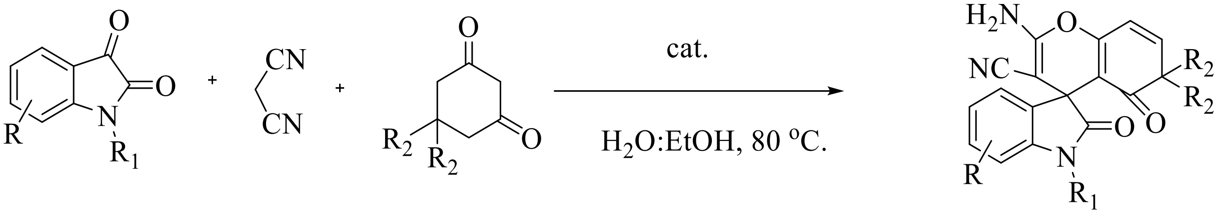
In 2019, Hemmat and co-workers studied the synthesis of spirooxindoles **33** using malononitrile **15** and isatin **1** and 1,3-dicarbonyl compounds **32** as starting materials **(Scheme 14)**. The reaction was carried out at 80° C, using an ethanol-water mixture as the solvent, in the presence of a heterogeneous catalyst, $CoFe_2O_4@SiO_2$. Excellent yields (97%), recoverability, reusability, and stability of the catalyst are some important features of this methodology (Hemmat et al., 2019).

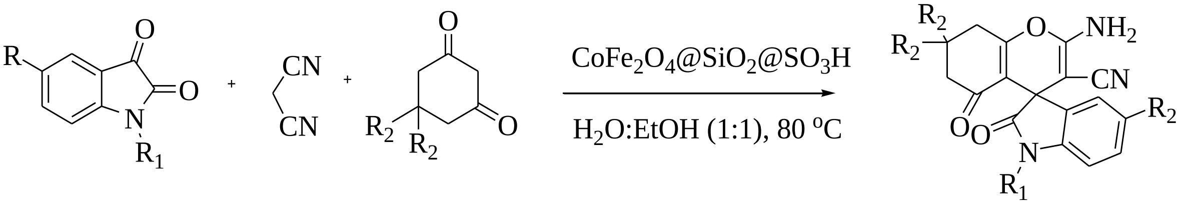


1 **15** **32** **33**

Yield : 97%

Scheme 14. Synthesis of spirooxindole derivatives by $CoFe_2O_4@SiO_2$.

Bardia et al. synthesized spirooxindole derivatives **33** with biological applications that can be used as anticancer and antimicrobial drugs. An efficient one-pot, three-component reaction has developed using malononitrile **15**, dimedone **32,** and isatin **1** at 80° C under reflux conditions using a water/ethanol (1:1) mixture as the solvent **(Scheme 15)**. A solid acid, $CoFe_2O_4@SiO_2@SO_3H$ has been used as an efficient and green catalyst which can be recycled. Additionally, this work demonstrates distinct benefits, including straightforward catalyst synthesis, use of affordable and readily available starting materials, short reaction times, the use of a catalyst with high catalytic activity, and high yields (98%).etc (Zamani-Ranjbar-Garmroodi et al., 2019).



1 **15** **32** **33**

Yield : 98%

Scheme 15. Synthesis of spirooxindole derivatives catalyzed by $CoFe_2O_4@SiO_2@SO_3H$.

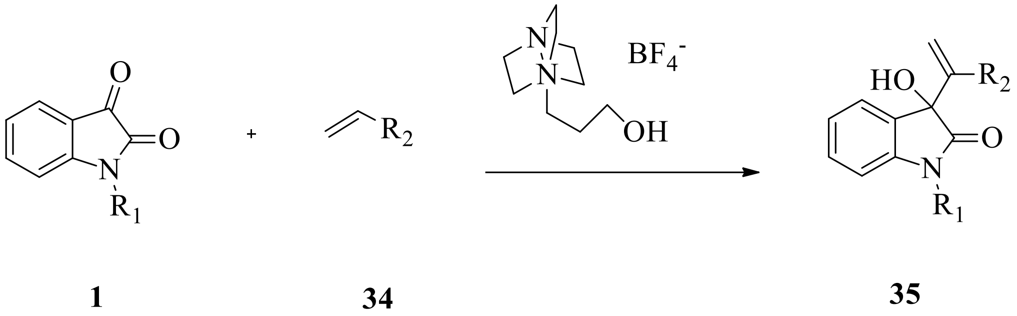
2.2. Novel green solvents

In this section, the properties and benefits of common green solvents that are widely used in the synthesis of oxindole derivatives other than water are discussed. Ionic liquids, green solvents such as polyethylene glycol, and deep eutectic solvents are some of the novel green solvents that are used.

- ***Ionic liquids***

Although water is the most abundant green solvent, there are some limitations to using water in some organic reactions. The use of moisture-sensitive catalysts and the hydrophobicity of organic molecules limit the use of water as a solvent in some reactions. Ionic solvents have many physiochemical advantages, including higher thermal and chemical resistance, non-inflammability, negligible vapor pressure, good solubility, and recyclability, allowing them to be used as ideal green solvents for many synthetic processes. It has both organic and inorganic characteristics and can form various interactions such as van der Waals interactions, ion-ion interactions, and ion-dipole interactions. Sometimes they can increase the yield and the rates of the reactions (Nasri et al., 2022).

In 2015, Ghodsi Mohammadi Ziarani and their co-workers found in their study that, 3-substituted 3-hydroxyindolin-2-ones **35** can be synthesized using 1-(2-hydroxypropyl)-4-aza1-azoniabicyclo [2.2.2]octane tetrafluoroborate [HPDABCO][BF_4] as the ionic liquid through Morita–Baylis–Hillman reaction of alkenes **34** and isatins **1** **(Scheme 16)**. They found that it's efficient to use ionic liquids because of their simplicity in operation, dual catalyst-solvent properties, the ability to recycle and reuse, and higher yields. These types of ionic liquids which are hydroxy ionic liquids, can be used to synthesize biologically active targets as they can act as tertiary amines and protic solvents as well (Ziarani et al., 2015).



Scheme 16. The reaction carried out in [HPDABCO][BF_4] was reported by Ghodsi Mohammadi Ziarani *et al.*

Jun Tong and co-workers successfully discovered a highly efficient methodology for the first time, a solvent-controlled Friedel-Crafts reaction for the synthesis of 3-indolyl-3-hydroxy oxindoles **36** and 3, 3-diindolyl oxindoles **37** in THF and water respectively. The reaction was conducted using indole **20** and isatins **1** as starting materials and using Dabco-base ionic liquids as a recyclable catalyst **(Schemes 17** and **18)**. The lack of use of metals and dry solvents, high chemoselectivity, and simple procedures are some important benefits of the developed procedure (Tong et al., 2017).

