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Cite this: *RSC Adv.*, 2018, **8**, 12069

Recent advances in the application of indoles in multicomponent reactions

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Received 13th December 2017
Accepted 5th March 2018

DOI: 10.1039/c7ra13321a

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Indoles are some of the most versatile and common nitrogen-based heterocyclic scaffolds and are frequently used in the synthesis of various organic compounds. Indole based compounds are very important among heterocyclic structures due to their biological and pharmaceutical activities. The last decade, in particular, has witnessed considerable activity towards the synthesis of indole derivatives due to the possibilities for the design of polycyclic structures by the incorporation of multiple fused heterocyclic scaffolds in an attempt to achieve promising new heterocycles with chemical and biomedical relevance. In this study, we provide an overview on recent applications of indole in the multicomponent reactions for the synthesis of various heterocyclic compounds during the period of 2012 to 2017.

1. Introduction

Heterocyclic compounds are important tools in our daily life having an extensive variety of applications such as sanitizers,[1] pharmaceuticals[2,3] and antioxidant compounds,[4,5] corrosion inhibitors,[6,7] dye stuff,[8] copolymers,[9,10] and as building blocks in the synthesis of organic compounds and natural products. Multicomponent reactions (MCRs) have been extensively used for the synthesis of heterocyclic compounds.[11–13] MCRs represent a great tool in organic synthesis for the construction of variety-oriented series of building blocks with potentially interesting biological activities.[14–17] The attractiveness of the MCR approach is its easy operation, high selectivity and yield by using minimum synthetic requirements. Indole scaffolds have been known for their value in the development of new compounds of pharmaceutical interest.[18–20] Up to date, several

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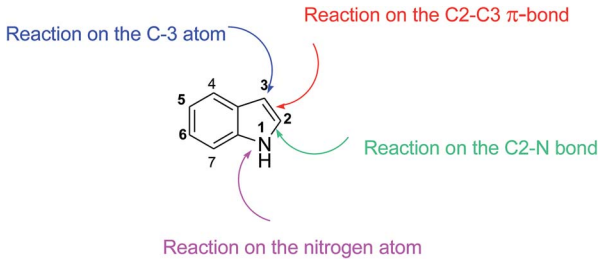
review articles have been published based on the reactions of indole.[21,22] Herein, in continuation of our studies towards the synthesis of heterocyclic compounds and multicomponent reactions,[23–32] and since there is a wide range of reactions that include indole in the preparation of heterocyclic compounds, this review presents the recent applications of indole in the synthesis of diverse heterocyclic compounds during the period from 2012 to 2017. This review first discusses indoles' C-3 carbon atom reactivity applicable to electrophilic reactions, followed by MCRs in which the N position of indole is reacted as a nucleophile to afford N-substituted indole products. In Section 2.3, indole cycloaddition reactions have been discussed including cycloaddition reactions of the C2–C3 π-bond (Section 2.3.1) and the C–N sigma bond (Section 2.3.2). Finally, in Section 2.4, miscellaneous reactions of indole will be reviewed.

2. Multicomponent reactions of indoles

The indole structure is a heterocyclic compound which easily participates in chemical reactions. Its bonding sites are analogous to pyrrole. As shown in Scheme 1, indole is reactive at four different positions including the carbon atom 3, nitrogen atom 1, the C2–C3 π-bond and the C2–N sigma bond. Indole can be protonated with strong acids such as hydrochloric acid, 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.

2.1. The C-3 position reactions of indoles

Gámez-Montaño's group reported the one-pot Ugi-azide[33] multicomponent reaction of indole **1**, isocyanides **2**, aldehydes **3** and $TMSN_3$ **4** (Scheme 2). In the first step, intermediate **A** was obtained, and then *N*-acylation was performed between **A** and



Scheme 1

chloroacetyl chloride to give the intermediate **B**, which underwent an S_N2 reaction with the potassium ethyl xanthogenate salt to give the final xanthates **5** (Scheme 2).[34]

The one-pot multicomponent reaction of 3-acetylindole **1**, aromatic aldehydes **3**, ethyl cyanoacetate **6**, and ammonium acetate **7** in the presence of piperidine as catalyst was established to access several 6-indolylpyridine-3-carbonitrile derivatives **8** (Scheme 3).[35] The anti-proliferative activities of products were evaluated and showed good results.

