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Research Article

Studies on Mechanism of Formation and Medicinal applications of structurally diverse Indole and Oxindole derivatives

Noor ud Din Zargar*, Khaliq uz Zaman Khan

Department of Chemistry University of Kashmir Srinagar (190006) J&K India

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✉: N. Zargar
nded.1092@rediffmail.com

ABSTRACT

The field of heterocyclic chemistry is vast and has played a significant role in synthetic organic chemistry. Heterocyclic compounds and methods for their synthesis form the bedrock of modern medicinal and pharmaceutical research. Indoles and Oxindoles are the most studied bicyclic nitrogen heterocycles. The selective acylation of indoles often requires sensitive and reactive acyl chloride derivatives. A chemo selective *N*-acylation of indoles**1** using thioesters **2** as a stable acyl source has been reported. Interaction of 1-acylindoles **10** with acetyl chloride in the presence of $AlCl_3$ yields the corresponding 1- acyl-3-acetylindoles **11** which upon hydrolysis affords 3-acetylindole**12.**Addition of (1*H*indol- 3-yl) magnesium iodide (**16**) to 2-(benzyloxy) acetyl chloride **17** in diethyl ether forms 3-benzyloxyacetylindole **18**. Acylation of Oxindole **20** with chloroacetyl chloride affords 5-chloromethyl ketone derivatives**31**whichwhen treated with thioureas and thioamides leads to the formation of 5-thiazole oxindoles**32**.This article focuses on various synthetic methods and suggested mechanism of different indole and oxindole derivatives. Apart from this, applications of medicinal importance of these heteroatom compounds have also been discussed.

Keywords: Acylation, Indole, Oxindole, Heterocycles, Synthesis, Mechanism

1. Introduction

Heterocyclic compounds are found in an enormous number of natural products possessing a wide range of physical, chemical, and biological properties. Indole and its derivatives are

found in an expansive number of bioactive natural products and molecules of pharmaceutical interest [1-6], coupled with the distinct nucleophilic chemistry revolving around the aromatic benzo-fused pyrrole system.3-acetylindole derivatives have attracted researchers due to their significant practical value and a spectrum of biological activities. 4- (1*H*-indol-3-yl)-2-hydroxy-4-oxobut-2-enoic acid has been found useful as an anti-HIV agent and other derivatives of 3-acetylindoles are used in the treatment of gastrointestinal and cardiovascular disorders. Chemoselective N- or C-functionalization of indoles is a challenging task for researchers[7,8]. Acylation of indoles frequently takes place at the C3position because of the relatively strong electron cloud density-acylated indoles are a widespread motif in a variety of pharmaceuticals and natural products [9-11].Screened N -acylation of indoles is very important but this process requires unstable and reactive acyl chloride, which results in a poor functional group tolerance. Thus the synthesis of *N*-acyl indoles becomes much attractive by developing elegant and effective methods. [12-15]. A dehydrogenative approach for the synthesis of a series of compounds has been developed using indoles and alcohols as starting materials catalyzed by tetrapropylammonium perruthenate[16].Chemoselective N-acylation of indoleamides has been carried out using a catalytic amount of DBU [17]. Oxindole is the core structure in a variety of natural products and drugs. Oxindole derivatives [18] have demonstrated significant potential for use in a wide range of biological applications such as NMDA antagonists 19] and calcium channel blockers[20] as well as antiangiogenic,[21] anti-cancer,[22] and analgesic effects[23].

This work highlights a series of mechanisms suggested /proposed for structurally diverse indole and oxindole derivatives. Although the compounds are known, however, the mechanisms were not discussed or developed earlier as revealed by the exhaustive literature survey. Aside from this, a wide range of recent and advanced applications of medicinal

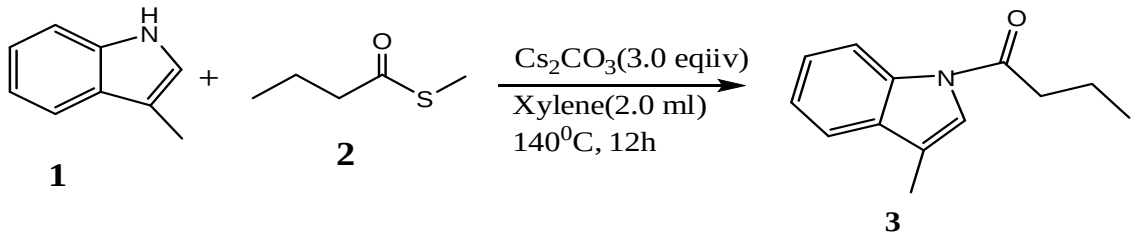
importance of various indole and oxindole derivatives have also been outlined in this manuscript.

2. Discussion

Indole and Oxindole mark central importance in the field of heterocyclic chemistry and medicinal chemistry with a vast number of derivatives widely distributed in nature. The ring system of indole is a well-designed feature in a variety of heterocyclic compounds. The broad spectrum of biological activities has been further facilitated by the synthetic versatility of Indole and Oxindole which allows the generation of a large number of structurally diverse derivatives.

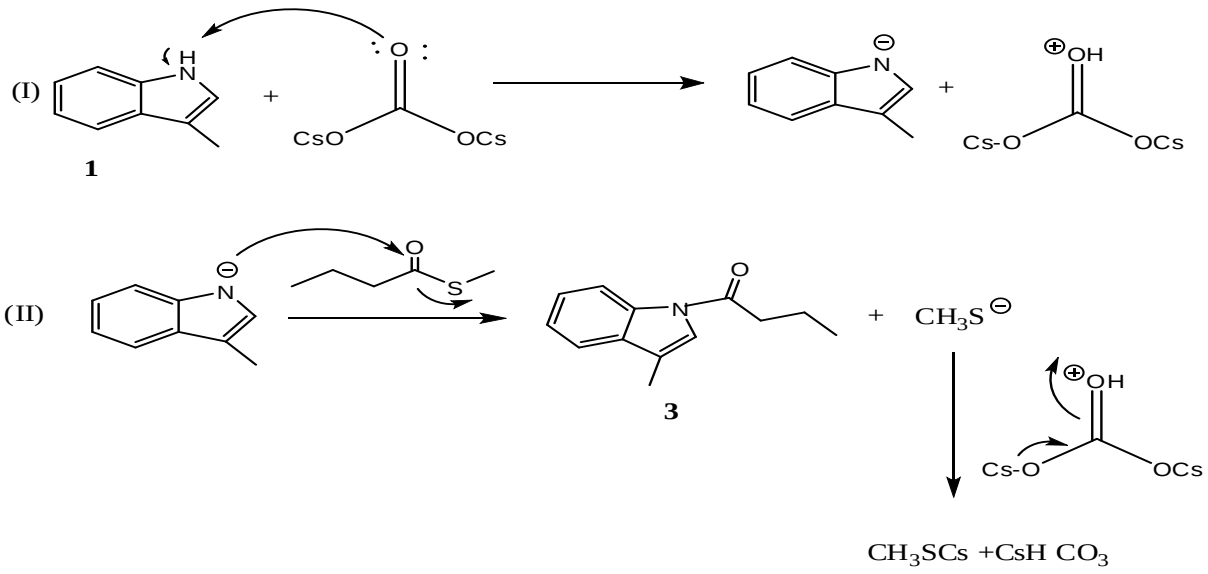
3-methyl-1H-indole **1** and *S*-methyl butanethioate **2** have been used as model substrates in various reactions. Different bases have been employed to improve the amide substitution but Cs_2CO_3 has been found the most suitable choice. NaO*t*-Bu can also be used in this reaction with excellent yields.

The reaction proceeded smoothly when carried out between 3-methyl-1*H*-indole **1** and *S*-methyl butanethioate **2**to afford 1-(3-methyl-1*H*-indol-1-yl)butan-1- one **3**in good yields.



