CHAPTER-2

Review of Literature

2.1. Introduction.

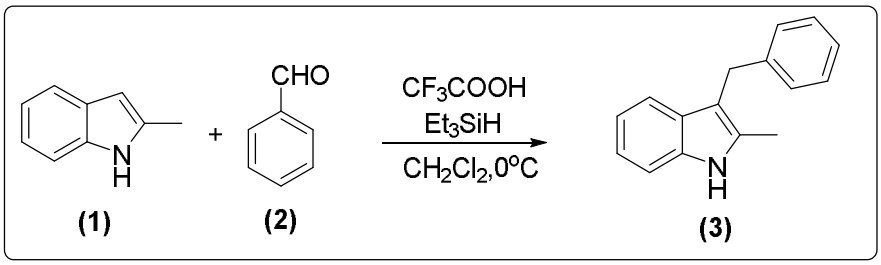
This chapter describes about the reviews on synthetic approaches of C3-alkyl/ aryl substituted indole derivatives, substituted 2-amino-3-cyanopyridine derivatives, substituted 2-amino-3-cyano-6-arylpyridine derivatives and 4, 5, 6, 7-tetrahydroindole-4-one derivatives.

2.2. Literature reviews on the synthesis of C3-alkyl/aryl substituted indole derivatives.

Synthetic methodologies for preparation of C3-substituted indole moiety has significantly enhanced from year to year, because of their high importance. All these conversions have rapid access to unique and novel C3-substituted indole compounds and offering the chance of enlarge the structural diversity in a very easy methods starting from readily available common substrates.

2.2.1. John Steele *et al*. approach.

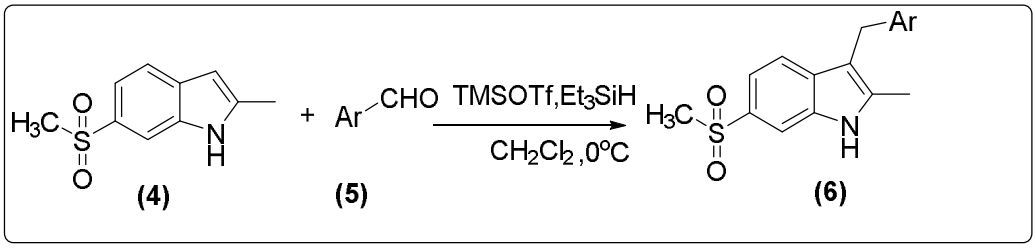
John Steele and co-authors prepared the 3-(aryl methyl) indoles (**3**) strating from 2-methyl indole (**1**) by reaction with aldehyde (**2**) in presence of triethylsilane and trifluoro acetic acid in dichloromethane at 0^{o}C [54] (**Scheme2.1**).



Sheme 2.1: Synthesis of 3-(aryl methyl) indoles catalyzed by trifluoro acetic acid.

2.2.2. Campbell *et al.* approach.

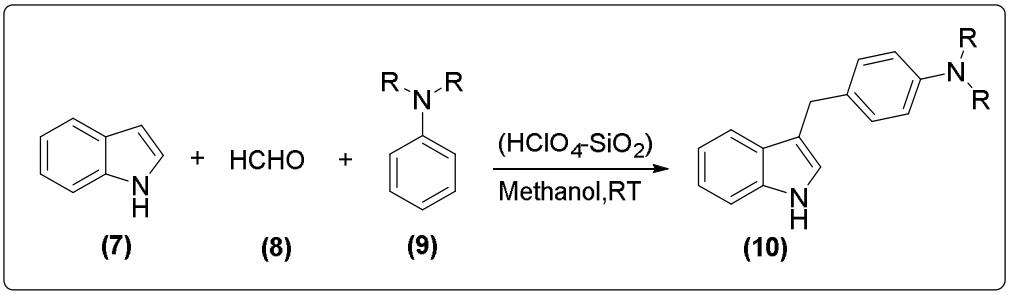
Jeffrey Campbell and co-authors described the 3-aryl methylation of indoles and its derivatives by using TMSOTf and Et_3SiH with different substituted benzaldehydes in dichloromethane solvent [55] (**Scheme 2.2**).