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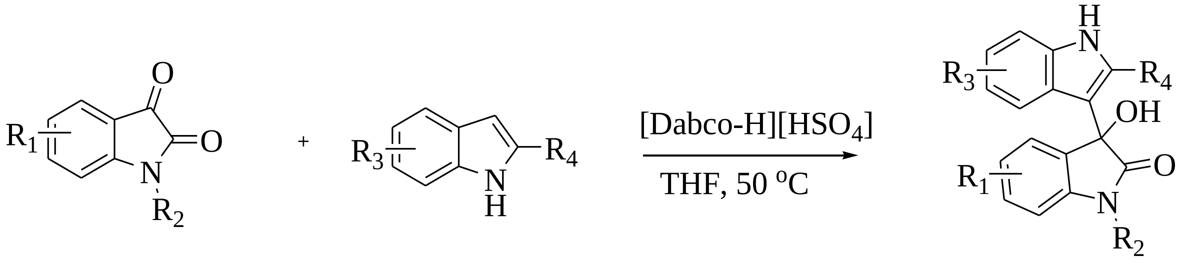
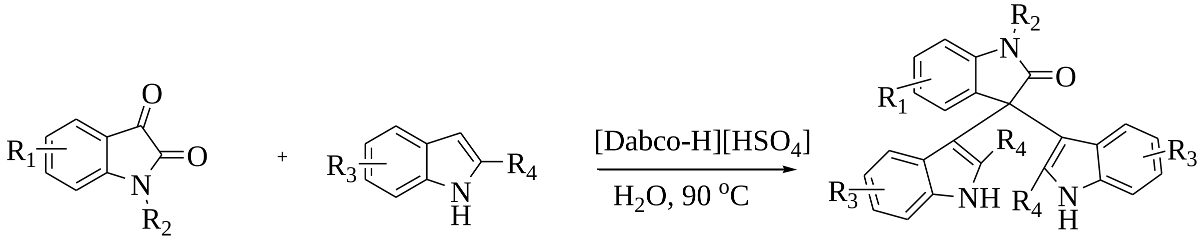


1 **20** **36**

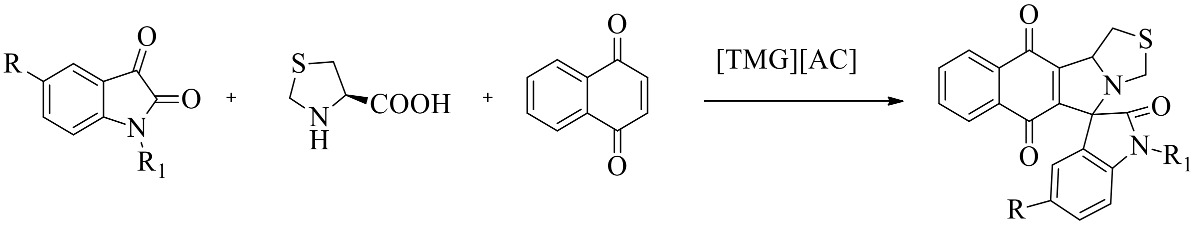
Scheme 17. Synthesis of 3-indolyl-3-hydroxy oxindoles in THF in the presence of [Dabco-H] [HSO₄]



1 **20** **37**

Scheme 18. Synthesis of 3, 3-diindolyl oxindoles in the presence of [Dabco-H] [HSO₄] in water.

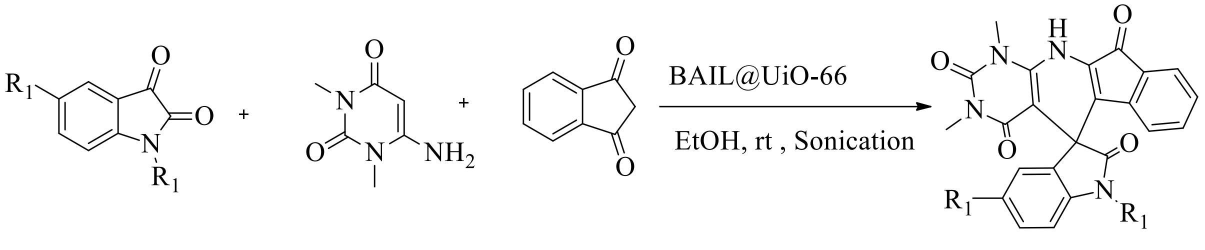
In 2018, Anshu Dandia and co-workers used ionic liquid 1,1,3,3-tetramethylguanidine acetate [TMG][Ac], to synthesize spiro[benzo[f]thiazolo[4,3-a]isoindole-5,3’-indoline]-2’,6,11-trione **40**, which is an important spirooxindole in medicinal chemistry, through multicomponent reaction of substituted isatin **1**, thiazolidine-4-carboxylic acid **38** and naphthoquinone **39** followed by spontaneous dehydrogenation (**Scheme 19)**. Excellent yields were obtained without additives or catalysts. In this study, it has been found that [TMG] [Ac] could be recovered and reused at least four times with the same activity (Dandia et al., 2018).



1 **38** **39** **40**

Scheme 19. Synthesis of spiro[benzo[f]thiazolo[4,3-a]isoindole-5,3’-indoline]-2’,6,11-trione.

Boshra and co-workers described an efficient approach for the rapid synthesis of spirocyclic 2-oxindole **43** using triethylenediamine/imidazole Brønsted acidic, ionic liquid supported in Zr metal–organic framework (TEDA/IMIZ- BAIL@UiO-66), through a one-pot condensation reaction of 6-amino-1,3-dimethyluracil **42**, isatins **1** and cyclic 1,3-diketone **41** (barbituric acid or 1,3-indanedione)(**Scheme 20),** under ultrasonic irradiation. Heterocyclic compounds such as pyrido[2,3-d:6,5-d′]dipyrimidines and indeno[2′,1′:5,6]pyrido[2,3-d]pyrimidines were synthesized using this developed method. Short reaction time, high yields, recyclability of the catalyst, and simple workup procedure are some attractive features of the developed approach (Mirhosseini-Eshkevari et al., 2019).



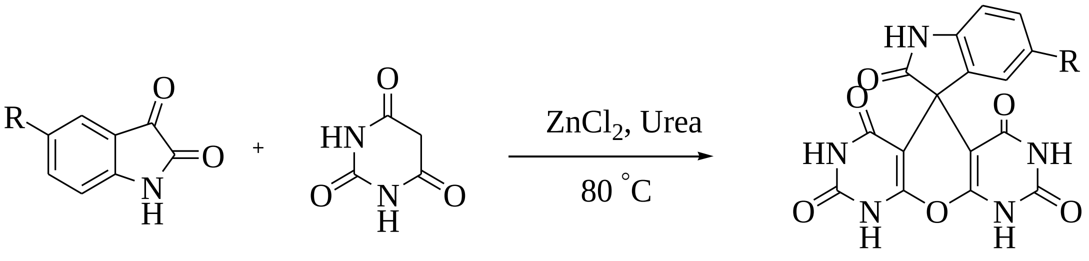
1 **42** **41** **43**

Scheme 20. Synthesis of spirooxindole derivatives using BAIL@UiO-66 under ultrasonic irradiation.

- ***Deep eutectic solvents (DES)***

Deep eutectic solvents are considered analogs of ionic liquids and are now frequently used as renewable green solvents. Deep eutectic solvents are environmentally benign ionic solvents with specific properties that are derived by combining a base with Lewis acids or Brønsted acids. They are typically used in various chemical reactions. The important features of deep eutectic solvents are their compatibility with water, nontoxicity, non-flammability, low transition temperature, and low volatility. In biotransformation, DES can be used as both solvents and catalysts. In addition, they can be used in electrodepositing metals and chemical reactions. Deep eutectic solvents generally form using metal halide and urea and important DES phenomena can be observed when they mix in a 1:2 mol ratio (Nasri et al., 2022)' (Nishtala and Basavoju, 2019).

In 2019, Venkata Bharat Nishtala and co-workers reported in their study, that the deep eutectic solvent of $ZnCl_2$ and Urea can be used as a productive solvent to synthesize spirooxindolopyrans **45** by a pseudo-three-component approach using isatin **1** and pyrimidine-2,4,6(1H,3H,5H)-trione **44** as starting materials **(Scheme 21)** Simplicity in operation, easy purification methods, higher yields, and higher reaction rate make DES, $ZnCl_{2+}$Urea an effective solvent to synthesize spirooxindoles (Nishtala and Basavoju, 2019).



