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AN EFFICIENT GREEN SYNTHESIS OF SPIRO-HETEROCYCLIC COMPOUNDS: A BRIF RIVIEW

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Abstract

Spiro- heterocyclic compounds are a class of compounds containing Spiro linkage and hetero atoms. Structural rigidity of spiro compounds makes them biologically a potent. Many Spiro-heterocyclic compounds are known for their biological activities. Number of Spiro-heterocyclic compounds exhibits various biological activities such as anticancer agents, antibacterial, anti-tubercular, anti-inflammatory, antipyretic, insecticidal and anthelmintic, insect anti-feedant , antibiotic and antifungal, cytotoxic, anti-food-deteriorating agent , anti-protozoal, CNS stimulant, cardiac glycoside, HIV-1 reverse transcriptase inhibitor, cholesterol absorption inhibitor, stimulant and convulsant, antitumor, anti-coagulant , antineoplastic, diuretic, antipsychotic, anti-broncho-constrictor, anxiolytic, anti-diabetic, anti-ulcer agent, antihypertensive. This aspect attract attention of the Chemist towards the synthesis of spiroheterocyclic compounds by using green environmental eco-friendly green synthesis.

There numerous methods are available for the synthesis of Spiro heterocyclic compounds and they are mentioned in the literature. In present study we have mentioned some of them which are environmental eco-friendly green synthesis. We have briefly reviewed the methods that are used for the solvent free green synthesis of spiroheterocyclic compounds.Fig.1

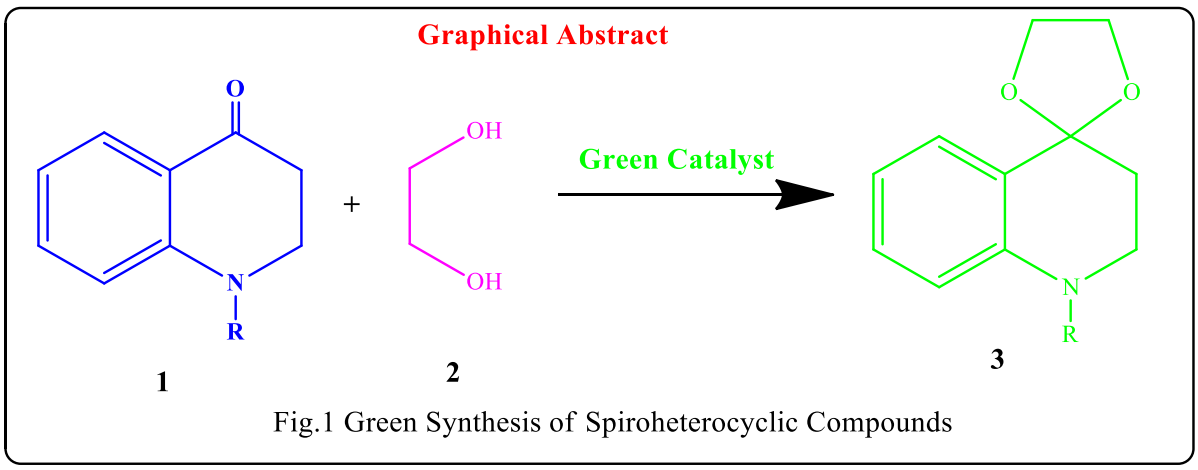


Fig.1 Green Synthesis of Spiroheterocyclic Compounds

Key Words: Green Synthesis, Biological Activities, Spiroheterocyclic Compounds, Environmental Eco-friendly etc.

Introduction:

Spiroheterocyclic compounds are the spiro compounds containing spiro linkage and one or more hetero atoms are the part of the cyclic ring. A synthetic approach of spiro-compounds containing hetero atoms is the interesting area of the most chemist due to their wide applications in the pharmaceutical field. A spiro compound is that compound which has at least two molecular ring with only one common carbon atom. The spiro compound containing hetero atom containing hetero atom such as Nitrogen, Oxygen and other hetero atoms are called as spiro-heterocyclic compounds. Many spiro compounds containing hetero atom such as Nitrogen, Oxygen are extensively used in the treatment of various disease due to their pharmacological and biological activities such as anticancer agents, antibacterial, anti-tubercular, anti-inflammatory, antipyretic, insecticidal and anthelmintic, insect anti-feedant , antibiotic and antifungal, cytotoxic, anti-food-deteriorating agent , anti- protozoal, CNS stimulant, cardiac glycoside, HIV-1 reverse transcriptase inhibitor, cholesterol absorption inhibitor, stimulant and convulsant, antitumor, anti-coagulant , antineoplastic, diuretic, antipsychotic, anti-broncho-constrictor, anxiolytic, anti-diabetic, anti-ulcer agent, antihypertensive etc.

In past number of Spiro & heterocyclic compounds were prepared by using various methodologies of synthesis[1]. These Spiro & heterocyclic compounds possess well biological activities such as anticancer agents[2,3], antibacterial[4,5], anti-tubercular[6], anti-inflammatory[7], antipyreti[8], insecticidal and anti-helminthic[9], insect anti-feedant[10], antibiotic and antifungal[11], cytotoxic[12], anti-food-deteriorating agent[13], anti- protozoal[14], CNS stimulant[15], cardiac glycoside[16], HIV-1 reverse transcriptase inhibitor[17], cholesterol absorption inhibitor[18], stimulant and convulsant[19], antitumor[20], anti-coagulant[21], antineoplastic[22], diuretic[23], antipsychotic[24], anti-broncho-constrictor[25], anxiolytic[26], anti-diabetic[27], anti-ulcer agent[28], antihypertensive[29-30], antimalarial[31], CCR antagonist[32], antiplatelet agents[33].

Some of the member from the Spiroheterocylic family such as Spiroindole and Spirooxindole in which the spiro linkage at C_2 and C_3 position of indole acts as an building block of the various drugs. It is core of the many drug moieties which acts as a pharmacophore and which exhibits potent pharmacological and biological activities. Many Spiroindole and spiroxindole core containing moieties well known for their pharmacological and biological activities such as Horsfline (S1), Mitraphylline (S2), Marefortine (S3), Welwitindolinone (S4), Elacomine (S5), and Alstonisine (S6) (Fig.2)[34-37]. Spiroindole possess connatural three dimensional and rigid structure which has good affinity towards protein this fact makes Spiroindole became a synthetic target in organic chemistry and drug discovery. Due to this fact Spiroindole exhibits potent broad spectrum biological activities such as antimicrobial, antitumor, antidiabetic, anticonvulsant, potential antileukemic, local anesthetic, and antiviral activities. Rather spirocyclic systems acts as a synthetic precursor for the synthesis and exploration of medicines. Spirotryprostatin S7A and Spirotryprostatin S8B shows microtubule assembly inhibition. While Pteropodine S9 and Isopteropodine S10 steepen the operation of muscarinic serotonin receptors. (Fig.3)[38, 39].