Scheme 2.2: TMSOTf catalyzed synthesis of 3-(aryl methyl) indoles.

2.2.3. Atul kumar *et al*. approach.

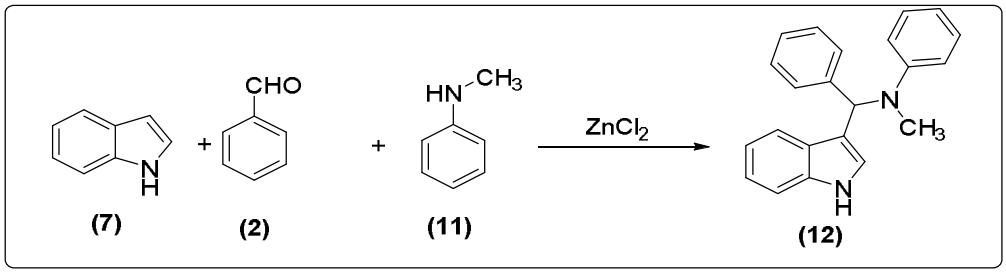
Atul kumar and co-authors prepared 3-alkyl arylindoles (**10**) by three-component reaction of indole (**7**), formaldehyde (**8**) and *N, N*-dialkylated aromatic amines (**9**) using ($HClO_4$–SiO_2) silica gel-supported perchloric acid as a highly efficient, inexpensive and recyclable catalyst in methanol at room temperature [56] (**Scheme 2.3**).



Scheme 2.3: Synthesis of 3-alkyl arylindoles catalyzed by $HClO_4$–SiO_2.

2.2.4. Ravindran *et al.* approach.

Ravindran and co-authors developed a new methodology [57] to synthesize several indole derivatives from indole (**7**), *N*-methyl aniline (**11**) and aldehyde (**2**) by Michael addition reaction (**Scheme 2.4**).



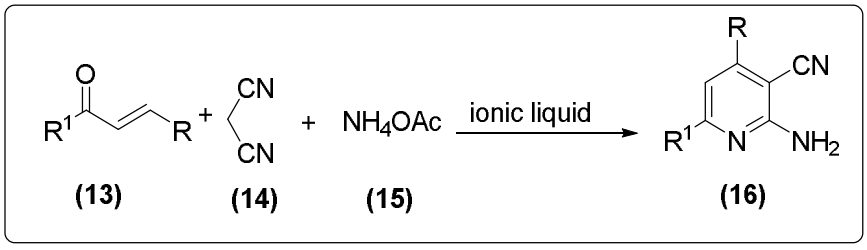
Scheme 2.4: Zinc (II) chloride catalyzed synthesis of 3- substituted indole derivatives.

2.3. Literature reviews on the synthesis of substituted 2-amino-3-cyanopyridine derivatives.

Several synthetic approaches were reported in the literature for the preparation of substituted 2-amino-3-cyanopyridine derivatives considering their high biological importance. Few of the approached are given below.

2.3.1. Sarda *et al.* approach.

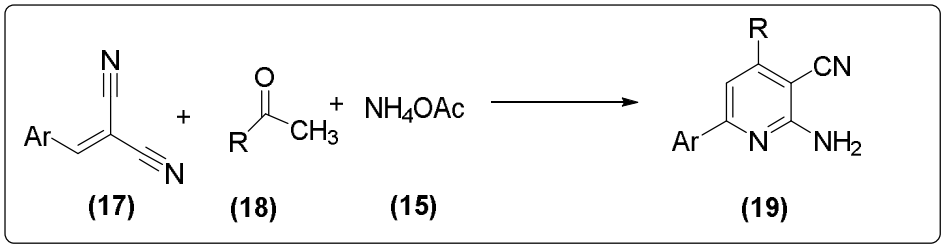
Sarda and co-workers reported the synthesis of 2-amino-3-cyanopyridine derivatives by the reaction of *α, β*-unsaturated ketones (**13**), malononitrile (**14**) and ammonium acetate (**15**) by using ionic liquid (Ethyl ammonium nitrate) [58] (**Scheme 2.5**).