1 **44** **45**

Scheme 21. Synthesis of spirooxindolopyrans.

Singh TP and co-workers developed a one-pot green methodology to synthesize spirooxindole derivatives **49** such as spiro[indoline-3,4′-pyrano[2,3-c] pyrazole products using a four-component reaction in a DES. The reactants were isatins **1**, active methylene compounds **48**, phenylhydrazine **46**, and ethyl acetoacetate **47** as β-ketoesters **(Scheme 22)**. To prepare the DES, urea, and choline chloride are used in a 2:1 ratio. The importance of this method is not to use toxic,

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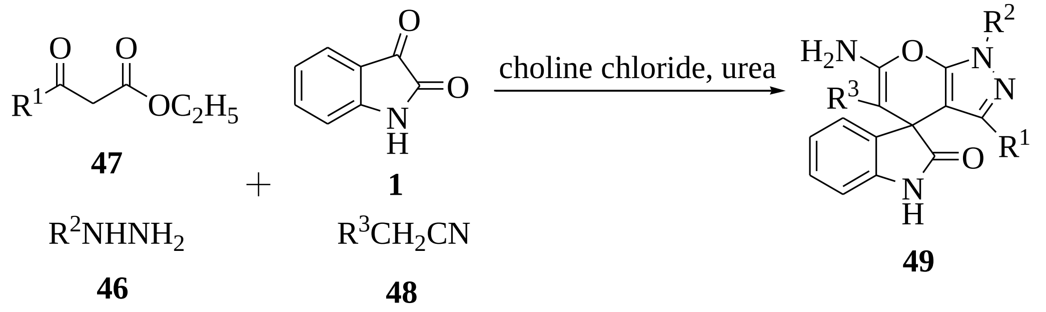
flammable, and expensive catalysts or solvents and observation of higher efficiencies. The method is highly sustainable because the deep eutectic solvent used is biodegradable (Devi et al., 2020).

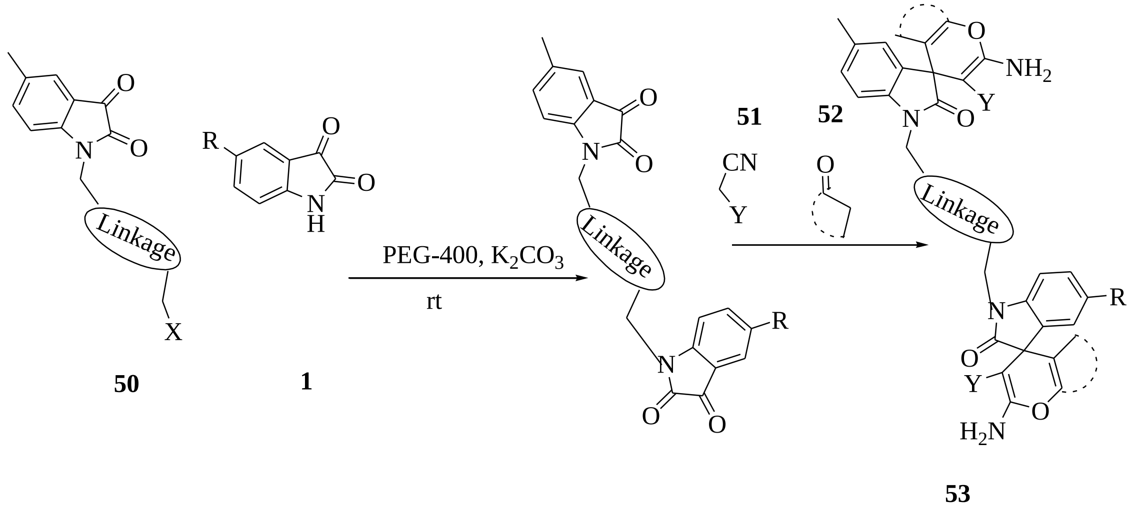


Scheme 22. Synthesis of spirooxindole derivatives in deep eutectic solvents.

- ***Polyethylene glycol (PEG)***

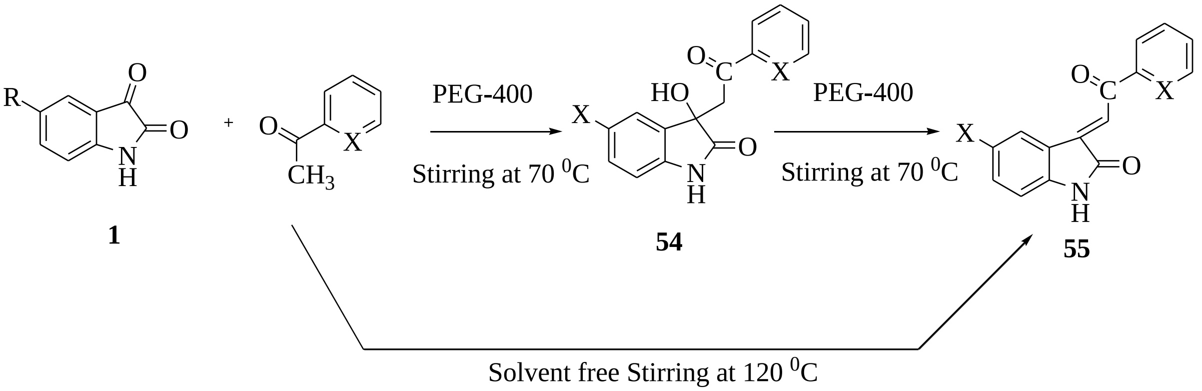
Polyethylene glycol is a widely used alternative sustainable solvent that has been mainly used in many organic reactions in recent years, as it is an eco-friendly and green solvent. Modified polyethylene glycol is also used other than ethylene glycol due to its important properties like biodegradability, non-toxicity, non-flammability, and biocompatibility. Polyethylene glycol is an inexpensive solvent and a soluble polymer matrix that dissolves in water and other organic solvents such as DMF and DMSO while being insoluble in less polar solvents such as hexane diethyl ether. The difference in solubility can be used as a phase separation device and polyethylene glycol-supported catalyst can be used under homogeneous catalyst conditions (Gupta et al., 2019).

In 2018, Hasaninejad et al. developed a one-pot, two-step, multicomponent reaction to synthesize novel asymmetrical bis-spirooxindole derivatives **53** using PEG-400 as a green and biodegradable reaction medium. The reaction was carried out at room temperature using isatin derivatives **1**, N-alkyl isatin **50**, alkylmalonates **51,** and C–H activated carbonyl compounds **52** as starting materials in the presence of K_2CO_3 (**Scheme 23)**. The reaction takes place via two steps; First condensation reaction between N-alkyl isatin and isatin derivatives resulting in bis-isatin derivatives, followed by desired asymmetrical bis-spirooxindole derivatives formation by the reaction between asymmetrical bis-isatin derivatives, alkyl malonates, and carbonyl compounds. Good to excellent yields were obtained using this developed procedure (Hasaninejad and Beyrati, 2018).



Scheme 23. Synthesis of novel asymmetrical bis-spirooxindole derivatives.

Alpana K. Gupta and co-workers described a method to synthesize a series of 3-hydroxy-2-oxindoles **54** and 3-methylene-2-oxindoles **55** using polyethylene glycol as a green solvent **(Scheme 24)** at 70°C. Excellent yields, the ability to use a large scope of substrates, low reaction time, and operational simplicity make this an efficient method over conventional synthetic methods. In addition to these advantages, an easy workup procedure, high atom economy, and catalyst-free reaction conditions make this protocol eco-friendly and sustainable for synthesizing a wide range of bioactive spiro oxindoles (Gupta et al., 2019).