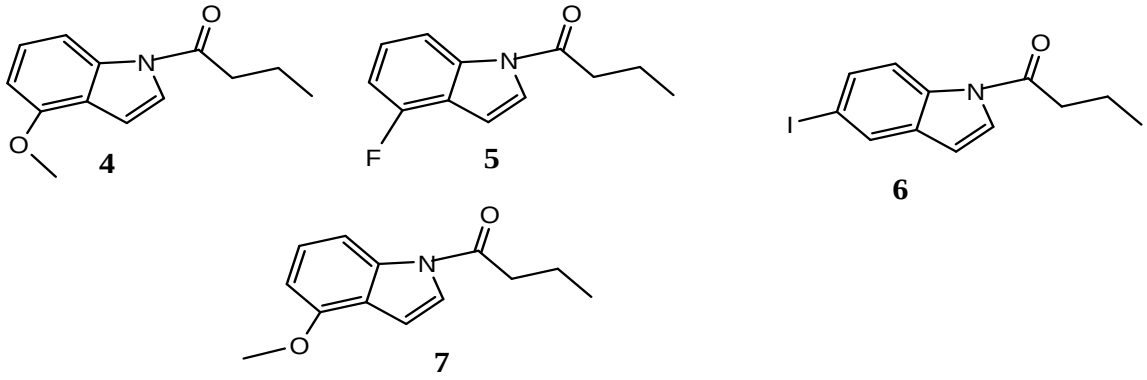
1 **2** **3**

Plausible mechanism proposed for the formation of**3** can be depicted as Scheme-1



Scheme-1. Synthesis of1-(3-methyl-1*H*-indol-1-yl) butan-1- one **3**

A series of products have been obtained by the variation of indoles and thio esters with moderate to excellent yields under different reaction conditions–Scheme-2

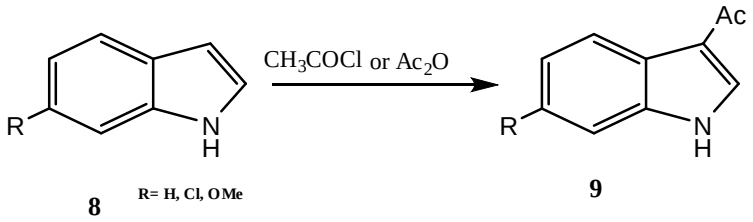


Scheme-2. Synthesis of substituted derivative (4-7)- of1-(3-methyl-1*H*-indol-1-yl)butan-1- one **3**

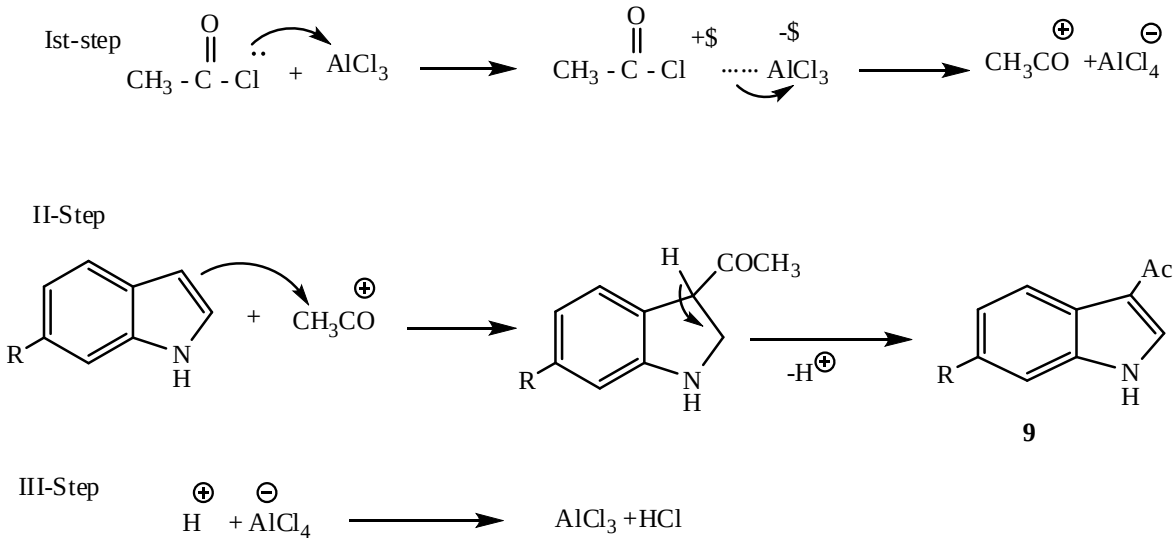
Mechanism of formation of the compounds**4-7** is analogous to that of compound**3**.

3. Friedel-Crafts Acetylation

3-Acetylindoles **9** have been synthesised by Friedel-Crafts acetylation of indoles **8** with acetyl chloride (AcCl) or acetic anhydride (Ac_2O) in the presence of a catalyst.

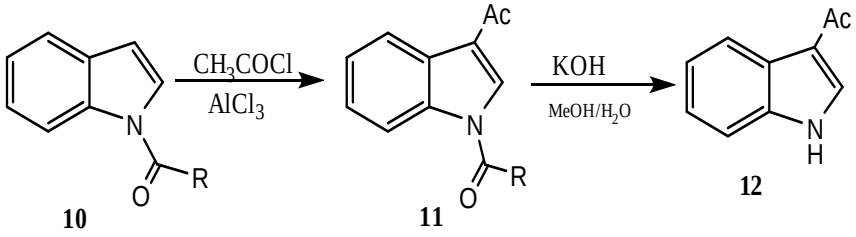


Mechanism developed for the formation of 3-acetyl indole **9** can be rationalised as shown in Scheme3

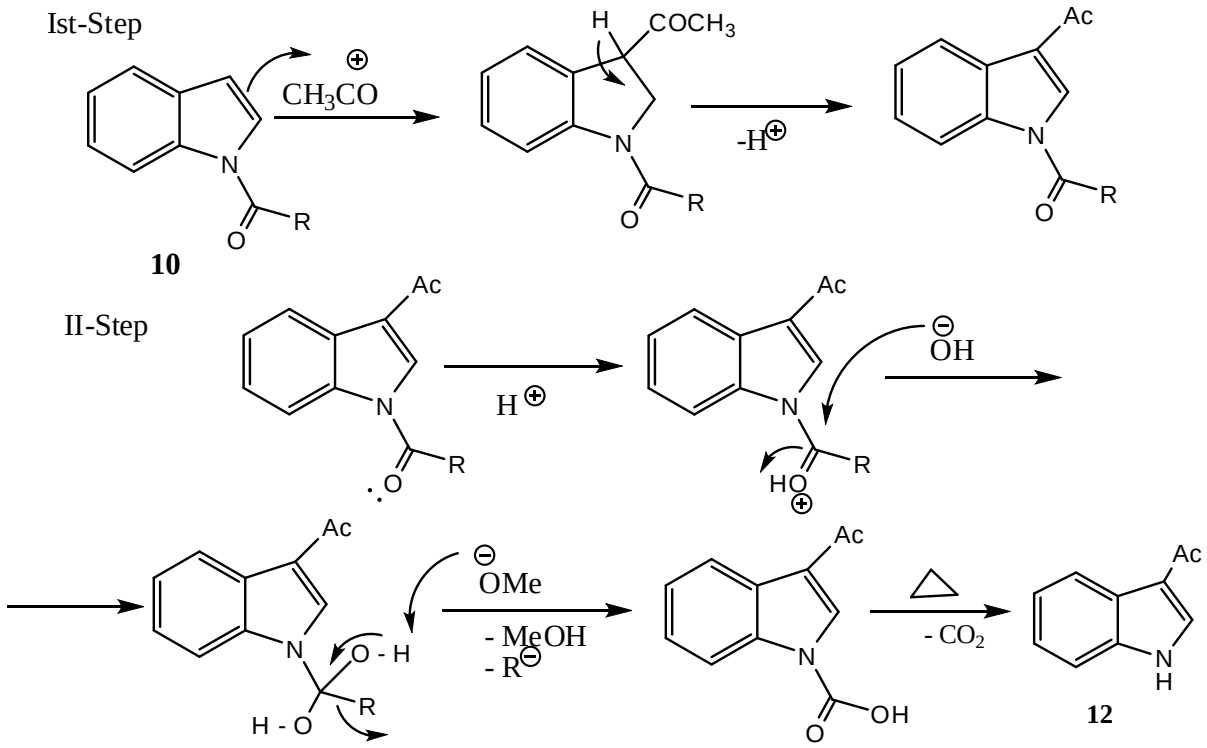


Scheme-3. Mechanism developed for the formation of 3-acetyl indole **9**

Interaction of 1-acylindoles **10** with acetyl chloride in the presence of $AlCl_3$ as catalyst resulted the corresponding 1- acyl-3-acetylindoles **11**inhighyields. Hydrolysis of **11**(R = Me) with KOH in aqueous MeOH produced 3-acetylindole **12**[24].

