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Chemistry of 3-cyanoacetyl indoles: synthesis, reactions and applications: a recent update

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Indole is a significant nitrogen-based heterocycle with particular importance in the synthesis of heterocyclic scaffolds. Indole based compounds have been recently attracting much attention due to their biological and pharmaceutical activities. 3-Substituted indoles such as cyanoacetyl indoles (CAIs) are nitrogen-heterocyclic compounds which are easily obtained from the reaction of indoles and cyanoacetic acid. They are versatile starting materials utilized for the construction of a wide variety of molecules containing indole moieties in organic synthesis. In this study, we provide an overview on the synthesis of 3-cyanoacetyl indoles (CAIs) and their recent applications in the multi-component reactions for the synthesis of various heterocyclic compounds such as pyranes, pyridines, dihydropyridines, pyrimidines, tetrahydropyrimidines, pyrazoles, pyrazolopyridines, pyrazolopyrimidines, pyridopyrimidines, tetrazolopyrimidines, triazolopyrimidines, furans, dihydrofurans, coumarins, pyrimido naphthyridines, chromenes, thiazoles, pyrimidoindazoles, pyrazoloquinolines, isoxazolopyridines, and carbazoles and their biological activities during the period of 2013 to 2022.

1 Introduction

Indole is also known as benzopyrrole which contains a bicyclic aromatic heterocyclic organic compound comprising a six membered benzene ring fused to a five-membered nitrogen-containing pyrrole ring and has 10 π-electrons which makes it aromatic in nature. Indole is a well-known privileged structure

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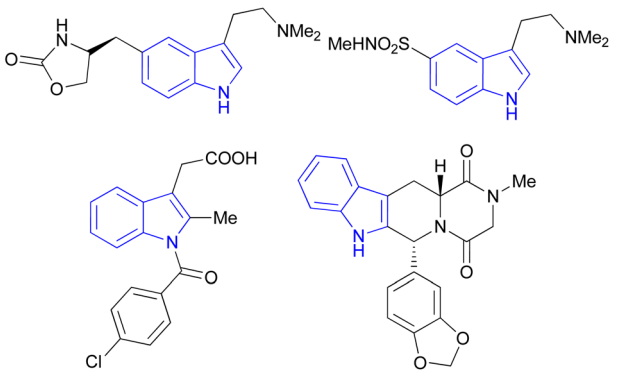


Fig. 1 The molecular structure of four drugs with indole moieties.

scaffold occurring in numerous natural products such as alkaloids and peptides, existing in different kinds of plants, animals and marine organisms.[1] Moreover, the addition of the indole nucleus to medicinal compounds that are biologically active made it an important heterocyclic compound having broad-spectrum biological and pharmaceutical activities (Fig. 1).[2–7] Due to this, researchers took interest to synthesize various scaffolds of indole for screening different pharmacological activities. Electrophilic substitution occurs readily on indole due to excessive π-electron delocalization.[8] Indole is reactive at four different positions including carbon atom 3,[9–13] nitrogen atom 1, the C2–C3 π-bond[14–17] and the C2–N sigma bond[18,19] (Fig. 2). Indole can be protonated with strong acids, which protonates the C3 position, more easily than the N atom. The cycloaddition reaction is another reaction of indole compounds. The C2–C3 π-bond of indole has a propensity towards cycloaddition reactions but cycloaddition reactions of the C2–N sigma bond are also observed. However, various methods for the synthesis and functionalization of indoles have been reviewed.[20–24] 3-Substituted indoles such as cyanoacetyl indoles (CAIs) are nitrogen-heterocyclic compounds which are versatile starting materials utilized for the construction of a wide variety of molecules containing indole moieties in organic synthesis. A large portion of these molecules exhibits promising biological activities such as against nicotinic acetylcholine receptors and prostaglandin-mediated disease,[25] antimicrobial,[26] antifungal,[27] anti-inflammatory and analgesic activities,[28] against prophylaxis and angiogenesis,[29] anticancer[30,31] and acts as inhibitors of JNK.[32] Up to date, two review articles have been published based on the synthesis and reactions of 3-cyanoacetyl indoles.[33,34] This review presents the recent applications of cyanoacetyl indoles in the synthesis of diverse organic compounds and their biological activities during the period from 2013 to 2022.

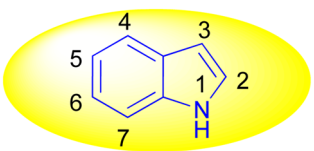
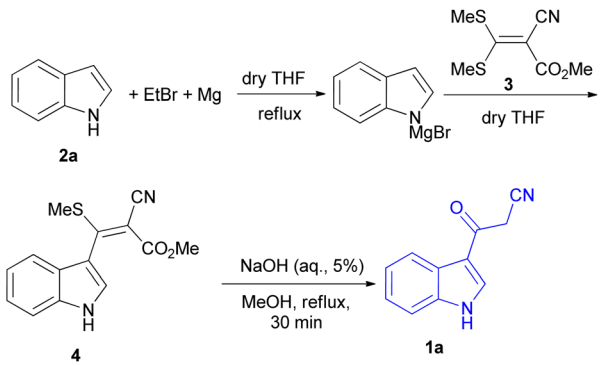


Fig. 2 Structure of indole.

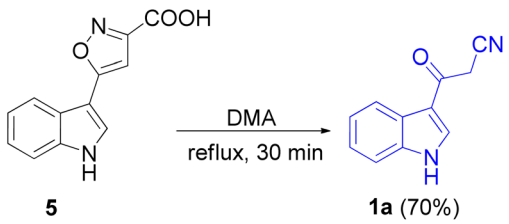
2. Synthesis of 3-cyanoacetyl indoles

In 1967, the first synthesis of 3-cyanoacetyl indole (**1a**) was reported by Washida and co-workers where an indole (**2a**) in the presence of Grignard reagent and the keten thioacetal **3**, followed by hydrolysis of the intermediate **4** in 5% NaOH solution afforded **1a** (Scheme 1).[35] In 1978, Gorbunova and Suvorov described synthesis of **1a** in 70% yield by heating of 5-(3-indolyl) isoxazole-3-carboxylic acid **5** in dimethylacetamide (DMA) under reflux condition for 30 min (Scheme 2).[36] In 1980, Kreher and Wagner provided a procedure for the synthesis **1a** in 84% yield *via* the reaction of indole, methanesulfonyl chloride and potassium cyanoacetate in acetonitrile at room temperature for 1 h (Scheme 3).[37] Next, Bergman *et al.* developed the use of acetic anhydride in the synthesis of 3-cyanoacetyl indole derivatives **1a–g** in 90–98% yields from the reaction of indoles **2** with cyanoacetic acid at 60–70 °C for 5 min (Scheme 4).[38]

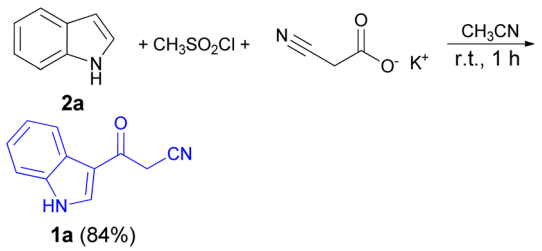
After that, 3-cyanoacetyl indole (**1a**) obtained *via* the reaction of cyanoacetic acid with indole in refluxing acetic anhydride for 30 min. Moreover, chloroacetylindole **6** readily converted into



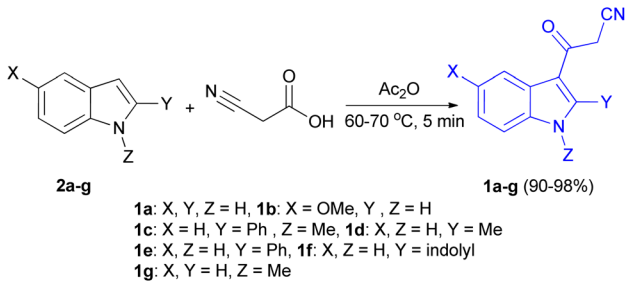
Scheme 1 Synthesis of 3-cyanoacetyl indole (**1a**).



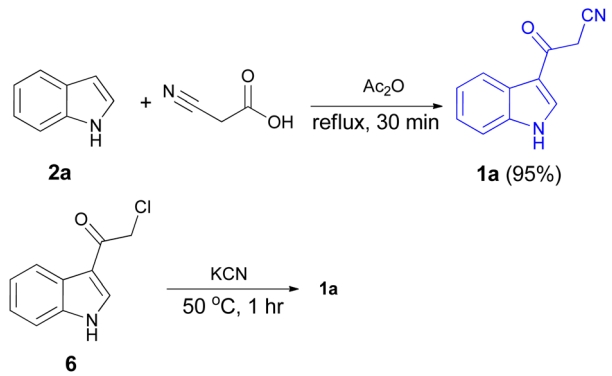
Scheme 2 Preparation of 3-cyanoacetyl indole (**1a**).



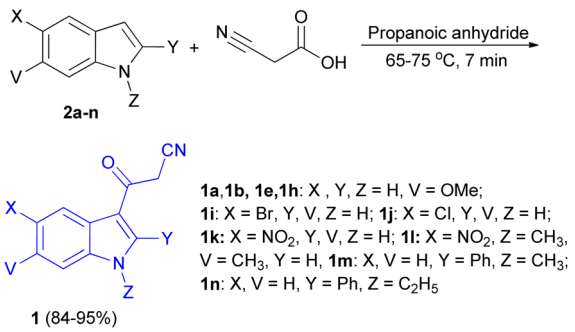
Scheme 3 Synthesis of 3-cyanoacetyl indole (**1a**).



Scheme 4 Synthesis of 3-cyanoacetyl indoles **1a–g**.



Scheme 5 Synthesis of 3-cyanoacetyl indole (**1a**).



Scheme 6 Synthesis of 3-cyanoacetyl indole derivatives **1**.

1a on treatment with potassium cyanide at 50 °C for 1 h (Scheme 5).[39]

In 2013, a facial method for the synthesis of 3-cyanoacetyl indole derivatives **1** in 84–95% yields reported by the reaction of indoles **2**, cyanoacetic acid and propanoic anhydride at 65–75 °C for 7 min (Scheme 6).[40]

3. 3-Cyanoacetyl indoles reactions

3.1. Pyran derivatives

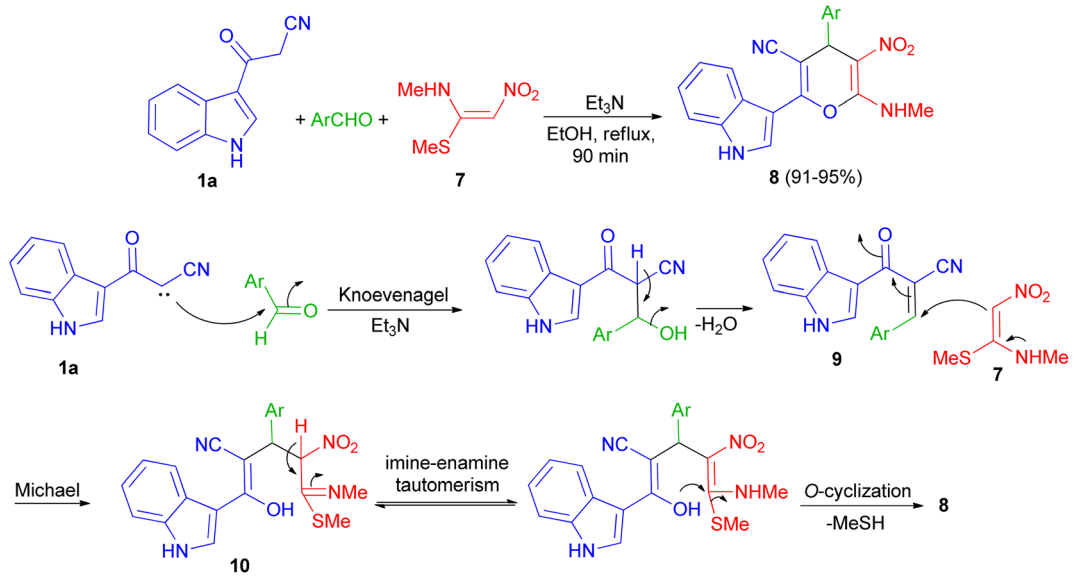
In 2013, Kumar and co-workers used 3-cyanoacetyl indole (**1a**), aromatic aldehydes and (*E*)-*N*-methyl-1-(methylthio)-2-nitroethenamine (**7**) for the synthesis of 2-(1*H*-indol-3-yl)-6-(methylamino)-5-nitro-4-aryl-4*H*-pyran-3-carbonitriles **8**. The corresponding products produced in 91–95% yields in the presence of Et_3N in EtOH under reflux conditions for 90 min. A plausible mechanistic pathway for the formation of **8** is outlined in Scheme 7. Initially, the Knoevenagel condensation between **1a** and aromatic aldehyde affords **9**, which undergoes Michael addition with **7** to give **10**. The intermediate **10** is susceptible to either an intramolecular o-cyclization which can afford penta-substituted 4*H*-pyrans **8**.[41]

Next, a series of polysubstituted indol-3-yl substituted pyran derivatives **11** synthesized in 74–94% yields *via* one-pot multi-component reactions of aromatic aldehydes, malononitrile with 3-cyanoacetyl indoles **1** in the presence of piperidine (20 mol%) in EtOH at room temperature under ultrasonic irradiation for 5–90 min. A plausible mechanism for the formation of **11** is shown in Scheme 8. Compound **11** could be produced from the intermediate **12** *via* Michael addition with the tautomer of 3-cyanoacetyl indole **1** followed by intramolecular cyclization.[42]

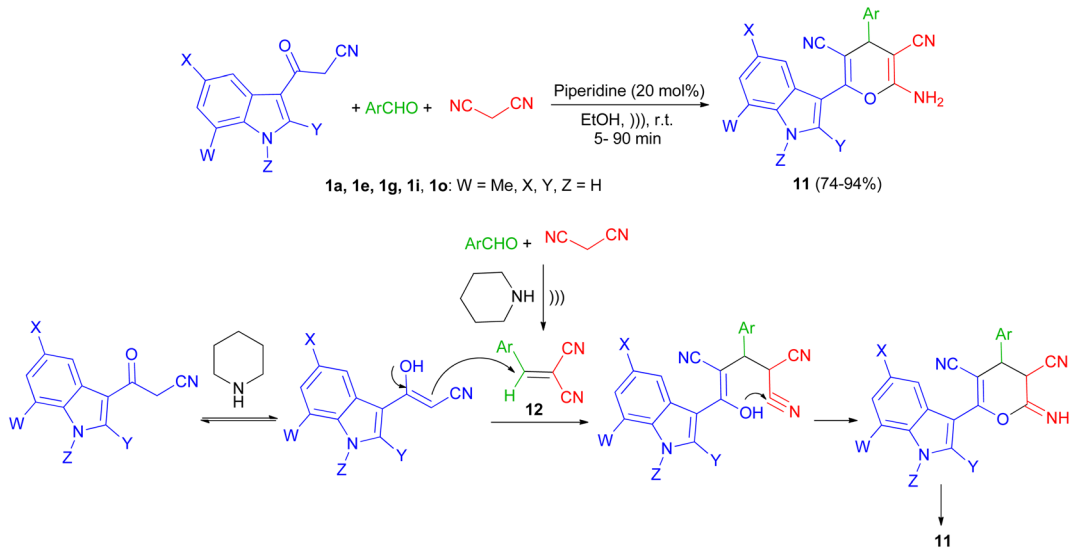
After that, Ji and co-workers reported an efficient multi-component reaction of 3-indolyl-3-oxopropanenitriles **1** with dialkyl acetylenedicarboxylates **13** and isocyanides **14** in CH_2Cl_2 under mild conditions leading to highly functionalized 6-(indol-3-yl)-4*H*-pyrans **15** in moderate to good yields (40–89%) for 48 h. A plausible mechanism was proposed as shown in Scheme 9. The reaction of isocyanide **14** and dialkyl acetylenedicarboxylate **13** *in situ* leads to the formation of zwitterionic intermediate **16**, which could be protonated by OH of **1′** to give intermediates **17** and **18**. Subsequently, ketenimine **19** could be formed by the reaction of enolate **17** with the nitrilium ion **18**. After tautomerization under the employed reaction conditions and cyclization, pyran derivative **15** is formed.[43]

One-pot multi-component reaction of 3-cyanoacetyl indoles **1**, aromatic aldehydes and ethyl acetoacetate in the presence of $InCl_3/NH_4OAc$ under microwave irradiation (540 W, 130 °C) for 2–7 min afforded highly functionalized 3-(pyranyl)- and 3-(dihydropyridinyl)indole derivatives and **20**, respectively, in good yields (55–86%). A plausible mechanism for the formation of compound **20** and **21** is shown in Scheme 10. 3-Cyanoacetyl indoles **1** reacts with aryl aldehyde to give a α,β-unsaturated ketone **22** which reacts with ethyl acetoacetate to give the Michael adduct **23** under microwave irradiation in the presence of $InCl_3$ and subsequently cyclizes by eliminating water molecule to give the 3-(pyranyl)indole derivative **20**. In the formation of compound **21**, β-ketoester first reacts with ammonia, generated from the dissociation of ammonium acetate under MW, to give amine **24**. The amine **24** then reacts with intermediate **22** to give the corresponding Michael adduct and finally undergoing cyclization/water elimination to afford product **21**.[44]

A series of highly functionalized indolylpyrans **25** has been synthesized in 84–93% yields *via* $InCl_3$ (20 mol%) catalyzed microwave irradiation (450 W) of 3-cyanoacetylindoles **1**, aromatic aldehydes with (*E*)-*N*-methyl-1-(methylthio)-2-nitroethenamine (NMSM) (**7**) under solvent-free condition for 3–7 min. Further, the synthesized azidoindolylpyrans **25a** undergo [3 + 2] cycloaddition reaction with different phenyl acetylenes in the presence of CuI (20 mol%) as catalyst in ACN : H_2O (1 : 1) at room temperature to give indolyltriazolylpyran hybrids **26** in 78–83% yields after 1–1.75 h (Scheme 11).[45]



Scheme 7 Synthesis of penta-substituted 4*H*-pyrans **8**.



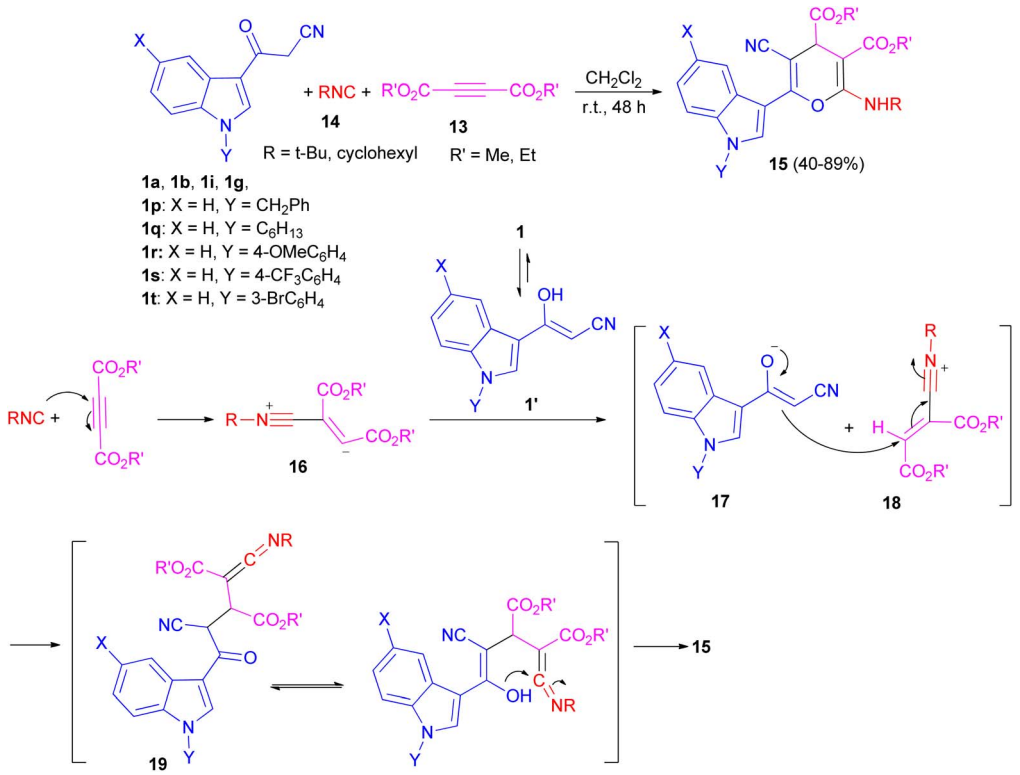
Scheme 8 Synthesis of indol-3-yl substituted pyran derivatives **11**.