R = H, F, Cl, Br, CH_3
X = H or N

Scheme 24. Synthesis of 3-hydroxy-2-oxindoles and 3-methylene-2-oxindoles.

- ***Renewable solvents***

In this section, renewable solvents are discussed as an alternative approach to avoid drawbacks like toxic solvent wastes, expensiveness, and sensitivity of metals to air. Ethanol, ethyl lactate, and bio-based solvents are some examples of renewable solvents that can be used for organic reactions (Kardooni and Kiasat, 2021).

Das and co-workers found a successful methodology for the synthesis of spiroindolineisoxazolopyridopyrimidine **59** and spiroindolinepyridopyrimidine **60** which are medicinally important spirooxindole derivatives by three-component reactions of various amino compounds **56**, substituted isatins **1** and 1,3-dicarbonyl compounds **57** or 3-phenylisoxazolone **58** at room temperature in ethyl L-lactate medium, under catalyst-free conditions **(Schemes 25 and 26).** A wide spectrum of biologically important oxindole-containing compounds can be synthesized using this green method. Mild reaction conditions, use of green solvents, low energy consumption, and high atom economy are some of the advantages of this protocol (Kausar et al., 2017).

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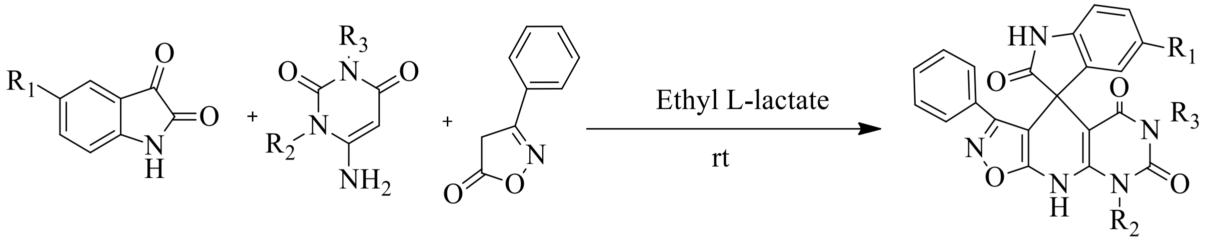
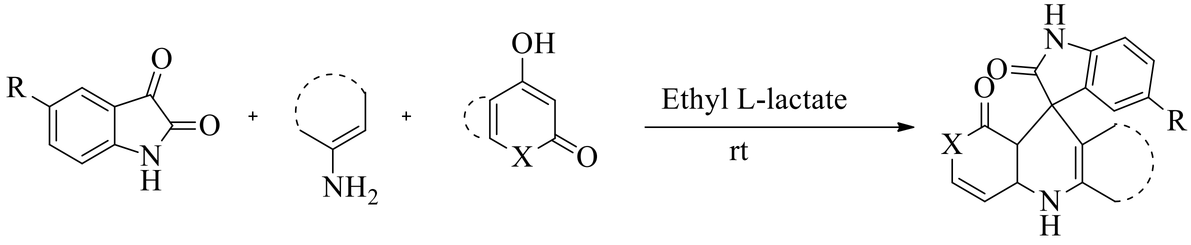


1 56 58 59

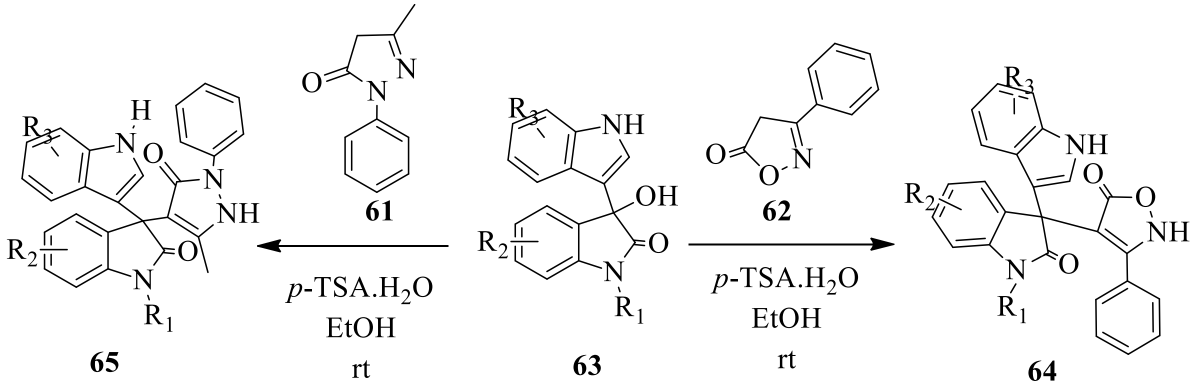
Scheme 25. Synthesis of spiroindolineisoxazolopyridopyrimidine in an ethyl L-lactate medium.



1 56 57 60

Scheme 26. Synthesis of spiroindolinopyrimidine in ethyl L-lactate medium.

Poomathi and co-workers successfully designed an eco-friendly technique to synthesize 3,3-disubstituted oxindoles named indolyl-3-methyl-5-oxo-1-phenyl pyrazolyl indolin-2-one **64** and indolyl-2-oxoindolinyl-3-phenylisoxazol-5-one **65** by using pyrazolone **62**, isoxazolone **61**, 3-hydroxy-2-oxindole **63** with *p*-TSA as a catalyst, at room temperature in ethanol medium **(Scheme 27)**. This approach has benefits including operational simplicity, cost-effectiveness, and reconciliation of structural complexity (Poomathi et al., 2018).



65 61 63 62 64

R^1 = H,CH_3,CH_3CH_2I, allyl,benzyl

R^2 = H,Cl,Br,F,CH_3,OCH_3

R^3 = H,5-Br,5-OH_3

Scheme 27. Synthesis of 3,3-disubstitueted oxindoles catalyzed by *p*-TSA. H_2O in EtOH.

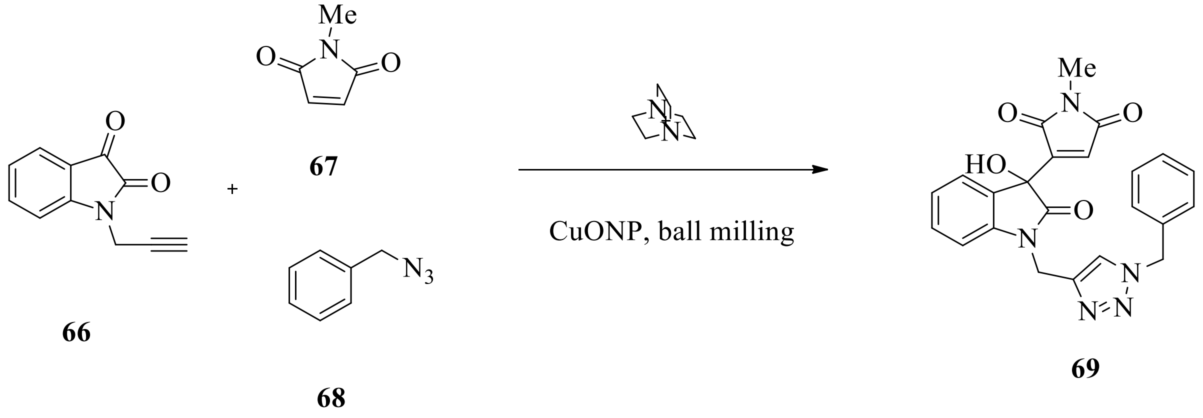
3. Green Techniques

The approaches discussed in this section are eco-friendly, green techniques that can be used for organic synthetic reactions. Increasing the rate of the process, avoiding the use of extreme conditions and toxic solvents, and preventing contamination are some of the benefits provided by green techniques. Among the chemicals used for the main reactions in synthetic processes, higher amounts around 80% are organic solvents. The large-scale chemical production of some compounds, using toxic compounds and volatile organic compounds has become a threat to both the environment and the health of living organisms. Therefore, the physical techniques discussed in this section can be identified as green alternatives to conventional methods (Häckl and Kunz, 2018). Examples of green techniques include the ball mill approach, microwave-assisted processes, and ultrasound-assisted processes.