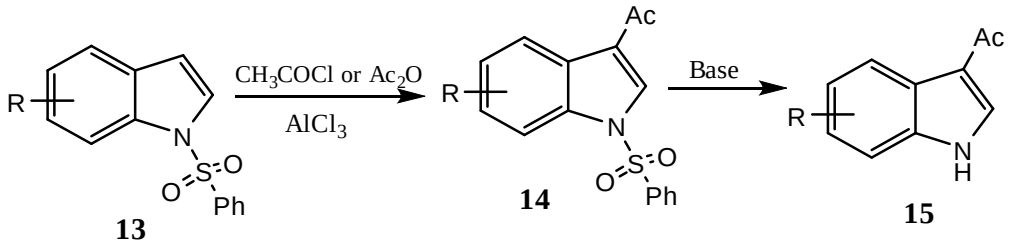


Probable mechanism proposed for the formation of **12** can be depicted as Scheme-4



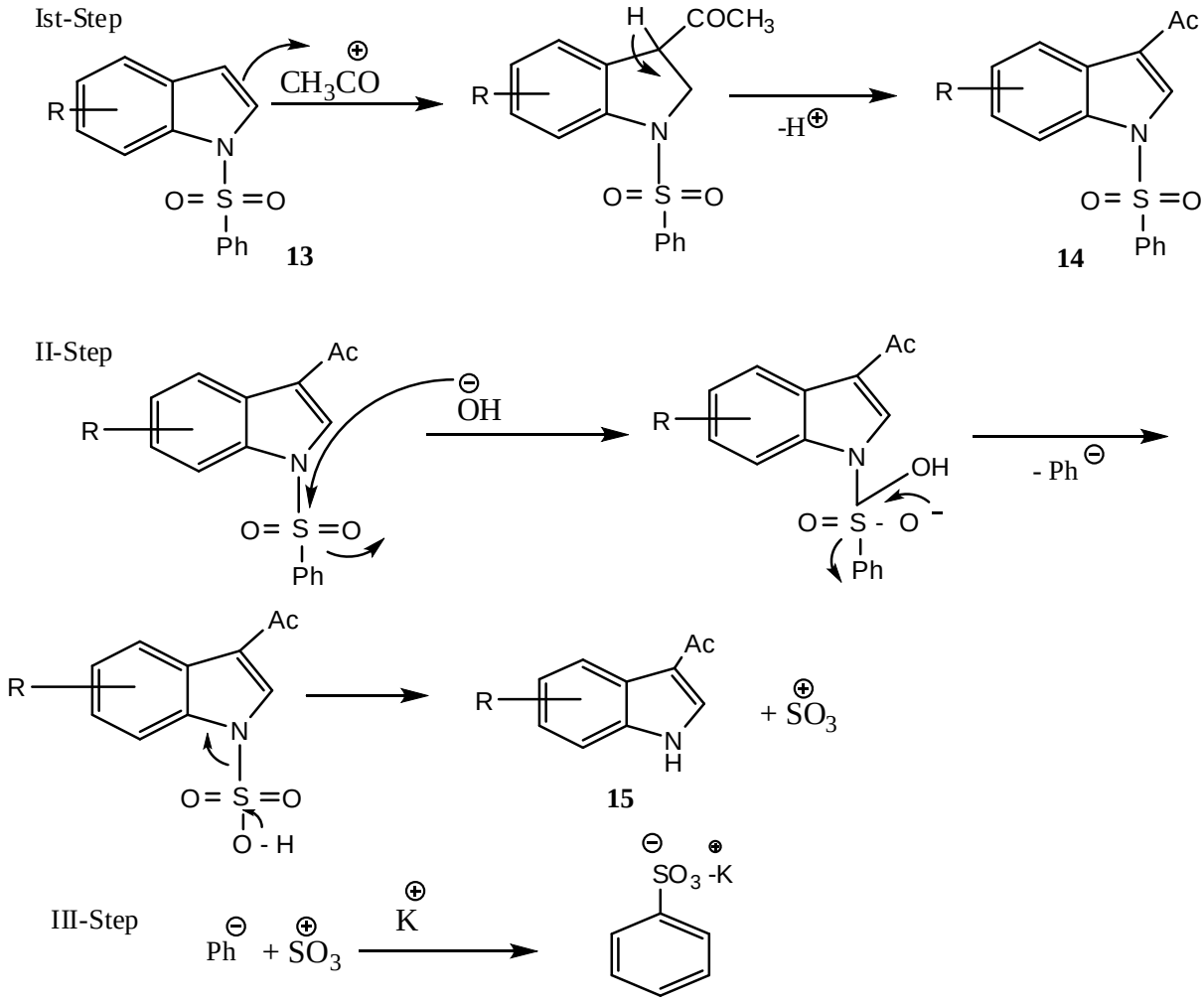
Scheme-4. Probable mechanism proposed for the formation of 3-Acetyl indole **12**

3-acyl-1-(phenylsulfonyl) indoles**14**have been synthesised by Friedel-Crafts acetylation of 1-(phenylsulfonyl) indoles**13** with acetic anhydride or acetyl chloride in the presence of aluminium chloride. Base hydrolysis of**14**resulted 3-acylindoles **15**in excellent yields [25].



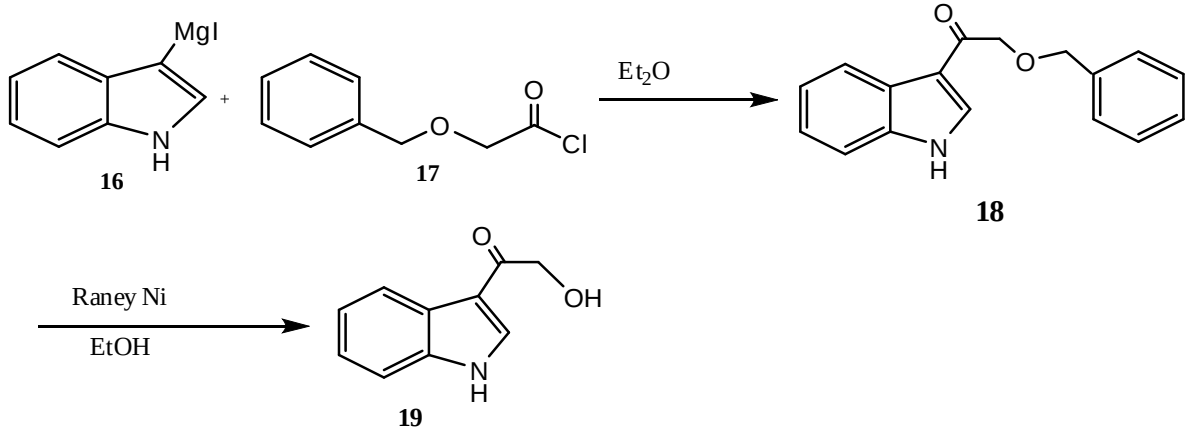
R = H,6-OMe, 5-OMe,5-F

Plausible mechanism developed for the formation of **15** can be discussed as –Scheme-5