Scheme 2.5: Ionic liquid catalyzed synthesis of 2-amino-3-cyanopyridine derivatives.

2.3.2. Satya *et al.* approach.

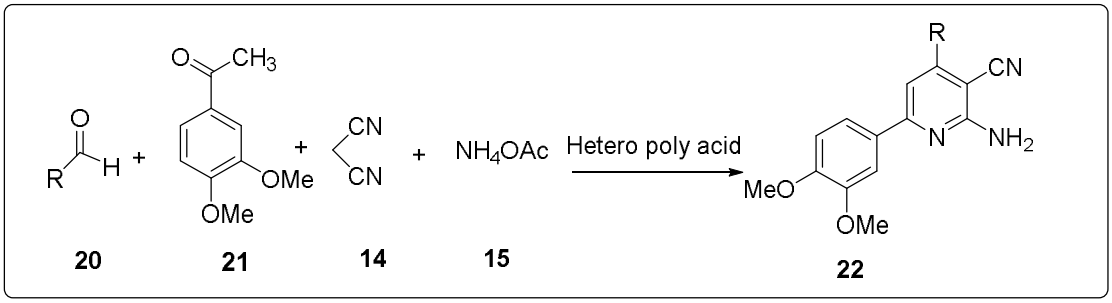
Satya and co-authors [59] synthesized the 2-amino-3-cyanopyridine derivatives by reacting arylidene malononitrile (**17**) with aldehyde (**18**) in presence of ammonium acetate (**15**) (**Scheme 2.6**).



Scheme 2.6: Synthesis of 2-amino-3-cyanopyridine derivatives by Satya *et al.* approach.

2.3.3. Heravi *et al.* approach.

Heravi and co-authous reported [60] a one pot and multi component synthesis of 2-amino-3-cyanopyridine derivatives from different aromatic aldehyde (**20**), malanonitrile (**14**), 3, 4-dimethoxyacetophenone (**21**) and ammonium acetate (**15**) using heteropoly acid as catalyst (**Scheme 2.7**).



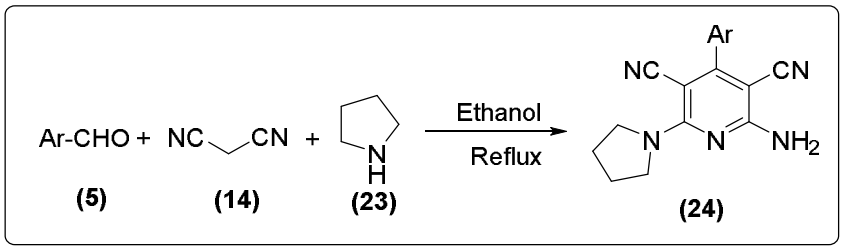
Scheme 2.7: Heteropolyacid catalyzed synthesis of 2-amino-3-cyanopyridine derivatives.

2.4. Literature reviews on the synthesis of *N*-substituted 2-amino-3-cyano-6-aryl pyridine derivatives:

Several synthetic approaches were reported in the literature for the preparation of *N*-substituted 2-amino-3-cyanopyridine derivatives considering their high biological importance. Few of the approached are given below.

2.4.1. Thirumurugan prakasam *et al.* approach.

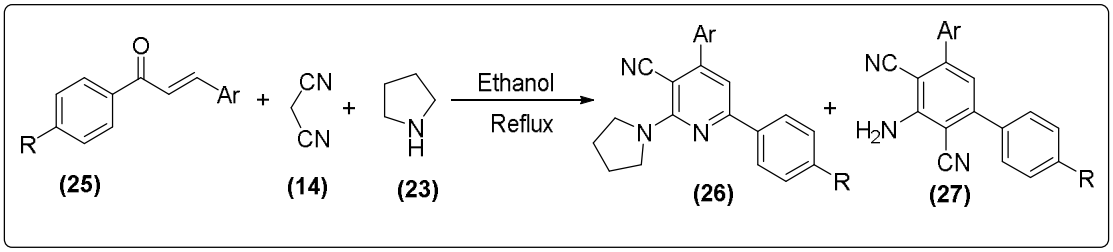
Thirumurugan prakasam and co-authors [61] prepared *N*-substituted 2-amino-3-cyanopyridine derivatives by reacting substituted benzaldehydes (**5**) with two moles of malononitrile (**14**) in presence of pyrrolidine (**23**) (**Scheme 2.8**).