3.1. Ball-milling

The method of mechanical force-induced chemical transformation or mechanochemistry (ball milling), has been widely used in many areas including supramolecular materials, inorganic and organic synthesis including organic scaffolds, common drugs, etc. These mechanochemical systems possess benefits like; the use of solvent-free conditions, the ability to recycle the catalysts, low energy usage, faster reaction rate, and provide considerably pure products(Egorov et al., 2020). Therefore this method can be considered as an ideal solvent-free technique for organic synthesis (Sharma et al., 2014, Raj et al., 2017).

Vadivelu and co-workers studied an efficient and green strategy under solvent-free ball milling conditions for the synthesis of new oxindole-triazole **69** pharmacophores by merging Baylis-Hillman and click chemistry by reacting N-propargyl isatin **66** (1.0 mmoL),18 N-methylmaleimide **67** (1.0 mmoL), benzyl azide **68** (1.0 mmol), DABCO (0.25 mmol) while using f CuONP as catalyst which can be recovered and recycled for almost 6 cycles **(Scheme 28)**. A short reaction time of approximately 30 min, good to excellent yield, good enantioselectivity, low reaction temperature, and 100% atom economy are some attractive benefits of the developed approach (Vadivelu et al., 2017).



Scheme 28. Synthesis of new oxindole-triazole.

In 2017, Hui Xu and co-workers developed a green, efficient, and solvent-free strategy to synthesize 3,20-pyrrolinyl spirooxindoles **72** using alkylidene oxindole **70** with enamine ester **71** by conducting the reaction for 1 hour (**Scheme 29**). During the study iodine-promoted cyclization of alkylidene oxindoles with enamino esters via C–C/C–N bond formation has been shown under

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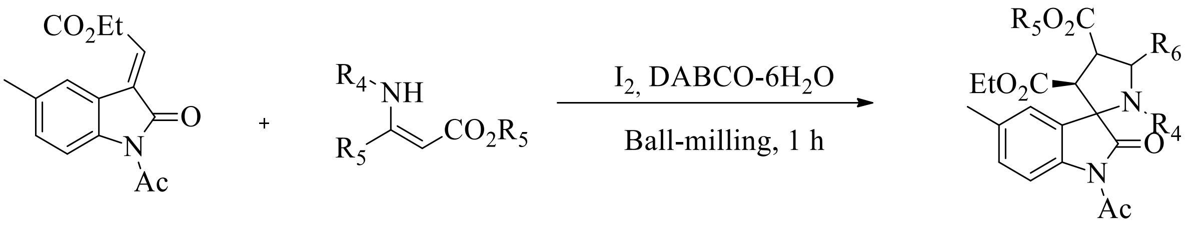
ball-milling conditions. Excellent diastereoselectivities, remarkable functional group tolerance, high yields up to 83% are some important features of the developed approach (Xu et al., 2017).

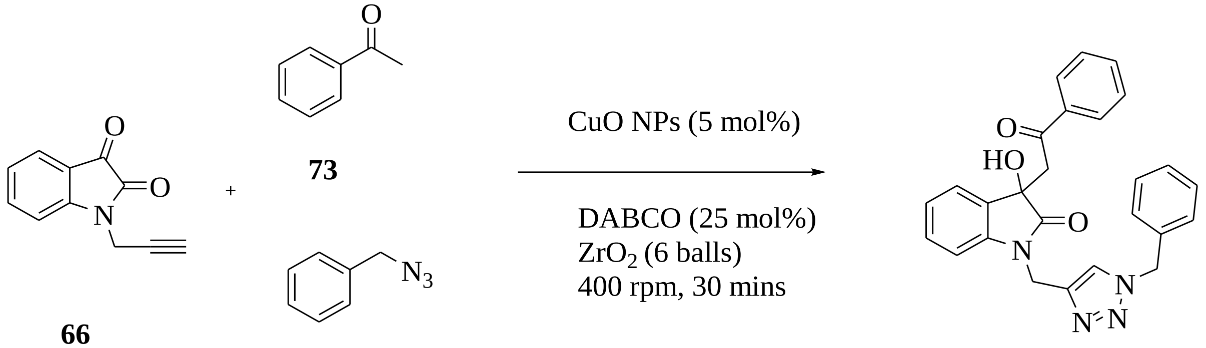


70 **71** **72**

Yields : up to 83%

Scheme 29. Synthesis of 3,20 -pyrrolinyl spirooxindoles.

In 2020, Sampath and co-workers carried out a reaction to synthesize a series of 1, 2, 3-triazole tethered 3-hydroxy-2-oxindoles **74,** which were found to be remarkable corrosion inhibitors with antifungal and antibacterial effects, using solvent-free ball-milling conditions. In this study, they have synthesized 1,2,3-triazoletethered 3-hydroxy-2-oxindoles using N-propargyl isatin derivatives **66**, substituted acetophenones/acetone **73,** and substituted benzyl azides **68** as the main starting materials by a combined concept of aldol condensation and click reaction **(Scheme 30).** ZrO_2 was used as the milling material with 400rpm milling speed. A short reaction time of approximately 30 min and an excellent yield of 80-92% are some important features of the developed protocol (Sampath et al., 2020).



66 **73** **68** **74**

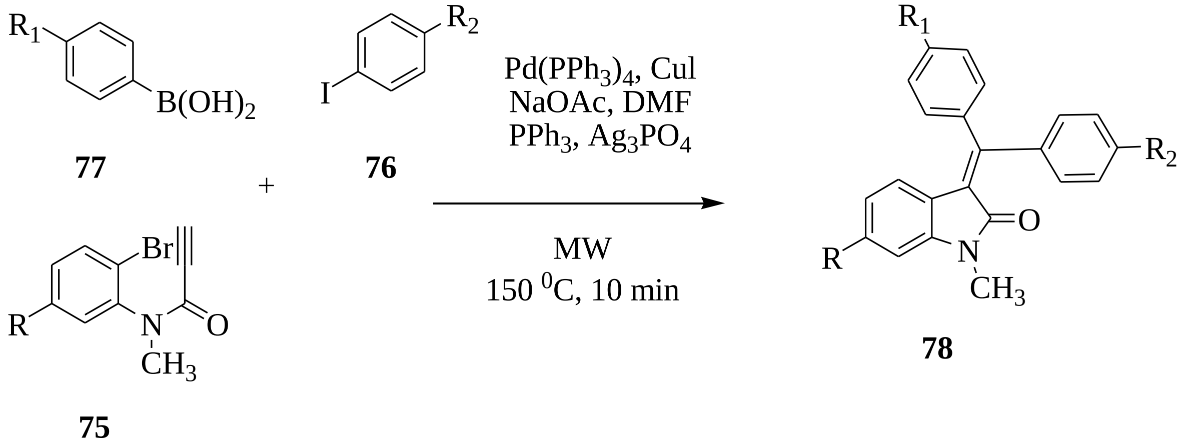
Yield : 80-92%

Scheme 30. The reaction was reported by Sampath *et al.* under mechanochemical conditions.