Indole **1**, carbon disulfide **9** and substituted α-bromo propiophenones **10** were reacted *via* a three component domino [3 + 2] heterocyclization reaction for the preparation of two-carbon-tethered 1,3-oxathiole–indole pair compounds **11** (Scheme 4).[36] The results showed that functional groups such as bromide and chloride provide ample opportunity for further functional group manipulations, for example, by modern cross-coupling reactions.

A regioselective Sonogashira[37] cyclization reaction was carried out in the presence of CuI as catalyst and 2,2′-(1*E*,1′*E*)-(1*R*,2*R*)cyclohexane-1,2-diylbis(azan-1-yl-1-ylidene)bis(methan-1-yl-1-ylidene)diphenol as ligand to obtain benzyl-3-(indol-3-yl)-2-phenyl-2,3-dihydroisoindolinones **14**. The reaction involved the one-pot multicomponent reaction of indoles **1**, 2-iodo-*N*-phenylbenzamides **12** and terminal alkyne **13** under

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Negar Lashgari was born in 1985 in Tehran, Iran. She received her B.Sc. degree in applied chemistry from the Kharazmi University, Karaj, Iran (2008) and her M.Sc. degree in organic chemistry at Alzahra University, Tehran, Iran (2011) under the supervision of Dr Ghodsi Mohammadi Ziarani. She obtained her Ph.D. degree in nanochemistry from the University of Tehran under the supervision of Dr Alireza Badiei and Dr Ghodsi Mohammadi Ziarani in 2017. Her research field is synthesis and functionalization of mesoporous silica materials and their application as nano-heterogeneous catalysts in multicomponent reactions and fluorescent chemosensors for detection of various anions and cations.

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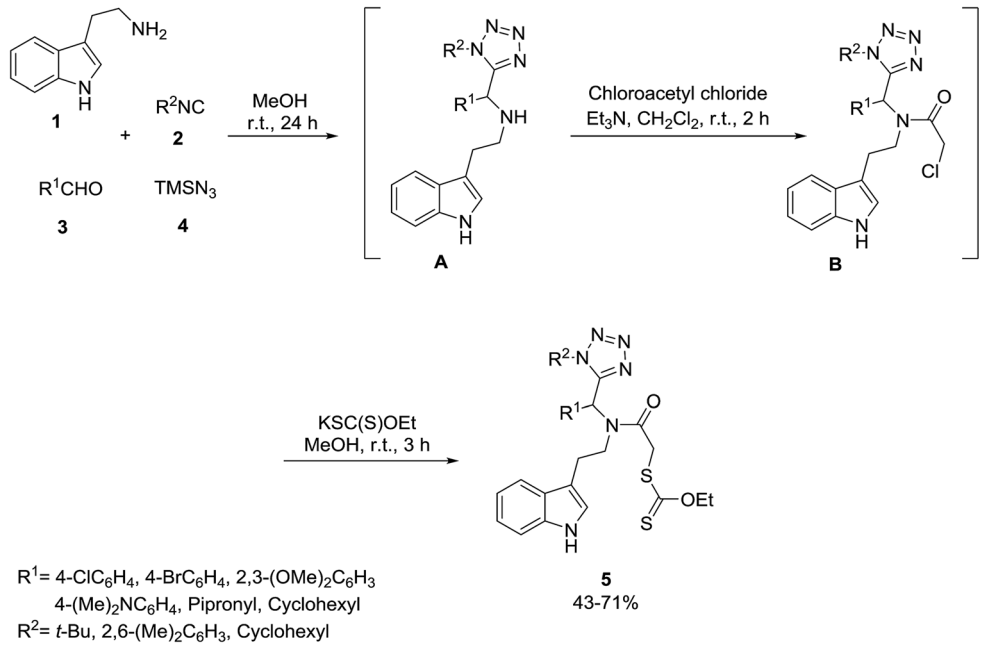
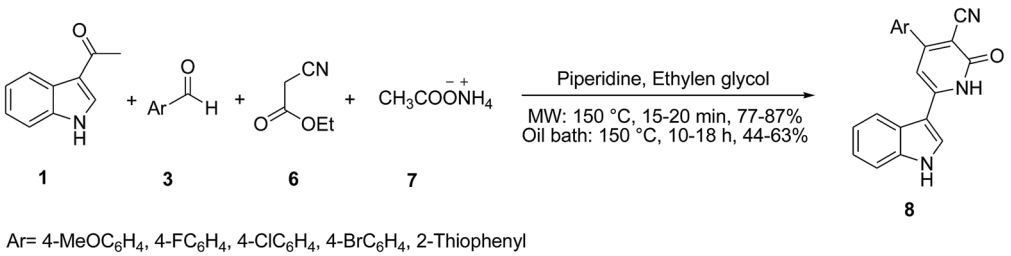