Scheme 2.8: Synthesis of *N*-substituted 2-aminopyridine derivatives by Thirumurugan prakasam *et al*. approach.

2.4.2. Raghu kumar *et al.*approach.

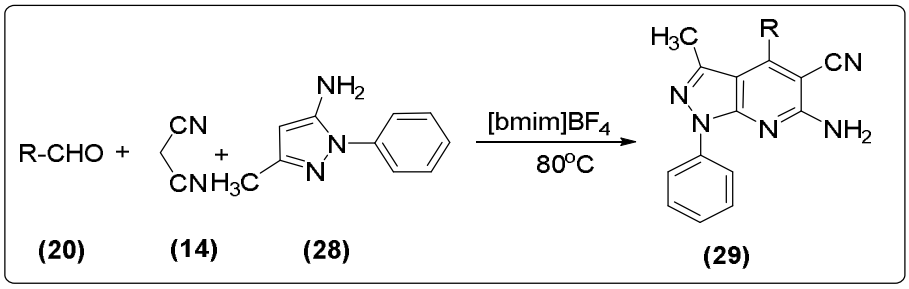
Raghu kumar and co-authors [62] prepared *N*-substituted 2-aminopyridine derivatives by multicomponent coupling of chalcones (**25**), malanonitrile (**14**) and pyrrolidine (**23**). Along with required product (**26**), 3-amino-2, 4-dicyano-5-(2-thienyl) biphenyl compound (**27**) also obtained (**Scheme2.9**).



Scheme-2.9: Raghu kumar *et al.* approach for synthesis of 2-amino-3-cyano-6-arylpyridine derivatives.

2.4.3. X. Zhang *et al.* approach.

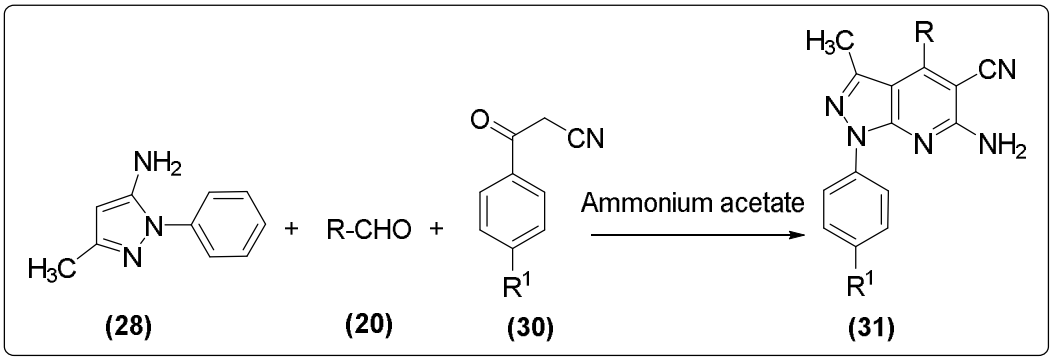
Zhang, Xinying and co-authors [63] prepared substituted pyrazolo [3, 4-b] pyridine derivatives (**29**) by multicomponent coupling of 5-amino-3-methyl-1-phenylpyrazole (**28**), substituted aldehyde (**20**) and malononitrile (**14**) in ionic liquid [bmim]BF_4 at 80^oC without any catalyst (**Scheme 2.10**).



Scheme 2.10: Ionic liquid ([bmim]BF_4) catalyzed synthesis of substituted pyrazolo [3, 4-b]pyridine derivatives.

2.4.4. M. N. Jachak *et al.* approach.

Jachak and co-authors developed a multicomponent methodology [64] to prepare the pyrazolo[3, 4-b]pyridine derivatives (**31**) by coupling of 1, 3-diphenyl- 1H-pyrazol-5-amine (**28**), substituted aldehyde (**20**) and *p*-substituted benzoylacetonitriles (**30**) by using ammonium acetate as catalyst (**Scheme-2.11**).