3.2. Microwave irradiation

Microwave irradiation is a novel technique that is commonly used as a heating method in organic synthesis. The microwave-assisted technique is significant because it can be carried out with less solvent or even under solvent-free conditions. It is a promising technique for many organic reactions and is consistent with the principle of green chemistry. Microwaves provide high heating and reaction rates; therefore, the expected products can be obtained rapidly. Microwave power can be considered as a possible reason for the rapid formation of the expected product. Under microwave irradiation, the molecules are directly exposed to radiation, and the reactant molecules interact with the electric vector of the radiation, increasing the stability of the transition state while lowering the activation energy compared to classical heating methods (Hossain et al., 2010). For some reactions, water cannot be used as the reaction medium due to the poor compatibility of organic substances in a water medium causing biphasic or immiscible reaction mixtures. Microwave irradiated process can be used as a remedy for that as the temperature and pressure reach a high value allowing proper mixing of the reactants in water and reducing the hydrophobic effects (Gawande et al., 2014).

In 2015 Sunhwa Park and co-workers improved a novel three-component, tandem reaction for the synthesis of 3-(diarylmethylene)oxindoles **78** under microwave irradiation. In this study, simple propiolamides **75**, aryl iodides **76**, and aryl boronic acids **77** were used as starting materials **(Scheme 31)**, and it was found that Ag_3PO_4 addition of has permits obtaining higher yields and increases the stereoselectivity of the tandem reaction. Some attractive benefits of this green approach are that the fast reaction takes only 10 min and the use of readily available starting materials. High tolerance to substituents in substrates, and simplicity of operation are other benefits of this method (Park et al., 2015).



Scheme 31. Synthesis of 3-(diarylmethylene)oxindoles **78.**

Pramod B. Thakur and co-workers have demonstrated rapid efficient, and eco-friendly protocol under catalyst-free conditions to synthesize a wide spectrum of 3-substituted, 3-hydroxy-2- oxindoles scaffold **79** under aqueous reaction media. Here 1, 3-diketone **80** with isatin **1** was used as the starting material under microwave irradiation **(Scheme 32)**. α-Regioselective aldol addition products have been studied using different structurally varied 1, 3-diketone as the nucleophile and different isatins as electrophiles. The γ C—H bond activation of 1,3-diketone can be carried out using this protocol under catalyst-free conditions, which have many applications in organic synthesis. This procedure can be considered a sustainable procedure due to its environmentally benign medium. Simplicity and excellent isolated yields are some other attractive features of this protocol (Al-Bogami and El-Ahl, 2015).

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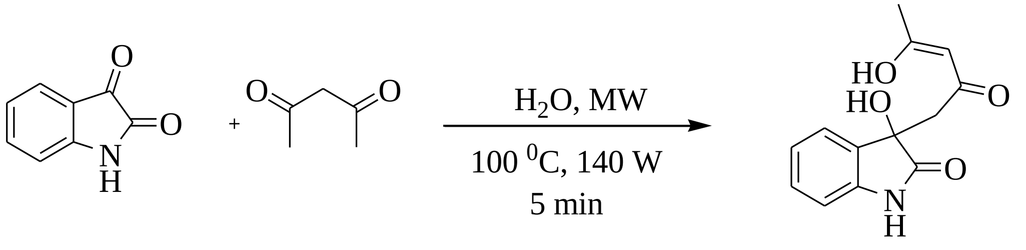
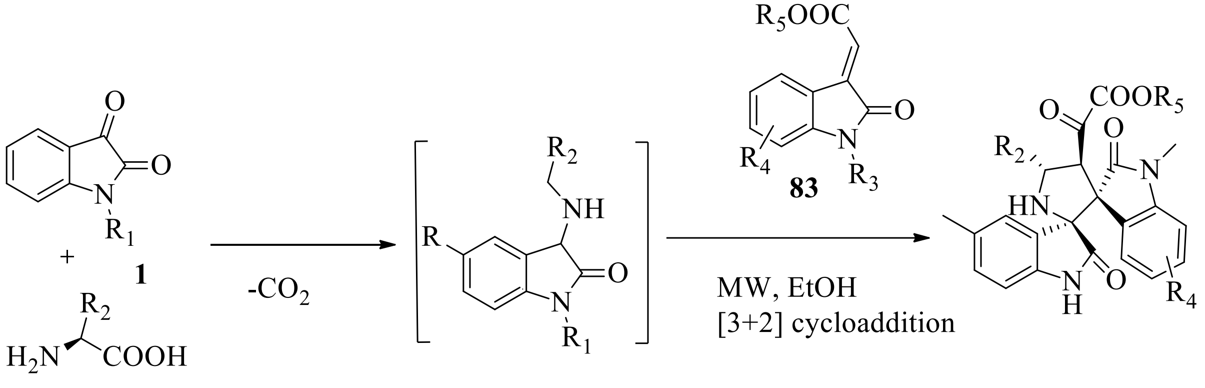


1 **80** **79**

Scheme 32. Synthesis of diversely functionalized 3-substituted, 3-hydroxy-2- oxindoles scaffolds **79.**

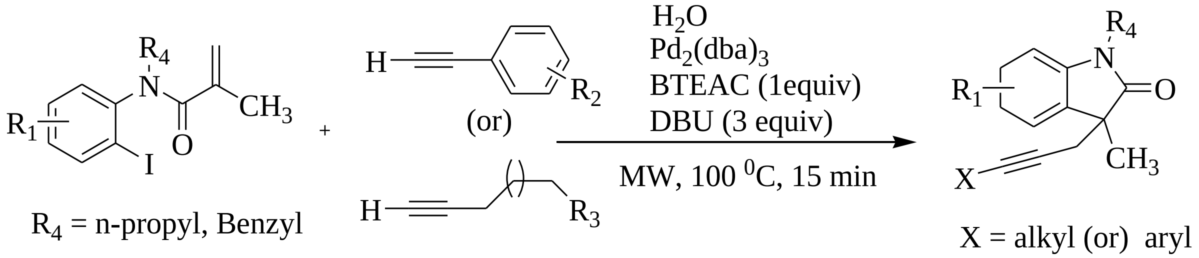
In 2019, Sonal Bhandari and co-workers developed an efficient, one-pot synthesis method to synthesize of pyrrolidine fused bis-spirooxindoles **84** using in-situ generated azomethine ylide **82** from decarboxylative condensation of isatins **1** and primary α-amino acids **81** with concomitant [3+2] cycloaddition of 3-alkenyl oxindoles **83** using ethanol as the solvent **(Scheme 33).** By this method, they have been able to obtain novel bis-spirooxindole skeletons with a single diastereomer also providing an effective method for the formation of C–C and C–N bonds with four stereocenters. The main benefits of this protocol are the ability to use catalyst and additive-free conditions, diverse substrate scope, high yields, and eco-friendliness (Bhandari et al., 2019).



81 **82** **84**

Scheme 33. Microwave-assisted synthesis of various bis-spirooxindoles.

Karu Ramesh and co-workers discovered an eco-friendly microwave-assisted domino [Pd]-catalyzed approach to synthesize a series of oxindole derivatives **87** using ortho-iodophenyl enamides **85** and terminal acetylenes **86** as the starting materials **(Scheme 34)**. They have reported that this reaction was suitable for different aryl or alkyl acetylenes and have obtained good yields. This method exhibits functional group tolerance, allowing the use of amino, hydroxyl, and carboxylic acid functionalities under protection-group-free conditions (Ramesh et al., 2018).