Scheme 2



Scheme 3

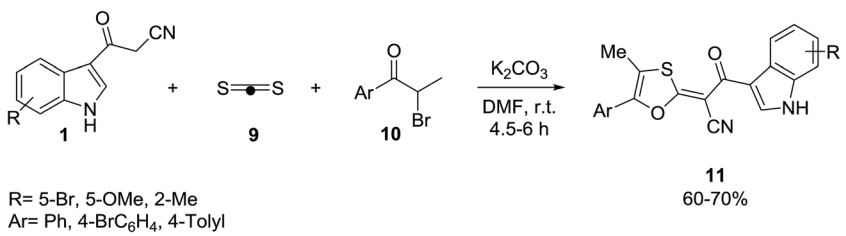
aerobic conditions followed by a nucleophilic addition (Scheme 5).[38]

Magnetic nanoparticles (Fe_3O_4-NPs) catalyzed the synthesis of pyrano[2,3-*d*]pyrimidines **17** and pyrido[2,3-*d*]pyrimidines **18**. The reactions were performed *via* the one-pot three component reaction of indole **1**, malononitrile **15** and barbituric acids **16a** or 6-amino uracil derivatives **16b** in EtOH (Scheme 6).[39]

Baruah *et al.* presented the synthesis of 3-alkylated indole derivatives **20** and **21** under a microwave-assisted three-component reaction of indole-3-aldehydes **1**, alkyl nitriles **15** or barbituric acids **16** with 1,4-dihydropyridine (DHP) derivative **19** (Scheme 7).[40] In each case, DHPs are converted to pyridines. In fact, 1,4-dihydropyridine is the reducing agent.

Preparation of a wide variety of new 6-(1*H*-indol-3-yl)-2-oxo-4-aryl-1,2,3,4 tetrahydropyrimidine-5-carbonitriles **23** was accessed by combining 3-(cyanoacetyl)-indoles **1** with an arylaldehyde **3** and urea **22** in the presence of PEG-400 and a catalytic amount of thiazolium anions (NHCs) (Scheme 8).[41]

A three-component reaction for the synthesis of functionalized 3-{1-[2-(1*H*-indol-3-yl)ethyl]-4,5,6,7-tetrahydro-1*H*-indol-3-