Next, a green method was developed for one pot synthesis of 3-pyranyl indole derivatives **27** in 85–94% yields by reaction of 3-cyano acetyl indole (**1a**), aromatic aldehydes and malanonitrile in an aqueous media under reflux for 25–40 min by using [Hmim]HSO_4 as a green and reusable catalyst (Scheme 12).[46]

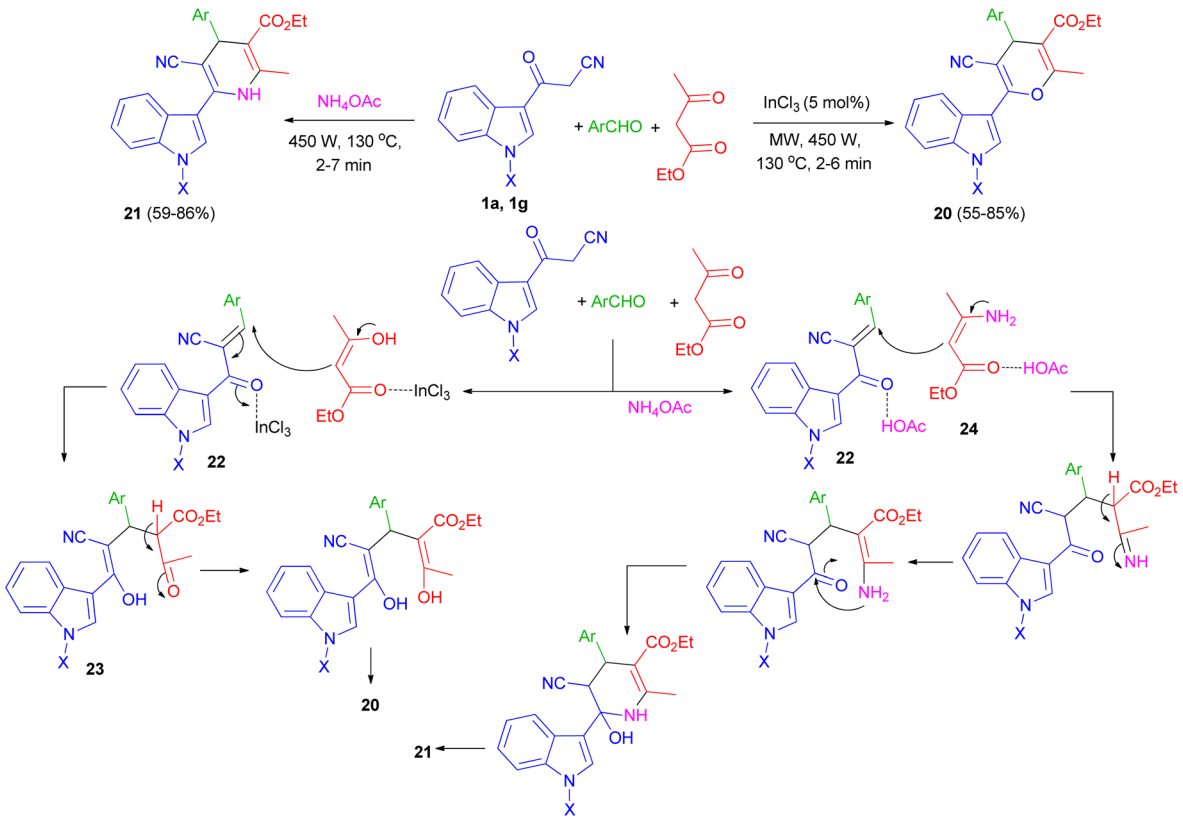
Green synthetic method for preparation of functionalized indol-3-yl pyran derivatives **28–30** in 70–88% yields was developed by one-pot three-component synthesis of 3-cyanoacetyl indoles **1**, malononitrile/cyanoacetate and various aldehydes/isatins/acenaphthenequinone in the presence of L-proline (20 mol%) in refluxing EtOH for 1–3 h (Scheme 13).[47]

In 2021, Zarei and his group described synthesis of 2-amino-6-(2-methyl-1*H*-indol-3-yl)-4-phenyl-4*H*-pyran-3,5-dicarbonitriles **31** in 65–95% yields by the one-pot reaction of various aromatic aldehydes, 3-(1*H*-indol-3-yl)-3-oxopropanenitrile derivatives **1** and malononitrile using CQDs-N$(CH_2PO_3H_2)_2$ as catalyst in refluxing EtOH and/or ultrasonic irradiation conditions (Scheme 14).[48]

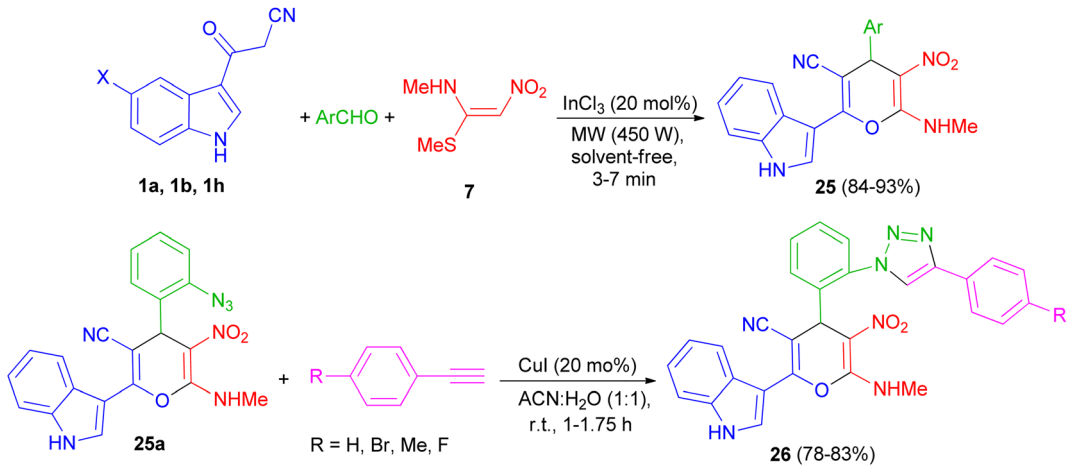
A protocol for the synthesis of 4-perfluoroalkylated 2*H*-pyran-2-ones **32** in 44–99% yields bearing indole skeleton reported *via* the reaction of 3-(1-methyl-1*H*-indol-3-yl)-3-oxopropanenitriles **1** and methyl perfluoroalk-2-ynoates in the presence of Et_3N in THF at 40 °C in air for 24 h. A plausible reaction mechanism is proposed in Scheme 15. In the presence of the base, deprotonation of **1** generates the anion **33**, which undergoes Michael addition to afford the intermediate **34** through an attack to the carbon atom at the β-position of the alkyne, which has a less electron density compared to the carbon atom at α-position. Subsequent enolization of **34** leads to the formation of oxygen



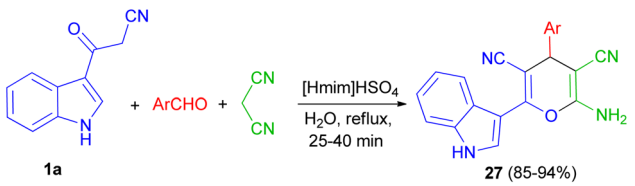
Scheme 9 Synthesis of 6-(indol-3-yl)-4*H*-pyrans **15**.



Scheme 10 Synthesis of 3-(pyranyl)- and 3-(dihydropyridinyl)indole derivatives **20** and **21**.



Scheme 11 Microwave assisted $InCl_3$ mediated synthesis of indolylpyrans **25** and indolyltriazolylpyran hybrids **26**.

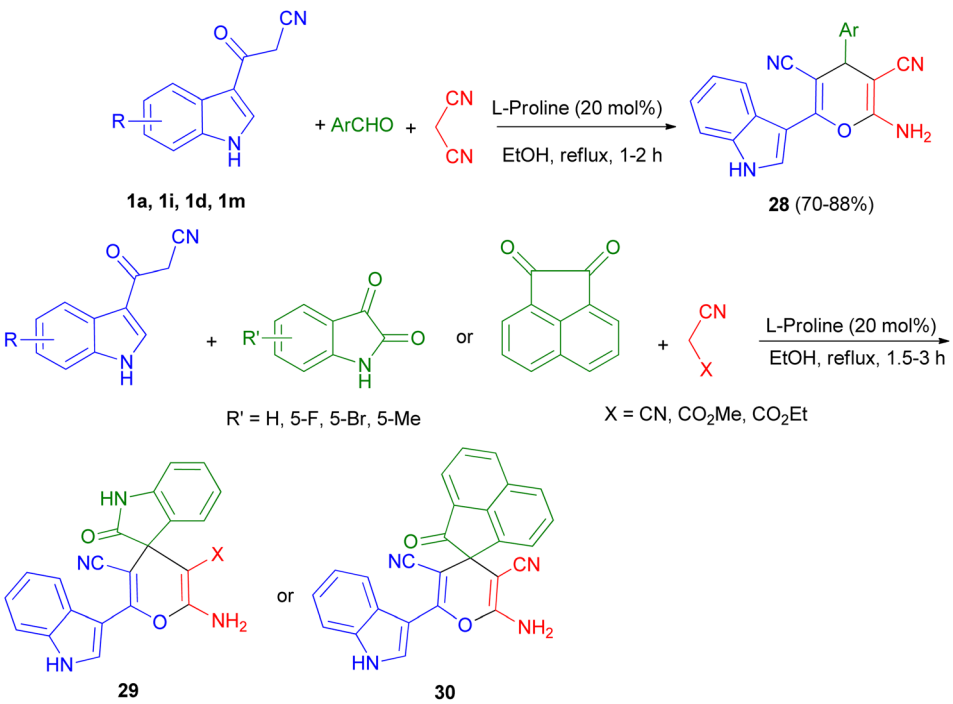


Scheme 12 Synthesis of 3-pyranyl indole derivatives **27** by using ionic liquid.

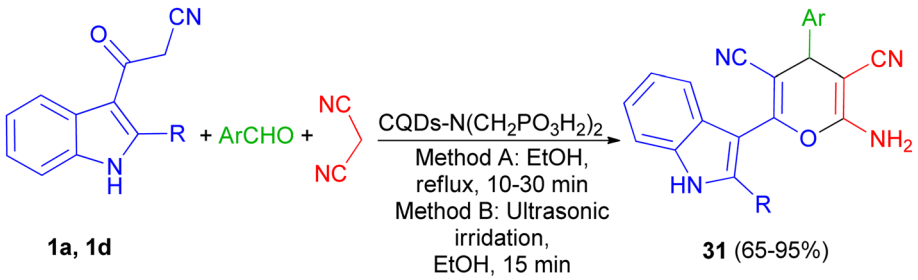
anion **35**, followed by intramolecular oxygen nucleophilic attack to carbonyl carbon to accomplish the cyclization, and final elimination of methoxide anion furnishes the target product **32**.[49]

3.2. Pyridine and dihydropyridine derivatives

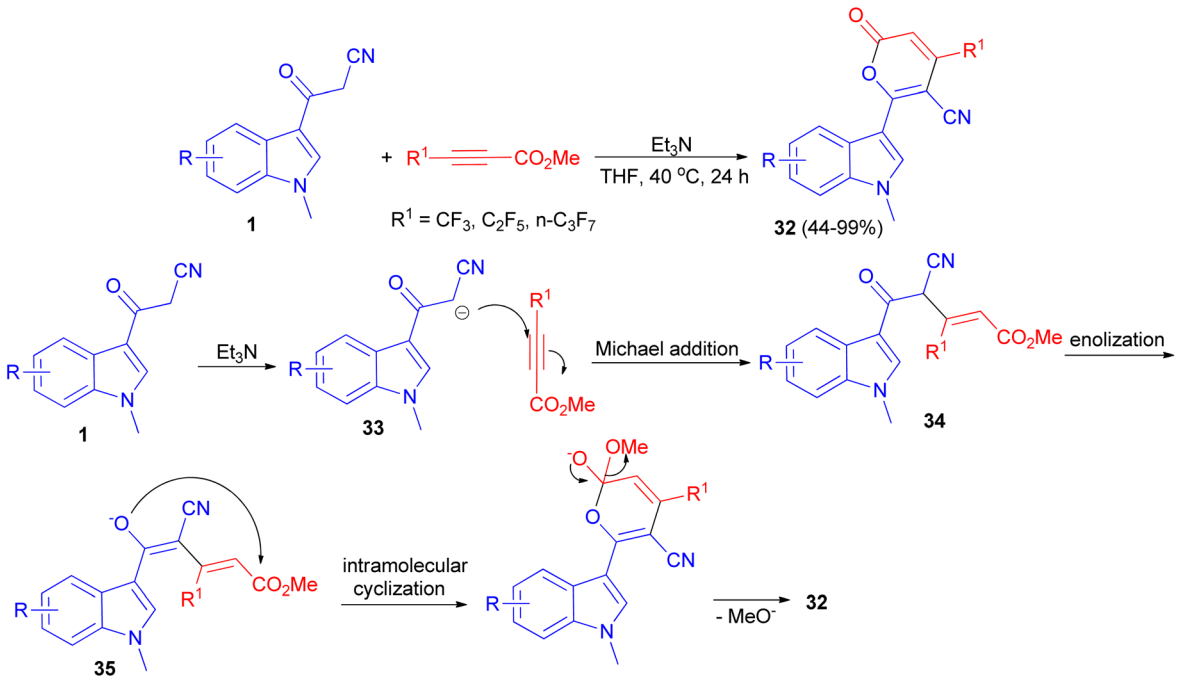
In 2013, preparation of a series of 3-cyano-2-(1*H*-indol-3-yl)-6-(9-butylcarbazol-3-yl)pyridine derivatives **36** in 75–86% yields reported through the one-pot four-component coupling of aromatic aldehydes, 1-(9-butylcarbazol-3-yl)ethanone (**37**), 3-(cyanoacetyl)indole (**1a**) and ammonium acetate in HOAc-glycol under irradiation at 300 W for 4 min. A possible mechanism is depicted in Scheme 16. 3-(Cyanoacetyl)indole reacts with ammonia from ammonium acetate to give intermediate **38**, which further reacts with the corresponding chalcones **39**, to yield **40**. Michael addition product **40** was then cyclised to afford the Hantzsch dihydropyridine derivative **41** with elimination of water.



Scheme 13 Preparation of functionalized indol-3-yl pyran derivatives **28**–**30**.



Scheme 14 Synthesis of multisubstituted 4*H*-pyran with indole moieties **31**.



Scheme 15 Synthesis of 4-perfluoroalkylated 2*H*-pyran-2-ones **32**.

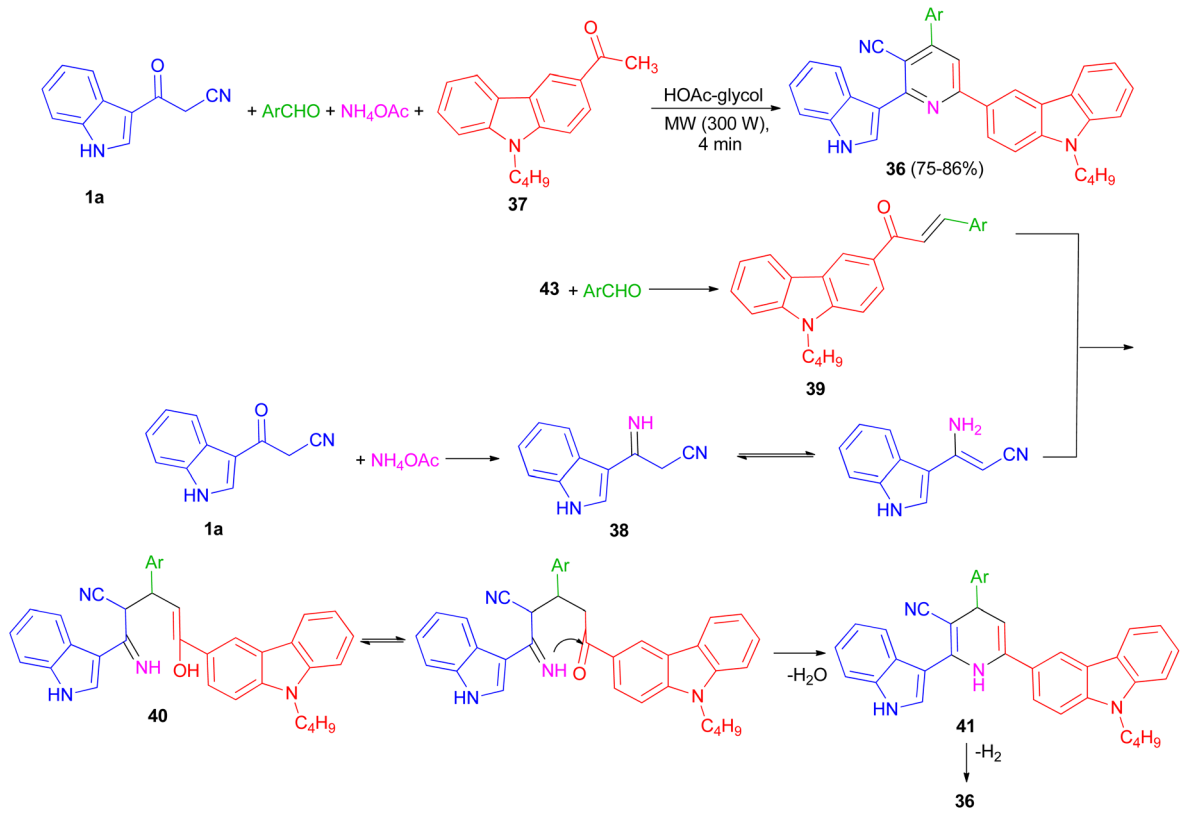
Subsequent dehydrogenation of **41** leads to formation of the highly substituted pyridine derivative **36.**[50]

A one-pot four-component reaction of **1a**, aromatic aldehydes, aromatic ketones **42**, and NH_4OAc in the presence of iodine as a catalyst was explored for the preparation of 2-(indol-3-yl)pyridine derivatives **43** in 43–87% yields under two different conditions (solvent-free and using AcOH as solvent) (Scheme 17).[51]

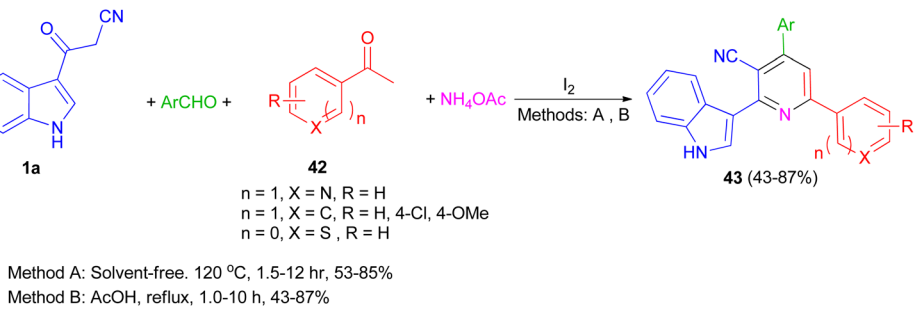
Perumal *et al.* explored the one-pot three-component reaction of 3-formylchromones **44**, cyanoacetylindoles **1** and ammonium acetate for the synthesis of functionalized indole-3-yl pyridines **45** in 80–94% yields in the presence of stannous chloride in DMF at 120 °C for 3–5 h (Scheme 18).[52]

In 2014, a series of 2,6-diaryl-4-(1*H*-indol-3-yl)-3-cyanopyridines **46** was obtained in good yields (64–76%) from the domino reactions of **1a**, 4,4,4-trifluoro-1-arylbutane-1,3-diones **47**, and aromatic aldehydes in the presence of ammonium acetate under solvent-free condition at 110 °C for 3–9 h (Scheme 19).[53]

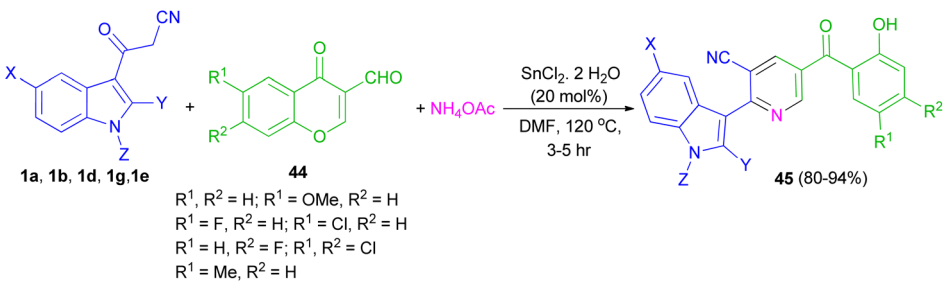
Singh *et al.* have developed one-pot synthesis of 2-amino-6-(1*H*-indol-3-yl)-4-arylpyridine-3,5-dicarbonitriles **48** in 90–94% yields *via* four-component reaction of 3-cyanoacetyl indoles, aromatic aldehydes, ammonium acetate, and malononitrile in aqueous micellar conditions in the presence of VB_1 (5 mol%), and cetyltrimethylammonium bromide (CTAB) (10 mol%) at 57 °C. From the mechanistic point of view, it is proposed (Scheme 20) that first step is the formation of the intermediate **49** from the Knoevenagel condensation between aldehyde and malononitrile. Simultaneously **1** reacts with NH_3 generated *in situ* by decomposition of ammonium acetate to give intermediate **50.** Both **49** and **50** further react to give intermediate **51**, which on cyclization and dehydration give the product **48** *via* intermediate **52.** The role of VB_1 as a catalyst may be postulated in terms of the NH-proton of the VB_1, leading to its interaction with the carbonyl oxygen atom of aldehyde as well as (3-cyanoacetyl)-indole, thereby facilitating the polarization and promoting the cyclocondensation reaction.[54]



Scheme 16 Synthesis of 3-cyano-2-(1*H*-indol-3-yl)-6-(9-butylcarbazol-3-yl)pyridines **36**.

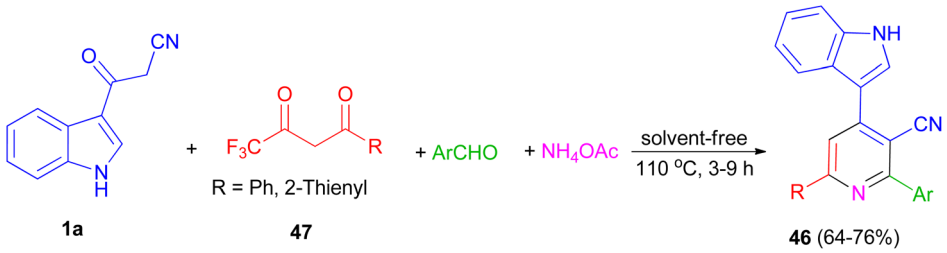


Scheme 17 Preparation of 2-(indol-3-yl)pyridine derivatives **43**.



Scheme 18 Synthesis of functionalized indole-3-yl pyridines **45**.