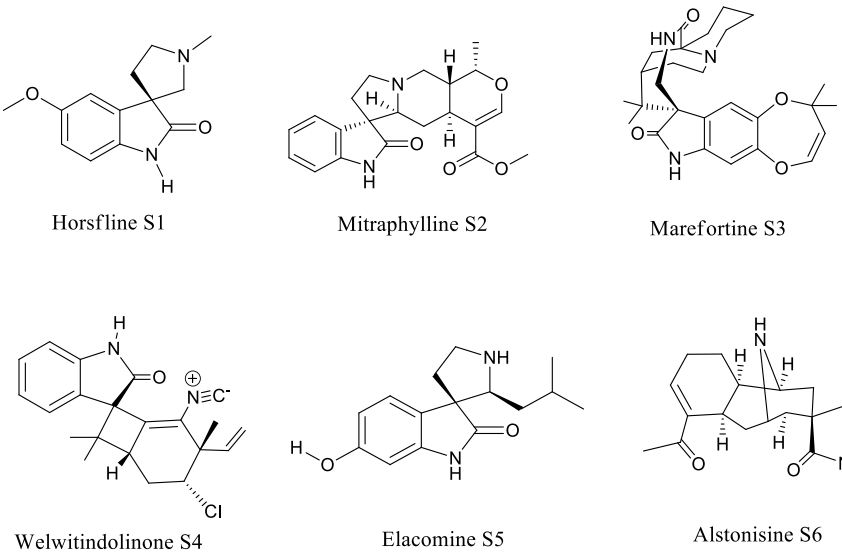


Fig.2 Biologically active Spiroheterocyclic Compounds

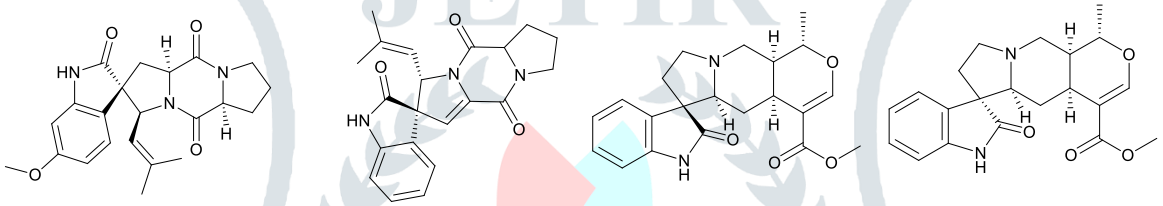


Fig.3 Pharmacologically Active Sirooxindole Moieties

Spirocyclic oxindoles are valuable synthetic intermediates and constitute many pharmacological activities like antimicrobial, antitumor, antimicrobial, antibacterial, antifungal, anti-viral and local anesthetics.

Review of literature reveals that Spirochromone Scaffold shows diverse broad spectrum biological activities such as antimicrobial activity[40], anticancer[41], anti-tubercular and anticonvulsant[42] anti-HIV[43], antiulcer[44] , anti-inflammatory[45], antidiabetic[46], analgesic[47], antimalarial[48], wound healing[49], immune-stimulator[50], antiplatelet[51], insecticidal[52], gastro protective[53], antihistamine[54], antihypertensive[55], calpain inhibitor[56], enzyme and receptor agonist/antagonist[57], antioxidant[58].

Spirochromone containing the coromone moiety and cromene ring widely occurred in many natural product and the variety of spirochromone moieties and its derivatives are the precursor for drug discovery. Many spirochromones were known for their potent biological and pharmaceutical applications such as Nedocromil (SC1), ethuliacoumarion (SC2), Khellin (SC3), apigenin (SC4), flavoxate (SC5) etc used in the treatment of Asthama, anthelmintic related problems, coronary disease and kidney related diseases , cancer related diseases, muscle spam related problems respectively.(Fig.4)[59]. Some of the spirochromone and chromone derivatives were used for the treatment of tuberculosis.[60]

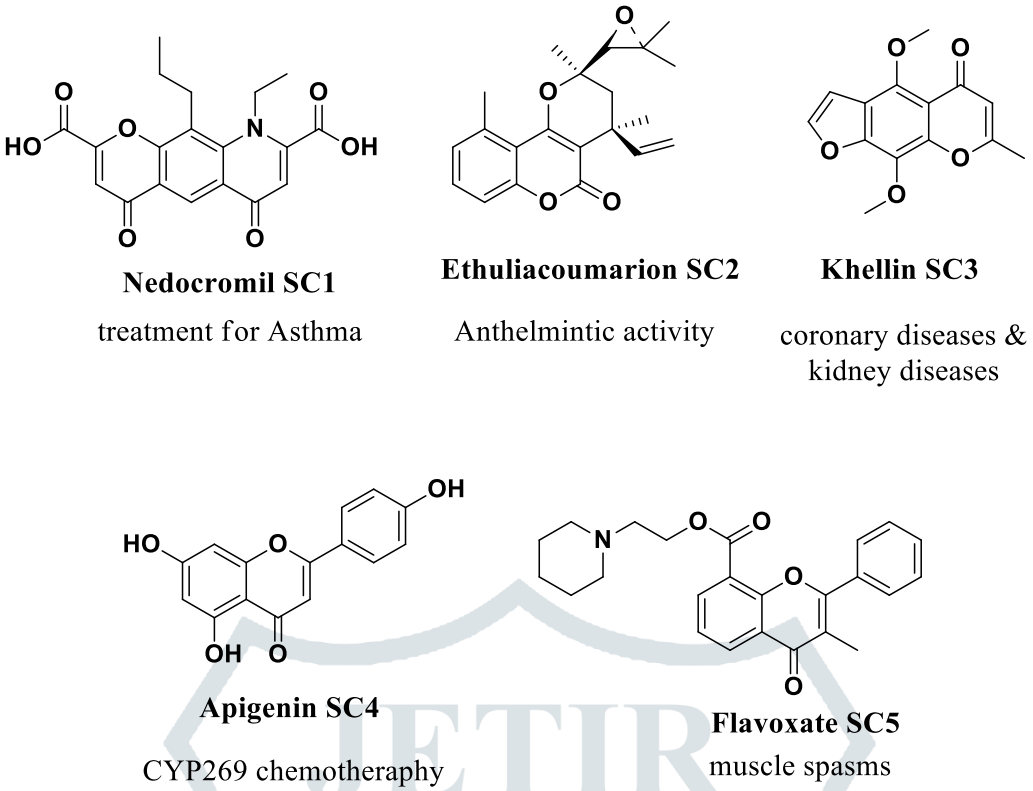


Fig.4 Spirochromone Scaffold moeties bearing different Biological Activities

Recently many methods were used for the synthesis of Spiro as well as heterocyclic compounds such as 1) Three component tandem cyclo-addition, 2) Microwave assisted synthesis, 3) 1,3, dipolar cycloaddition also known as Huisgen cycloaddition or Huisgen reaction, 4) Reductive lithilation,, 5) Alkylation and reductive cyclization, 6) Rig closing metathesis,7) [3+2] Annulation followed by reductive cleavage, 8) ring expansion, 9) Waters' ring closing metathesis, 10) Palladium-mediated cyclisation, 11) asymmetric Michael additions, 12) cycloaddition, and multicomponent reactions, 13) Prins/ene cascade process, 14) Fischer indole synthesis followed by Ugi reaction, 15) intramolecular cyclization using Eaton's Reagent, 16) Curtius rearrangement, 17) Regioselective Mizoroki–Heck cyclization for the synthesis of spirooxindoles,[61-62] 17) Aldol cascade method by using (R)-pyroglutamic acid as catalyst.[63] In the literature there are numerous methods were mentioned for the synthesis of Spiroheterocylic compounds containing hetero atoms like Nitrogen and Oxygen became a part of Spirocyclic ring. In last decade wide verities of Spiroheterocylic compounds and their derivatives were known such Spiroindoles, Spirooxindoles, Spirochromones, spiroperimidones, Spiroheterocylic compounds prepared from isatin, five membered, six membered spirocomepounds prepared from various precursors bearing heterocyclic Scaffold moieties.

Spiroheterocylic system containing one carbon atom common two rings are structurally interesting. The presence of the sterically constrained Spiro compounds represent an important class of naturally occurring substances. Most of the methods used for the synthesis of spirocompouds are chemical methods which is not environment ecofriendly or they not follow the green approach.

In present study brief review about the green synthesis of Spiroheterocylic compound is done. In this article we try to collect some methods used for the synthesis of Spiroheterocylic compounds by using green approach.

Green synthesis deals with the 12 Principles of Green Chemistry i.e. 1) Prevent Waste, 2) Atom Economy, 3) Less hazardous synthesis, 4) Design benign Chemicals, 5) Beginning Solvent and auxiliaries, 6) Design for energy efficiency,7) Use of Renewable Feedstock's, 8) Reduce Derivatives, 9) Catalysis, 10) Design of degradation, 11) Real Time Analysis for Pollution Prevention, 12) Inherently Benning Chemistry for Accident Prevention. Some of the principles were utilized and synthesized some Spiro compounds and following methods were reported for the green synthesis.