Scheme 4

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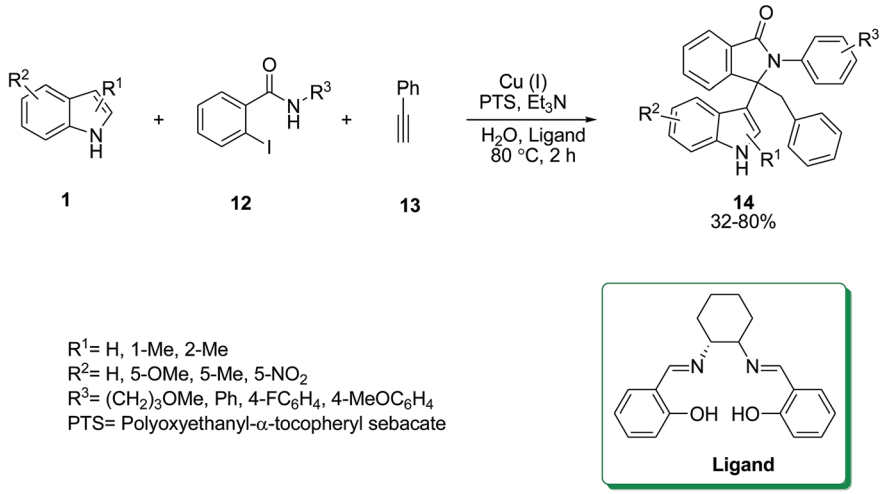
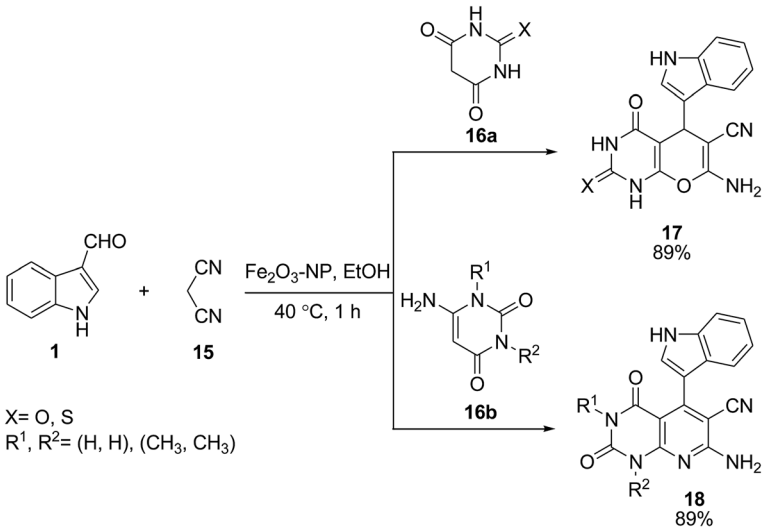


Scheme 5



Scheme 6

yl}indolin-2-ones **26** has been described by Jiang and Yan. The reaction involves a one-pot condensation of indole **1** with dimedone **24** and 3-phenacylideneoxindoles **25** in refluxing acetonitrile with *p*-toluenesulfonic acid as catalyst (Scheme 9).[42]

Modha and co-workers provided a novel procedure for the synthesis of diversely substituted spiroindolines **30** *via* the post-Ugi gold-catalyzed diastereoselective domino cyclization. In this methodology, the Ugi reaction of indole-3-aldehydes **1**, propargylamine **27**, acids **28** and isocyanides **2** gave the products **29** in good yields which reacted with $Au(PPh_3)SbF_6$ in chloroform to produce spiroindolines **30** in moderate yields (Scheme 10).[43] In another study, the same group used other amines instead of propargylamine for the synthesis of analogues of these products.[44]

The indolylmalonamides **33** have been prepared *via* the three-component reaction of indole derivatives **1**, chromene-3-carboxylates **31** and amines **32** in the presence of $La(OTf)_3$ as a Lewis acid catalyst (Scheme 11).[45] Indolylmalonamide products **33** showed notable fluorescence activities when they are exposed to long wave UV light (366 nm).

Polyfunctionalized indole derivatives **35** and **36** were generated from the Yonemitsu-type[46] trimolecular condensation of indoles **1** with aldehydes **3** and 1,3-dicarbonyl compounds **34**, such as malonates and acetoacetates using Lewis acid catalysts under microwave irradiation. The formation of bis-indolic derivative **36** can be easily rationalized in the one pot reaction, where a double addition of indole to the aldehyde is assumed. As already suggested by Gao and Wu,[47] the adduct **35** is probably converted into a reactive indolenine derivative **A**[48] by the loss of an active methylene fragment, which reacts with another molecule of indole (Schemes 12 and 13).[49] Macroporous copper oxide (mpCuO) was also used as catalyst in this reaction and the same products were isolated in good yields.[50] Docking studies against enoyl acyl carrier protein reductase predicted