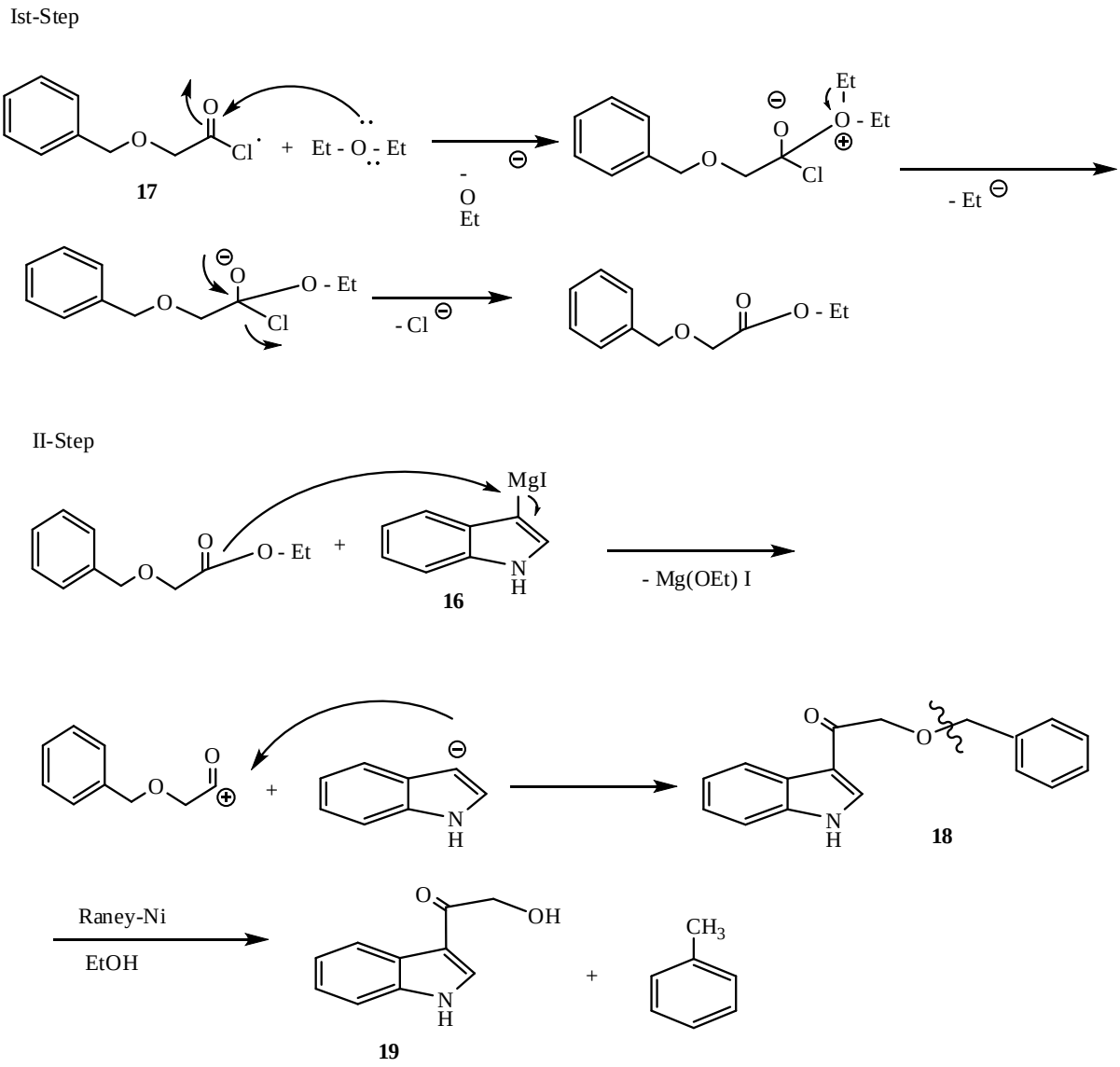


Scheme-5. Mechanism developed for the formation of 3-acylindoles **15**

Reaction of 2-(benzyloxy)acetyl chloride **17** with (1*H*indol- 3-yl)magnesium iodide **16** in diethyl ether afforded 3-benzyloxyacetylindole **18** which upon reduction with Raney Ni in absolute ethanol yielded 2-hydroxy-1-(1*H*indol- 3-yl)ethanone **19** [26].



Mechanism suggested for the formation of **19** can be explained as–Scheme-6

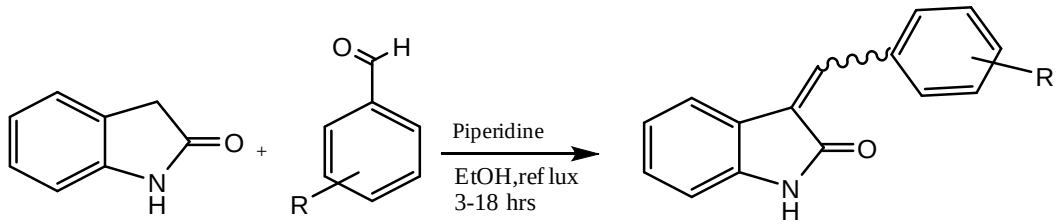


Scheme-6 .Suggested mechanism for the formation of 2-hydroxy-1-(1*H*indol- 3-yl) ethanone**19**

Oxindole is the key structure in a variety of natural products and pharmacologically active compounds. Its derivatives find a wide range of biological applications such as calcium channel blockers as well as anti-cancer, and analgesic effects .In oxindole, C-3 has two acidic hydrogen atoms which form the active sites for condensation reactions, Michael addition reactions, as well as reactions with alcohols, nitriles and other compounds.

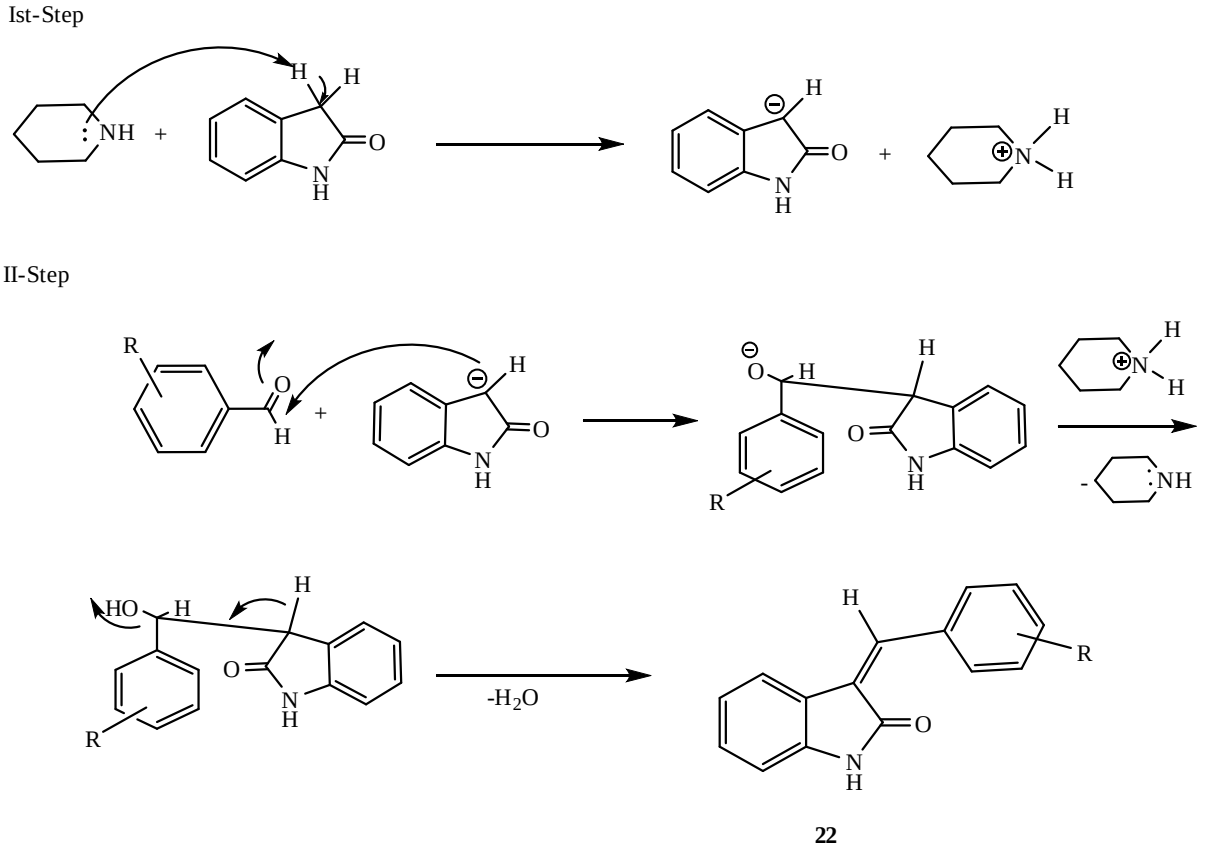
4. Condensation reactions

4.1. Knoevenagel condensations:-Condensation reactions of oxindole **20**and benzaldehyde derivatives **21**in the presence of piperidene as base to yield **22**have been reported and then re-examined under reflux conditions in EtOH in the presence and absence of piperidene.[27-32].