The one-pot four-component reaction of 3-(1*H*-indol-3-yl)-3-oxopropanenitriles **1**, aromatic aldehydes, cycloalkanones and ammonium acetate reported *via* a six-step tandem Knoevenagel condensation-nucleophilic addition to carbonyl-Michael addition-*N*-cyclization-elimination-air oxidation sequence to afford structurally intriguing indole–cycloalkyl[*b*]pyridine-3-carbonitrile



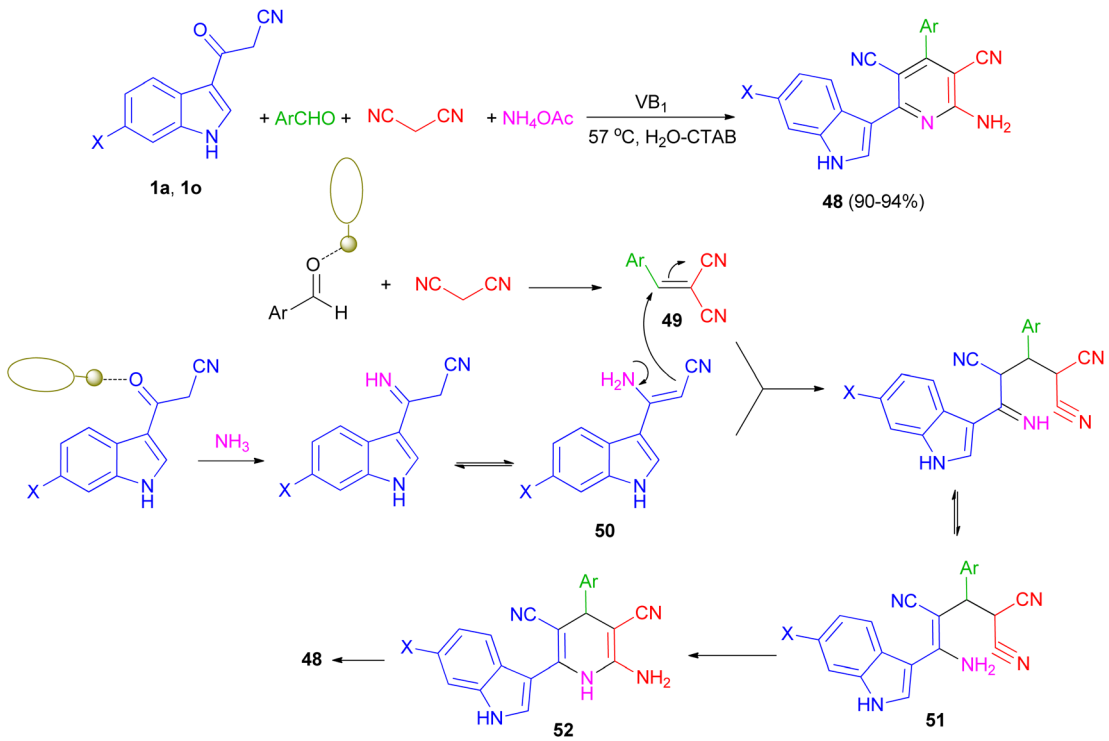
Scheme 19 Synthesis of 2-aryl-4-(1*H*-indol-3-yl)-6-phenyl-3-cyanopyridines **46**.

hybrid heterocycles **53–56** in 80–95% yields in refluxing EtOH for 2 h (Scheme 21).[55]

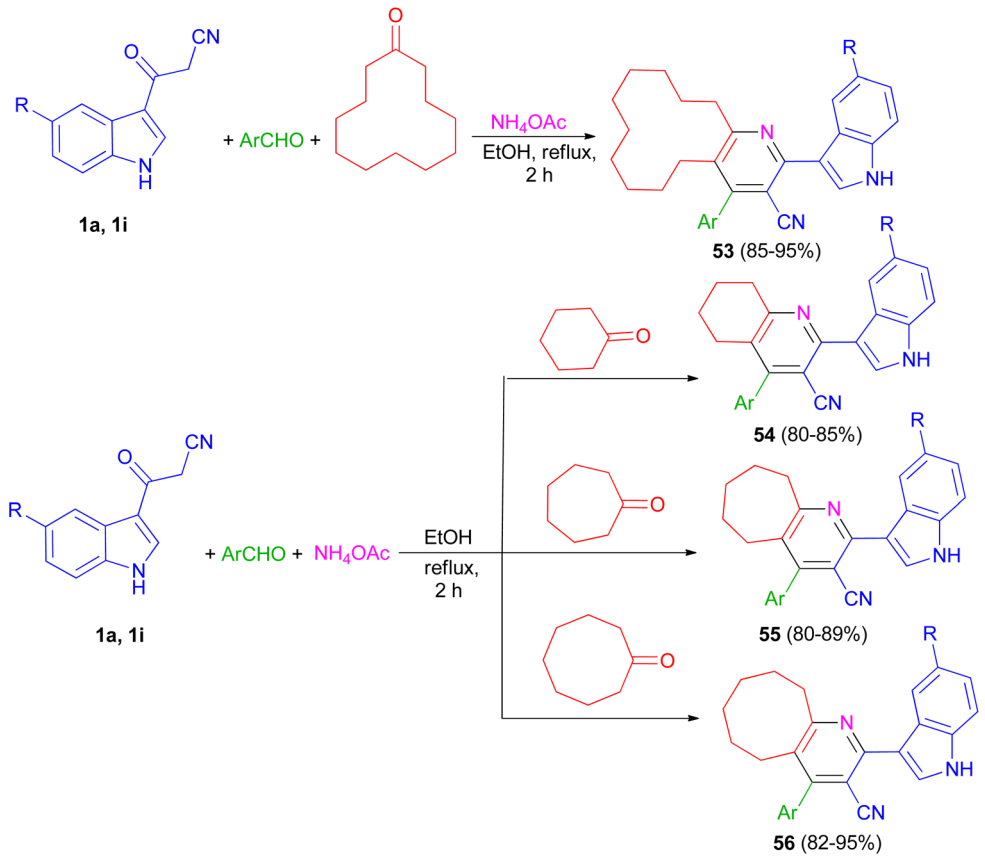
Priya and co-workers reported synthesis of 4-(4-fluorophenyl)-2-(1*H*-indol-3-yl)-5,6,7,8,9,10-hexahydrocycloocta[*b*] pyridine-3-carbonitrile (**57**) in 94% yield and 2-(1*H*-indol-3-yl)-4-(thiophen-2-yl)-5,6,7,8,9,10-hexahydrocycloocta[*b*]pyridine-3-carbonitrile (**58**) in 94% yield by one-pot four-component reaction of **1a**, aromatic aldehydes (4-fluorobenzaldehydealdehyde, thiophene-2-carboxaldehyde), cyclooctane and ammonium acetate in EtOH at reflux for 2 h (Scheme 22). Crystal structure, Hirshfeld surface analysis, DFT calculations and molecular docking studies on pyridine derivatives as potential inhibitors of nicotinamide phosphoribosyltransferase (NAMPT) of the synthesized compounds were investigated.[56]

An efficient and simple procedure for the synthesis of a class of diversely functionalized indole and coumarin containing pyridine-3-carbonitrile derivatives **59** in 85–92% yields has been described through one-pot four-component condensation reaction of 3-(1*H*-indol-3-yl)-3-oxopropanenitrile (**1a**), various aldehydes, 3-acetyl-2*H*-chromenones, and ammonium acetate in acetic acid at 120 °C for 3 h. The plausible mechanism pathway depicted in Scheme 23. Initially, Knoevenagel condensation reaction between **1a** and aldehyde gave intermediate **60** (acts as Michael acceptor) and 2-acetylchromenes and ammonium acetate gave intermediate **61**. Then, intermediate **60** undergoes Michael addition with **61** to give the intermediate **62**, which could apparently isomerizes to intermediate **63**. Intramolecular N-cyclization of **63** gave the dihydro intermediate **64**, which could further undergo dehydrogenation to afford the fully aromatized product **59**.[57]

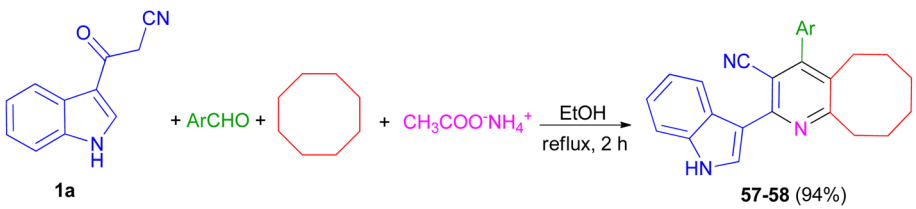
El-Sawy and co-workers utilized the one-pot four-component condensation of 3-cyanocarbomethylindole (**1a**), various aldehyde, 3-acetylindole, and ammonium acetate in glacial acetic acid at 120 °C for the synthesis of 2,6-bis(1*H*-indol-3-yl)-4-(substituted-phenyl)pyridine-5-carbonitriles **65**. Additionally, 2,6-bis(1*H*-indol-3-yl)-4-(benzofuran) pyridine-5-carbonitriles **66**



Scheme 20 Thiamine-hydrochloride catalyzed synthesis of 2-amino-6-(1*H*-indol-3-yl)-4-arylpyridine-3,5-dicarbonitriles **48**.



Scheme 21 Synthesis of indole-cycloalkyl[*b*]pyridine hybrids **53–56**.

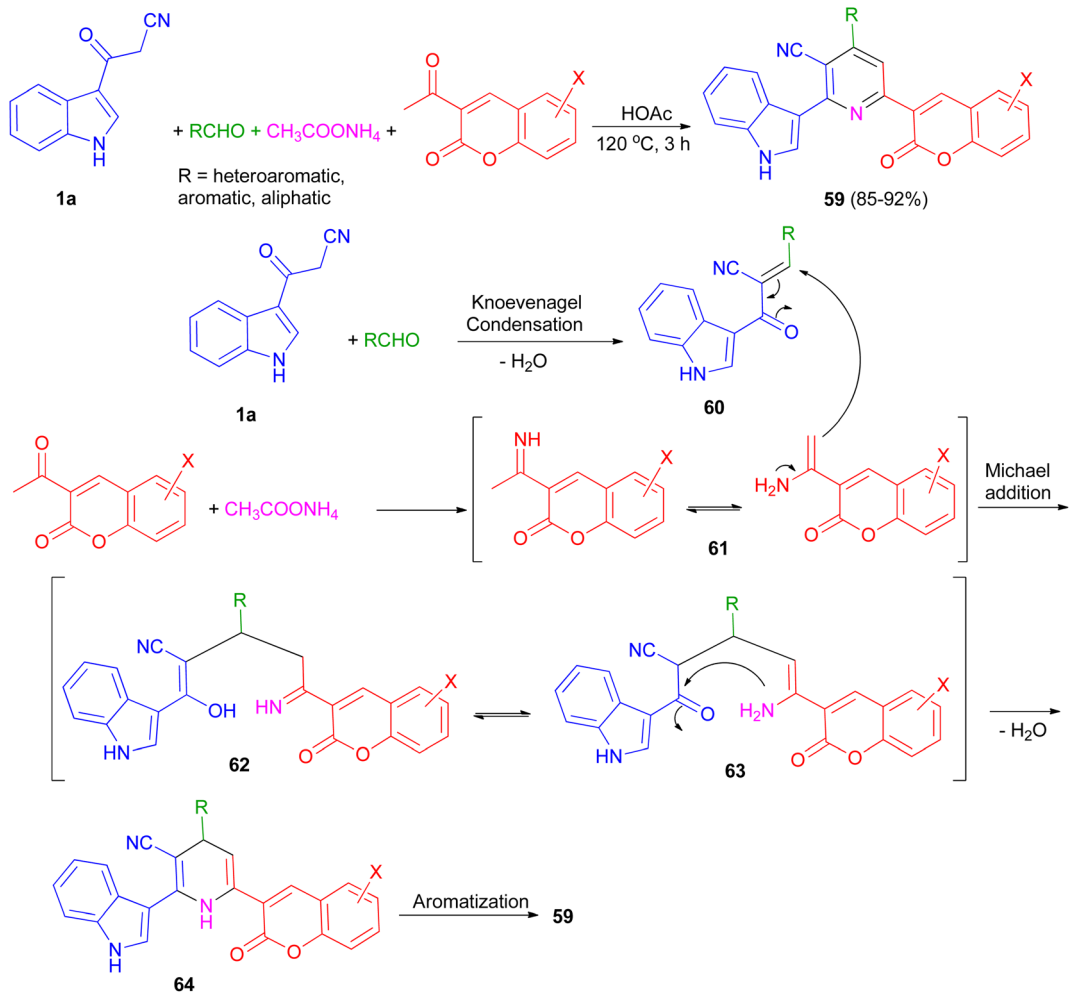


Scheme 22 Synthesis of pyridine derivatives **57** and **58**.

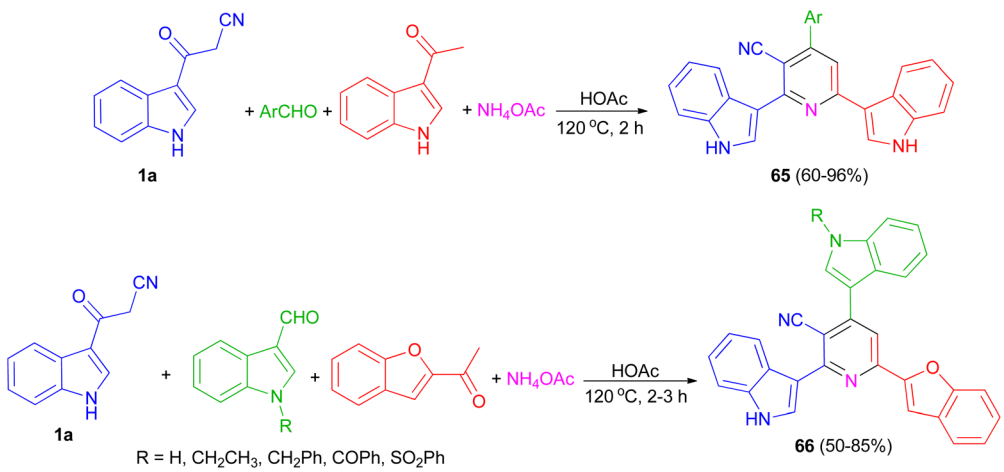
prepared *via* a one-pot four-component condensation of 3-cyanocarbomethylindole, various *N*-substituted-indole-3-aldehydes, 2-acetylbenzofuran, and ammonium acetate in glacial acetic acid at 120 °C for 2 h (Scheme 24). The synthesized compounds exhibited *in vitro* antimicrobial (MIC, MBC), anti-biofilm properties.[58]

Ammonium acetate as a dual rule reagent-catalyst used for the synthesis of symmetrical terpyridines **67** in 60–83% yields by the reaction of 1,1′-(2,6-dimethylpyridine-3,5-diyl)bis(ethan-1-one) (**68**), 3-(1*H*-indol-3-yl)-3-oxopropanenitrile (**1a**) and aromatic aldehydes under solvent-free conditions at 100 °C for 35–70 min. The proposed mechanism is displayed in Scheme 25. Initially, carbonyl groups of **68** are activated by AcOH (derived from thermal dissociation of ammonium acetate) and reacted with ammonia which leads to related imine intermediate **69**. Then, *via* a tautomerization process, intermediate **69** converted to intermediate **70**. Meanwhile, intermediate **71** is obtained from a Knoevenagel condensation reaction between aldehyde and **1a**. After that, intermediate **70** reacts with intermediate **71** which results to formation of intermediate **72**. In the next step, through successive tautomerization process, and intramolecular nucleophilic attack intermediate **73** is formed. In the next step, intermediate **73** through dehydration converted to the related intermediate **74**. Finally, the corresponding product **67** is produced *via* a cooperative vinylogous anomeric based oxidation mechanism both in the presence and absence of oxygen.[59]

Further, an eco-friendly, efficient and cost effective procedure described for the synthesis of 1,4-dihydropyridine **75** in 64–86% yields by a solvent and catalyst free Hantzsch reaction's condensation of **1a**, 2-fluoroacetophenone and substituted aldehyde in the presence of ammonium acetate under



Scheme 23 Synthesis of indole and coumarin containing pyridine-3-carbonitriles **59**.

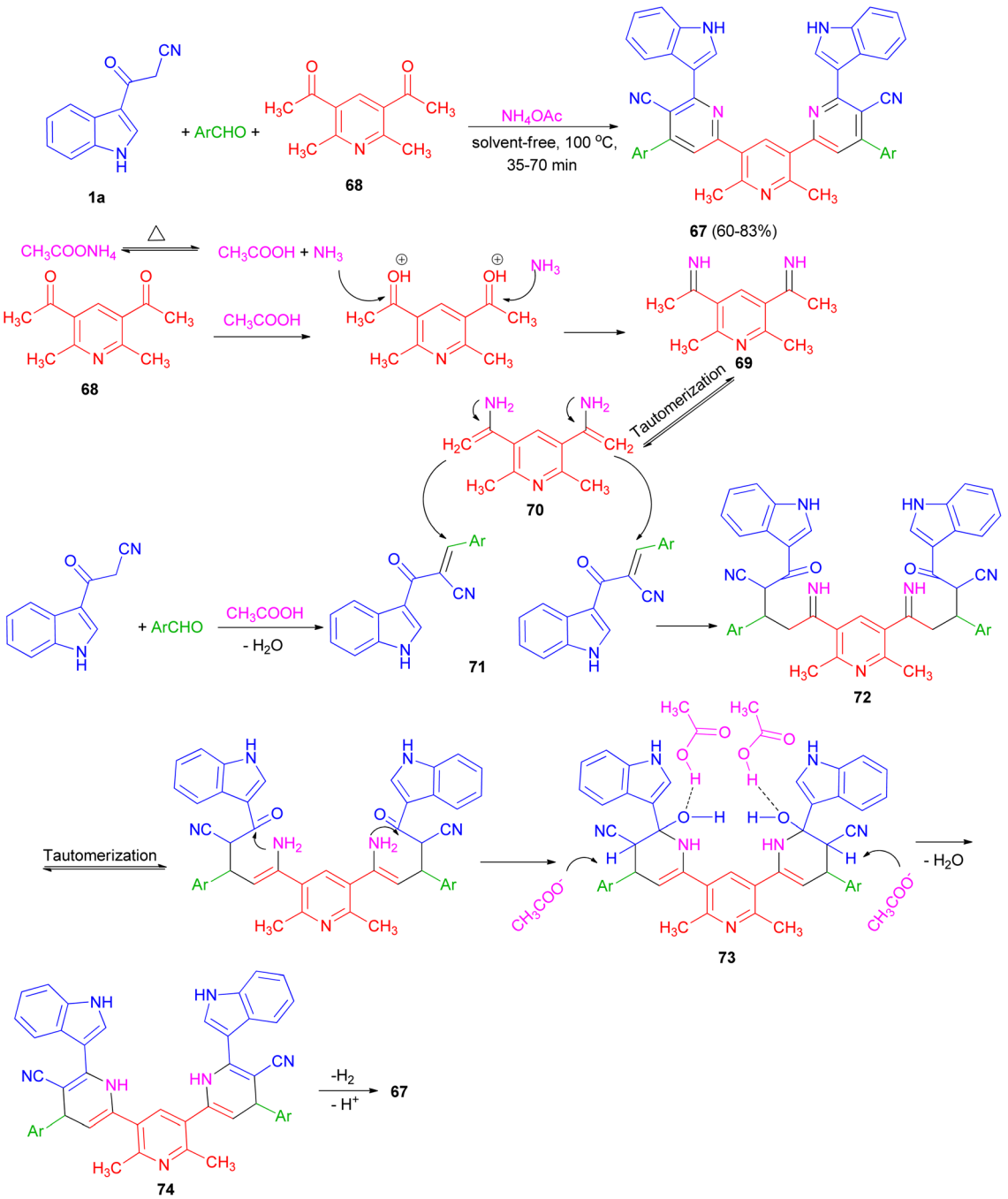


Scheme 24 Preparation of bis(indolyl)pyridines **65** and **66**.

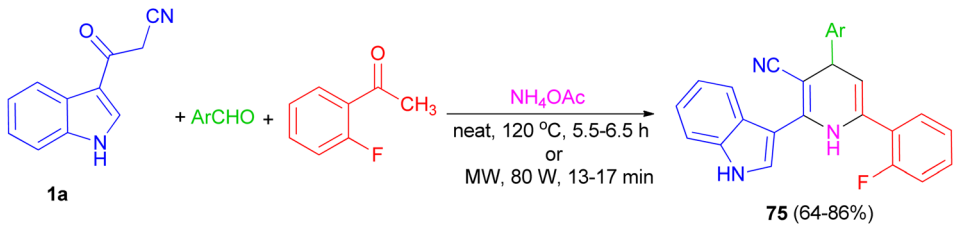
conventional heating at 120 °C for 5.5–6.5 h and microwave irradiation at 80 W for 13–17 min (Scheme 26). Also, anti-bacterial and anti-fungal of the synthesized compounds were investigated.[60]

3.3. Pyrimidine and tetrahydropyrimidine derivatives

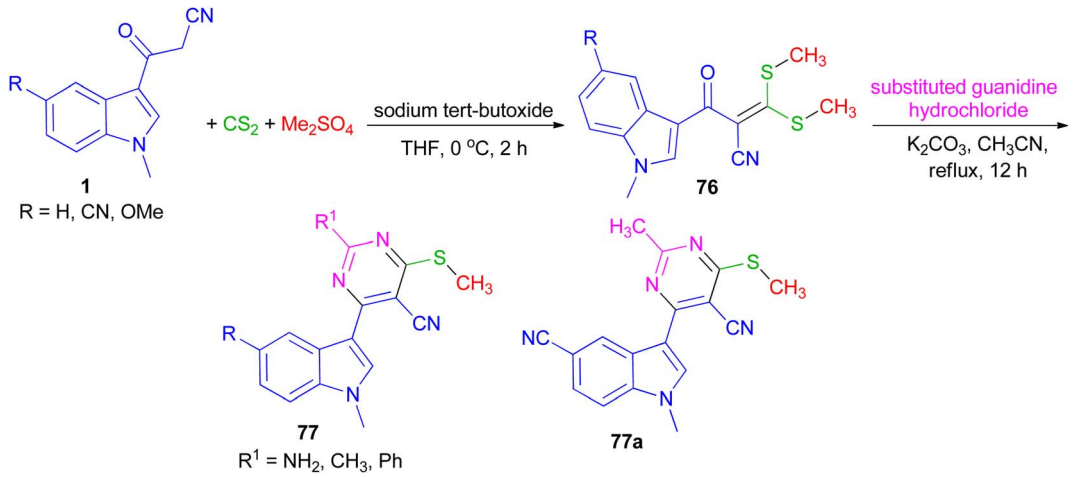
In 2022, Patil *et al.* converted 3-(1-methyl-1*H*-indol-3-yl)-3-oxopropanenitriles **1** to 2-(1-methyl-1*H*-indole-3-carbonyl)-3,3-bis(methylthio)acrylonitriles **76** by the reaction of carbon



Scheme 25 Synthesis of symmetrical terpyridines **67**.



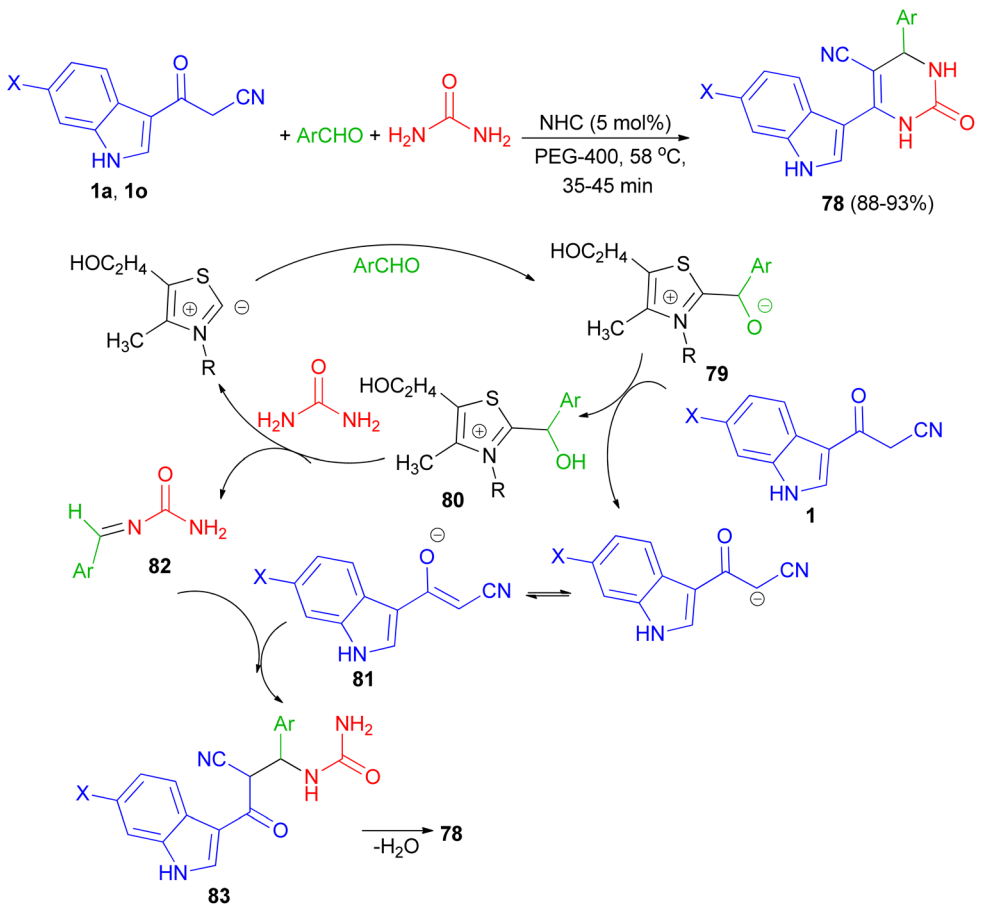
Scheme 26 Synthesis of indole containing 1,4-dihydropyridines **75**.