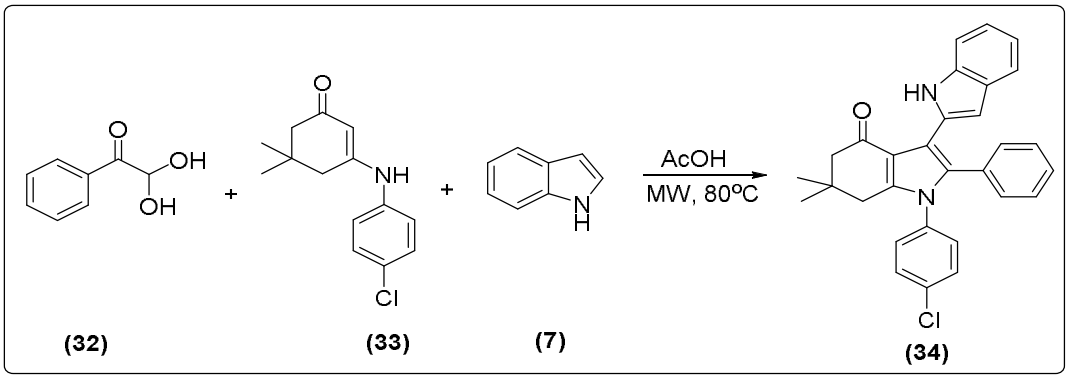
Scheme 2.11: Synthesis of pyrazolo[3, 4-b]pyridine derivatives catalysed by NH_4OAc.

2.5. Literature reviews on the synthesis of 4-oxo-4, 5, 6, 7-tetrahydroindole derivatives.

There are several synthetic approaches available to prepare various 4-oxo-4, 5, 6, 7-tetrahydro indole derivatives.

2.5.1. F. Li-Ping *et al.* approach.

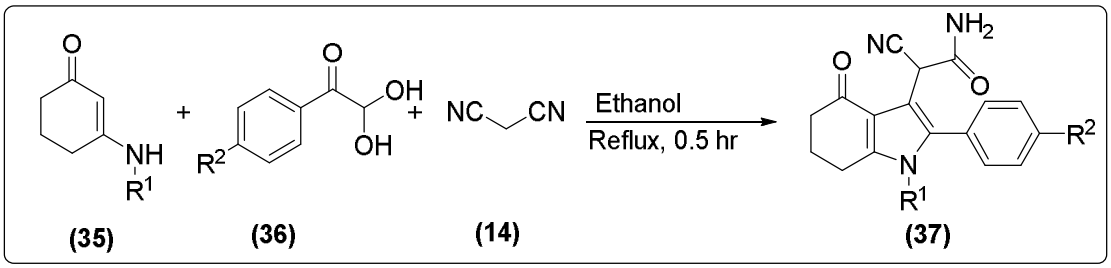
Li-Ping *et al*. developed the multicomponent methodology [65] to synthesize the 3-indole substituted 4-oxo-4, 5, 6, 7-tetrahydroindole derivatives (**34**) by reacting phenylglyoxalmonohydrate (**32**), 3-((4-chlorophenyl)amino)-5,5-dimethyl cyclohex-2-enone (**33**) and indole (**7**) in presence of acetic acid under microwave irradiation at 80^{o}C (**Scheme 2.12**).



Scheme 2.12: Microwave assisted acetic acid catalysed synthesis of 4-oxo-4, 5, 6, 7-tetrahydroindole derivatives.