20 **21** **22**

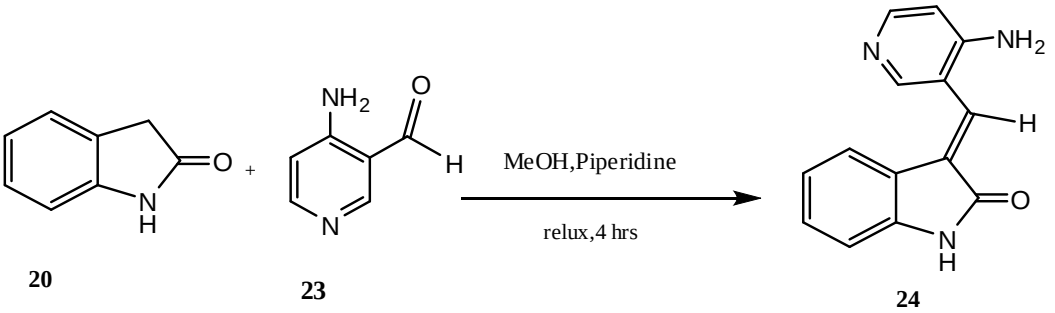
Plausible mechanism developed for the formation of **22** can be justified as-Scheme-7



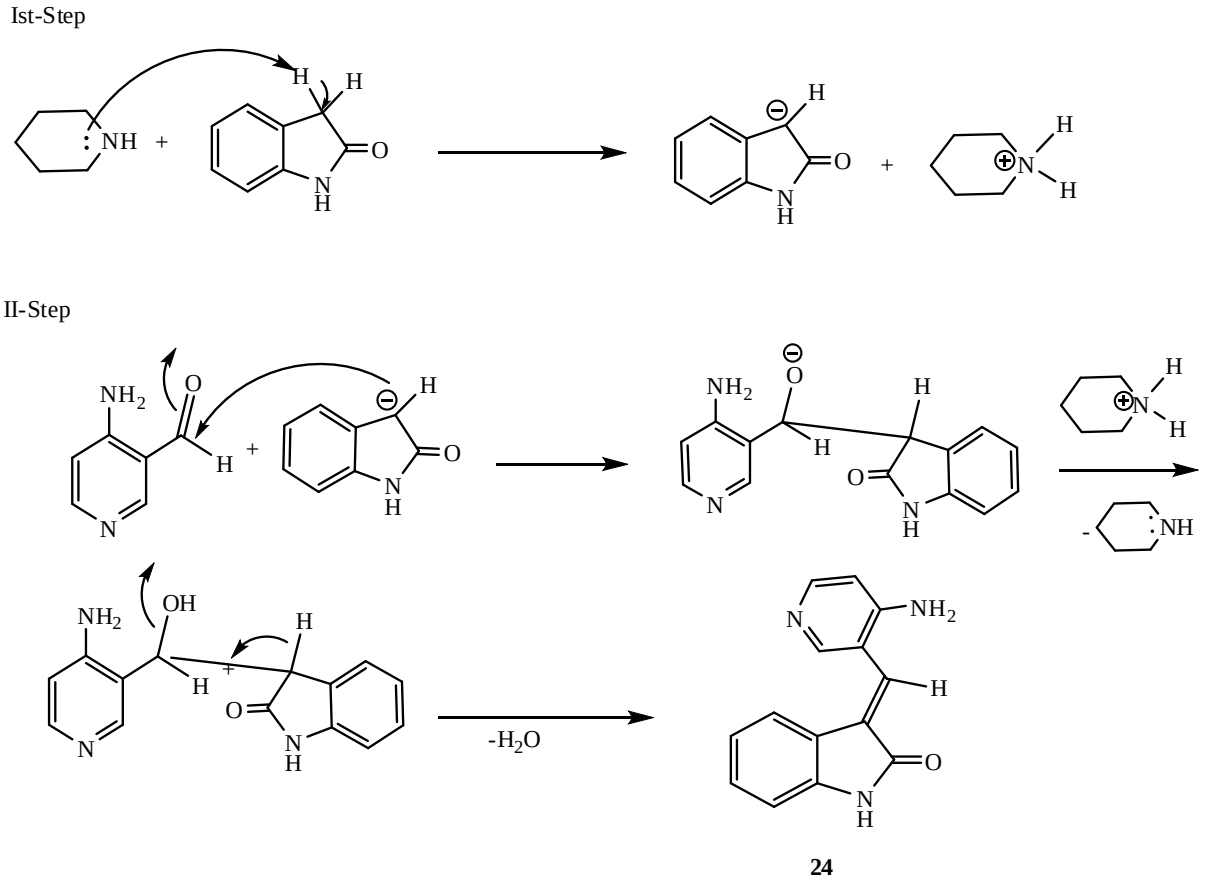
22

Scheme-7. Mechanism developed for the formation of **22**

When oxindole**20** is condensed with4-aminonicotinaldehyde **23**in methanol in presence of piperidine base, it affords **24** with anti-amnesic effects [33].

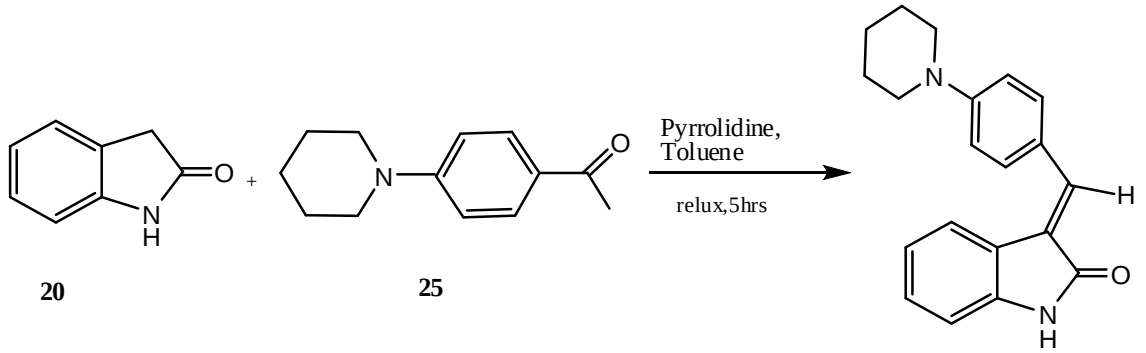


Mechanism suggested for the formation of **24** can be illustrated as –Scheme-8



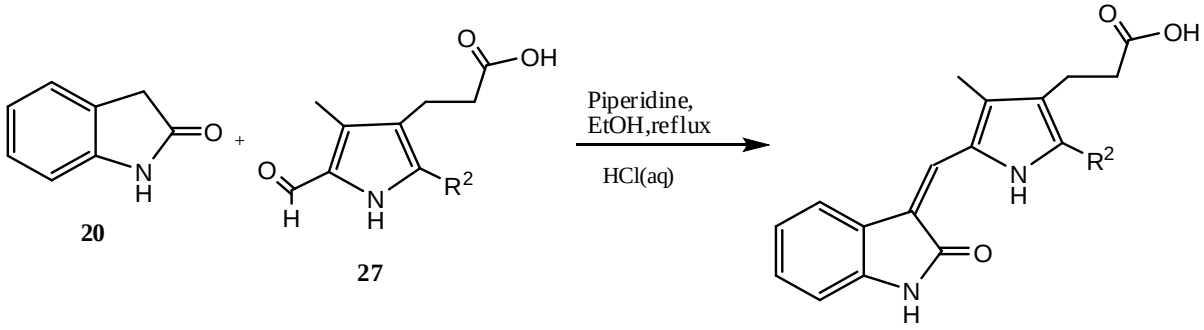
Scheme-8. Mechanism suggested for the formation of **24**

Refluxing oxindole(**20**) with 4-(piperidin-1-yl) phenyl acetone (25**)**in toluene in the presence of pyrrolidine resulted the desired (*E*)-3-[1-[4-(Piperidin-1-yl) phenyl] ethylidenyl]indolin- 2-one **26 [**34].