Scheme 27 Synthesis of 4-(1-methyl-1*H*-indol-3-yl)-6-(methylthio) pyrimidine-5-carbonitriles **77**.

disulfide in the presence of sodium tert-butoxide followed by alkylation with dimethyl sulfate in dry THF at 0 °C for 2 h. Further, **76** on cycloaddition with substituted guanidine hydrochloride under an alkaline condition in refluxing acetonitrile for 12 h furnished desired 4-(1-methyl-1*H*-indol-3-yl)-6-(methylthio) pyrimidine-5-carbonitriles **77** in 90–96% yields. All the synthesized compounds exhibited potent anticancer activity against breast cancer cell line, which was significantly altered with the substitution of indole and pyrimidine. In addition, compound **77a** was found to be an effective anti-inflammatory agent (Scheme 27).[61]

In 2013, Singh *et al.* developed a three-component, one-pot, direct and highly efficient cyclocondensation method for the synthesis of 6-(1*H*-indol-3-yl)-2-oxo-4-aryl-1,2,3,4-



Scheme 28 NHC catalyzed synthesis of 6-(1*H*-indol-3-yl)-2-oxo-4-aryl-1,2,3,4-tetrahydropyrimidine-5-carbonitriles **78**.

tetrahydropyrimidine-5-carbonitriles **78** in 88–93% yields by combining an aryl aldehyde with 3-(cyanoacetyl)-indoles **1** and urea in the presence of the PEG-400 and a catalytic amount of thiazolium anion (NHC) at 58 °C for 35–45 min. The plausible mechanistic pathway for the synthesis of product **78** is illustrated in Scheme 28. The aldehyde initially reacts with NHC (as thiazolium ion) to give an intermediate **79**, which further reacts with cyanoacetylindole **1** to give species **80** and corresponding anion of **1**, *i.e.*, **81** by removal of acidic hydrogen. Species **80** further reacts with urea to give intermediate **82.** Intermediate **81** and **82** further reacts to give intermediate **83**, which upon intramolecular cyclocondensation reaction yields the desired product of series **78.**[62]

Singh *et al.* employed thiamine hydrochloride (5 mol%) as catalyst for the preparation of 6-(1*H*-indol-3-yl)-2-oxo-4-aryl-1,2,3,4-tetrahydropyrimidine-5-carbonitriles **84** in 82–92% yields *via* the one-pot three-component reaction of **1a**, aryl aldehydes and urea in the presence of the cationic surfactant (CTAB, 20 mol%) in water at 60 °C for 20–30 min (Scheme 29).[63]

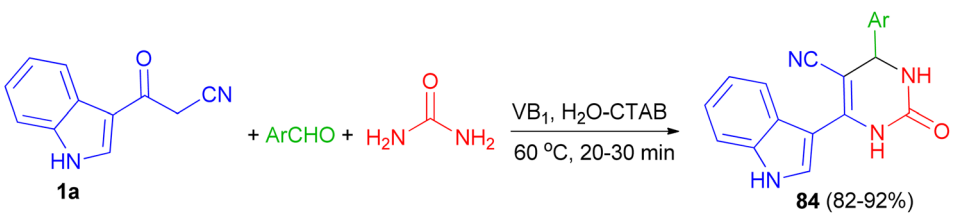
3.4. Pyrazole derivatives

In 2013, Ghosh *et al.* described synthesis of 5-(1*H*-indol-3-yl)-pyrazolyl derivatives **85a–b** as colorimetric sensor for anions in 72–80% yields by the reaction of **1a** with hydrazine hydrate in the presence of *p*-TSA as catalyst in CH_3CN at 82 °C for 8–20 h under nitrogen atmosphere (Scheme 30). Compound **85a** as colorimetric sensor shows a drastic change in absorption spectrum and colour upon addition of F^- in DMSO solution due to the deprotonation of indole-NH proton. Moreover, **85b** binds with F^-, CN^-, $H_2PO_4^-$, $AcO^-$and $PhCOO^-$ ions exploiting hydrogen-bonding interaction with the shifting of absorption band to longer wavelength and subsequent colour change of the solution.[64]

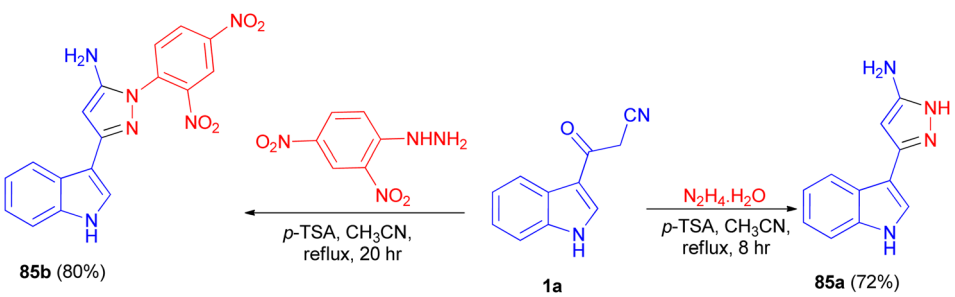
Ketene dithioacetal mediated chemo- and regioselective synthesis of a series of 1,3,4,5-tetrasubstituted pyrazole derivatives **86** in 82–88% yields integrated with a bioactive indole nucleus was achieved by reacting substituted 2-(1-methyl-1*H*-indole-3-carbonyl)-3,3-bis-(methylthio)-acrylonitrile **87** and substituted phenyl hydrazine hydrochloride in the presence of a catalytic amount of anhydrous K_2CO_3 in EtOH under reflux conditions for 3 h. All the synthesized compounds were *in vitro* evaluated for their anti-inflammatory, antioxidant and cytotoxic potential against breast carcinoma (MCF-7). Among the compounds under investigation, 5-(5-bromo-1-methyl-1*H*-indol-3-yl)-1-(4-cyano-phenyl)-3-methylsulfanyl-1*H*-pyrazole-4-carbonitrile (**86a**) and 5-(1,2-dimethyl-1*H*-indol-3-yl)-3-methylsulfanyl-1-phenyl-1*H*-pyrazole-4-carbonitrile (**86b**) exhibited significant antitumor and anti-inflammatory activities, respectively (Scheme 31).[65]

3.5. Pyrazolopyridine derivatives

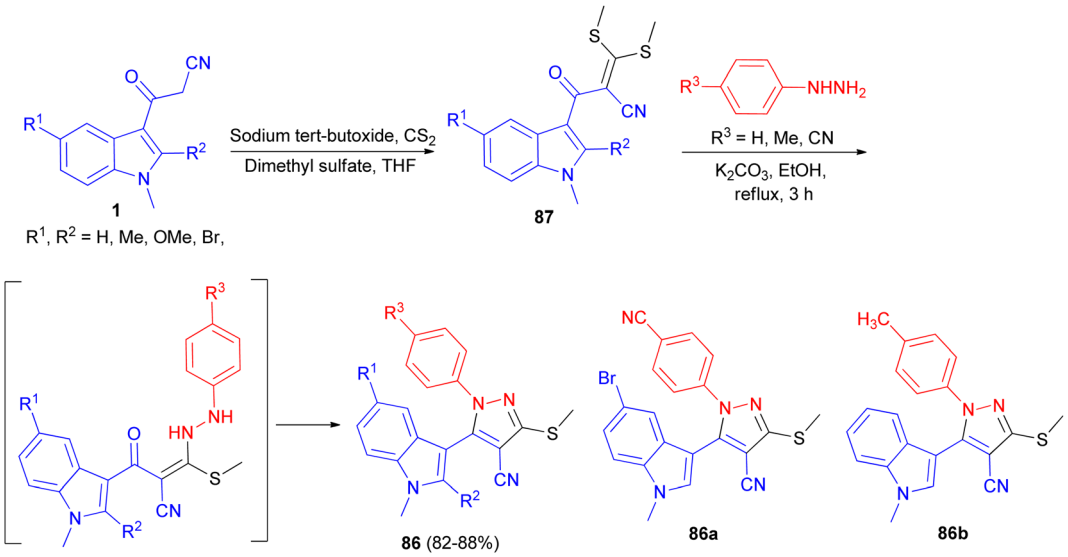
In 2013, Mamaghani and his group synthesized polyfunctional pyrazolo[3,4-*b*]pyridines **88** *via* a regioselective one-pot three-component reaction of 3-(cyanoacetyl)indoles **1**, 5-amino-3-methylpyrazole (**89**) and aryl aldehydes in 85–98% yields using Fe^{3+}-montmorillonite as a reusable catalyst under conventional conditions in refluxing EtOH for 20–40 min and ultrasonic irradiation (40 kHz, 60 °C and 3–7 min). The plausible mechanism for the formation of **88** is outlined in Scheme 32. The formation of these products can be visualised by initial Knoevenagel condensation of aldehyde and 3-cyanoacetylindoles (**1**). The Fe^{3+}@Mont. activated arylidene intermediate, seems to be a good acceptor for the Michael addition of **1** *via* attack of the nucleophilic C-4 of the pyrazole, followed by cyclisation and loss of H_2O to furnish the desired pyrazolopyridines **88**. These products were also evaluated for their antibacterial activities.



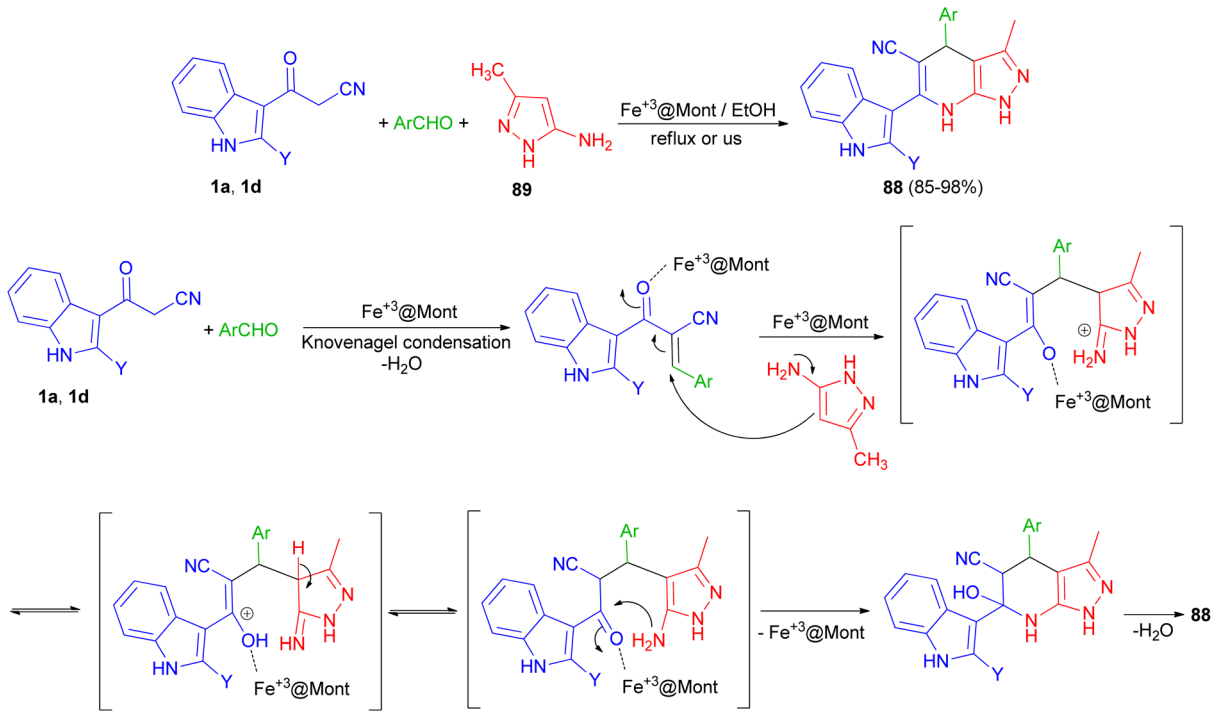
Scheme 29 Preparation of 6-(1*H*-indol-3-yl)-2-oxo-4-aryl-1,2,3,4-tetrahydropyrimidine-5-carbonitriles **84**.



Scheme 30 Synthesis of 5-(1*H*-indol-3-yl)-pyrazolyl derivatives **85a–b**.



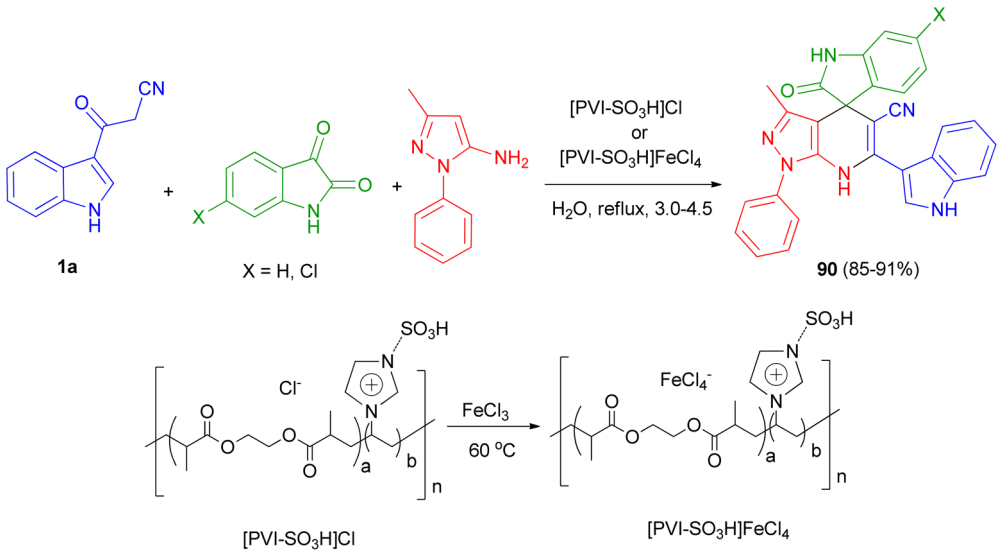
Scheme 31 Synthesis of a series of 1,3,4,5-tetrasubstituted pyrazole derivatives **86**.



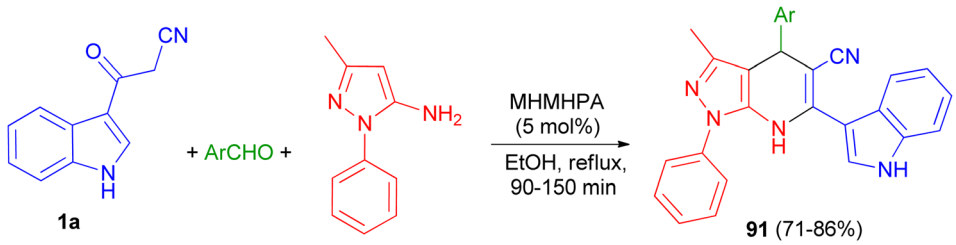
Scheme 32 Polyfunctional pyrazolo[3,4-*b*]pyridines **88**.

Most of the compounds exhibited excellent antibacterial activity against both Gram-negative and Gram-positive bacteria.[66]

Mesoporous cross-linked poly(vinyl imidazole)s with sulfonic acid tags, [PVI-SO_3H]Cl and [PVI-SO_3H]$FeCl_4$, were successfully applied as reusable and efficient catalysts for the preparation of N-heterocycle spiropyrans **90** *via* the one-pot reaction of isatin derivatives, 3-methyl-1-phenyl-1*H*-pyrazol-5-amine and 3-(1*H*-indol-3-yl)-3-oxopropanenitrile (**1a**) in water under reflux conditions 3.0–4.5 h (Scheme 33). In the proposed mechanism, initially, the acidic groups (SO_3H) of [PVI-SO_3H]$FeCl_4$ or [PVI-SO_3H]Cl activate the carbonyl group of isatin, and **1a** are enolized. Then, the reaction of **1a** with isatin leads to a removal of one molecule of H_2O to give first intermediate. In the next step, 3-methyl-1-phenyl-1*H*-pyrazol-5-amine as a nucleophile attacks to the intermediate, which acts as a Michael acceptor, to give second intermediate. Finally, the cyclocondensation reaction of second intermediate affords third intermediate, which is converted into the corresponding N-heterocycle spiropyran derivatives **90**.[67]



Scheme 33 Preparation of *N*-heterocycle spiropyrans **90**.



Scheme 34 Synthesis of (3′-indolyl)pyrazolo[3,4-*b*]pyridines **91**.

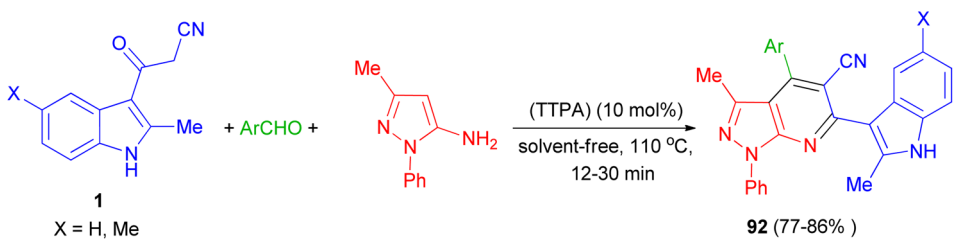
In 2020, Zolfigol and his group described preparation of (3′-indolyl)pyrazolo[3,4-*b*]pyridines **91** in 71–86% yields *via* an one-pot reaction between cyanoacetylindole, 3-methyl-1-phenyl-1*H*-pyrazol-5-amine, and an aromatic aldehyde in the presence of melamine hexakis(methylene)hexakis(phosphonic acid) (MHMHPA) as a heterogeneous nanocatalyst under refluxing ethanol for 90–150 min (Scheme 34).[68]

Zolfigol and his group synthesized (3′-indolyl)pyrazolo[3,4-*b*] pyridine derivatives **92** in 77–86% yields by the reaction of 3-methyl-1-phenyl-1*H*-pyrazol-5-amine, aryl aldehyde and 3-cyanoacetyl indoles **1** using the acrine tetrakis (phosphonic acid) (TTPA) (10 mol%) as nanocatalyst under solvent-free condition at 110 °C for 12–30 min. Also, bis aromatic aldehydes (terephthaldehyde and iso-terephthaldehyde) produced their corresponding bis(2-methyl-1*H*-indol-3-yl)-pyrazolo[3,4-*b*]pyridines (Scheme 35).[69]

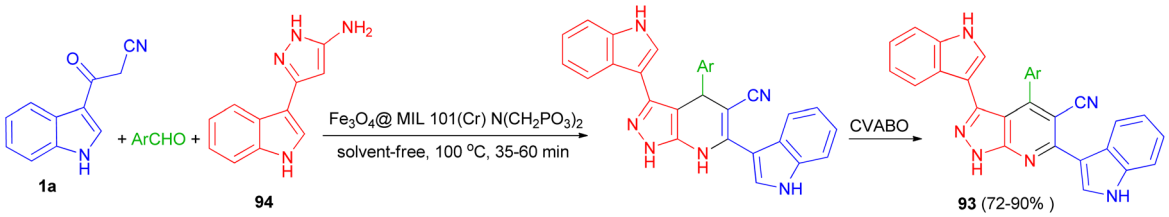
A nano-magnetic metal–organic frameworks based on Fe_3O_4 namely Fe_3O_4@ MIL-101(Cr)–$N(CH_2PO_3)_2$ was used as catalyst in the synthesis of pyrazolo [3,4-*b*] pyridines **93** in 72–90% yields by condensation reaction of aldehydes, 5-(1*H*-indol-3-yl)-2*H*-pyrazol-3-ylamine (**94**) and 3-(cyanoacetyl)indole (**1a**) *via* a cooperative vinylogous anomeric-based oxidation (CVABO) at 100 °C and under solvent-free conditions for 35–60 min (Scheme 36).[70]

3.6. Pyrazolopyrimidine derivatives

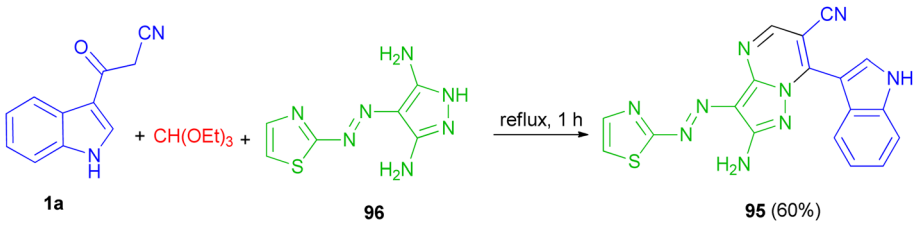
In 2015, El-Mekabaty and co-worker presented the synthesis of pyrazolo[1,5-*a*]pyrimidine derivative **95** in 60% yield by the



Scheme 35 Synthesis of (3′-indolyl)pyrazolo[3,4-*b*]pyridine derivatives **92**.



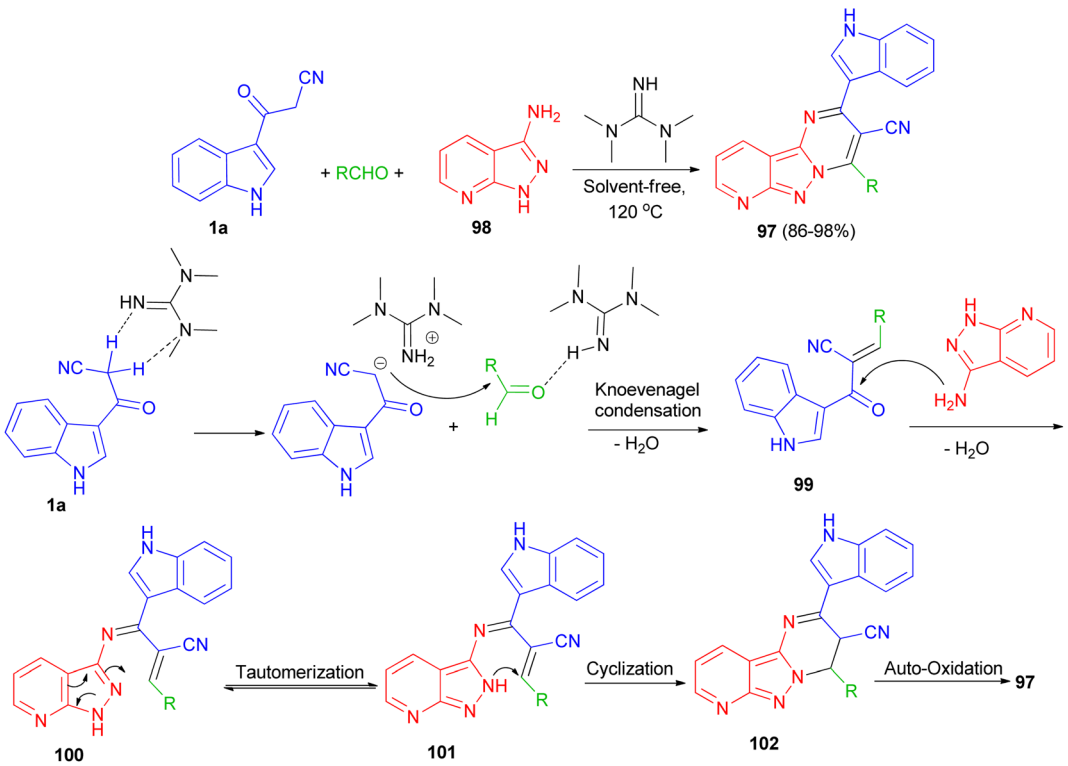
Scheme 36 Synthesis of pyrazolo[3,4-*b*] pyridines **93**.