In present review the observation is divided into different synthetic methods by adopting green approach. Fig .5 depicts the different methodologies used for the synthesis.

1) Microwave Assisted Synthesis :

Wide varieties of Spiro heterocyclic compounds were synthesized by using different starting material and reagent at different conditions like solvent, temperature etc. By adopting Microwave assisted synthesis. Microwave assisted facile synthesis has tremendous importance in the area of green synthesis. This method facilitates the easier, safe, and environmentally eco-friendly as well less time consuming and high yield synthesis of various types of drug by one pot synthesis. This method bears good atom economy. Microwave (MW) irradiation is a solo tool in modern organic synthesis[64].

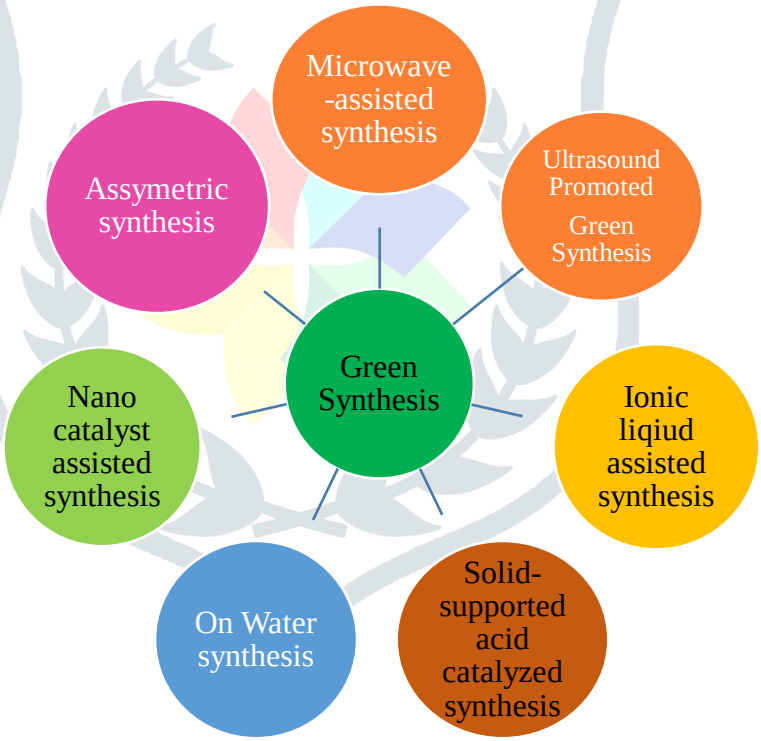
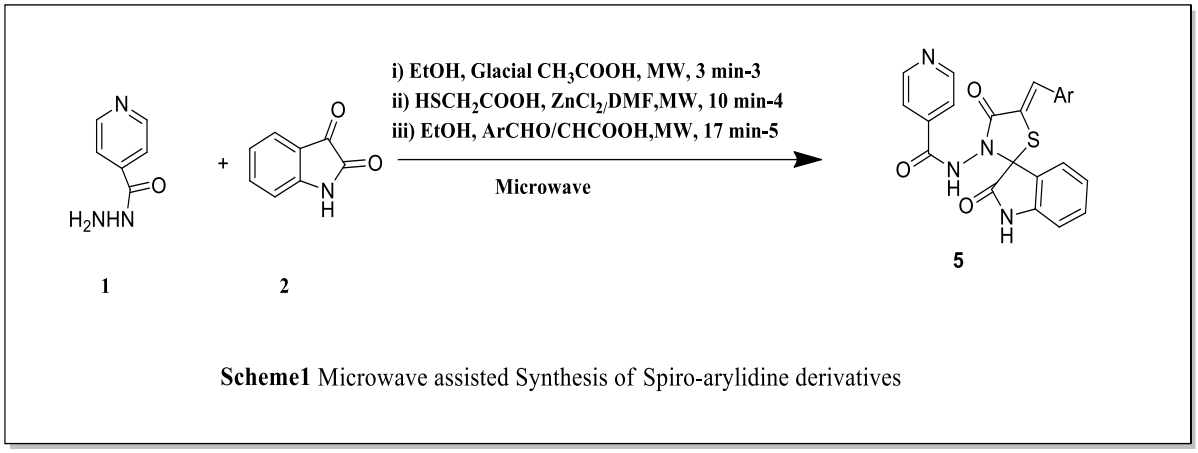


Fig 5: Different methodologies used for green synthesis

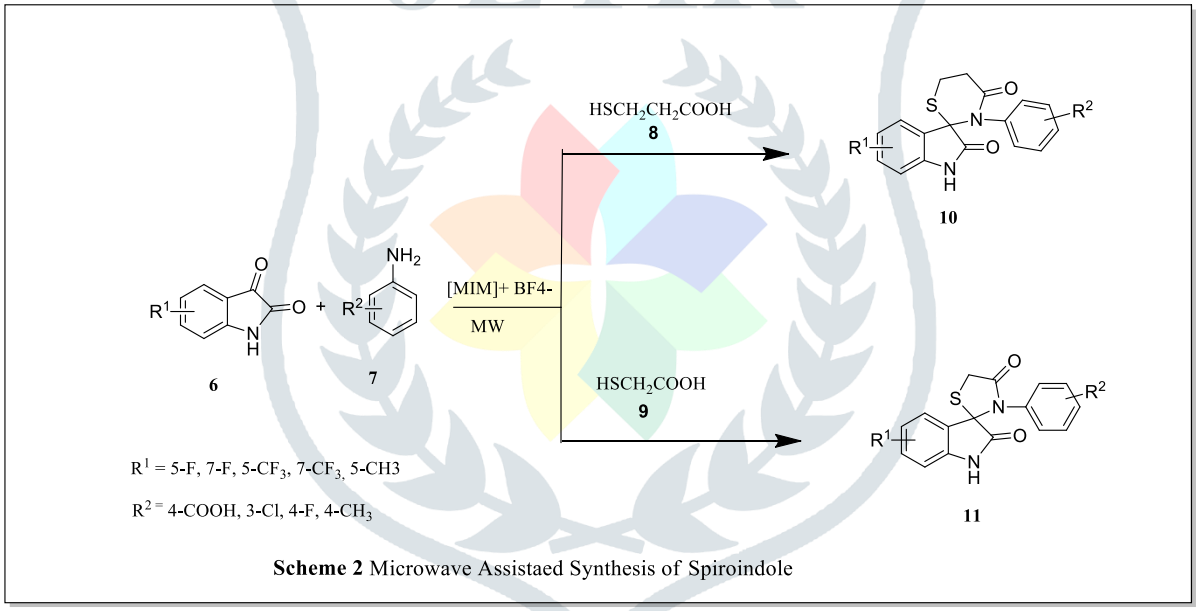
P. N. Shinde et al.[65] outlined the synthesis of spiro-[indole-thiazolidine] derivatives (5) by the reaction of isoniazid (1) and isatin (2) in the presence of the catalytic amount of glacial acetic acid gives N-(2-oxo-1,2-dihydro-3′ H-indol-3-ylidene) pyridine-4-carbohydrazide (3), which on further undergo cyclocondensation with mercaptoacetic acid and anhydrous ZnCl2 to results spiro-[indole-thiazolidine] derivatives (4). Later on compound (4) was abridged with aromatic aldehydes to provide arylidene derivatives (5) (Scheme 1). The synthetic methodology and the procedure used for the production of this moieties facilitates: operational simplicity, reduced reaction time, and simple work-up. The Author also investigated the antimicrobial activity of the resulted Spiro-

[indole-thiazolidine] moieties against the gram positive and gram negative bacteria and he found that some moieties exhibit the potent antimicrobial activities.