20 **25** **26**

A wide range of 3-substituted oxindoles **28**containing propionic acid functionality attached to the pyrrole ring at the C-3 position of the core have been synthesized by the reaction of oxindoles **20**with 4-carboxyethyl-3-methylpyrrol-2-carboxaldehyde derivatives **27.**



20 **27** **28**

R^1 = H,5-COOH,5-SO_2NH_2,6-OMe,6-Ph etc.
R^2 =H,Me

R^2 = H(4h)
R^2 = Me(overnight)

Mechanism suggested for the formation of compounds **26** and**28**is analogous to that of mechanism developed for the formation of compound **22** and **24.**

5. Reactions on the Aromatic Ring

5.1. Acylation of oxindole

Selective acylation of Oxindole has been achieved by exploiting different acyl chlorides and employing aluminium chloride as catalyst in DMF to yield **30**. Acylation of Oxindole**20** with

chloroacetyl chloride readily afforded the 5-chloromethyl ketone derivative**31**which when treated with thioureas and thioamides afforded functionalized 5-thiazole oxindoles**32**[35].

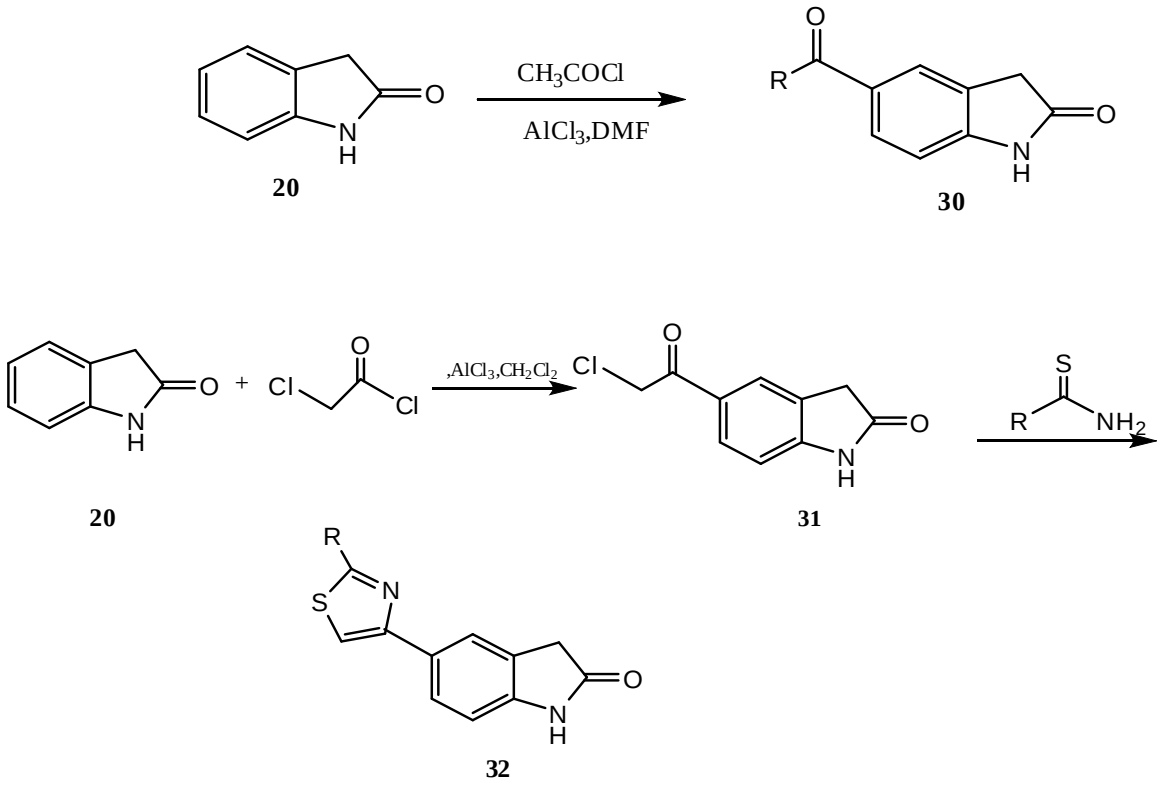
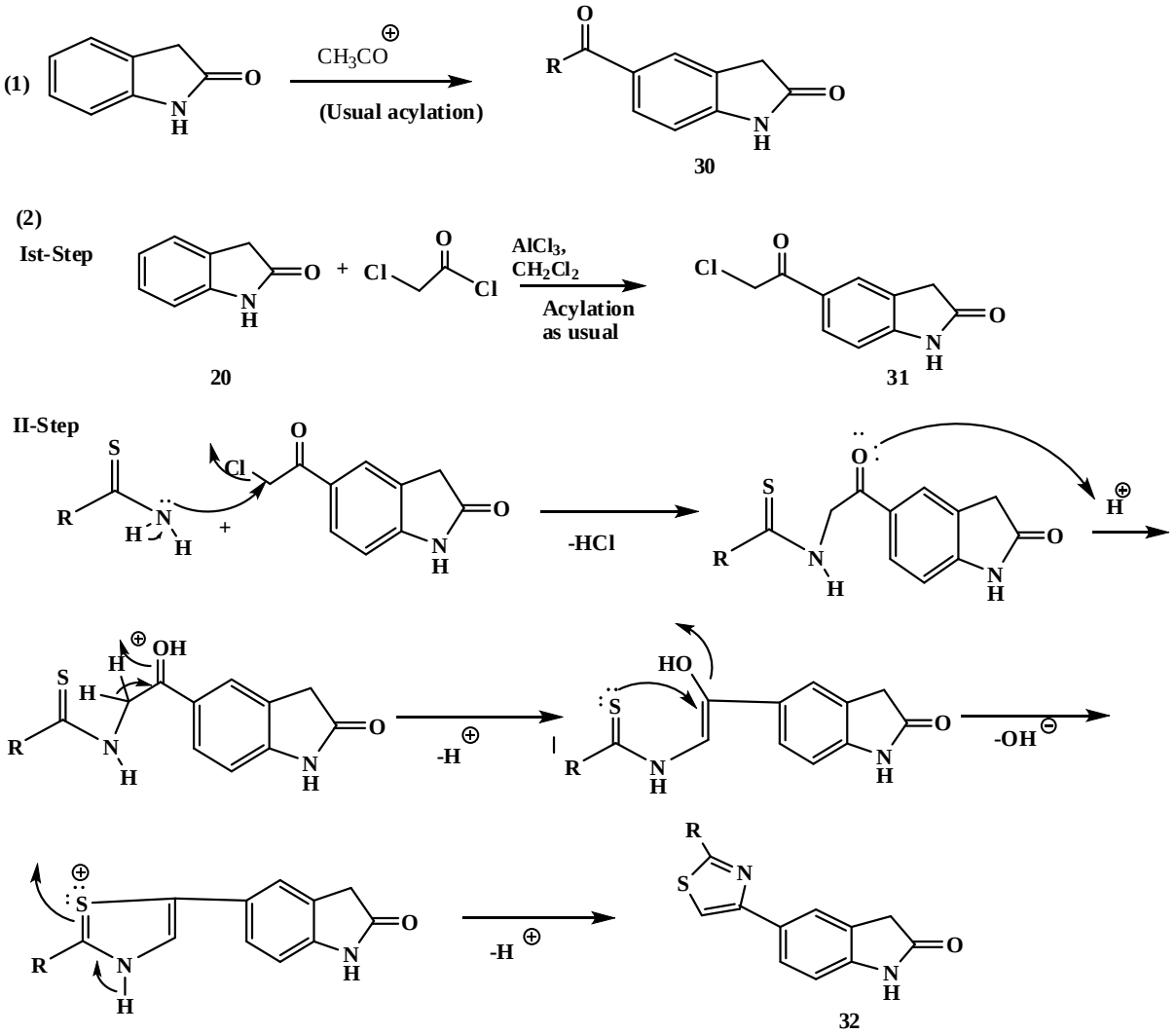