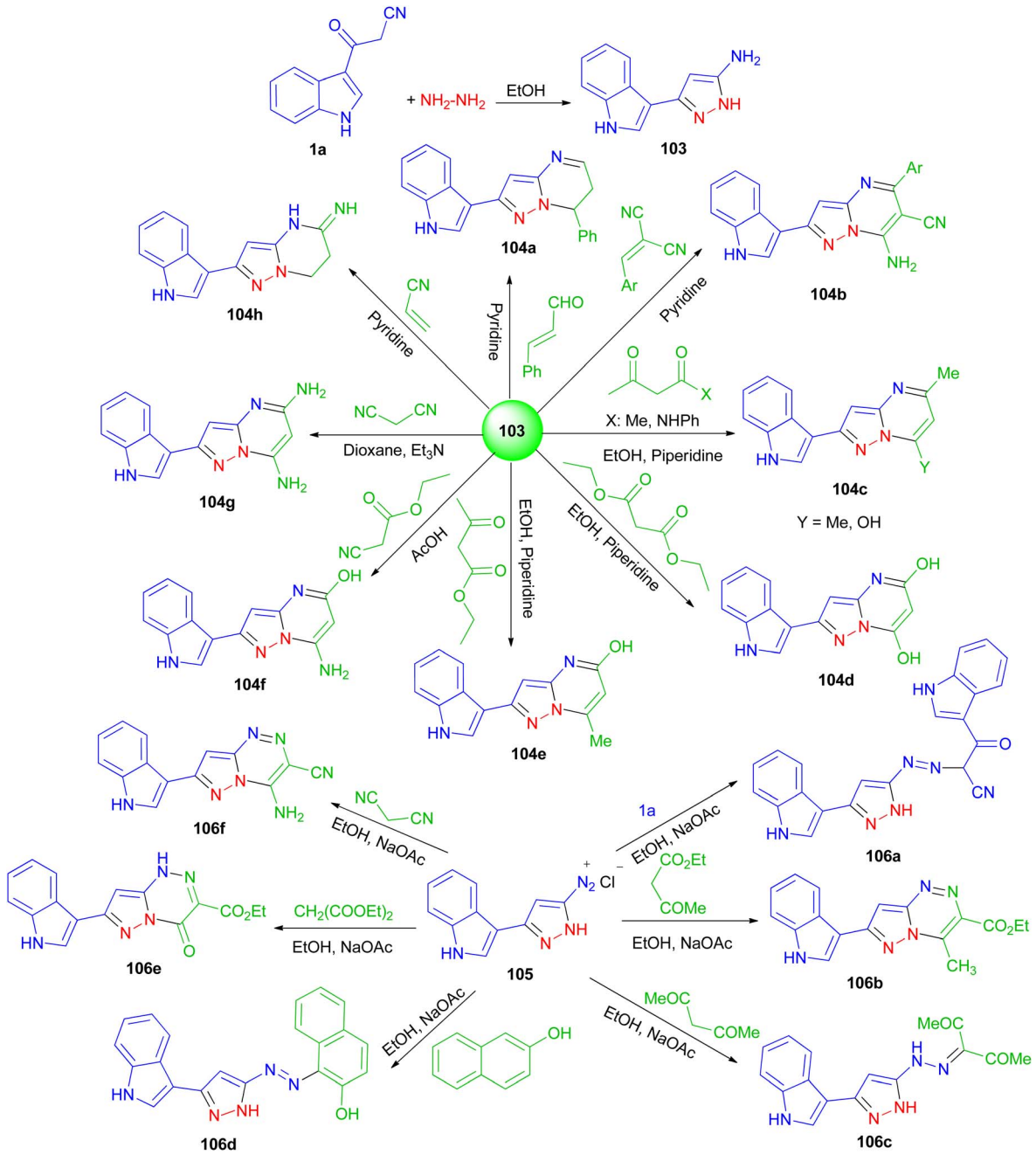
Scheme 37 Synthesis of pyrazolo[1,5-*a*]pyrimidine derivative **95**.

reaction of 3-(1*H*-indol-3-yl)-3-oxopropanenitrile **1a** with 4-(thiazol-2-yldiazenyl)-1*H*-pyrazole-3,5-diamine **96** and triethyl orthoformate under reflux conditions for 1 h (Scheme 37).[71]

Jeong and co-workers described an efficient solvent-free access towards highly substituted pyrido[2′,3′ : 3,4]pyrazolo [1,5-*a*]pyrimidine-3-carbonitrile derivatives **97** in 86–98% yields through multi-component reaction of 1*H*-pyrazolo[3,4-*b*] pyridin-3-amine **98**, aldehyde and **1a** catalyzed by 1,1,3,3-tetramethylguanidine (TMG) at 120 °C. A plausible mechanism is proposed in Scheme 38. Initially, TMG activate aldehydes through hydrogen binding to start the nucleophilic addition of **1a**, to provide a nucleophilic TMG *via* capturing a proton of **1a** to form corresponding carbanions. Activation of the starting aldehydes by hydrogen bonding increases the electrophilicity of the aldehyde and assists the formation of the corresponding adduct **99** (Knoevenagel product) with **1a**. This adduct **99**



Scheme 38 Synthesis of highly substituted pyrido[2′,3′ : 3,4]pyrazolo[1,5-*a*]pyrimidines **97** using TMG.



Scheme 39 Synthesis of pyrazolo[1,5-*a*]pyrimidines **131** and pyrazolo[5,1-*c*]triazines **133**.

undergoes Michael type addition reaction with **98** to form an adduct **100** intermediate. The intermediate **100** further tautomerization *via* proton transfer N–N to give **101**. After that intermediate **101** underwent intramolecular cyclization leading to the C–N bond formation and gave intermediate **102**, which was followed by the auto-oxidation leading to the formation product **97**.[72]

Next, El-Mekabaty and co-workers prepared 3-(1*H*-indol-3-yl)-1*H*-pyrazol-5-amine **103** in a quantitative yield by heating **1a** in dry ethanol with hydrazine hydrate, and utilized as key intermediate for the synthesis of some new pyrazolo[1,5-*a*]pyrimidines and pyrazolo[5,1-*c*]triazines. The reaction of **103** with acetylacetone, acetoacetanilide, diethylmalonate, ethylacetoacetate, ethyl cyanoacetate, malononitrile, 2-(4-methoxybenzylidene)malononitrile, cinnamaldehyde or acrylonitrile, under various conditions afforded pyrazolo[1,5-*a*]pyrimidines **104a–h** in 37–81% yields after 4–22 h. Also, the reaction of diazotized **105** (prepared from **103** and the appropriate quantities of conc. HCl and sodium nitrite) with malononitrile, ethyl acetoacetate, diethylmalonate, 3-(1*H*-indol-3-yl)-3-oxopropanenitrile, β-naphthol or acetylacetone gave pyrazolo[5,1-*c*]triazines **106a–f** in 44–81% yields after 6–9 h (Scheme 39). Most of the tested compounds belonging to the pyrazolo[1,5-*a*]

pyrimidine series exhibited better antioxidant activities than members of the pyrazolotriazine one.[73]

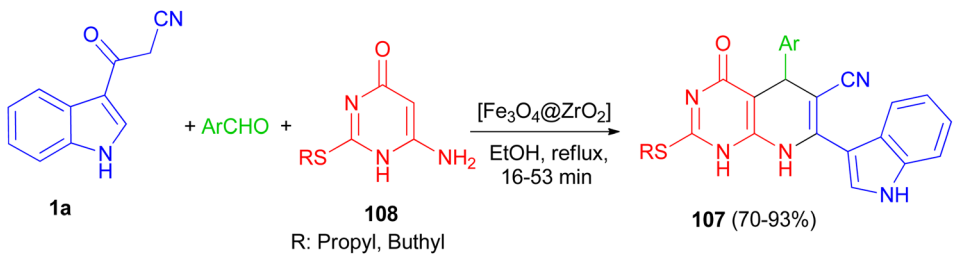
3.7. Pyridopyrimidine derivatives

In 2016, Mamaghani and his group established a new synthetic protocol for the preparation of pyrido[2,3-*d*]pyrimidine derivatives **107** in 70–93% yields *via* one-pot multicomponent reactions of 6-amino-2-(alkylthio)pyrimidin-4(3*H*)-one **108**, **1a** and arylaldehydes using [Fe_3O_4@ZrO_2] as magnetically recyclable nanocatalyst in EtOH under reflux conditions for 16–53 min. The reaction proceeds *via* Knoevenagel condensation, Michael addition, cyclization and dehydration (Scheme 40).[74]

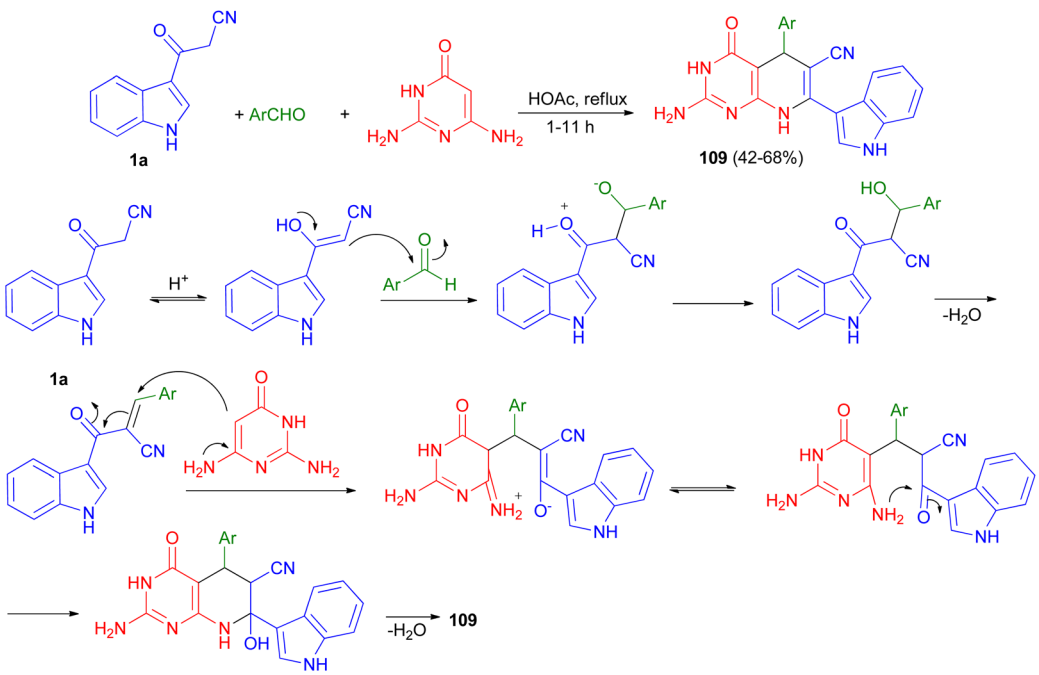
A series of pyrido[2,3-*d*]pyrimidine indole derivatives **109** were synthesized in 42–68% yields by one-pot three-component cyclocondensation Michael reaction between 2,6-diaminopyrimidine-4(3*H*)-one, **1a** and aromatic aldehydes in boiling acetic acid as solvent for 1–11 h. A plausible mechanism is presented in Scheme 41. Initially, a conventional Knoevenagel condensation occurs which is initiated by a nucleophilic attack of the 3-(2-cyanoacetyl)indole methylene carbon atom towards the aldehyde carbonyl (C) atom. The second stage starts again *via* a nucleophilic attack, this time of the C-5 carbon atom of the aminopyrimidine towards the aryl-substituted center (former carbonyl carbon of the reactant aromatic aldehyde). An intermediate is generated which then undergoes intramolecular cyclization mediated by nucleophilic attack of the amino group of the aminopyrimidine towards the carbonyl (C) atom. Dehydration at the latter then finally leads to the desired product **109**.[75]

After that, bioactive 2-methylindole-substituted pyrido[2,3-*d*]pyrimidine derivatives **110** in 70–90% yields were synthesized through one-pot three-component reaction of aromatic aldehydes, 6-amino-*N*,*N*-dimethyluracil, 3-(2-methyl-1*H*-indol-3-yl)-3-oxopropanenitrile (**1**) in the presence of Fe_3O_4@SiO_2-IL nanocatalyst as an efficient and magnetically retrievable catalyst in DMF at 120 °C for 50–120 min. The antibacterial activity of synthesized compounds was also examined and most of them showed good antibacterial activity against the tested strains (Scheme 42).[76]

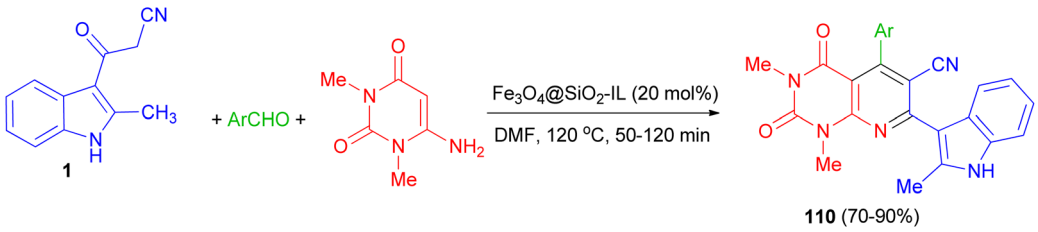
Zhu and co-workers established an efficient and catalyst-free protocol for the synthesis of a series of indole substituted or spirooxindole-consisted dihydropyrido[2,3-*d*]pyrimidine



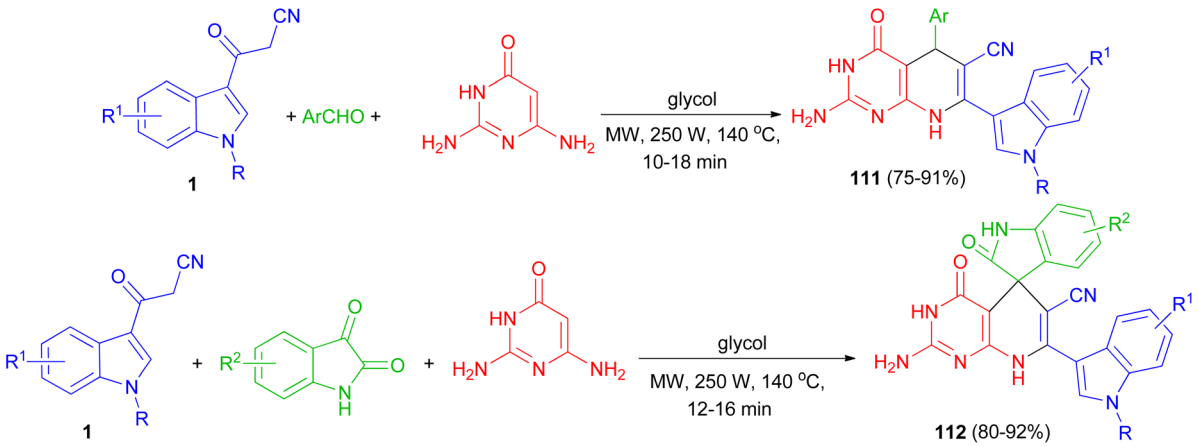
Scheme 40 [Fe_3O_4@ZrO_2] catalyzed synthesis of pyrido[2,3-*d*]pyrimidine derivatives **107**.



Scheme 41 Synthesis of pyrido[2,3-*d*]pyrimidine indole substituted derivatives **109**.



Scheme 42 Synthesis of indole-substituted pyrido[2,3-*d*]pyrimidines **110**.

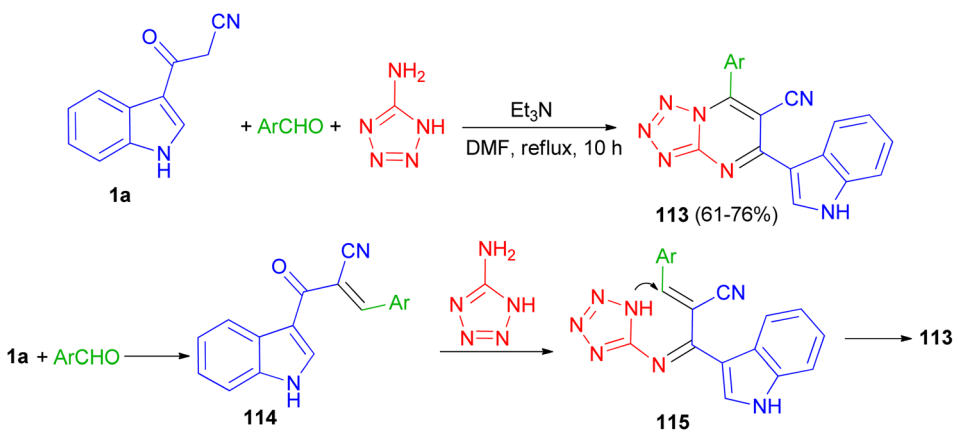


Scheme 43 Synthesis of indolyl substituted and spirooxindole pyrido[2,3-*d*]pyrimidine derivatives **111** and **112**.

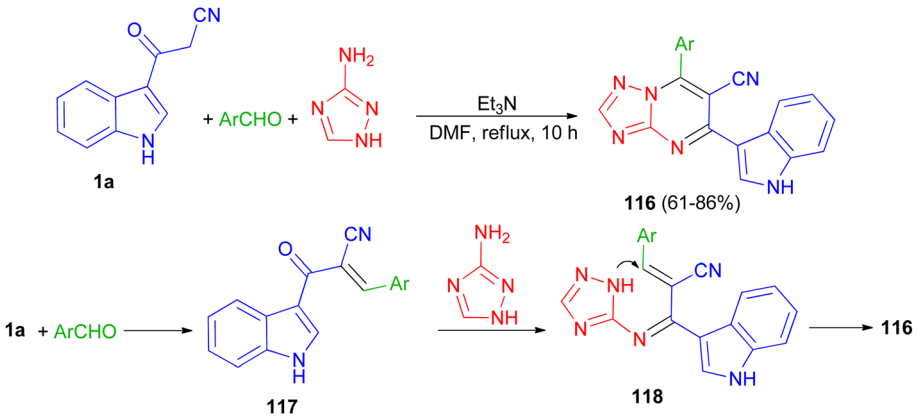
derivatives **111** and **112** in 75–92% yields by one-pot three-component reaction of 2,6-diaminopyrimidine-4-one, various aryl aldehydes or isatins, and 3-cyanoacetyl indoles **1** in glycol under microwave irradiation at 250 W and 140 °C for 10–18 min (Scheme 43).[77]

3.8. Tetrazolopyrimidine and triazolopyrimidine derivatives

In 2020, a series of 7-substituted-5-(1*H*-indol-3-yl)tetrazolo[1,5-*a*]pyrimidine-6-carbonitrile **113** was synthesized in 61–76% yields *via* a one-pot, three-multicomponent reaction of appropriate aldehydes, 1*H*-tetrazole-5-amine and 3-cyanoacetyl indole (**1a**) using triethylamine as catalyst in DMF under reflux condition for 10 h. A probable mechanism is suggested in Scheme 44. Firstly, TEA initiates aldehydes through hydrogen binding to start the nucleophilic addition of **1a**. Activation of the starting aldehydes by hydrogen bonding increases the electrophilicity of the aldehyde and supports the production of the corresponding intermediate **114** (Knoevenagel product) with compound **1a**. This adduct undergoes a Michael type addition reaction with 1*H*-tetrazol-5-amine to yield an adduct **115** intermediate. After that, intermediate **115** underwent intramolecular cyclization leading to the C–N bond formation



Scheme 44 Preparation of 7-substituted-5-(1*H*-indol-3-yl)tetrazolo[1,5-*a*]pyrimidine-6-carbonitriles **113**.



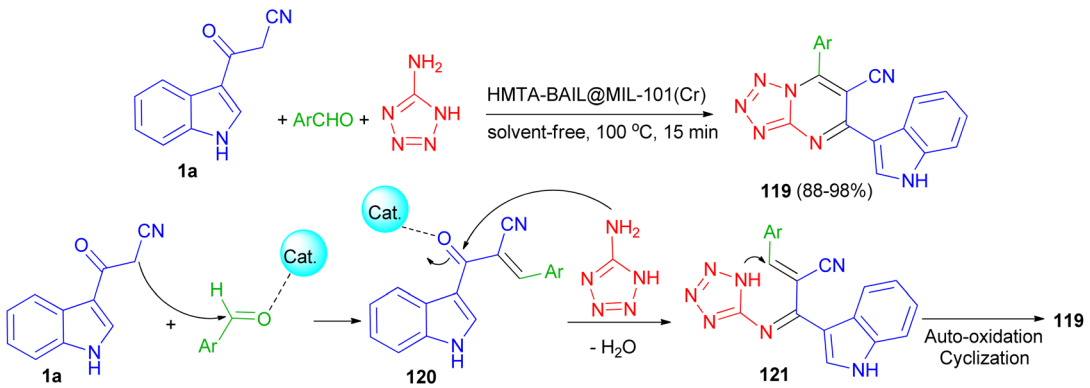
Scheme 45 Preparation of triazolopyrimidine derivatives **116**.

followed by the auto-oxidation leading to the formation product **113**. The synthesized compounds showed potent anticancer activities against human colon and human lung cancer.[78]

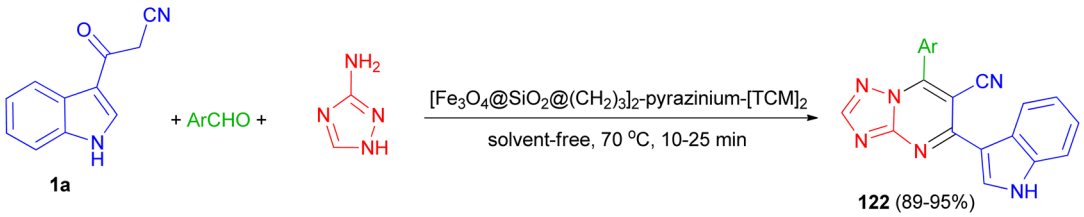
A series of triazolopyrimidine derivatives **116** was produced *via* three-component reactions of suitable aromatic or hetero-aromatic carboxaldehyde, 3-amino-1,2,4-triazole, and 3-indolyl-3-oxopropanenitrile (**1a**) using triethylamine as a catalyst in DMF at 120 °C for 10 h. Antiproliferative activity of the compounds has been examined toward four different human cancer cells and one human healthy cell line. Some of synthesized compounds are active against the human colon cancer; all triazolopyrimidines are active toward MCF-7; and are effective anticancer applicants on hormone-dependent instead of hormone-independent MCF-7. A possible mechanism proposed in Scheme 45. First, triethylamine activated the nucleophilic reaction of **1a** *via* hydrogen bonding to excite carboxaldehyde. The initiation of carboxaldehyde by H-bond enhances the electrophilicity of the carboxaldehyde and improves the building of a transitional **117**. Intermediate **117** and 3-amino-1,2,4-triazole then undergo Michael's reaction to form intermediate **118** *via* intramolecular cyclization reaction to form a C–N bond. Subsequently, compound **116** obtained in 61–86% yields by autoxidation.[79]

Next, Ghasemzadeh *et al.* utilized the one-pot three-component reaction of benzaldehydes, 1*H*-tetrazole-5-amine, and 3-cyanoacetyl indole (**1a**) in the presence of a new hexamethylenetetramine-based ionic liquid/MIL-101(Cr) metal–organic framework as a recyclable catalyst for the synthesis of tetrazolo[1,5-*a*]pyrimidine-6-carbonitriles **119** in 88–98% yields under solvent-free conditions at 100 °C for 15 min. A plausible mechanism is shown in Scheme 46. It is suggested that HMTA-BAIL@MIL-101(Cr) serves as a dual Brønsted/Lewis acid catalyst (IL/Cr^{3+} active sites), increasing the electrophilicity of the carbonyl groups of the aldehyde and the intermediates. Firstly, the activated carbonyl of the benzaldehyde undergoes a Knoevenagel condensation reaction with 3-cyanoacetyl indole to afford the intermediate **120**, followed by the condensation reaction with 1*H*-tetrazole-5-amine to produce the intermediate **121**. The intramolecular cyclization of the intermediate **121** with a subsequent auto-oxidation reaction finally gives the desired product **119**.[80]

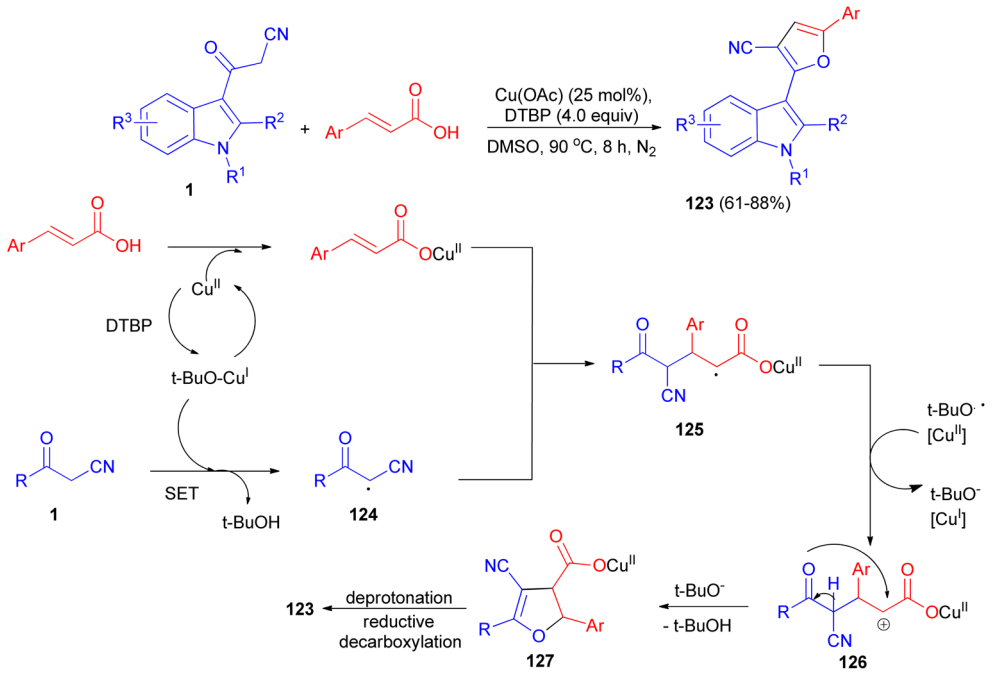
In 2022, Baghery and his group developed three-component reaction of aromatic aldehydes with 3-(1*H*-indol-3-yl)-3-oxopropanenitrile (**1a**) and 1*H*-1,2,4-triazol-5-amine under the solvent-free condition at 70 °C in the presence of polyionic magnetic nanoparticles with pyrazine bridge [Fe_3O_4@SiO_2@(-CH_2)$_3$]$_2$-pyrazinium-[TCM]$_2$ as a catalyst for the synthesis of 7-aryl-5-(1*H*-indol-3-yl)-[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carbonitriles **122** in 89–95% yields *via* a cooperative anomeric-based oxidation (Scheme 47).[81]



Scheme 46 Synthesis of tetrazolo[1,5-*a*]pyrimidine-6-carbonitriles **119**.