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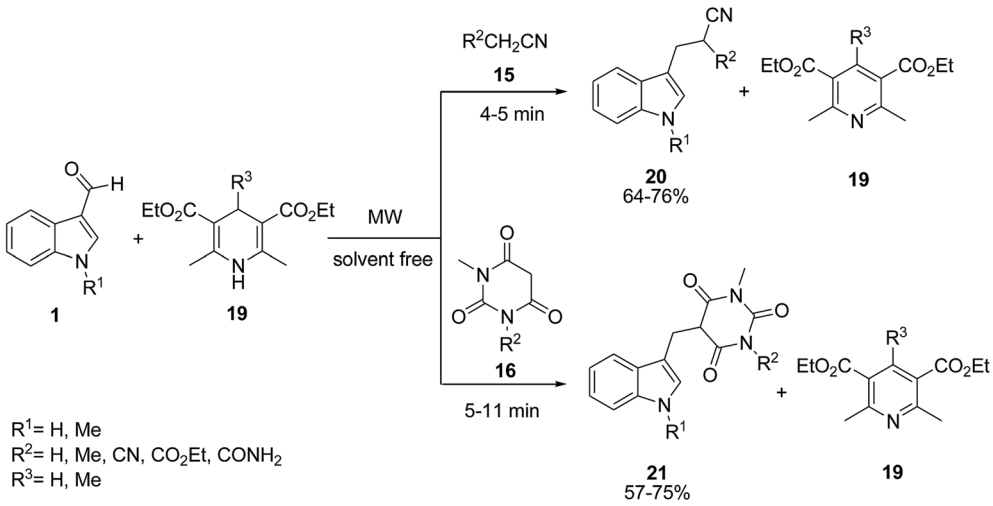
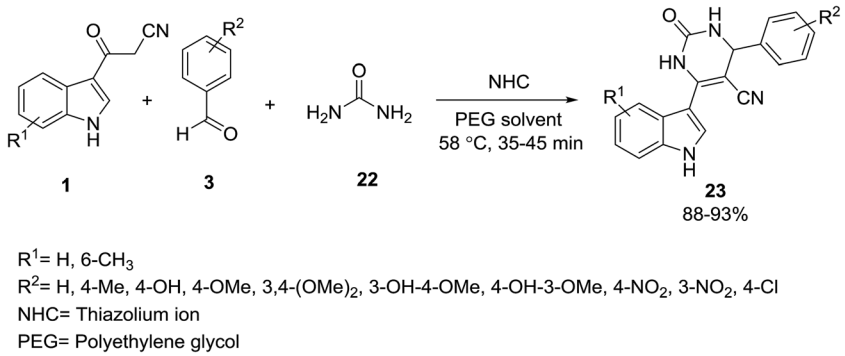
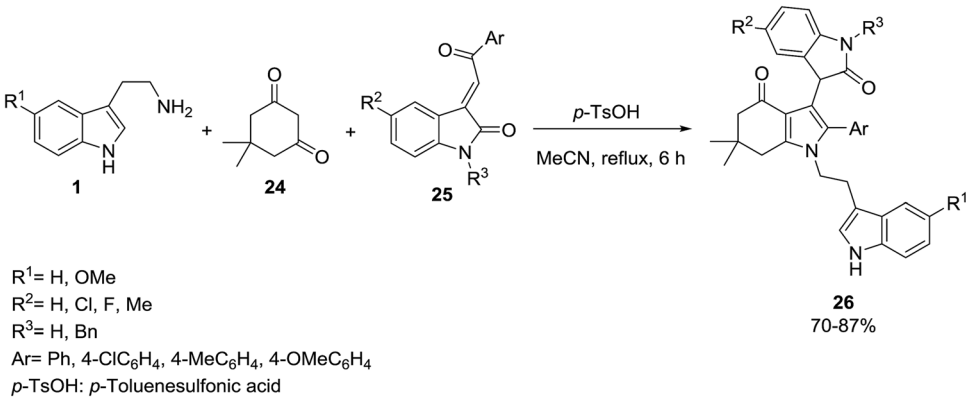


Scheme 7



Scheme 8



Scheme 9

that the compounds bind at the active site with high binding affinity values. In another study, Li *et al.* used L-proline as catalyst in this reaction.[51] The results are summarized in Table 1.

Khalafi-Nezhad *et al.* developed the use of trimethylsilyl iodide (TMSI) as a multifunctional agent in the one-pot synthesis of 9-(1*H*-indol-3-yl)xanthen-4-(9*H*)-ones **37** from the reaction of indoles **1**, 2-methoxybenzaldehydes **3** (as *O*-methyl protected salicylaldehydes) and β-dicarbonyl compounds **24** (Scheme 14).[52]

The functionalized indole-3-yl pyridines **40** were prepared *via* an efficient one-pot condensation of cyanoacetylindoles **1**, 3-