Fig. 1. Functionalized 5-thiazole oxindoles

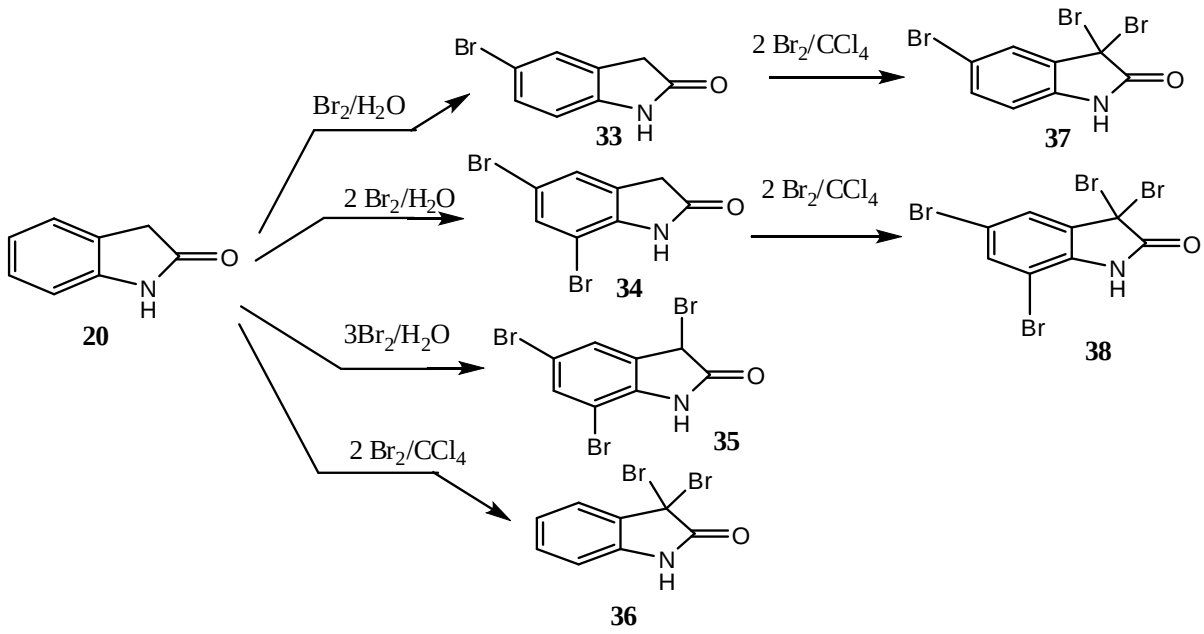
Plausible mechanism proposed for the formation of **32** can be discussed as- Scheme-9



Scheme-9-Proposed mechanism for the formation of compounds**30,31**and**32**

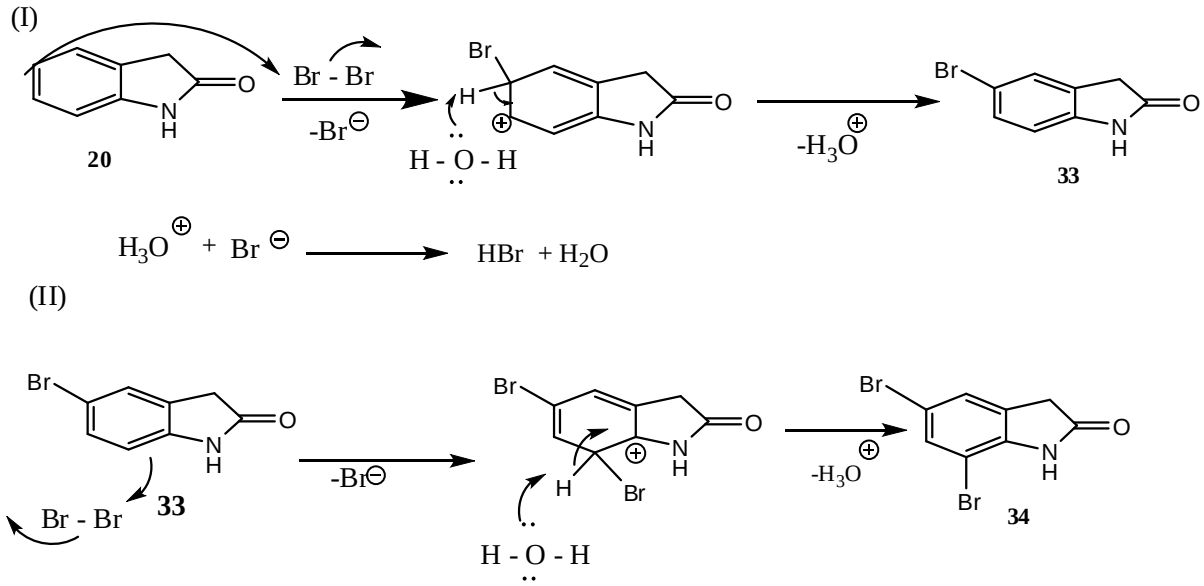
5.2. Bromination of oxindole

Bromination of oxindole **20**with bromine water in presence of one, two and three equivalents of bromine resulted 5-bromooxindole **33**, 5,7-dibromooxindole **34**and 3,5,7-tribromooxindole **35** respectively. However, addition of bromine in CCl_4 to oxindole **20**and its derivatives**33**and **34**yielded the corresponding 3,3-dibromooxindole derivatives **36**, **37**and **38**, respectively [36].Scheme-10

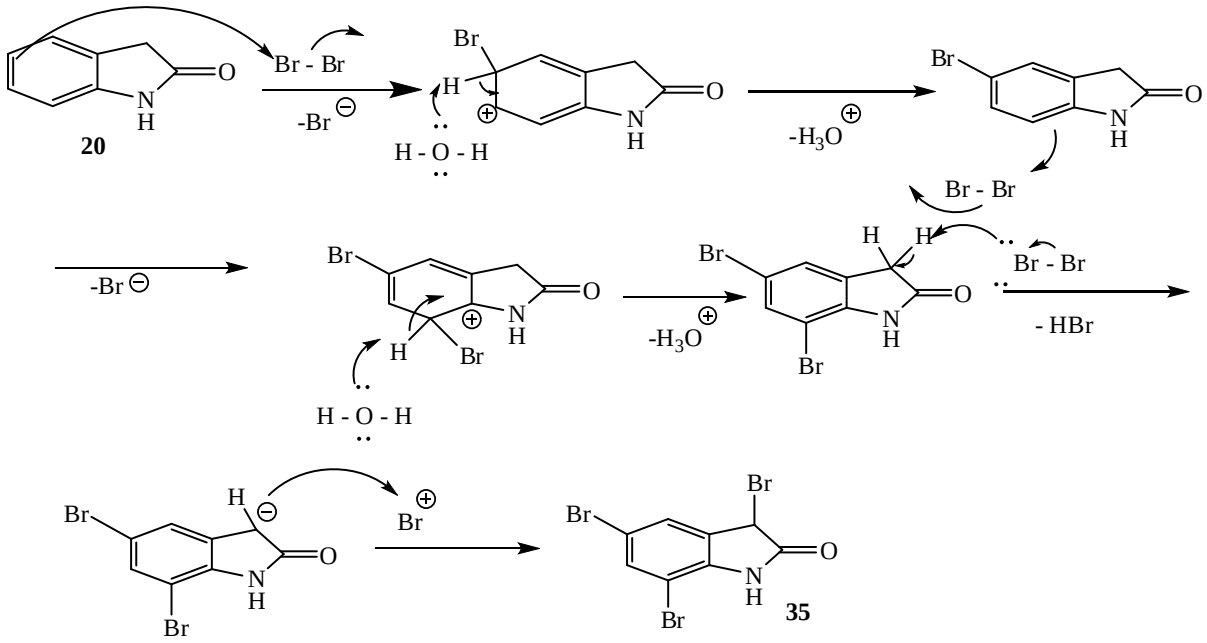


Scheme-10. Bromination of Oxindole **20**

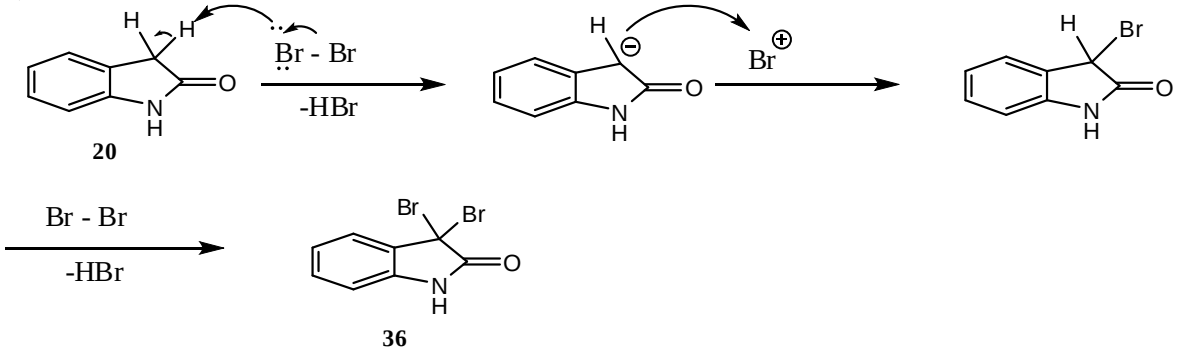
Most plausible mechanism suggested for the formation of derivatives **33-38** can be depicted as –Scheme-11