Scheme 47 Synthesis of 7-aryl-5-(1*H*-indol-3-yl)-[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carbonitriles **122**.



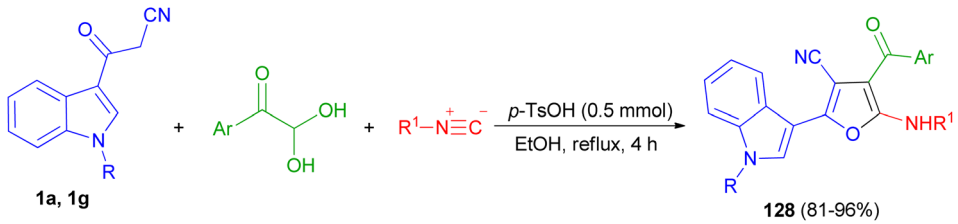
Scheme 48 Regioselective synthesis of 3-(2-furanyl) indole derivatives **123**.

3.9. Furan and dihydrofuran derivatives

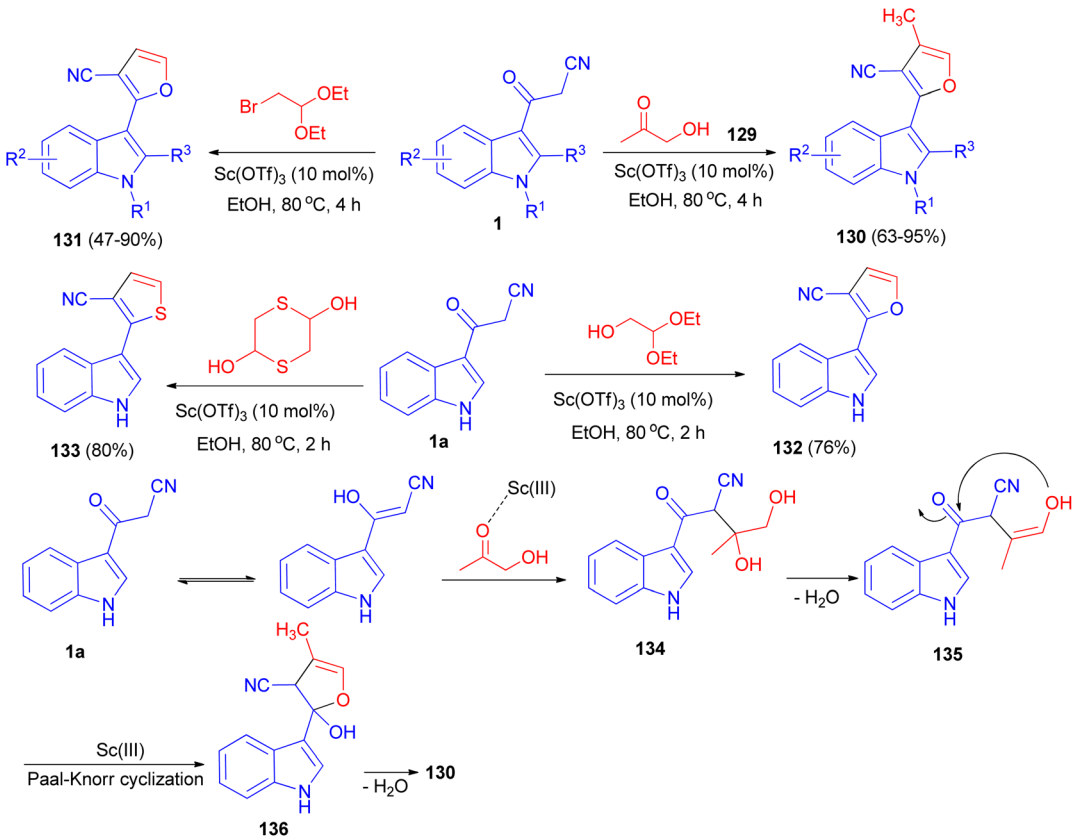
Sashidhara *et al.* developed the reaction between 3-cyanoacetyl indoles and α,β-unsaturated carboxylic acids in the presence of Cu $(OAc)_2$ as catalyst and di-*tert*-butyl peroxide as an external oxidant in DMSO at 90 °C. This reaction undergoes radical addition, decarboxylative processes, and provides a facile regioselective 3-(2-furanyl) indole derivatives **123** in 61–88% yields after 8 h. A plausible reaction mechanism is depicted in Scheme 48. Initially, cinnamic acid reacts with $Cu(OAc)_2$ to form cupric cinnamate. Then, 3-cyanoacetyl indole reacts with *t*-BuO radical to generate the carbon center radical **124**. Subsequently, the addition of radical **124** to the α-position of the double bond in cupric cinnamate would give the intermediate **125**. This intermediate **125** undergoes single electron oxidation, and gets converted into intermediate **126**, which on further intramolecular cyclization resulted in the formation of intermediate **127**. Finally, intermediate **127** undergoes deprotonation and reductive decarboxylation to generate the product **123**.[82]

In 2019, Jeong *et al.* developed a facile and efficient acid-catalyzed cascade reaction for the synthesis of biheteroaryl structural motifs containing densely functionalized furans in refluxing EtOH for 4 h. The reaction sequence involves a Knoevenagel condensation of arylglyoxals with 3-(1*H*-indol-3-yl)-3-oxopropanenitriles **1** and subsequently an isocyanide insertion *via* formal [4 + 1] cycloaddition followed by rapid [1,3]-H shift to afford uniquely decorated biheterocycles **128** in 81–96% yields after 4 h (Scheme 49).[83]

A [3 + 2] cyclization reaction of arylacetonitriles **1** and hydroxyacetone **129** was developed by using $Sc(OTf)_3$ as a catalyst to synthesize some furan derivatives **130.** Bifunctional C2-based acetals, such as α-bromoacetaldehyde acetal, 1,4-dithiane-2,5-diol and glycolaldehyde diethyl acetal, also reacted readily as alternative counterpart reagents to arylacetonitriles. The reactions were performed in refluxing ethanol for 2–4 h and afforded the desired products **131–133**. The prepared furan compound **131a** (R^1=R^2=R^3=H) exhibited a highly potential fungicidal agent against *Botrytis cinerea*, *Verticillium dahliae*, *Fusarium culmorum* and *Septoria nodorum* Berk. A plausible mechanism is depicted in Scheme 50. Incipiently, the activated acetol with $Sc(OTf)_3$ was triggered form the indolyl diol intermediate **134** by the enol form of **1a** to, followed by dehydration to generate intermediate **135**. Subsequently, the intramolecular nucleophilic addition of the hydroxy onto the keto-carbonyl would then occur, enabling the formation of an intermediate **136** with a five-



Scheme 49 Synthesis of furan based densely substituted biheteroaryls **128**.



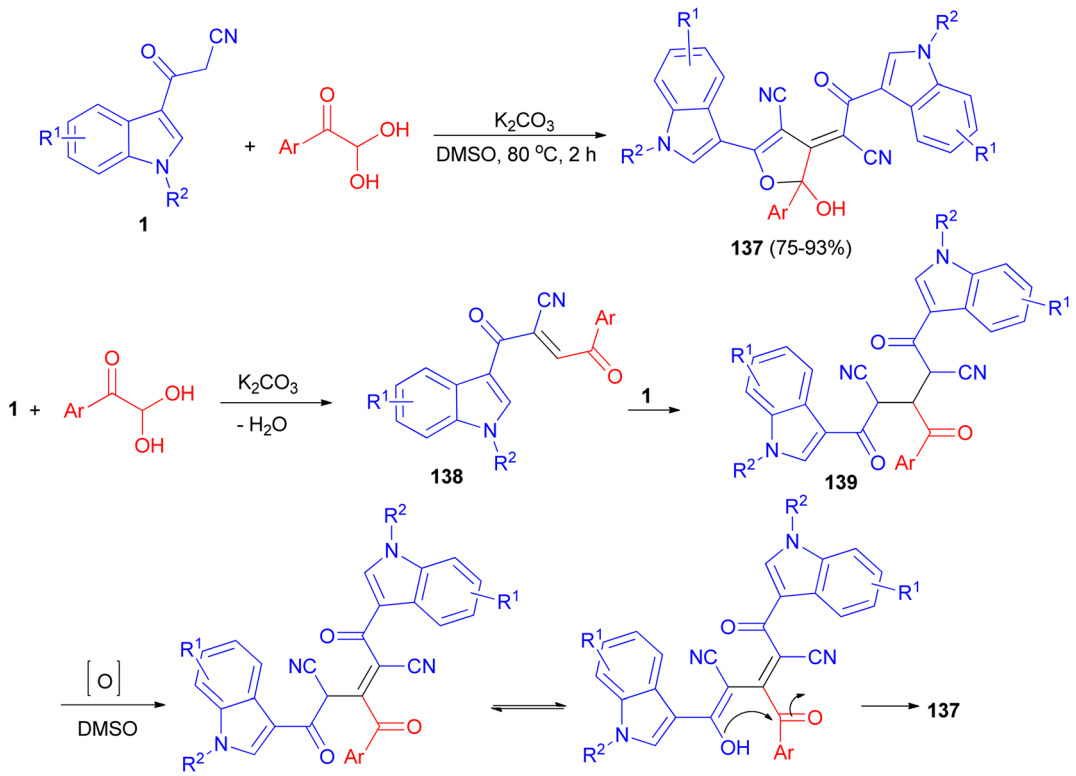
Scheme 50 $Sc(OTf)_3$-catalyzed synthesis of polysubstituted furans **130–133**.

membered ring system. Finally, the furan product was formed through the dehydration of intermediate **136**.[84]

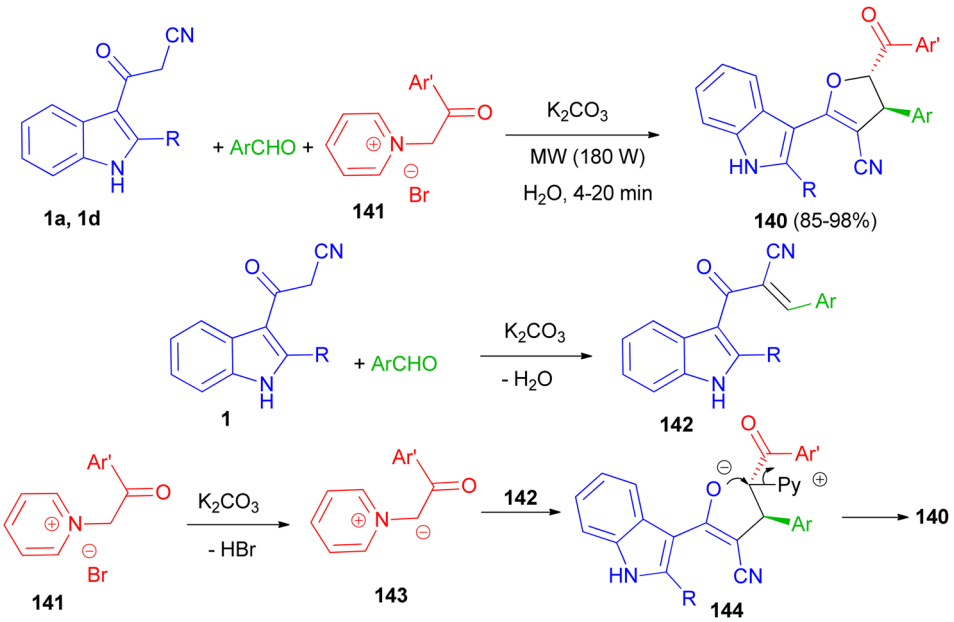
Wu *et al.* established an efficient base-promoted tandem cyclization for the synthesis of polyfunctional 2-hydroxy-2,3-dihydrofurans **137** in 75–93% yields from arylglyoxal monohydrates and 3-(1*H*-indol-3-yl)-3-oxopropanenitriles **1** in DMSO at 80 °C for 2 h. A tandem process is illustrated for the formation of **137** in Scheme 51. Initially, intermediate **138** was formed by means of a Knoevenagel condensation between phenylglyoxal monohydrate and **1**. Subsequently, another amount of **1** reacted with **138** to form intermediate **139** *via* a Michael addition. Finally, the intermediate **139** underwent oxidation, tautomerization, and intramolecular cyclization to form the final product **137**.[85]

Baharfar *et al.* developed an ecofriendly approach for the diastereoselective synthesis of indole-based 4,5-dihydrofurans **140** in 85–98% yields through a three-component reaction of 3-cyanoacetyl indoles **1** with various aldehydes and *N*-phenacylpyridinium bromides **141** in the presence of potassium carbonate as an inexpensive and non-toxic base in water under low power microwave irradiation (180 W) for 4–20 min. The proposed mechanism is outlined in Scheme 52. The Knoevenagel condensation between **1** and aldehyde in the presence of K_2CO_3 generates benzylidene 3-cyanoacetyl indole **142**. Deprotonation of pyridinium salt **141** by K_2CO_3 forms pyridinium ylide **143**, which undergoes Michael addition to intermediate **142** to afford dipolar adduct **144**. Lastly, the attack of enolate moiety **144** on the electrophilic carbon bearing the leaving pyridyl group gives the final product **140**.[86]

Next, 1,1,3,3 *N*,*N*,*N*′,*N*′-tetramethylguanidine as catalyst was used for the diastereoselective synthesis of *trans*-indolyldihydrofurans **145** in 85–95% yields by three-component reaction of 3-cyanoacetyl indoles **1** with various aromatic aldehydes and *N*-phenacylpyridinium bromides **141** under solvent-free conditions at 80 °C for 20–60 min. The synthesized compounds exhibited good antioxidant activity, which can be attributed to



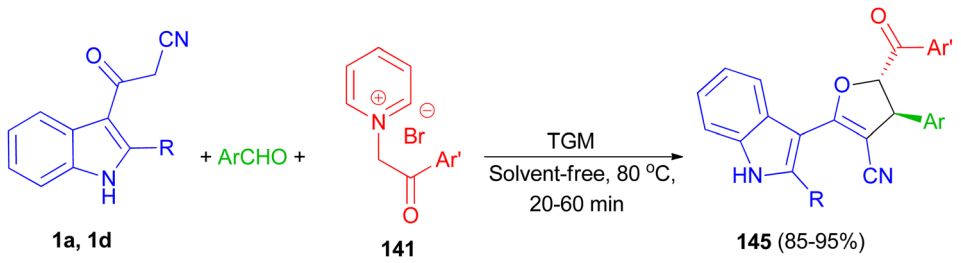
Scheme 51 Synthesis of polyfunctional 2-hydroxy-2,3-dihydrofurans **137**.



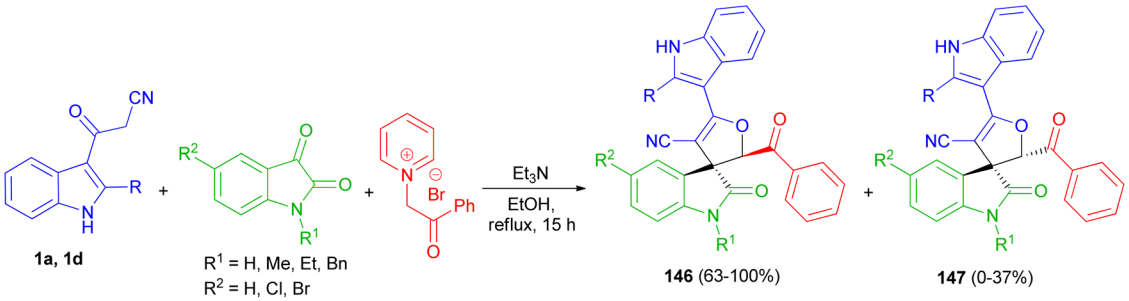
Scheme 52 Synthesis of indole-based 4,5-dihydrofurans **140**.

the acidic hydrogens of their N–H and methine groups. Additionally, presence of either electron-withdrawing or electron-donating substituents on the aromatic ring effectively increased the antioxidant capacity (Scheme 53).[87]

A facile and efficient protocol developed for the diastereoselective synthesis of spirooxindole-dihydrofurans **146** and **147** by the three-component condensation of isatin derivatives, 3-cyanoacetyl indoles **1**, and *N*-phenacylpyridinium bromide in the presence of triethylamine base in ethanol under reflux conditions for 15 h. In this transformation, a mixture of diastereomers was detected in most cases (Scheme 54).[88]



Scheme 53 Synthesis of highly functionalized indole based 4,5-dihydrofurans **145**.



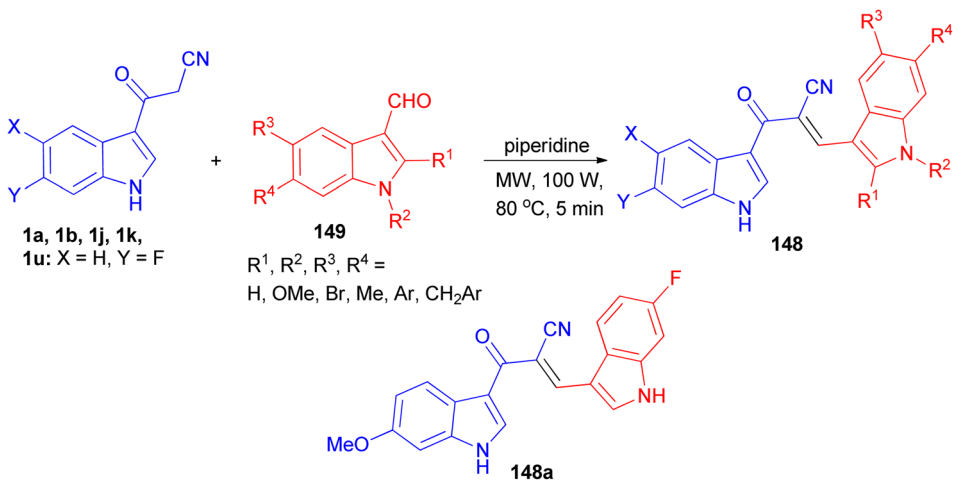
Scheme 54 Synthesis of dihydrofuranyl spirooxindoles **146** and **147**.

3.10. Other derivatives

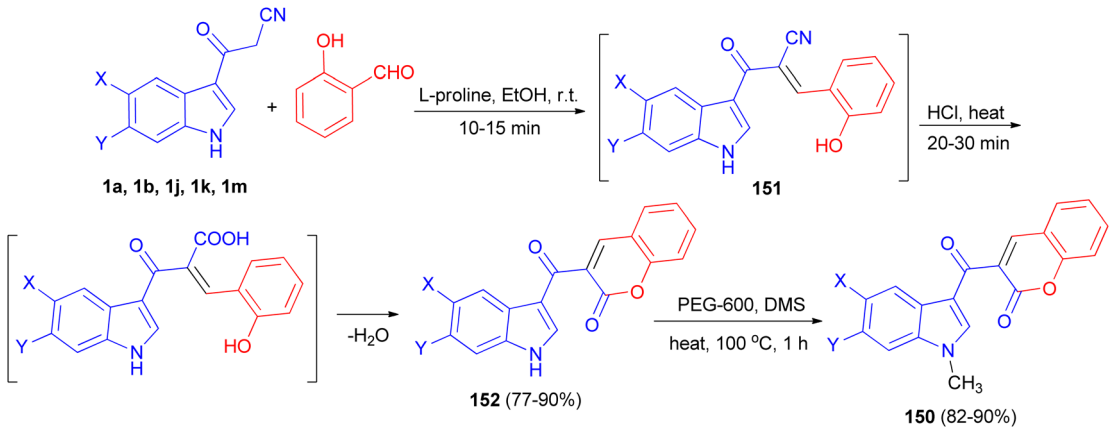
Ito *et al.* presented the synthesis of α-cyano bis(indolyl)chalcones **148** in good yields by the reaction of 3-cyanoacetylindole 1 and indole-3-carboxaldehyde **149** in ethylene glycol and piperidine under microwave irradiation with $P = 100$ w/100 psi at 80 °C for 5 min (Scheme 55). Among the synthesized chalcones, compound **148a** was found to be the most potent and selective against A549 lung cancer cell line ($IC_{50} = 0.8$ μM). In a preliminary mechanism of action studies some α-cyano bis(indolyl)chalcones were found to enhance tubulin polymerization suggesting these compounds could act as microtubule stabilizing agents.[89]

A tandem synthesis of 3-acetylcoumarinoindoles **150** in the presence of catalytic amount of L-proline in ethanol medium is reported. L-Proline has been utilized as an efficient and eco-friendly catalyst for the Knoevenagel condensation of 3-cyanoacetylindoles **1** with 2-hydroxybenzaldehyde to afford the corresponding substituted 3-(1*H*-indol-3-yl)2-(2-hydroxybenzylidene)-3-oxopropanenitriles **151**, which without isolation were treated with hot conc. HCl to afford 3-acetylcoumarinoindoles **152** in 77–90% yields. Subsequently, these were reacted with dimethyl sulfate in the presence of PEG-600 as an efficient and green solvent at 100 °C for 1 h to afford the corresponding *N*-methyl-3-acetylcoumarinoindoles **150** in 82–90% yields (Scheme 56).[90]

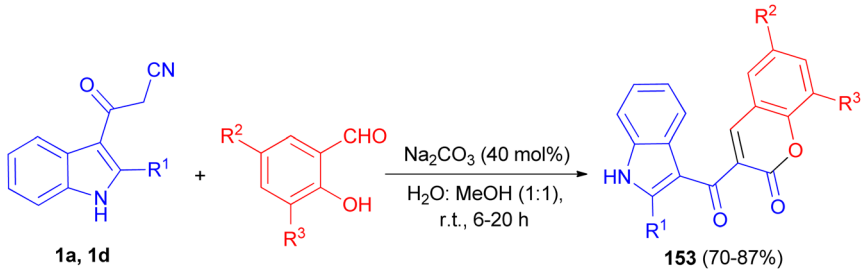
A simple and convenient method described for the one-pot synthesis of 3-(1*H*-indole-3-carbonyl)-2*H*-chromen-2-one



Scheme 55 Synthesis of α-cyano bis(indolyl)chalcones **148** as anticancer agents.