Scheme1 Microwave assisted Synthesis of Spiro-arylidine derivatives

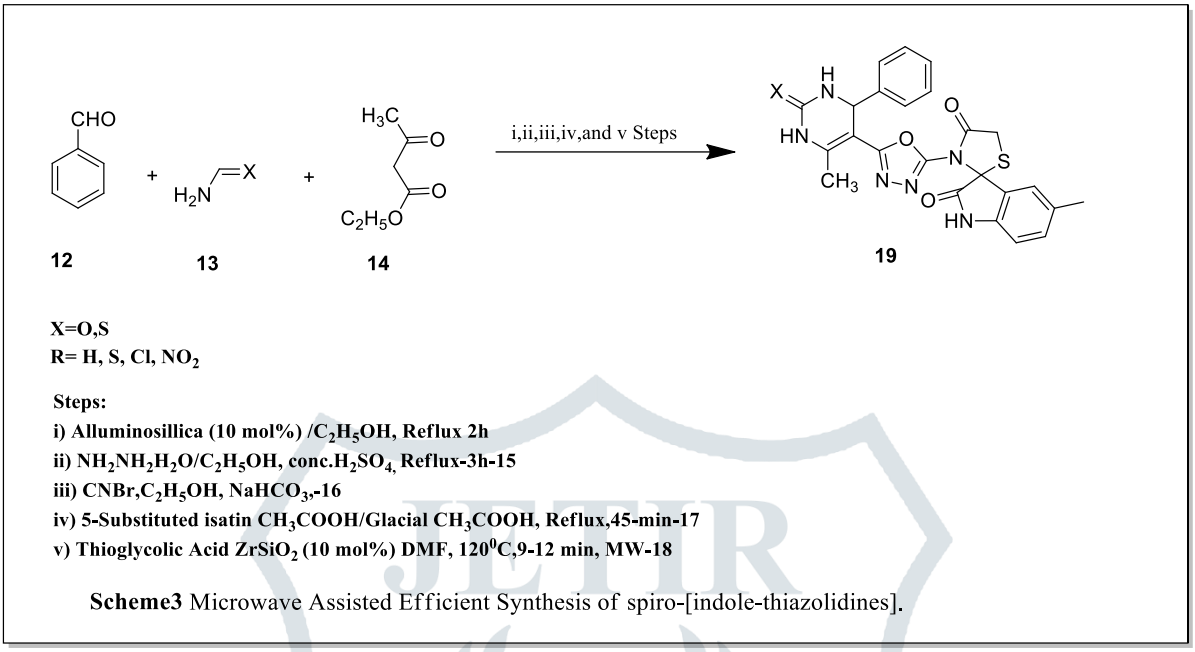
Arya et al.[66] also reported the microwave assisted synthesis of fluorinated spiro indole (10), (11) by cylocondensation. By reaction of different isatin (6) with heterocyclic amines (7) using thioacids (8), (9) and 1-methylimidazolium tetrafluoroborate ([MIM]+ BF4-) on microwave irradiation about 2-4 minutes gives 90-97% yield of respected fluorinated Spiro compound. (Scheme2) .



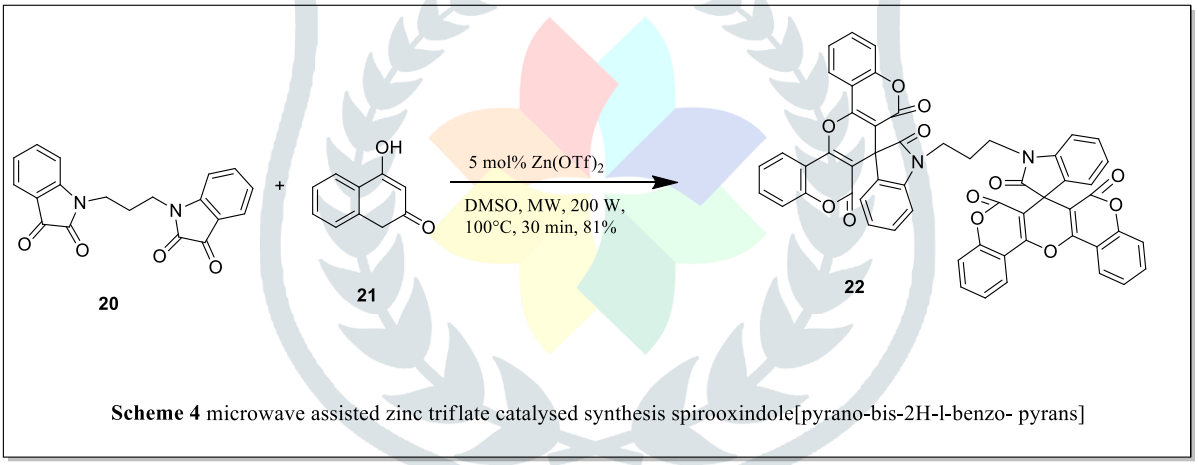
Scheme 2 Microwave Assistaed Synthesis of Spiroindole

M. A. Borad and co-authors[67] reported the synthesis of several manifold novel spiro-[indolethiazolidines] (19) derivatives from substituted isatins and thioglycolic acid (TGA) catalysed by ZrSiO2 under microwave influence (18). (Scheme 3) Spirosynthesized precursors by the previously reported methods namely 6-methyl-4-phenyl-2-oxo/ thioxo-1, 2, 3,4-tetrahydropyrimidine-5-carbohydrazide(15),5-(5-amino-1,3,4-oxadiazol-2-yl)-6-methyl-4-phe-ny 3,4dihydropyrimidin-2(1H)-one/thione (16) and 5-substituted-3-[{5-(6-methyl-2-oxo/ thioxo-4-phenyl-1,2,3,4-tetrahydropyrimidin-5-yl)-1,3,4-oxadiazol-2-yl}imino]-1,3dihydro2H-indol-2-one (17). Author also explored the advantages of this method i.e. operational simplicity, expeditious workup, appreciable product yield, reusable and recyclable catalyst. Author also screened the synthesized derivative for their antimicrobial activities such as anti- tuberculosis activity. They found that most of the scaffold shows potent anti-tubercular activity.

Parthasarathy et.al.[68] reported microwave assisted zinc triflate catalysed synthesis spirooxindole[pyrano-bis-2H-l-benzo- pyrans] (22) by tandem double condensation between isatin (20) and 4-hydroxycoumarin (21) under microwave irradiation (220 W) in DMSO solvent for 30 minute at 100^0C results 86-95% yield.(Scheme 4).

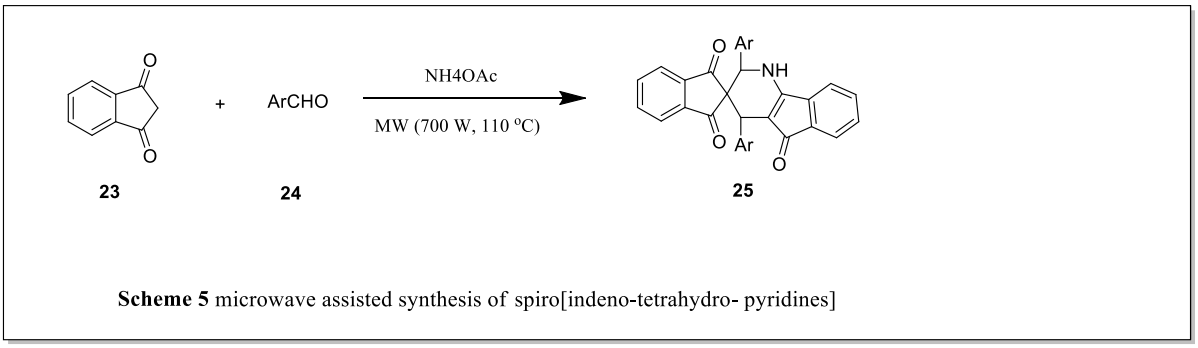


Scheme3 Microwave Assisted Efficient Synthesis of spiro-[indole-thiazolidines].