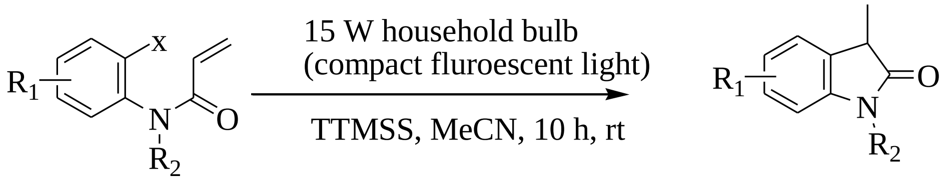
85 **86** **87**

Scheme 34. Synthesis of oxindole derivatives under microwave irradiation.

3.3. Visible-light irradiation and photo redox catalysis

One of the main aims of green chemistry is to minimize the formation of chemical waste and make full use of renewable materials. In recent years, in the field of synthetic organic chemistry, visible light has attracted considerable attention as a clean energy source owing to its advantages, such as low cost, wide substrate suitability, eco-friendliness, safety, good compatibility with functional groups, and availability. In processes such as classical radical generation methods that use toxic reagents, explosive oxidants, and expensive transition-metal catalysts, this protocol helps create environmentally benign procedures.

Gustavo Piva da Silva and co-workers successfully developed a new metal and additive-free photochemical process for the synthesis of oxindole derivatives **89** via a combined tris(trimethylsilyl)silane (TTMSS) and visible-light-promoted intramolecular reductive cyclization protocol using N- protected 2-halophenylacrylamides as substrates **88 (Scheme 35).** The reaction was carried out for 10 hours at room temperature and simple household fluorescent light bulbs were used as the visible light source while using tris(trimethylsilyl)silane as hydride source. The developed methodology can be considered as a rapid and practical synthesis of functionalized nitrogen-based heterocycles. The use of inexpensive reagents, high functional group tolerance, and mild reaction conditions are some attractive features of the developed approach (da Silva et al., 2015).



88 **89**

Scheme 35. Synthesis of oxindole derivatives **89.**

Visible-light-induced radical cyclization of N-aryl acrylamides has used by Guojie Yin and co-workers in 2016, for the synthesis of difluoromethylenephosphonated oxindoles **91**. Difluoromethylenephosphonated oxindoles were synthesized via tandem radical cyclization using

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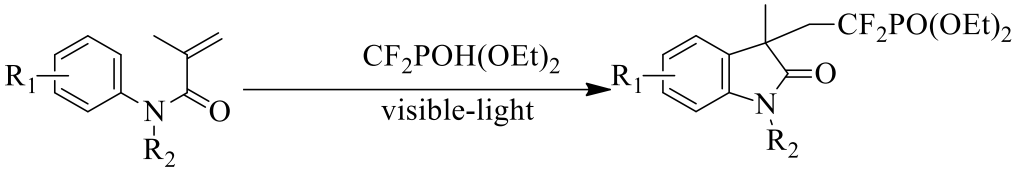
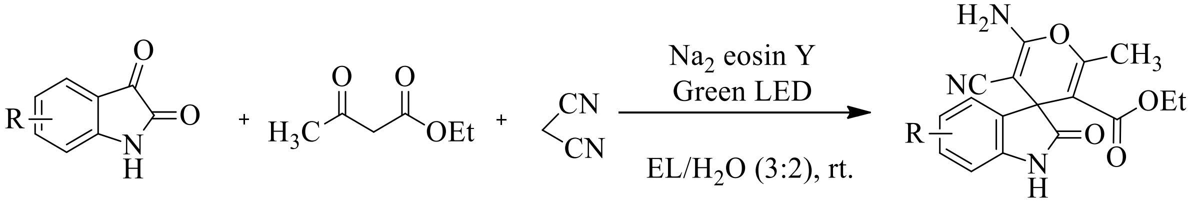
in-situ generated phosphonodifluoromethyl radicals and N-arylacrylamides **90 (Scheme 36).** Operational simplicity, mild conditions, non-toxic reagents, and compatibility with various functional groups are some attractive features of this green protocol. This study is very useful as this protocol can be successfully applied in many fields including drug discovery research, laboratory methods, and also in industrial processes (Yin et al., 2016).



90 **91**

Scheme 36. Photochemical strategies for radical difluromrthylenephosphonation.

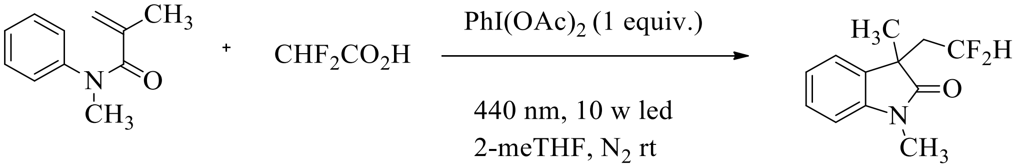
In 2020, Meng-Nan Chen and co-workers developed a green and effective method to synthesize spiro[oxindole-3,4'-(40 H-pyran)] derivatives **94** which are biologically important molecules via one-pot, three-component reaction under visible light. For this reaction, malononitrile **92**, 1,3-dicarbonyl compounds **93,** and isatins **1** were used as the starting materials in an aqueous ethyl lactate medium at room temperature **(Scheme 37)**, while using cost-effective organic dye and Na_2 eosin Y, as the photocatalyst. They have stated that the classical methods of synthesizing spiro[oxindole-3,4'-(40 H-pyran)] derivatives have some limitations such as the use of toxic solvents, poor yields, poor substrate scope, high temperature, long reaction time, and complex catalyst preparation. These problems can be avoided by this visible light irradiated green protocol (Chen et al., 2020).



1 **93** **92** **94**

Scheme 37. Synthesis of spiro[oxindole-3,4'-(40 H-pyran)].

Gui et al. designed an effective and environmentally benign method for the synthesis of difluoromethylated oxindoles **97** via a one-pot tandem reaction of N-arylacrylamides **95**, difluoroacetic acid **96**, and $PhI(OAc)_2$ under visible light irradiation **(Scheme 38)**. Very mild conditions which are metal catalyst-free, additive-free, and external photosensitizer-free conditions can be used for this reaction. Here easily available and cheap CHF_2CO_2H has been used as the difluoromethylation reagent. They have been able to obtain higher yields for about 26 types of N-arylacrylamide substrates (Gui et al., 2021).



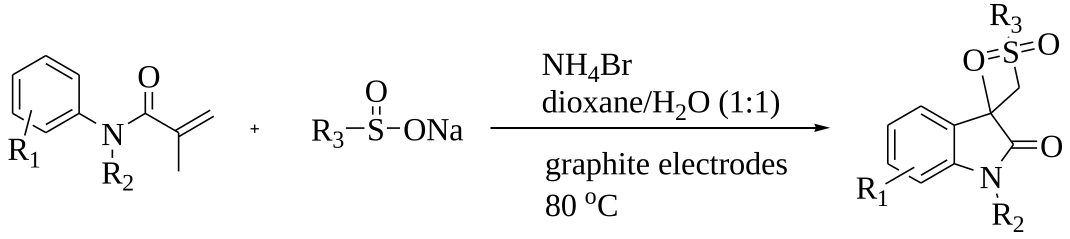
95 **96** **97**

Scheme 38. Synthesis of difluoromethylated oxindoles **97.**

3.4. Electrochemical method

The electrochemical method is one most convenient and efficient methods with multiple benefits in organic synthesis. The advantages of the electrochemical approach include cost-effectiveness, low energy consumption, high selectivity, low temperature, readily available precursors, and a high atom economy. It can be considered a sustainable method as it doesn't release hazardous waste and can be used to produce heterocyclic compounds, concerning the function of hetero atoms in electron transfer processes in various reactions (Frontana-Uribe et al., 2010).