2.5.2. Maity *et al.* approach.

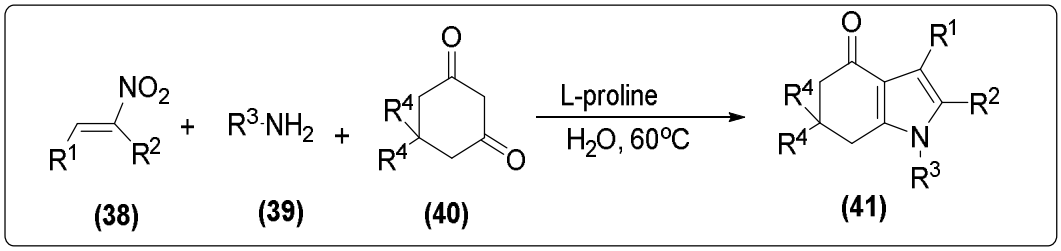
Subhendu Maity and co-authors [66] synthesized substituted 4, 5, 6, 7- tetra hydro-4-oxo-1*H*-3-indolyl)-2-cyano acetamide derivatives (**37**) by three-component coupling of substituted enamine (**35**), arylglyoxalmonohydrate (**36**) and malanonitrile (**14**) in ethanol at reflux (**Scheme 2.13**).



Scheme 2.13: Maity *et al.* approach for synthesis of 4, 5, 6, 7-tetra hydro-4-oxo-1*H*-3-indolyl)-2-cyano acetamide derivatives.

2.5.3. Furen Zhang *et al.* approach.

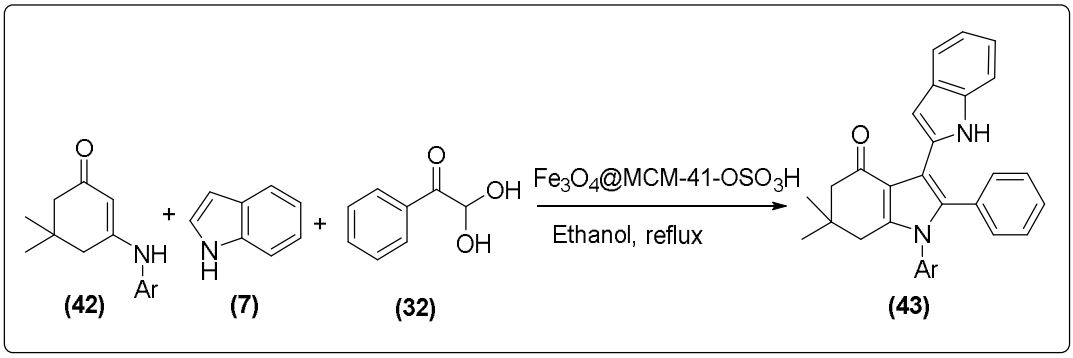
Furen Zhang and co-authors developed a methodology [67] to prepare 4, 5, 6, 7-tetrahydro-4*H*-indole-4-one derivatives (**41**) by reacting the 1, 3-dione (**40**), nitro olefine (**38**) and substituted amine (**39**) in presence of L-proline in water at 60°C (**Scheme 2.14**).



Scheme 2.14: L-proline catalysed synthesis of 4, 5, 6, 7-tetrahydro-4*H*-indole-4-one derivatives.

2.5.4. Alireza Khorshidi *et al.* approach.

Alireza Khorshidi and co-authors reported [68] the synthesis of 3-indolyl-4, 5, 6, 7-tetrahydroindole-4-one derivatives (**43**) by reacting indole (**7**), *N*-arylenaminone (**42**) and phenylglyoxal monohydrate (**32**) in presence of Fe_3O_4@MCM-41-OSO_3H in ethanol at reflux (**Scheme-2.15**).



Scheme 2.15: Synthesis of 3-indolyl-4, 5, 6, 7-tetrahydroindole-4-one derivatives by Alireza Khorshidi *et al.* approach.

2.6. Conclusion:

While many of the above mentioned approaches are useful and efficient, most of the approaches involve non-environmentally benign catalysts and solvents. In some approaches catalysts are moisture and air sensitive, required anhydrous conditions and catalyst is not recyclable.

Thus the development of more environmentally benign process to the synthesis of 3-diarylmethyl/arylmethylindole derivatives, 2-arylamino-3-cyanopyridine derivatives, 2-arylamino-3-cyano-6-arylpyridine derivatives and 4-oxo-4, 5, 6, 7-tetrahydroindole derivatives is extremely desirable.