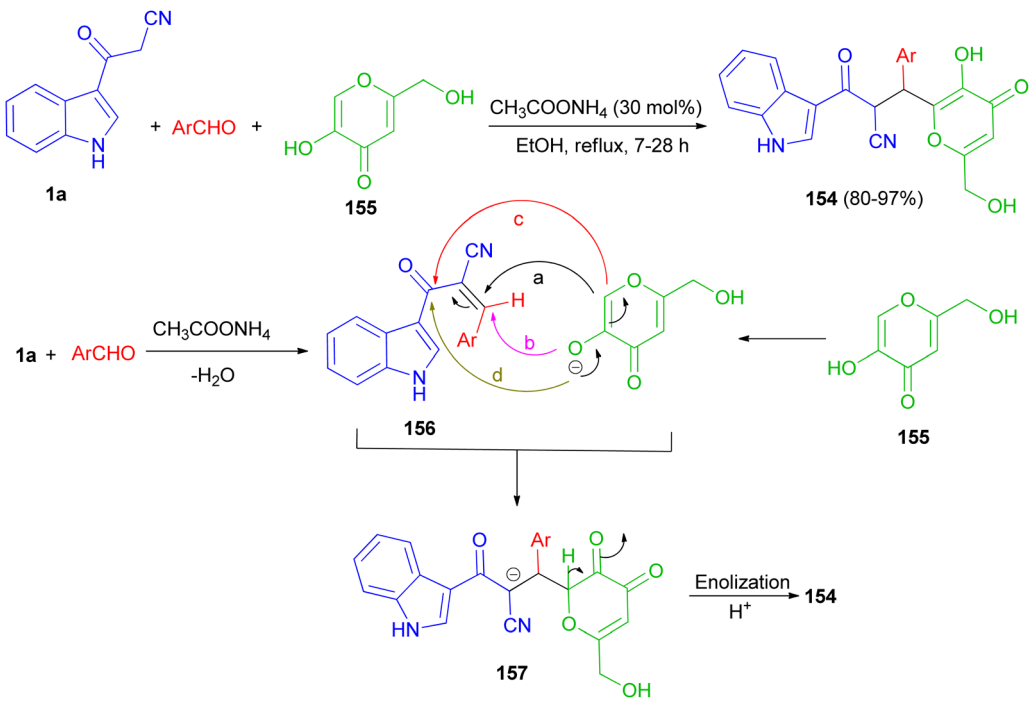


Scheme 56 Synthesis of 3-acetylcoumarinoindoles **150**.

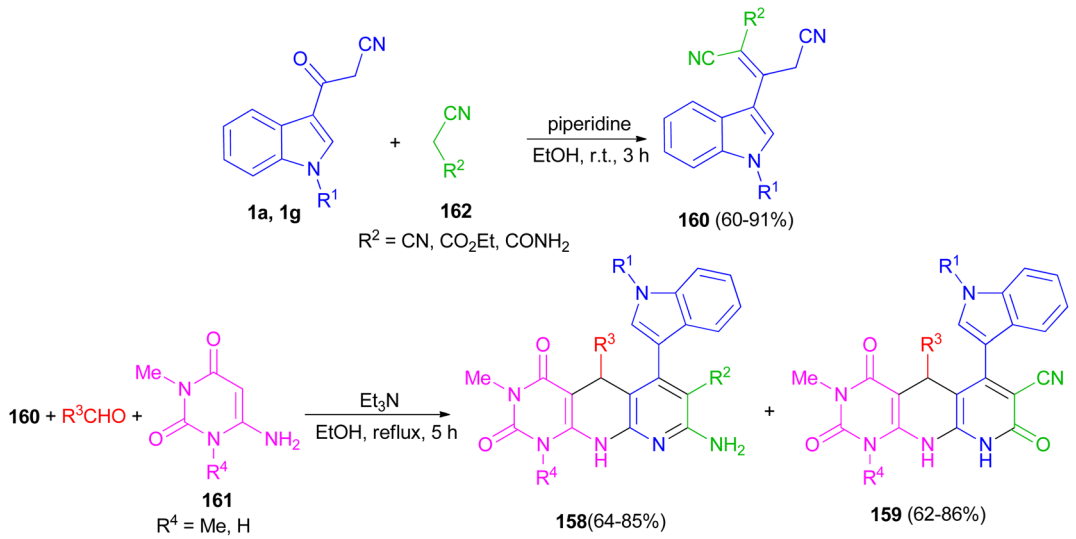


Scheme 57 Preparation of 3-(1*H*-indole-3-carbonyl)-2*H*-chromen-2-one derivatives **153**.

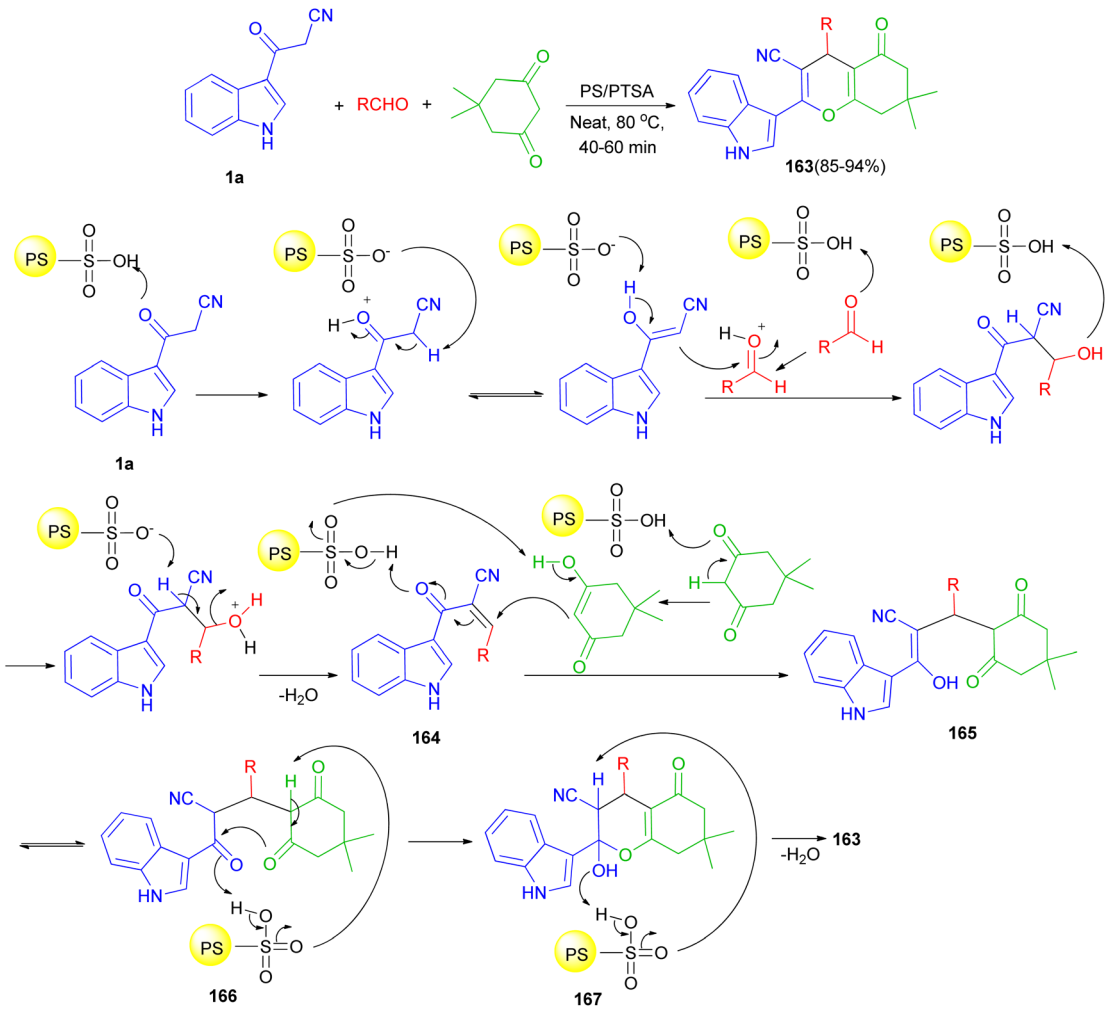
derivatives **153** in 70–87% yields from the reaction of 3-cyanoacetyl indoles (**1**) and salicylaldehyde derivatives in the presence of Na_2CO_3 in water: methanol (1 : 1) at room temperature for 6–20 h (Scheme 57). The synthesized compounds exhibited good radical scavenging ability against DPPH free radical, antibacterial activity against Gram-positive bacteria (MRSA), *Bacillus* sp.



Scheme 58 Regioselective synthesis of 3-(cyanoacetyl)indole derivatives **154**.



Scheme 59 Synthesis of hexahydropyrimido[4,5-*b*]-1,8-naphthyridines **158** and **159**.



Scheme 60 Schematic illustration of reaction mechanism for the product **163**.

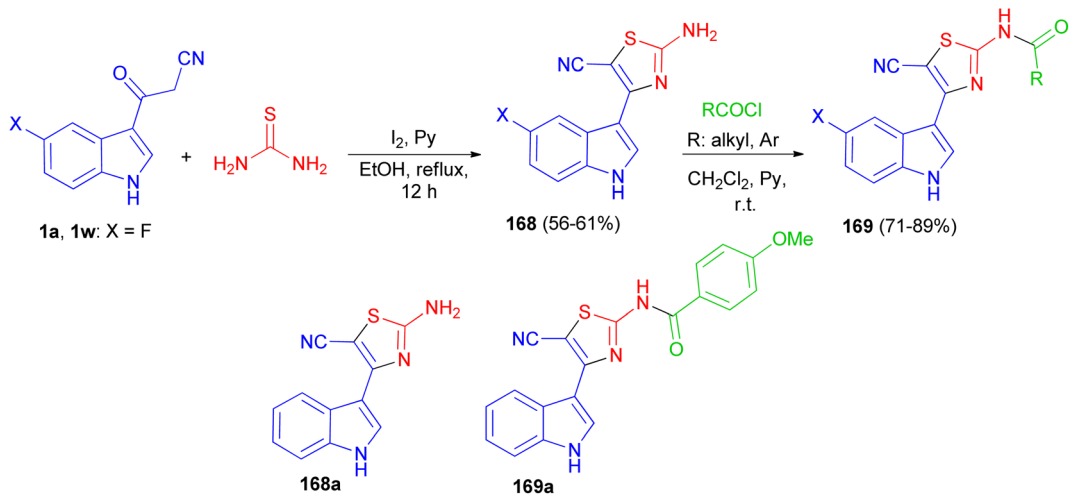
and Gram negative bacterial strains (*Escherichia coli*, *Klebsiella pneumoniae*) and antifungal activity against *Candida albicans*.[91]

A protocol for the regioselective synthesis of diastereomeric 3-substituted indole derivatives **154** in 80–97% yields was described by the three-component condensation of 3-(cyanoacetyl)indole (**1a**), aromatic aldehydes, and kojic acid (**155**) in the presence of ammonium acetate as catalyst in refluxing EtOH for 7–28 h. Some of the synthesized compounds demonstrated excellent activity against *S. aureus*, *B. subtilis*, antibacterial activities against *P. aeruginosa* and good activity against *E. coli*. A plausible mechanism is given in Scheme 58. The formation of these products can be rationalized by initial formation of intermediate **156** by Knoevenagel condensation of the aldehyde and **1a**. The anion of kojic acid can attack to intermediate **156** in four routes: Michael-type addition (route a), direct addition (route b), *C*-alkylation (route c), or *O*-alkylation (route d). Among these four routes, the reaction proceeded regioselectively *via* route a, and led to intermediate **157**. Then, enolization and protonation of **157** in the reaction conditions result in final product **154**.[92]

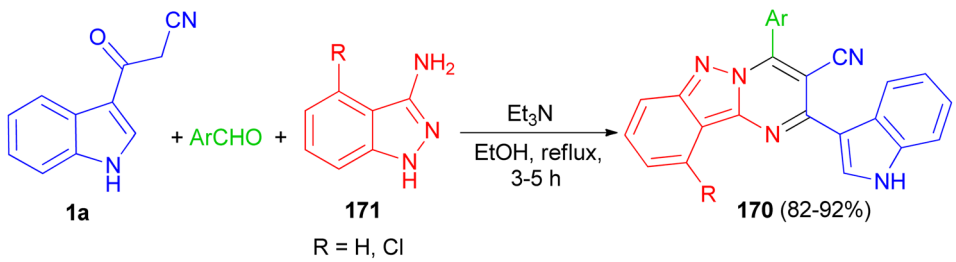
Naidu and co-workers provided a procedure for the synthesis of hexahydropyrimido[4,5-*b*]-1,8-naphthyridine derivatives **158** and **159** in 62–86% yields by a one-pot three-component reaction of a 2-cyano-3-(1*H*-indol-3-yl)-pent-2-enedinitrile or ethyl-2,4-dicyano-3-(1*H*-indol-3-yl)but-2-enoate derivative **160** with an aryl aldehyde and a 6-aminouracil derivative **161** in the presence of Et_3N in refluxing EtOH for 5 h. Indoles **160** were synthesized by treating the corresponding **1** with the appropriate acetonitrile derivative **162** in the presence of piperidine as a catalyst in EtOH at room temperature for 3 h (Scheme 59).[93]

In 2016, Reddy *et al.* described an efficient and environmentally benign protocol for the synthesis of diversely functionalized 1*H*-indol-3-yl-4*H*-chromene-3-carbonitriles **163** in 85–94% yields through one-pot three-component condensation reaction of **1a**, 5,5-dimethylcyclohexane-1,3-dione and various aromatic, aliphatic and heterocyclic aldehydes in the presence of polystyrene-supported *p*-toluenesulfonic acid (PS/*P*TSA) under solvent-free conditions at 80 °C for 40–60 min. A plausible mechanism is shown in Scheme 60. Initially in the presence of PS/*P*TSA catalyst **1a** is reacts with aldehydes to give an α,β-unsaturated ketone **164**. On subsequent Michael addition of enolic form of 5,5-dimethylcyclohexane-1,3-dione to this conjugated intermediate, **164**, forms enolic intermediate **165** which on keto–enol tautomerisation (K.E.T.) gives triketone, **166**, intermediate. In the presence of catalyst, this intermediate undergoes intramolecular cyclisation and gives unstable, **167**, which on dehydration affords the desired product **163**.[94]

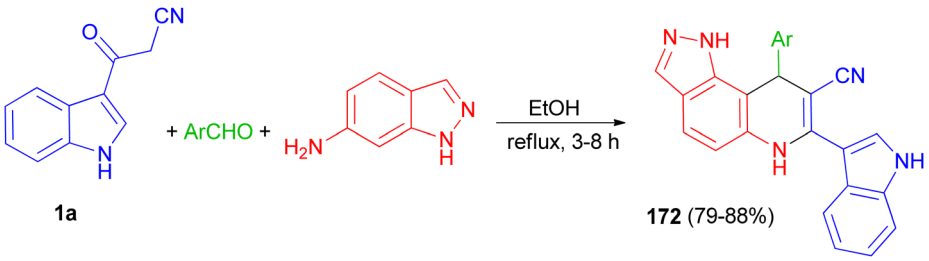
After that, Gururaja and co-workers reported synthesis of 2-amino-4-(1*H*-indole-3-yl) thiazole-5-carbonitrile derivatives **168** in 56–61% yields by the reaction of 3-(1*H*-indole-3-yl)-3-oxopropanenitrile derivatives **1** and thiourea in the presence of pyridine and iodine in refluxing EtOH for 12 h. Then, the reaction of **168** with carboxylic acid chloride in CH_2Cl_2 in the



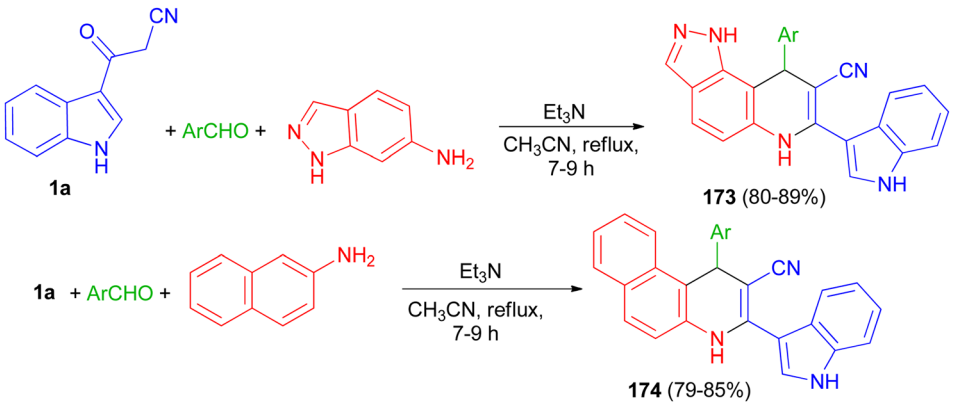
Scheme 61 Synthesis of thiazole derivatives containing indole moiety **168** and **169**.



Scheme 62 Synthesis of 4-arylpyrimido[1,2-*b*]indazole-3-carbonitrile derivatives **170**.



Scheme 63 Synthesis of pyrazolo[3,4-*f*]quinoline-8-carbonitriles **172**.

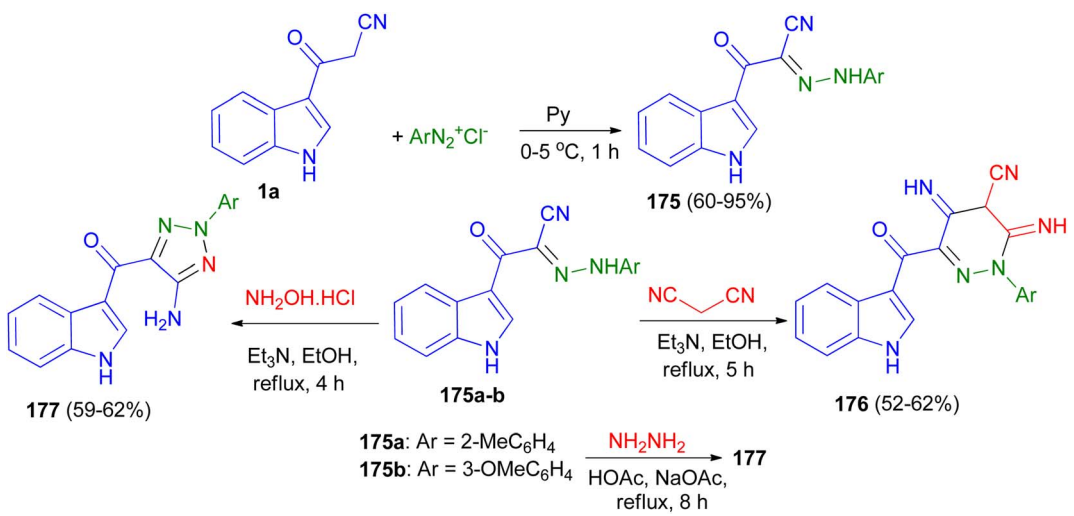


Scheme 64 Synthesis of 9-aryl-6,9-dihydro-1*H*-pyrazolo[3,4-f]quinoline-8-carbonitriles **173** and 1-aryl-1,4-dihydrobenzo[f]quinoline-2-carbonitriles **174**.

presence of pyridine at room temperature afforded *N*-(5-cyano-4-(1*H*-indole-3-yl)thiazol-2-yl) substituted amides **169** in 71–89% yields. The synthesized indole-thiazole derivatives were evaluated for cytotoxicity effect on breast cancer cells and found that, compounds **168a** and **169a** are moderately toxic and the others are less toxic to the breast cancer cells (Scheme 61).[95]

In 2017, Rong *et al.* utilized an efficient metal-free cascade reaction to synthesize pyrimido[1,2-*b*]indazole-3-carbonitrile derivatives **170**. The reaction of aromatic aldehydes, 1*H*-indazol-3-amine (4-chloro-1*H*-indazol-3-amine) **171** and **1a** was carried out in refluxing EtOH in the presence of triethylamine to afford **170** in 82–92% yields after 3–5 h (Scheme 62).[96]

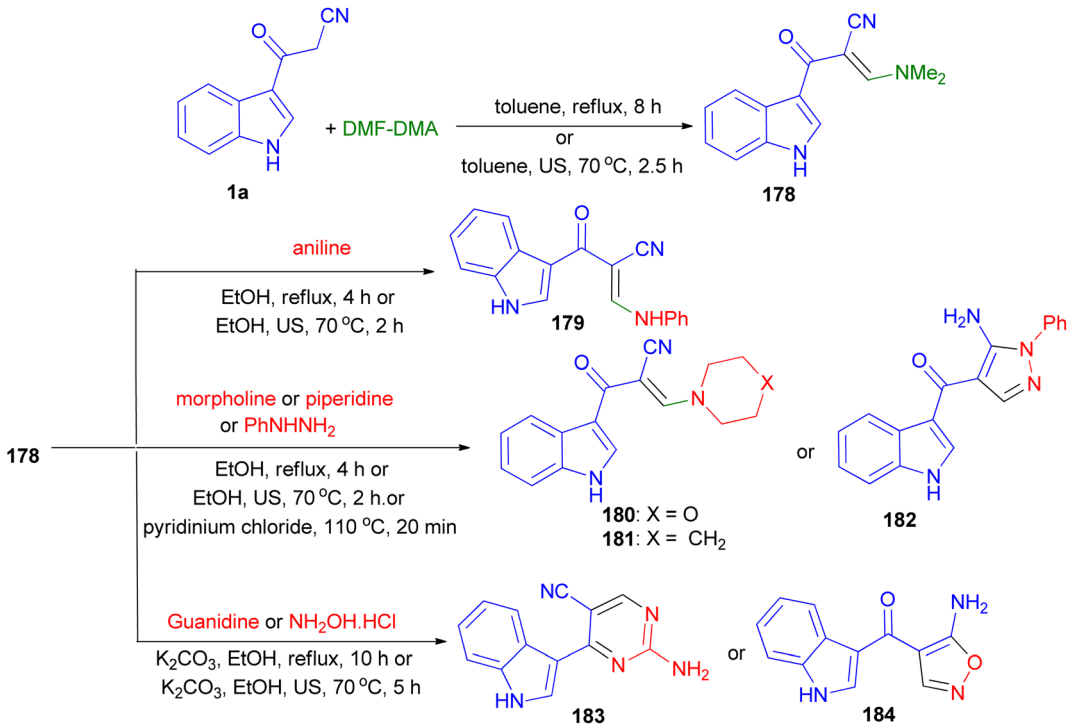
Liu and co-workers presented the synthesis of pyrazolo[3,4-*f*]quinoline-8-carbonitriles **172** in 79–88% yields by the reaction of an aromatic aldehyde, 1*H*-indazol-6-amine and **1a** in ethanol under reflux conditions for 3–8 h (Scheme 63).[97]



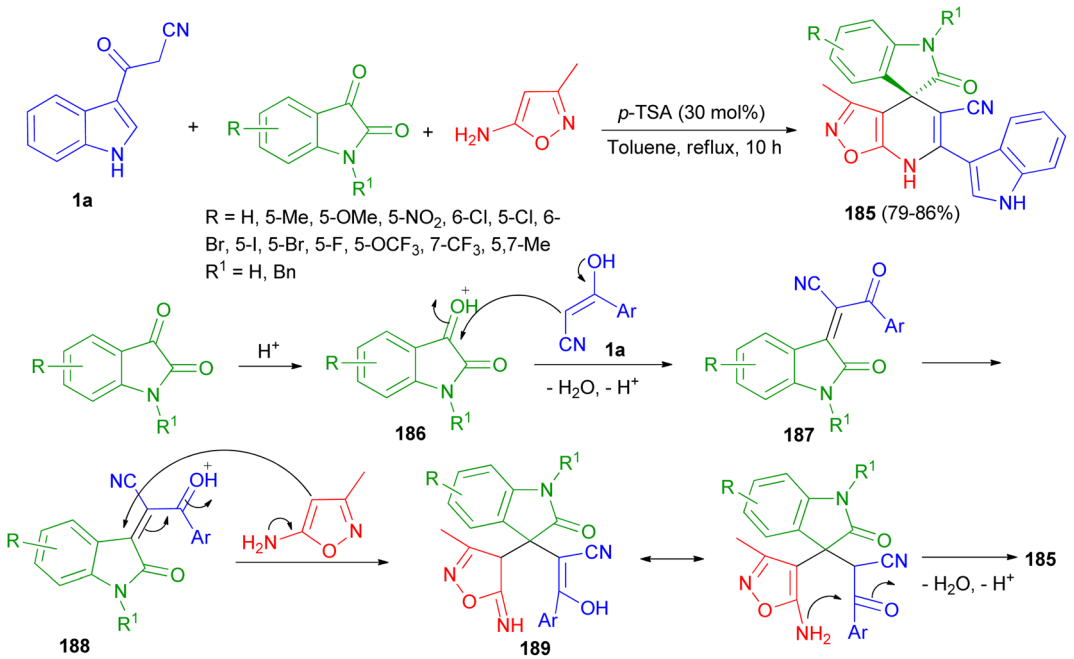
Scheme 65 Synthesis of hydrazo, dihydropyridazinyl and triazolyl derivatives containing indole nucleus **175–177**.