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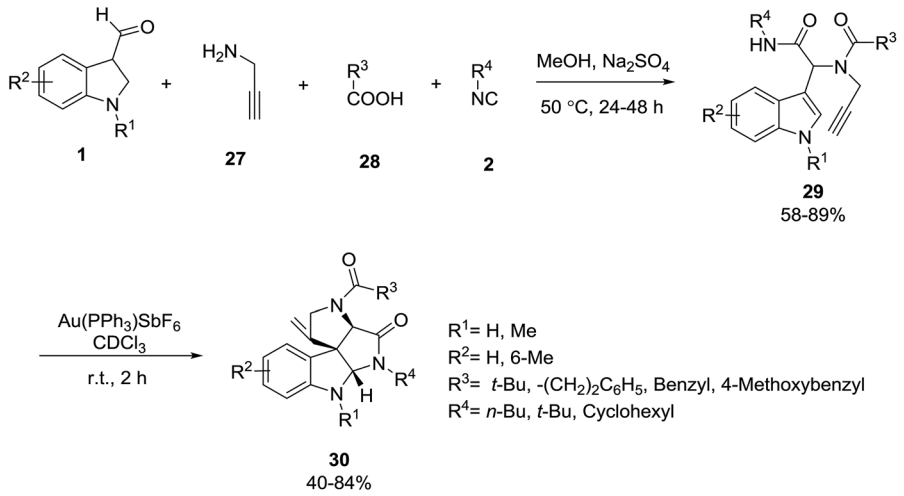
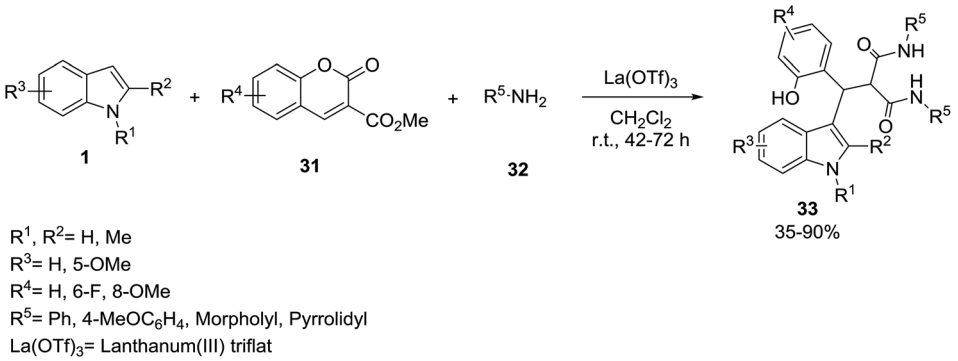


Scheme 10

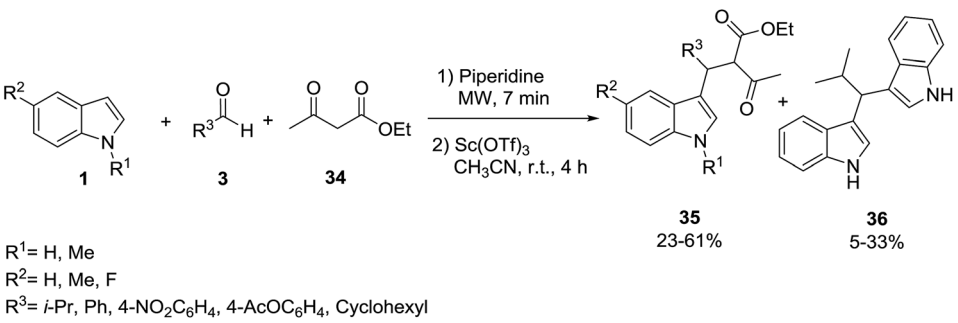


Scheme 11

formylchromones **38** and ammonium acetate **7** under stannous chloride **39** mediation in DMF (Scheme 15).[53]

Wan and co-workers used polyethylene glycol (PEG-200) in a three-component reaction of indoles **1**, aldehydes **3**, and malononitrile **15** to afford 3-indole derivatives **41** in good to excellent yields (Scheme 16).[54] L-Proline,[55] tetrabutylammonium fluoride (TBAF),[56] Zn-salphen,[57] $Cu(OAc)_2$ (ref. 58) and Cu(III)[59] were also used as catalysts in this reaction and the results are shown in Table 2.