In 2016, Sun and co-workers successfully developed for the first time an efficient electrochemical approach to synthesize 3-sulfonyloxindoles **100** via a one-pot, two-step procedure. The reaction was carried out by electrolyzing a mixture of acrylamide **98** and sodium sulfonate **99** at 80 ° C using graphite electrodes, in the presence of the catalytic amount of NH_4Br (10 mmol%) as a redox catalyst **(Scheme 39)**. Sulfonyl halides which are unstable and commercially unavailable were synthesized in situ during the reaction. Sulfonyl radicals are formed as sulfonyl halides undergo hemolytic cleavage regenerating bromide. The ability of the anode to act as a co-oxidant prevents the use of additional chemical co-oxidants. The ability of electrolysis to be carried out in an undivided cell, avoiding the use of a supporting electrolyte, can be considered an additional advantage of the developed protocol (Jiang et al., 2016).



98 **99** **100**

Yield : up to 85% **Scheme 39.** Synthesis of 3-sulfonyloxindoles.

Xin-Yu Wang and co-workers developed a practical, economical, and environmentally friendly method for the synthesis of Seleno oxindoles **103** with medicinal importance, by tandem cyclization of acrylamide with diselenides facilitated by electrochemical oxidation by constructing a C-Se bond. Diphenyl diselenide **102** and N-arylacrylamide **101** were used as starting materials for the reaction under a constant current of 15 mA for 2 h in the presence of nBu_4NPF_6 and CH_3CN/1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) = 8:2 as the co-solvent, and a yield of approximately 85% was obtained **(Scheme 40)** (Wang et al., 2021).

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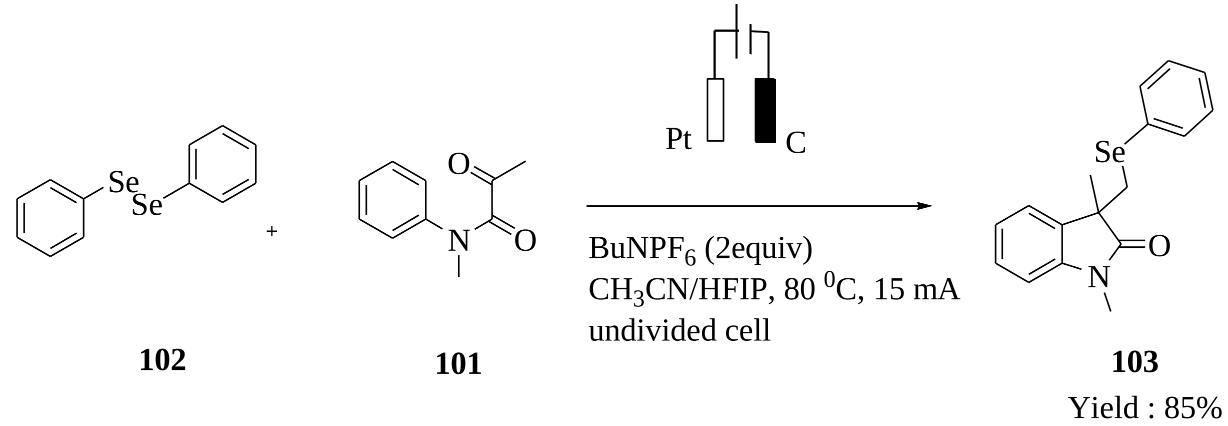
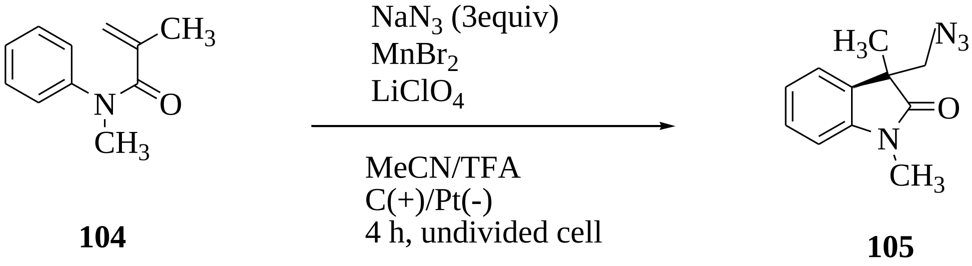


102 **101** **103**

Yield : 85%

Scheme 40. Synthesis of selenooxindoles **103.**

Debabrata Maiti and co-workers synthesized a series of oxindole derivatives **105** by manganese-catalyzed electrochemical reaction at room temperature via tandem azidation-radical cyclization strategy. For the reactions, a series of N-phenyl acrylamides **104** was used with sodium azide and $MnBr_2$ in an undivided cell equipped with a graphite anode and a platinum cathode under an ambient atmosphere **(Scheme 41)**. The ability to use cheap azide sources like NaN_3, diverse synthetic applications, and wide substrate scope are some of the major advantages of this procedure (Maiti et al., 2021).



104 **105**

Scheme 41. Synthesis of oxindole derivatives **105.**

4. Challenges and author recommendations

Finding green and efficient methods for the synthesis of biologically important compounds can be stated as one of the greater developments in the field of synthetic organic chemistry. Because the demand for oxindoles is very high, mainly in the field of medicine, synthesis should be carried out on a large scale. As a result, the need for eco-friendly methods has increased, owing to the negative impacts of conventional methods on the environment.

One of the major challenges faced during using of green solvents is the poor solubility and poor compatibility of some organic compounds. Hence attention must be paid in future studies to improve the compatibility of organic compounds in green solvents like water. This allows for an increase in the scope of reactions that use green synthesis techniques.

High time consumption and high cost of production are other challenges faced during the production of biologically important compounds such as oxindoles on a large scale. Hence, future studies should be carried out using biocatalysts to increase the rate and efficiency of the reactions. Reuse and recycling are two other techniques that support the concept of green chemistry. Therefore, studies should be carried out to find new methods that can recycle and reuse the solvents and other byproducts formed during the reactions.

5. Conclusion

Oxindole and its derivatives are a significant class of compounds with distinct structures and valuable pharmacological properties that have been highly considered by present researchers. Consequently, there has been an increase in the demand for sustainable processes that adhere to green chemistry principles. This review highlights several recent publications that discuss sustainable protocols for the synthesis of oxindole-containing molecules using green methods. All methods are summarized in two sections: green solvents and green techniques. Many researchers utilize water, ionic liquids, deep eutectic solvents, polyethylene glycol, and renewable solvents as the green solvents of choice. Some studies have shown the ability to use water as a reaction medium without any catalysts and with homogeneous/heterogeneous catalysts. This discovery represents one of the most significant turning points in the process of synthesizing medicinally important oxindole derivatives because water is the most environmentally friendly and abundant solvent on the earth. Using the ball mill approach, microwave irradiation, visible-light irradiation, ultrasound-assisted synthesis, electrochemical methods, and multi-component synthesis are discussed. Most of these methods allow the reaction to proceed rapidly without releasing significant waste into the environment.

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List of abbreviations

PEG- Polyethylene glycol
DES- Deep eutectic solvents

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