Rong *et al.* reported synthesis of 9-aryl-6,9-dihydro-1*H*-pyrazolo[3,4-f]quinoline-8-carbonitrile derivatives **173** in 80–89% yields by the one-pot three-component reaction of aromatic aldehydes, 1*H*-indazol-6-amine and 3-cyanoacetyl indole (**1a**) and 1-aryl-1,4-dihydrobenzo[*f*]quinoline-2-carbonitrile derivatives **174** in 79–85% yields *via* the reaction of various aromatic aldehydes, 2-naphthylamine and **1a** using Et_3N in CH_3CN at 80 °C for 7–9 h (Scheme 64).[98]

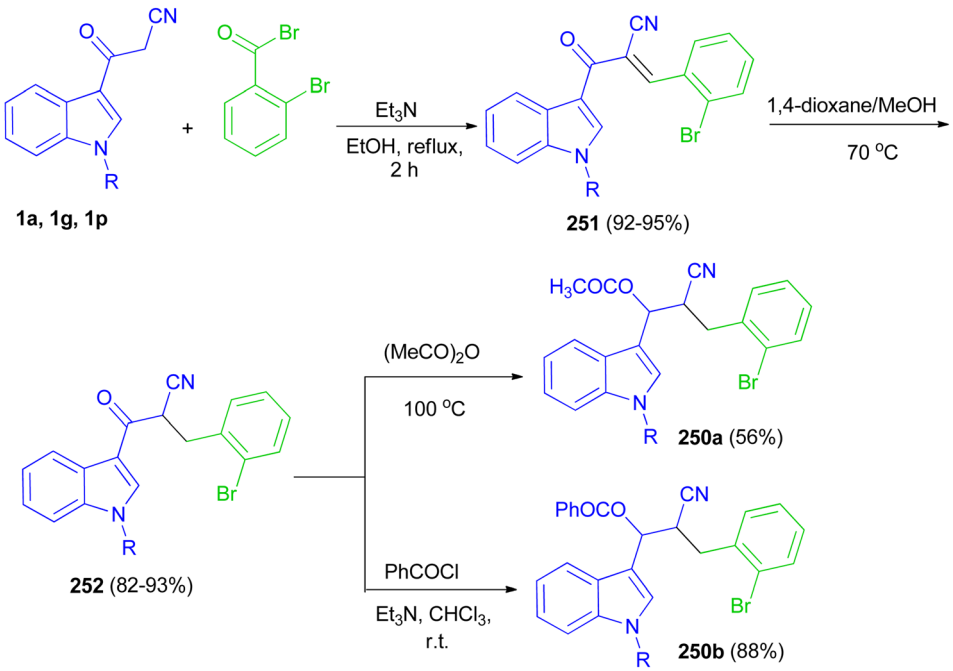
Fadda *et al.* designed the synthesis of *N*-aryl-2-(1*H*-indol-3-yl)-2-oxoaceto hydrazonoyl cyanide derivatives **175** in 60–95% yields utilizing the reaction of **1a** and aryl diazonium salts in pyridine at 0–5 °C for 1 h. Also, synthesis of 2-aryl-3,5-diimino-6-



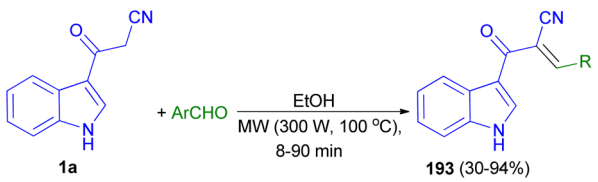
Scheme 66 Synthesis of enaminones **178–181** and heterocyclic compounds **182–184**.



Scheme 67 Chemo-selective synthesis of indoline-3,4′-isoxazolo[5,4-*b*]pyridine fused spirooxindole derivatives **185**.



Scheme 68 Synthesis of indole-based cyano derivatives **250–252**.

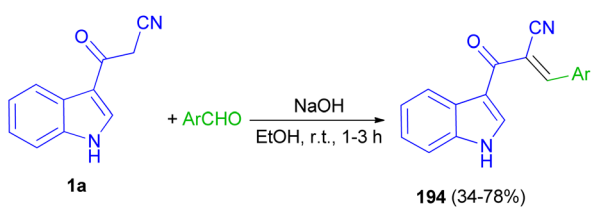


Scheme 69 Synthesis of (*E*)-2-(1*H*-indole-3-ylcarbonyl)-3-hetero-aryl-acrylonitriles **193**.

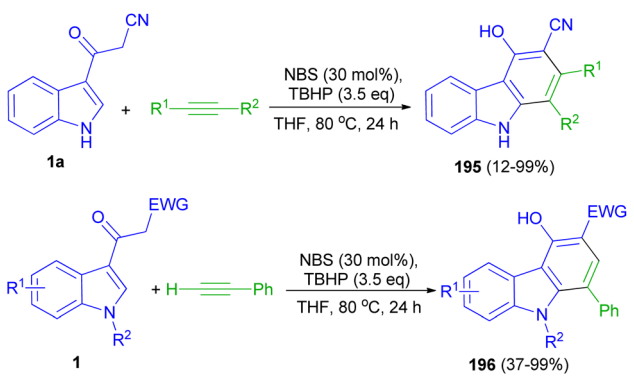
(1*H*-indole-3-carbonyl)-2,3,4,5-tetrahydropyridazine-4-carbonitrile derivatives **176** in 52–62% yields accomplished by the reaction of **175a–b** with malonitrile in ethanol in the presence of triethylamine as catalyst under reflux conditions for 5 h. The same research group also reported synthesis of (5-amino-2-aryl-2*H*-1,2,3-triazol-4-yl)(1*H*-indol-3-yl)methanone derivatives **177** in 59–62% yields *via* the reaction of **175a–b** with hydroxylamine hydrochloride in refluxing ethanol in the presence of catalytic amount of triethylamine for 4 h or with hydrazine hydrate in acetic acid in the presence of sodium acetate under reflux conditions for 8 h (Scheme 65). The obtained results clearly revealed that arylazo derivatives with electron withdrawing group exhibited better antimicrobial activity than compounds not containing this groups.[99]

The condensation reaction of **1a** with dimethylformamide-dimethylacetal (DMF-DMA) gave the corresponding enaminone **178**. Nucleophilic substitution of **178** with different amines (aniline, piperidine and morpholine) resulted enaminones **179–181**. Treatment of compounds **178** with phenylhydrazine afforded the pyrazole derivatives **182**. On the other hand, reacting **178** with guanidine gave the pyrimidine **183**. Treatment of compound **178** with hydroxylamine hydrochloride afforded the aminoisoxazoles **184**. The foregoing reactions were carried out with conventional heating and under green conditions [ultrasound (US) irradiations or ionic liquids (ILs)] (Scheme 66).[100]

A highly convergent and efficient protocol reported for the facile chemoselective synthesis of a library of indoline-3,4′-isoxazolo[5,4-*b*]pyridine fused spirooxindole derivatives **185** in 79–



Scheme 70 Synthesis of indole acrylonitriles **194**.



Scheme 71 Synthesis of carbazoles **195** and **196**.

86% yields by three-component reaction of **1a**, isatin derivatives and 3-methylisoxazol-5-amine using *p*-TSA (30 mol%) in refluxing toluene for 10 h. A plausible mechanism is outlined in Scheme 67. First, the nucleophilic addition of aryl acetonitrile into protonated isatin **186** followed by elimination of water gives intermediate **187**, which upon further protonation at ketone to yield intermediate **188**. The intermediate **188** on Michael addition with isooxazole-5-amine to generate intermediate **189**, which undergoes intra-molecular cyclisation and dehydration to afford desired product **185**.[101]

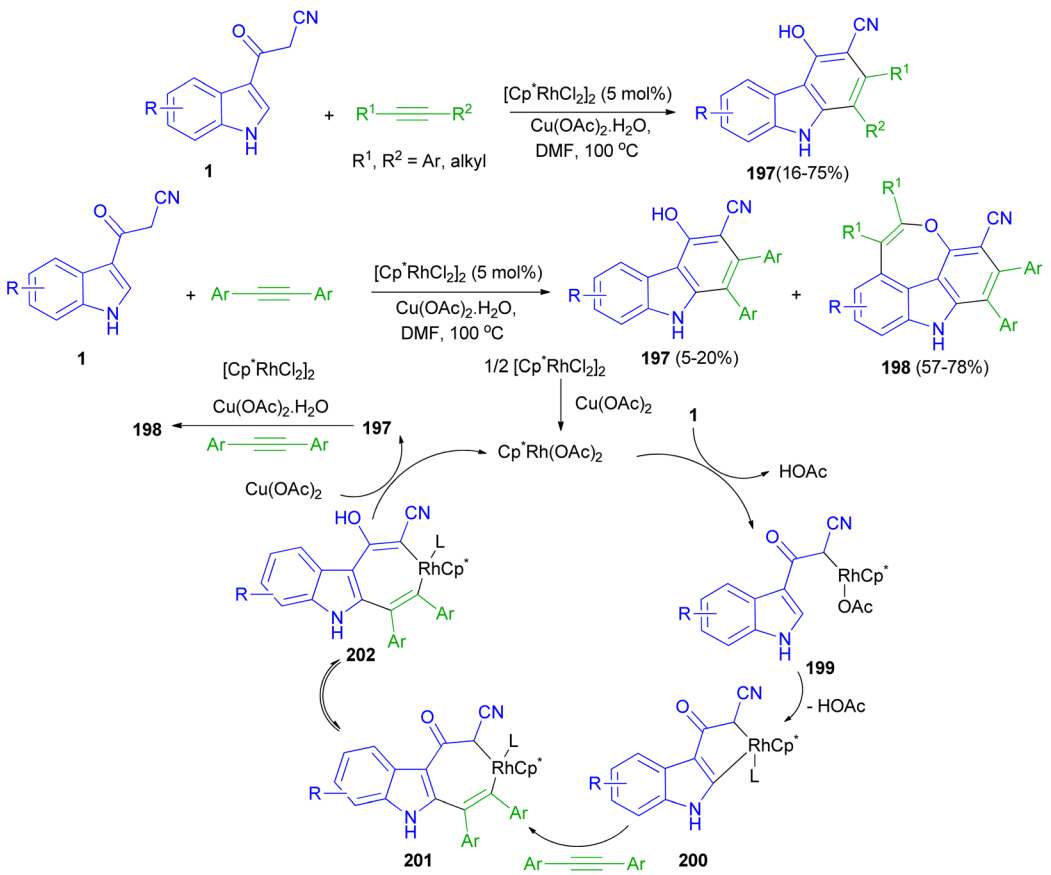
Glidewell and co-workers developed three-step sequence for the preparation of the esters **190** starting by the reaction of 3-(indol-3-yl)-3-oxopropanenitriles **1** with 2-bromobenzaldehyde in the presence of Et_3N in refluxing EtOH for 2 h to form the corresponding chalcones **191** in 92–95% yields; these are readily reduced to dihydrochalcones **192** in 82–93% yields in the presence of $NaBH_4$ in 1,4-dioxane and methanol at 70 °C, which are in turn acylated to form the enolate esters **190** in 56–88% yields (Scheme 68).[102]

Stereoselective synthesis of (*E*)-2-(1*H*-indole-3-ylcarbonyl)-3-heteroaryl-acrylonitriles **193** obtained in 30–94% yields from the reaction of **1a** with heteroaryl-aldehydes in EtOH under microwave assisted Knoevenagel reaction at 300 W of potency and 100 °C for 8–90 min (Scheme 69).[103]

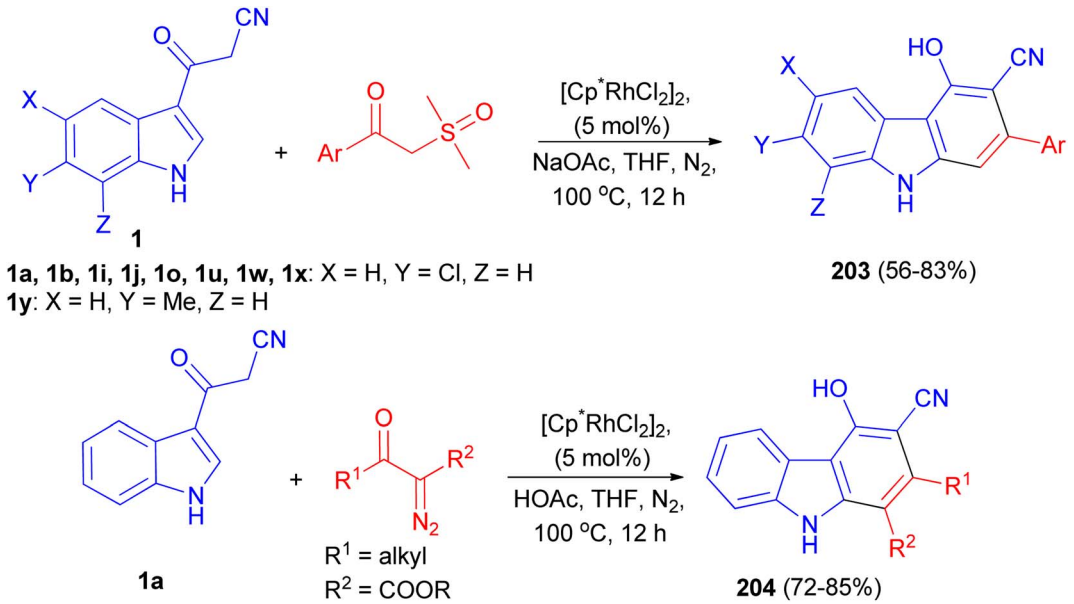
Mohammed Khan and co-workers reported synthesis of indole acrylonitriles **194** in 34–78% yields by the reaction of **1a** and aryl aldehydes in the presence of NaOH in absolute ethanol at room temperature for 1–3 h (Scheme 70). The synthetic molecules have shown promising α-glucosidase enzyme inhibitory activity in the range of (IC_{50} = 0.53 ± 0.01–1.36 ± 0.04 μM) as compared to the standard acarbose (IC_{50} = 2.91 ± 0.02 μM).[104]

Wang and co-workers applied *N*-bromosuccinimide for the intermolecular annulation of acetyl indoles **1** with alkynes in the presence of TBHP in THF at 80 °C for 24 h, allowing for regioselective formation of valuable carbazoles **195–196** (up to 99% yield) through direct C–H bond functionalization (Scheme 71). Mechanistic investigations indicate that the bromination of acetyl indole takes place to generate a bromide intermediate, followed by coupling with an alkyne and intramolecular cycloaromatization to furnish carbazole products.[105]

Rh(III)-catalyzed [4 + 2] cycloaddition reactions of 3-(1*H*-indol-3-yl)-3-oxopropanenitriles **1** with alkyne in the presence of Rh(III) as catalyst in DMF at 100 °C afforded substituted carbazoles **197** in 16–75% yields. Also, the reaction of **1** with two molecules of alkynes resulted 4*H*-oxepino[2,3,4,5-def]carbazoles **198** (57–78% yields) and **197** (5–20 mol% yields) *via* tandem [4 + 2] and [5 + 2] cycloaddition under the same reaction conditions. A possible mechanism is proposed as shown in Scheme 72. The first step is likely to be the acidic C(sp^3)–H bond activation process affording intermediate **199**, then C(sp^2)–H bond activation through the CMD mechanism gives a five membered



Scheme 72 Rh(III)-catalyzed synthesis of carbazoles **197** and 4*H*-oxepino[2,3,4,5-def]carbazoles **198**.

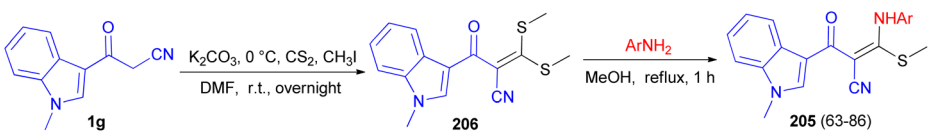


Scheme 73 Synthesis of polysubstituted carbazoles **203** and **204**.

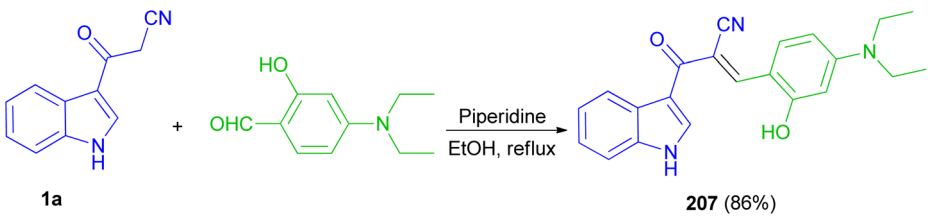
rhodacycle **200**. The coordination and insertion of an alkyne into **200** leads to the seven-membered rhodacycle intermediate **201**. After ketone enolization intermediate **202** is formed and undergoes reductive elimination to afford product **197** and Cp*Rh(I). Cp*Rh(I) is oxidized by $Cu(OAc)_2 \cdot H_2O$ to $Cp^*Rh(OAc)_2$ for the next catalytic cycle. The mechanism for the second-step annulation of **197** with an alkyne to form **198** is similar to the [5 + 2] cycloaddition reaction of *o*-vinylphenol with an alkyne.[106]

A rhodium-catalyzed annulation of 3-(1*H*-indol-3-yl)-3-oxopropanenitriles with sulfoxonium ylides or diazo compounds has been developed, leading to a series of polysubstituted carbazoles **203** and **204** in moderate to good yields. This procedure proceeded with formal Rh(III)-catalyzed [4 + 2] cycloaddition, with the functionalization of 2-C–H bonds of indole in a step-economical procedure. Additionally, this reaction could also be conducted under acidic conditions in THF at 100 °C for 12 h when diazo compounds were employed as the reaction partners, which was a complement to the annulation of sulfoxonium ylides under weak basic conditions in the presence of NaOAc in THF at 100 °C for 12 h (Scheme 73).[107]

Patel *et al.* described synthesis of 3-((substitutedphenyl) amino)-2-(1-methyl-1*H*-indole-3-carbonyl)-3-(methylthio) acrylonitrile derivatives **205** in 63–86% yields. At first, the reaction of 3-cyanoacetyl *N*-methyl indole **1g** with carbon disulphide and methyl iodide in basic condition affords 2-(1-methyl-1*H*-indole-3-carbonyl)-3,3-bis(methylthio)acrylonitrile **206** as a scaffold. Subsequent, the scaffold when reacts with substituted various amine derivatives *via* desulfitative displacement forms the desired product **205** (Scheme 74). The antibacterial activity of all compounds showed promising activity in comparison to standard drug streptomycin and ciprofloxacin, while the antifungal activity of all compounds



Scheme 74 Synthesis of *N*-methyl indole derivatives **205**.



Scheme 75 Synthesis of fluorescent probe based on cyanoacetyl indole derivative **207**.

showed higher to moderate activity against standard drug nystatin.[108]

Recently, a fluorescent probe based on cyanoacetyl indole derivative **207** was designed and synthesized by the reaction of 3-cyanoacetylindole (**1a**) with 4-diethylaminosalicylic aldehyde using anhydrous ethanol as solvent and piperidine as a catalyst under reflux temperature. Probe displayed good stability, highly selectivity and sensitivity for detection of HPO_4^{-2} through fluorescence quenching, and other thirteen anions including $H_2PO_4^-$, NO_3^-, NO_2^-, HSO_3^-, SO_3^{-2}, SO_4^{-2}, $S_2O_3^{-2}$, AcO^-, F^-, Cl^-, Br^-, I^-, SCN^- was basically undisturbed and only occurred weak fluorescence changes. The protonation of nitrile may afford nitrilium ion (Scheme 75).[109]

4. Conclusion

This review represents a comprehensive documentation to the recent development for the synthesis of 3-cyanoacetyl indoles (CAIs) and applications for the construction of variety of novel molecules containing indole moieties such as pyranes, pyridines, dihydropyridines, pyrimidines, tetrahydropyrimidines, pyrazoles, pyrazolopyridines, pyrazolopyrimidines, pyridopyrimidines, tetrazolopyrimidines, triazolopyrimidines, furans, dihydrofurans, coumarins, pyrimidonaphthyridines, chromenes, thiazoles, pyrimidoindazoles, pyrazoloquinolines, isoxazolopyridines and carbazoles *via* the different classical methods with green approach, homogeneous, heterogeneous and metal-catalyzed reactions, ultrasound-mediated and microwave irradiation reactions during the period of 2013–2022. A large portion of these molecules exhibits promising biological and pharmaceutical activities such as antioxidant, anticancer, antiproliferative, antimicrobial, α-glucosidase enzyme inhibitor, anti-inflammatory, antibacterial activity against both Gram-negative and Gram-positive bacteria, antibiofilm, cytotoxic potential against breast carcinoma (MCF-7) and as potential inhibitors of Nicotinamide phosphoribosyltransferase (NAMPT). It is hoped that more interesting results in this review will help not only to the synthetic chemists but also to the medicinal and pharmaceutical chemists to update information on recent developments in this field as well as to study the potential biological activities of such compounds reported in this review.

Conflicts of interest

There are no conflicts to declare.

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