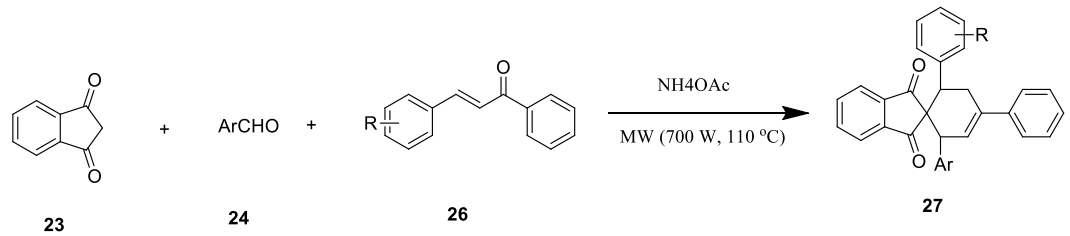


Scheme 4 microwave assisted zinc triflate catalysed synthesis spirooxindole[pyrano-bis-2H-l-benzo- pyrans]

Bhuyan et al[69] reported spiro[pyridines/piperidines] synthesis on irradiation with microwave yields 76-85% spiro[indeno-tetrahydro- pyridines] (25,27) when 1,3-indanedione (23), substituted benzaldehyde (24) and ammonium acetate in closed vessel is reacted in the microwave reactor about (700W) under 14 bar pressure at 110^0C for 7 min (Scheme 5). By using Chalcone (26) instead of benzaldehyde get differently substituted product. (Scheme 6).

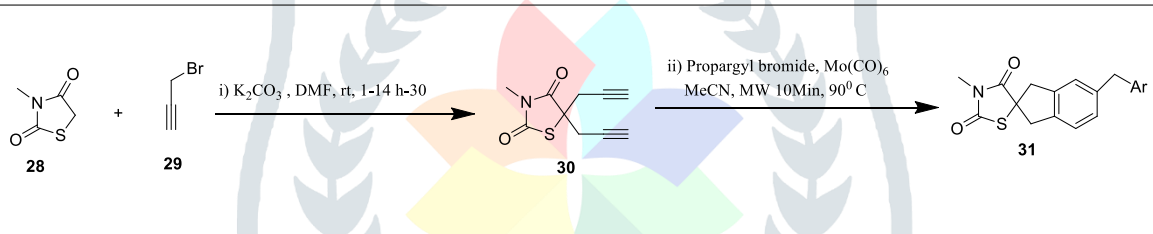


Scheme 5 microwave assisted synthesis of spiro[indeno-tetrahydro- pyridines]



Scheme 6 microwave assisted synthesis of substituted spiro[indeno-tetrahydro- pyridines] by using Chalcone

S. Kotha and colleagues[70] reported a novel synthetic methods for spirothiazoli-dinediones using [2 + 2+ 2] cyclotrimerization, followed by functionalization with DA chemistry and click reaction. (Scheme 7). In this method the Spirothiazolidinedione is produced from the starting material i.e. precursor thiazolidinedione which is synthesized form N-methylthiazolidine-2,4-dione (28) and propargyl bromide (29) in DMF in the presence of K_2CO_3 to obtain dipropargylated intermediate thiazolidinedione (30) in 85% yield. The final product i.e. Spirothiazolidiones (31) was further produced by cyclotrimerization when dyne (30) and propargyl bromide (29) reacted in presence of acetonitrile and catalyst Mo $(CO)_6$ at 90^0C by Microwave irradiation. Authors also investigated anticancer activity.



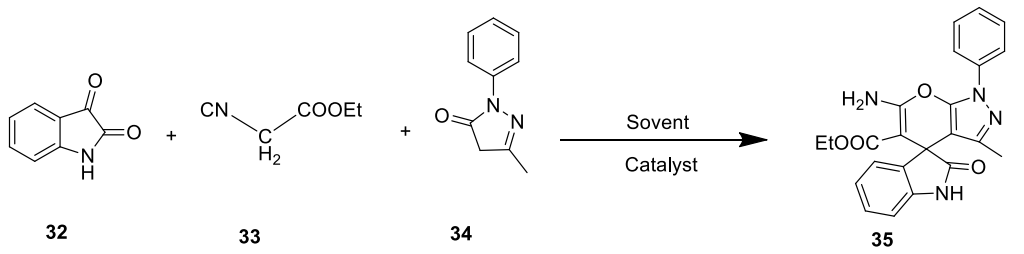
Sheme 7 Microwave Assisted Synthesis of Spirothiazolidiones

2) Ultrasound Promoted Green Synthesis :

Literature survey reveals that wide verities Spiro compounds was synthesized by ultrasound promoted synthesis which follows some principle of green synthesis.

Anshu Dandia and co-authors[71] reported ultrasound promoted cerium ammonium nitrate catalysed sustainable synthesis of spiro[indoline3,4–pyrano[2,3-c]pyrazole] derivatives. Further synthesized derivative were screened for antioxidant activities. Free radical scavenging effect on diphenylpicryl hydrazine (DPPH•), 2, 2-azino-bis-(3-ethyl-benzthiazoline-6-sulphonic acid) (ABTS•) and nitric oxide (NO) radicals.

spiro[indoline3,4 -pyrano[2,3- c]pyrazole] derivative (35) was prepared by reacting Isatin (32), malanonitrile (33) and 3-methyl-1-phenyl-2-pyrazolin-5-one (34) by using different reaction conditions.(Scheme 8). Variety of solvents were tested and proven that water is the better solvent of choice both in terms of time and yield of the spiro[indoline3,4 -pyrano[2,3-c] pyrazole] derivatives.

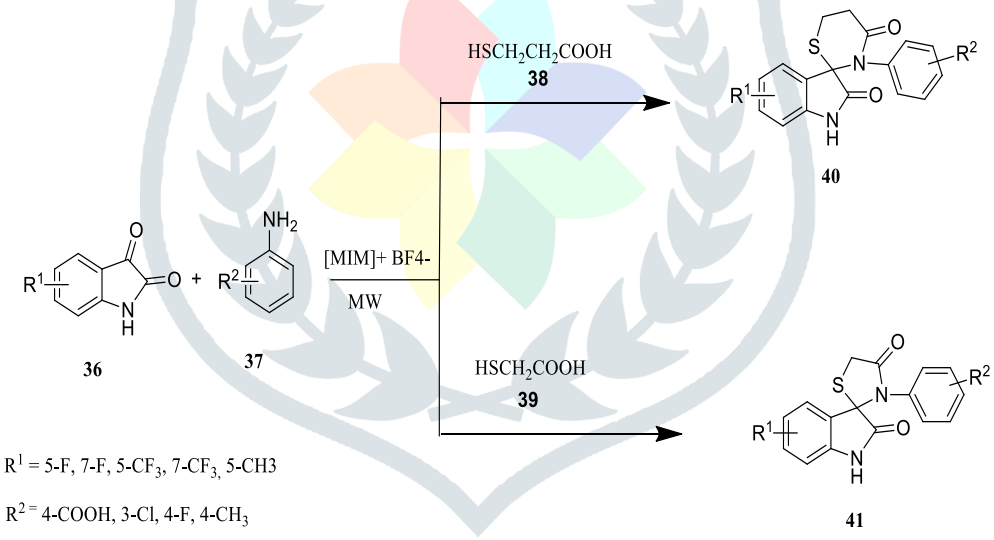


32 33 34 35

Sheme 8 Utrasound promoted green synthesis of spiro[indoline3,4-pyrano[2,3-c]pyrazole] derivatives

3) Ionic Liquid Assisted Synthesis:

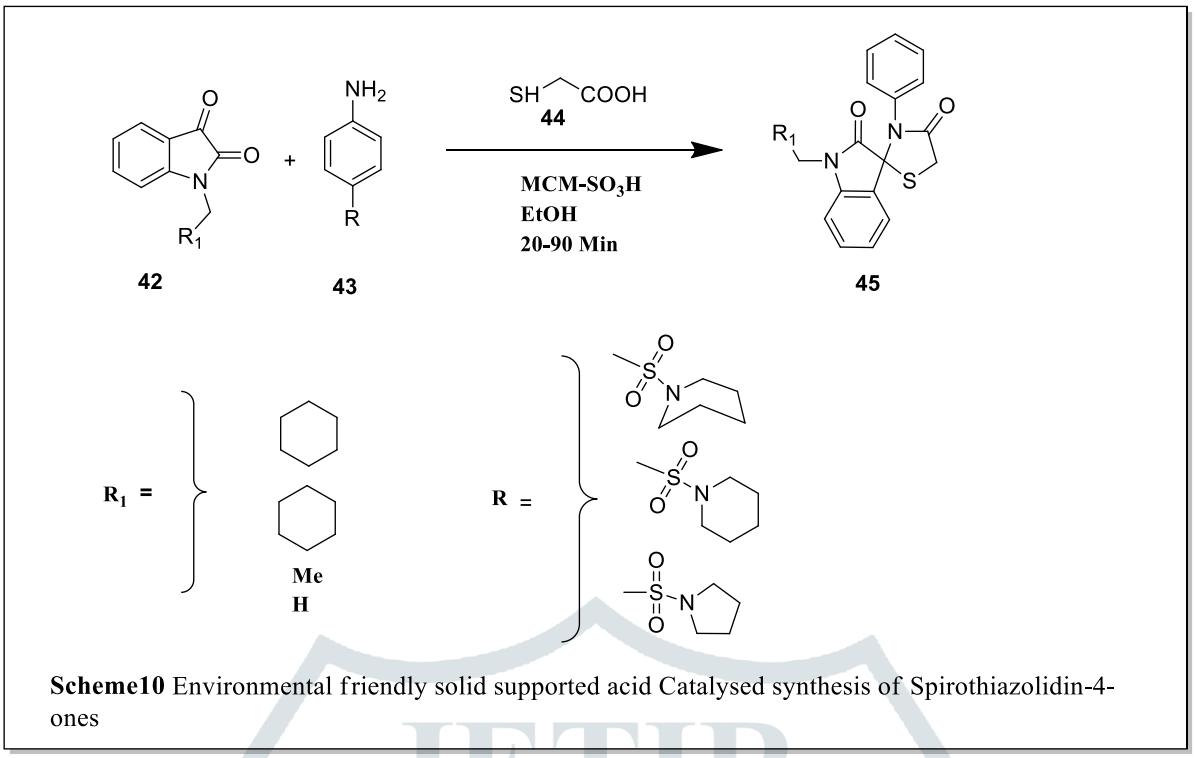
Ionic liquid has tremendous importance and interest of many researchers due to eco-friendly favourable characteristics insignificant vapour pressure, high thermal stability and reusability.[72-75] Arya et al.[66] also reported the microwave assisted synthesis of fluorinated spiro indole (40), (41) by cylocondensation. By reaction of different isatin (36) with heterocyclic amines (37) using thioacids (38), (39) and 1-methylimidazolium tetrafluoroborate ([MIM]+ BF4-) on microwave irradiation about 2-4 minutes gives 90-97% yield of respected fluorinated Spiro compound. (Scheme 9).



Scheme 9 Ionic Liquid Assisted Synthesis Spiroindole

4) Solid Supported Acid Catalysed Synthesis :

E.M. Hussein and Co-workers[76] reported environmental friendly solid supported acid Catalysed synthesis of Spirothiazolidin-4-ones (45) by using sulfonated mesoporous silica (MCM- SO_3H) heterogeneous and reusable catalyst. One pot synthesis of scaffold is done by avoiding the use of harmful solvent which results an optimal yield. Spirothiazolidin-4-one is synthesized by reaction of 1,3-dione derivative (42) with aromatic amines (43) results respected imine derivative followed by a reaction with thioglycolic acid (44) finally yield Spirothiazolidin-4-ones(45).(Scheme 10). This approach is fully green approach which facilitates environment friendly, quick reaction time, high yield, ease of workup and catalyst reusability.

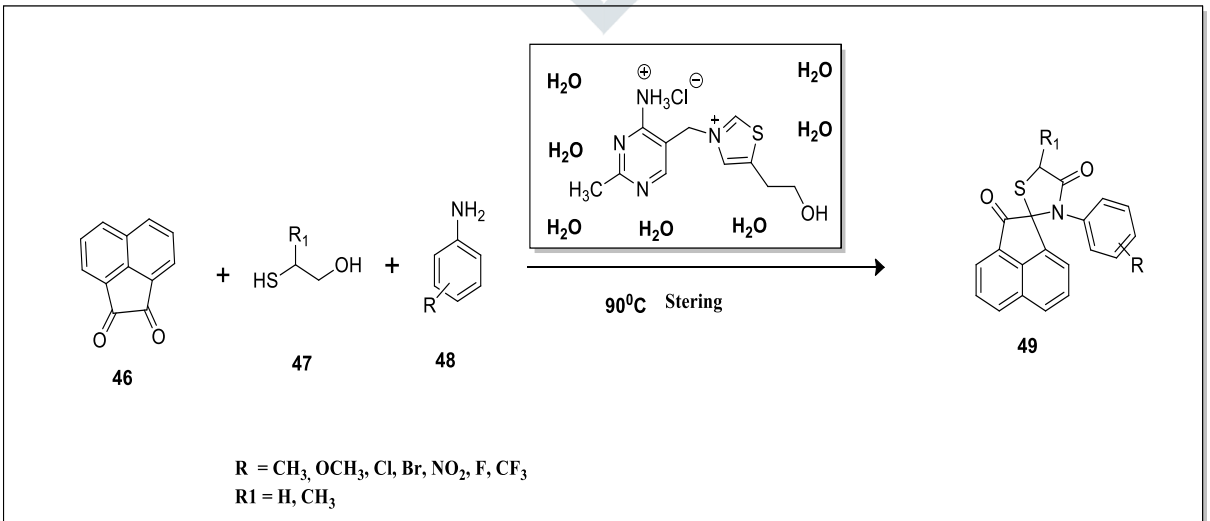


Scheme10 Environmental friendly solid supported acid Catalysed synthesis of Spirothiazolidin-4-ones

5) On water synthesis:

Survey of literature reveals that water is suitable solvent for the green synthesis due to their many versatile characteristics such as water acts as universal solvent due to their solvation capability and temperature range, inexpensive, easily availability, no harmful effect, easy isolation and purification of synthesized compounds i.e. filtration, extraction etc. due to these characteristic water plays an excellent role in the green synthesis of spirocompounds in fact one can call water is potent and excellent solvent for green synthesis.[77-81]

R. Sing and Co-authors[82] reported one pot multicomponent environment friendly water facilitated and thiamine hydrochloride promoted efficient synthesis of spiro[acenaphthylene-1,2'[1,3]-thiazolidine]-2,4′(1H)-diones. Spiro[acenaphthylene-1,2'[1,3]-thiazolidine]-2,4′ (1H)-diones(49) was synthesized by water facilitated and thiamine hydrochloride promoted multicomponent reaction between acenaphthylene-1,2-dione(46), α-mercaptocarboxylic acid(47) and substituted aniline(48) at 80^0C upon condensation and cyclization results the respected product with green approach.(Scheme 11).

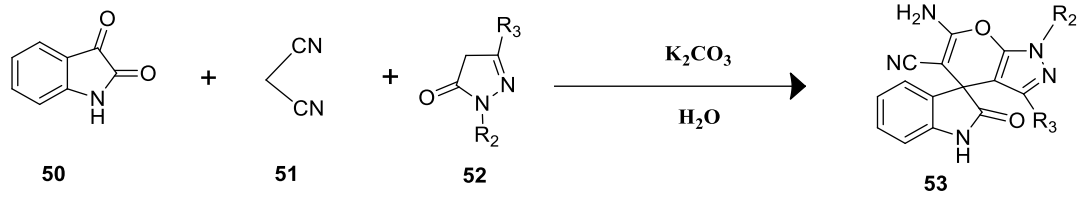


Scheme 11one pot multicomponent environment friendly water facilitated and thiamine hydrochloride promoted efficient synthesis of spiro[acenaphthylene-1,2'[1,3]-thiazolidine]-2,4-(1H)-diones.