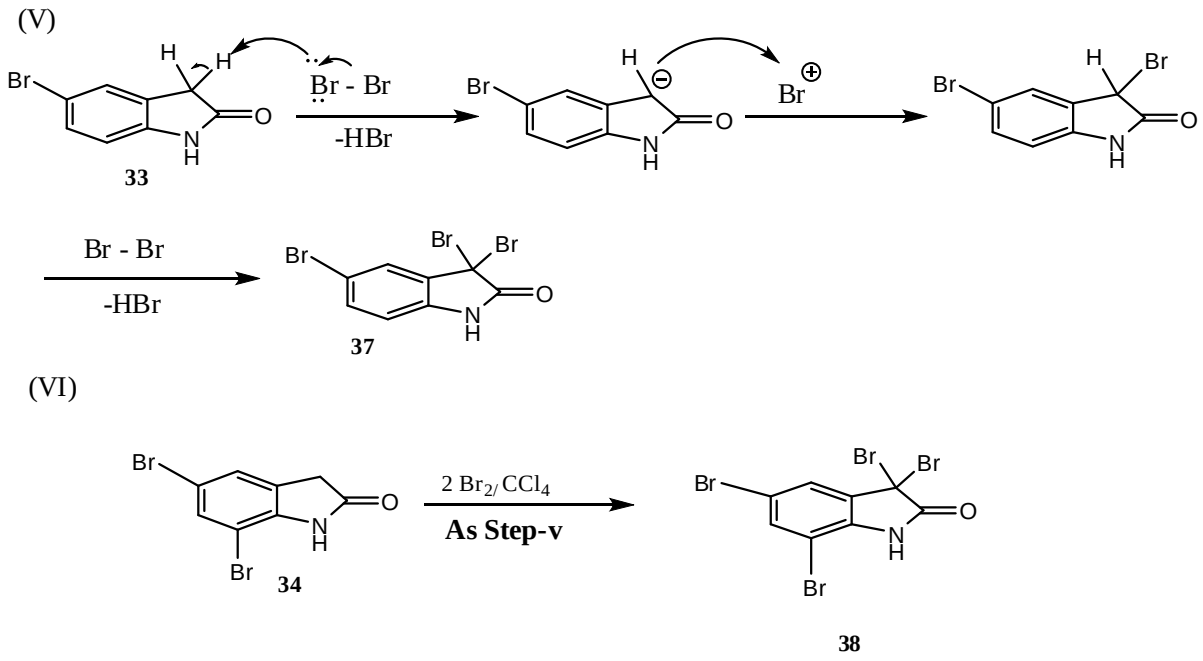


(III)


Br - Br
-Br
H - O - H
-H3O
Br - Br
-Br
-H3O
Br - Br
- HBr
H - O - H
Br
35

(IV)


Br - Br
-HBr
Br
Br - Br
-HBr
36



Scheme-11. Mechanism developed for the formation of oxindole derivatives **33-38**

6. Applications of Medicinal Importance

Heterocyclic compounds display a broad spectrum of biological activities. Indole is an important member of fused heterocyclic compounds. Indoles and their derivatives exhibit a wide range of anti-tuberclosive, anti-malarial, anti-cancer and anti-hypertensive properties.3-bromo-4-(4-oxo-3,4-dihydro-1*H*-carbazol-9(2*H*)-yl)benzamide has been found as ant-proliferative agent.6-Amino-4-substitutedalkyl-1H-indole-2-substitutedcarboxylate derivatives are reported as antiviral agents and showed inhibitory activity against influenza.4-((3-(ethoxycarbonyl)-1-methyl-5-(pyrrolidin-1-ylmethyl)-1H-indol-2 yl)methyl)benzenesulfinate has been found the most active compound against hepatitis C virus (HCV). Compounds 3,3'-([1,1'-biphenyl]-4- yl methylene)bis(1H-indole) **,** 3,3'-((1H-imidazol-2-yl)methylene)bis(1H-indole)and 3,3'-((5-methylpyridin- 2-yl)methylene)bis(1H-indole) show anti-inflammatory activity.4-(3-(1H- indol-3- yl)-4, 5-dihydro-1H-pyrazol-5-yl) phenol has been reported the most effective anti-inflammatory chalcone.Compound (E)-N'-(3-nitrobenzylidene)-2-(5-methoxy-2-methyl-1Hindol- 3-yl) acetohydrazide is reported an active analgesic and anti-inflammatory agent.A series of 2, 4-disubstituted furo[3,2-b]indoles

have been presented for anticancer activity against the tumor cell lines but the compound (5-((2-(hydroxymethyl)- 4H-furo[3,2-b]indol-4-yl)methyl)furan-2- yl)methanol demonstrated the best anticancer activity.4-(1*H*-Indol-3-yl)-2-(4-methoxyphenyl)-2,3 dihydrobenzo[*b*][1,4]thiazepine and 3-[(3-chlorophenyl) diazenyl]-4-(1*H*-indol-3-yl)-2-(4-methoxyphenyl)-2,3-dihydrobenzo[*b*][1,4]oxazepine are useful as antipsychotic agents. (E)-1-(substitutedphenyl)-2-((2-(4-fluorophenyl)-1Hindol- 3-yl) methylene) hydrazine derivatives have been tested for antioxidant activity in human erythrocytes. Compounds (E)-1-(2-chlorophenyl)-2-((2- (4-fluorophenyl)-1H-indol-3-yl) methylene) hydrazine and (E)-1-(4-chlorophenyl)-2-((2-(4-fluorophenyl)-1H-indol- 3-yl)methylene)hydrazine exhibit significant activity. Indole-3-glyoxyl tyrosine derivatives have been reported as ant-malarial agents against the pathogen *Plasmodium falcipa*. Ribofuranosylindole is communicated as a potential antiviral agent. Pyridazino [4,5-*b*]indol-4-ones, are a class of heterocycles containing indole moieties. The pyridazino [4,5-*b*]indole scaffold has attracted particular attention due to its bio-isosterism with β-carboline as well as γ-carboline, as the core structure of a wide variety of bio-active compounds. Pyridazino [4,5-*b*]indole derivatives have neurotrophic activity and can be used for treating diseases and disorders related to the peripheral benzodiazepine receptor. Pyridazino [4,5-*b*]indole derivatives exert antihypertensive activity and can act as inhibitors of thromboxane synthetase. 11*H*-1,2,4-triazolo[4´,3´:2,3]pyridazino[4,5-*b*]indoles and 11*H*- 1,2,3,4-tetrazolo[4´,3´:2,3]-pyridazino[4,5-*b*]indoles are useful as *antihypertensives.* The 3,5-disubstituted pyridazino[4,5-*b*]indole shows anti-inflammatory and antihistaminic activity. Oxindole derivatives display diverse biological activities such as anti-tumor, anti-HIV, anti-viral, anxiolytic, anti-inflammatory and CNS-stimulating activities.

7. Conclusion

This article summarizes the various new methods developed for the synthesis of a broad range of indole and oxindole derivatives. Mechanism for the formation of a series of indole and oxindole derivatives has been developed/suggested which confirmed the designed structure of various molecules. Indole and oxindole derivatives have attracted the attention of researchers because of different biological activities like antidiabetic, anticancer, antimicrobial, antiviral, anti-inflammatory, antioxidant, ant- tubercular, and ant-malarial activities.

Acknowledgement

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