Ying Liu and Colleague[83] reported way to green and efficient synthesis spiro[indoline-3,4'(1 H')-pyrano[2,3-c]pyrazol]-2-one derivatives. Highly efficient method of synthesis of spiropyranopyrazole using water as a green solvent is introduced. In this method spiro[indoline-3,4'(1 H')- pyrano[2,3-c]pyrazol]-2-one (53a) derivatives was produced by the Knoevenagel condensation and Michael addition reaction . Starting material i.e. isatin (50a), malononitrile (51) and 1-phenyl-3- methyl-5-pyrazolone (52a) undergoes Knoevenagel condensation and Michael addition reaction in presence of water as a green solvent and various bases like K_2CO_3, $NaHCO_3$, $KF{\cdot}2H_2O$ which results a spiro[indoline-3,4'(1 H')- pyrano[2,3-c]pyrazol]-2-one derivatives with yield 79.5%, 75.8%, and 77.2% respectively. Time required for the completion of the reaction is also different i.e. 10, 75, 240 minutes respectively.(Scheme12).

Zhansheng Wang and Co-Authour[84] mentioned Green synthesis of novel spiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,3'(7'H)- dione, spiro[indeno[1,2-b]pyrazolo[4,3-e]pyridine-4,3'-indoline]-2',3-dione, and spiro[benzo[h]pyrazolo[3,4-b]quinoline-7,3'-indoline]-2',8(5H)-dione derivatives in aqueous medium. They observed the variation in the amount of produced compound in different conditions of using mixture of solvents in various proportions. spiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,3'(7'H)- dione is produced by reacting isatin (54), 3-amino-1-phenyl-1H-pyrazol-5(4H)-one (55) and 1,2-diphenylethan-1-one (56) in presence of water and small amount of acetic acid. By mixing two different solvent with varying the proportion and temperature gives variable yield of resulted product.(Scheme 13).

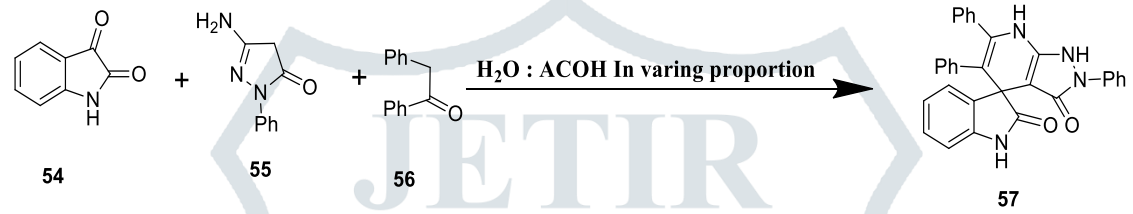
By altering the all three reactant and various solvent, time, temperature, solvent condition results the remaining two derivatives i.e. spiro[indeno[1,2-b]pyrazolo[4,3-e]pyridine-4,3'-indoline]-2',3-dione, and spiro[benzo[h]pyrazolo[3,4-b]quinoline-7,3'-indoline]-2',8(5H)-dione derivatives. (Scheme14, 15, 16)



50 51 52 53

53a-53d R2 = Ph, 53e-53l R2 = H
53a-53h R3 = CH3, 53i-4l R3 = Ph

Scheme 12 Efficient synthesis spiro[indoline-3,4'(1 H')- pyrano[2,3-c]pyrazol]-2-one derivatives



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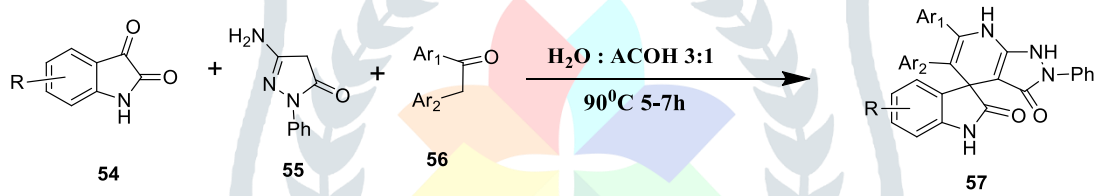
Scheme 13 Efficient synthesis spiro[indeno[1,2-b]pyrazolo[4,4,3-e]pyridine-4,3'-indoline]-2',3-dione,



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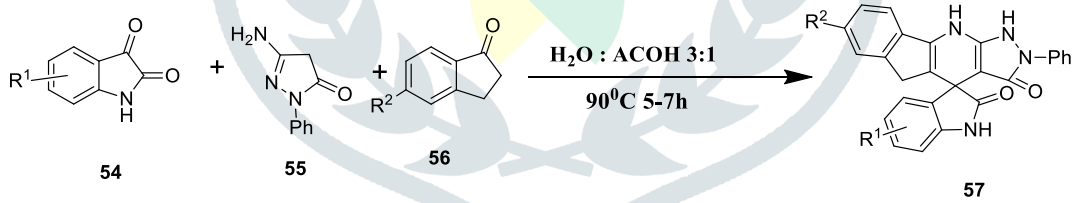
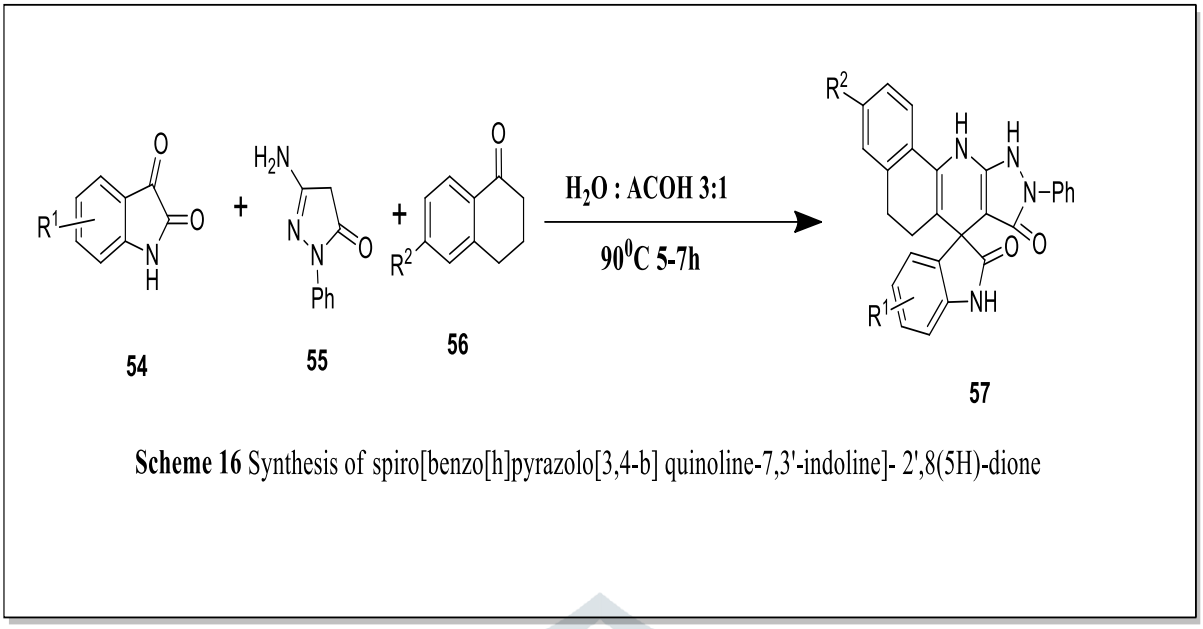
Scheme 14 Synthesis of spiro[indoline-3,4'-pyrazolo[3,4-b]pyridine]-2,3' (7'H)-dione



54 55 56 57

Scheme 15 Synthesis of spiro[indeno[1,2-b]pyrazolo[4,3-e]pyridine-4,3'-indoline]-2',3-dione



Scheme 16 Synthesis of spiro[benzo[h]pyrazolo[3,4-b] quinoline-7,3'-indoline]- 2',8(5H)-dione

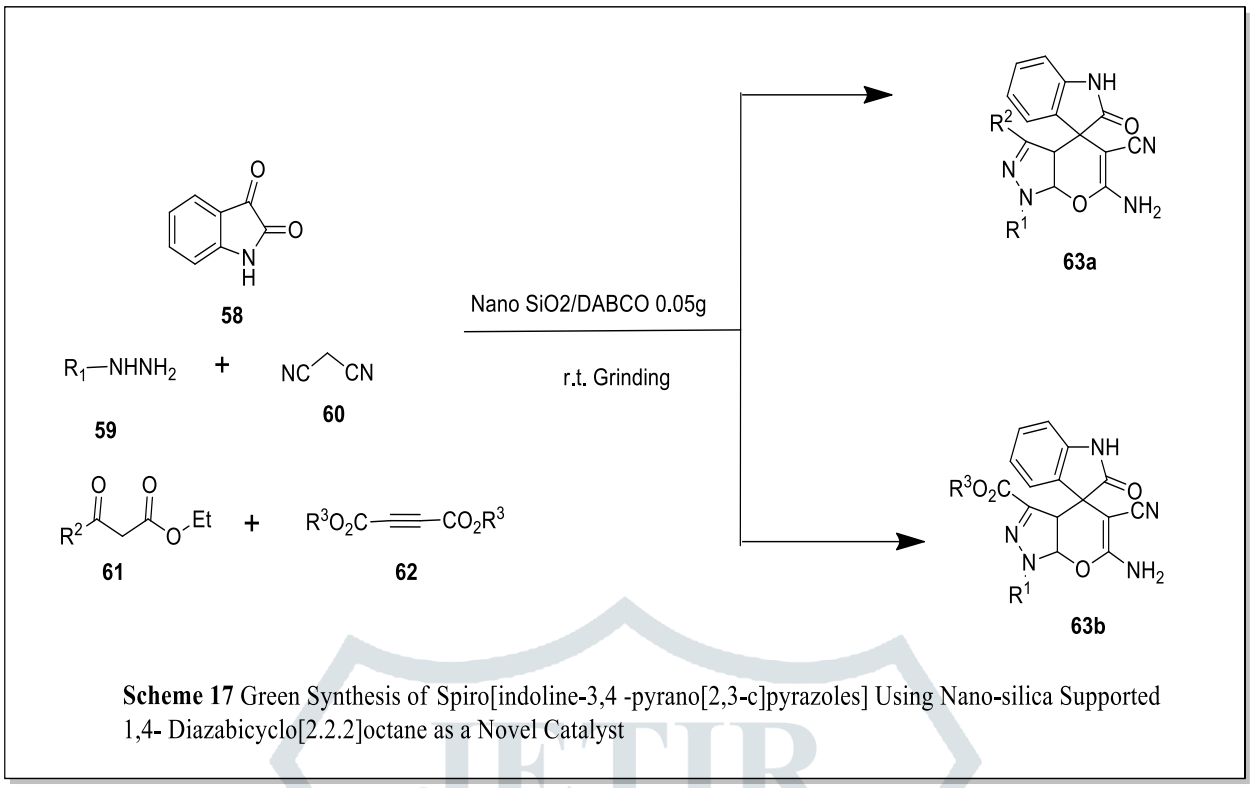
6) Nano catalyst Assisted Synthesis:

Now a days Nano science got tremendous importance due to the particle size i.e. nano size which increases researchers interest in the synthesis of nano catalyst, nano composites. Due to this fact every branch of science is doing research in the nanofield. In resent mostly green synthesis is done by using nano catalyst assisted synthesis of the various biologically active spirheterocyclic compouds.

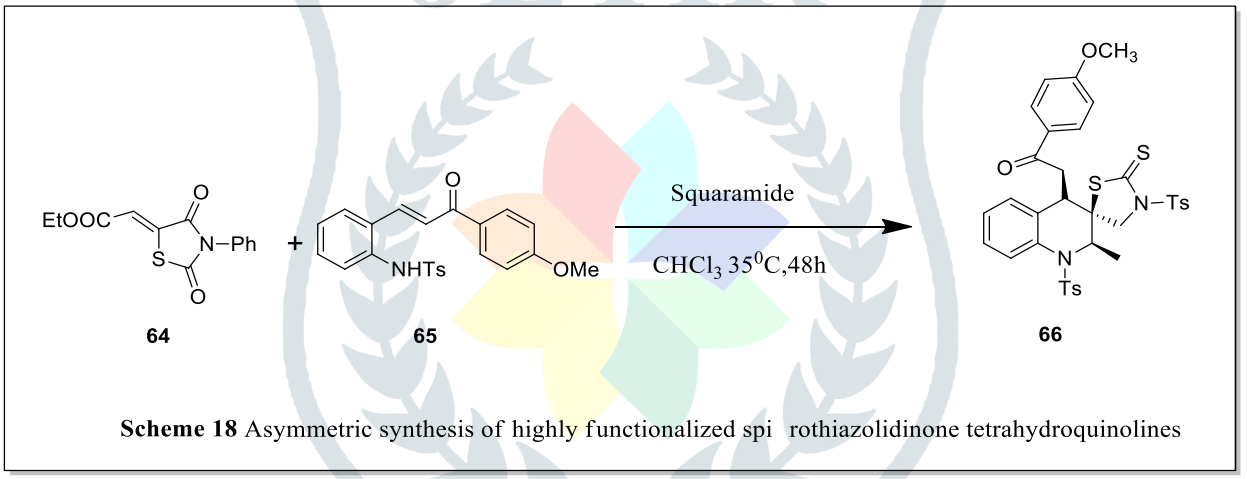
Naeimeh Salehi and Co-worker [85] reported Green Synthesis of Spiro[indoline-3,4 -pyrano[2,3-c]pyrazoles] Using Nano-silica Supported 1,4- Diazabicyclo[2.2.2]octane as a Novel Catalyst. Synthesis of Spiro[indoline-3,4 -pyrano[2,3-c]pyrazoles] was done by grinding mixture of β-ketoester or dialkyl acetylenedicarboxylate (1 mmol) and hydrazine hydrate 50-60% (0.1 ml) with mortar and pestle at room temperature for 1 minute. Then, the aldehyde or isatin (1 mmol), malononitrile (1 mmol) and nano-SiO2/ DABCO (0.05 g) were added to the reaction mixture and it was ground continuously at room temperature for the time. After completion of reaction the product is poured into cold water.(Scheme17).

7) Asymmetric synthesis:

D.M. Du et al.[86] reported a bifunctional squaramide catalysed asymmetric cascade aza-Michael/ Michael addition for the synthesis of chiral spirothiazolidinone tetrahydroquinolines (66) with three chiral centers. To produce spirothiazolidinone tetrahydroquinolines (66) various functionalized rhodanine derivatives (64) and 2-tosylaminochalcone (65) with squaramide catalyst were reacted in chloroform solvent and stirred at 35^{0}C for 18 h yield final assymetric compound with high disteroselectivity and enantioselectivity. (Scheme18)



Scheme 17 Green Synthesis of Spiro[indoline-3,4 -pyrano[2,3-c]pyrazoles] Using Nano-silica Supported 1,4- Diazabicyclo[2.2.2]octane as a Novel Catalyst



Scheme 18 Asymmetric synthesis of highly functionalized spi rothiazolidinone tetrahydroquinolines

Conclusion: The current review briefly focus on the different methodologies and techniques used for the environment friendly green synthesis of spiroheterocyclic compounds. This review also aims to focus the current synthetic aspects of green chemistry as well as the research underwent in the field of green synthesis of spiroheterocyclic compounds having biological and pharmaceutical importance. This review will helps to develop new synthetic methodologies and it acts as a road map for the researchers in this area. This review also helpful for the synthesis of various biologically active and pharmaceutically potent scaffold Spiro heterocyclic. Compounds.

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