Singh's group described a highly efficient methodology for the synthesis of 3-amino-alkylated indoles **44** *via* the one-pot three-component Mannich[60] type reaction of amines **42**, alcohols **43** and indoles **1**. Treatment of amines **42** and alcohols **43** with KOH in toluene in the presence of ($Fe(NO_3)_3 \cdot 9H_2O$/TEMPO)[61] as catalyst, yielded iminium ion **A**. Then, the iminium ion **A** was reacted with indoles **1** to obtain novel 3-substituted indoles **44** (Scheme 17).[62] In another study, ferric hydrogen sulfate (FHS)[63] was applied as catalyst and the same



Scheme 12

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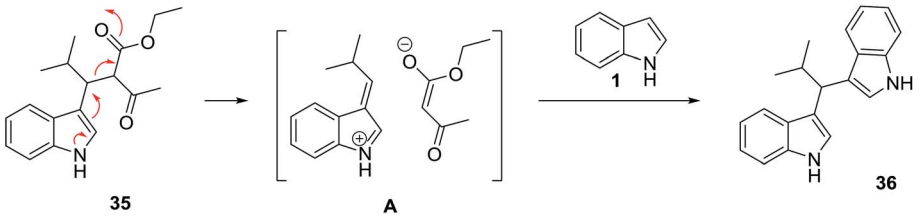


Scheme 13

Table 1 Comparison of different conditions for the synthesis of products 35 and 36

Entry	Solvent	Catalyst	Temperature	Time	Yield (%)
1	CH_3CN	$Sc(OTf)_3$	r.t.	4 h	58–79 (ref. 49)
2	H_2O	mpCuO	r.t.	15–31 min	78–95 (ref. 50)
3	EtOH	L-Proline	80 °C	0.25–4 h	70–99 (ref. 51)

products were prepared in 87–98%. It was observed that electron-withdrawing groups on the aldehyde reacted rapidly and were better reagents in this reaction. Furthermore, *N*-methylaniline showed better reactivity in comparison with *N*-ethylaniline due to the low steric effects. *N*-Alkylanilines were used in excess to avoid the formation of bis(indolyl)alkanes.[64] The reaction was also catalyzed by L-proline,[65] Amberlite, IRA-400 Cl resin[66] and polyaniline-fluoroboric acid-dodecyl hydrogen sulfate salt (PANI-HBF_4).[67] Catalyst-free conditions in MeOH have also been reported in 72 h by 28–99% yields.[68] A comparison of different catalysts and experimental setups is given in Table 3.

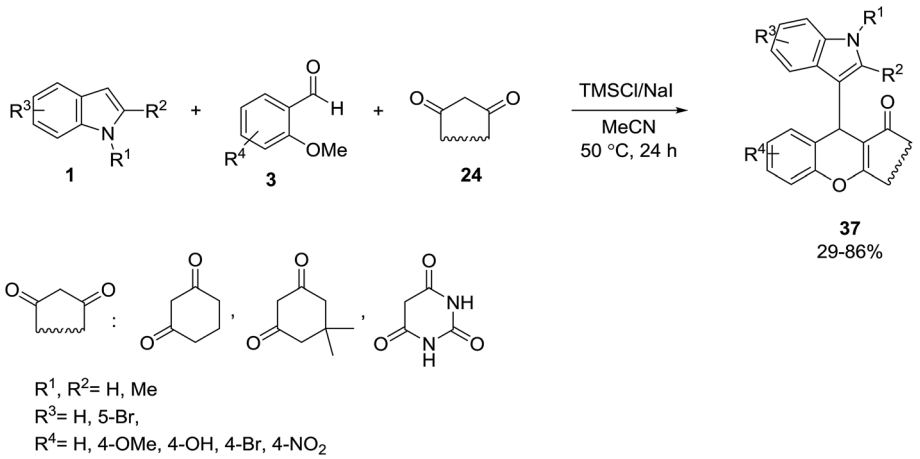
Mahmoodi and co-workers developed the one-pot cyclo-condensation of mono- or bis(indole-3-carbaldehyde) **1** or **45**,[69,70] thiosemicarbazide **46**, and phenacyl bromides **47** in the presence of a catalytic amount of AcOH for the preparation of the novel mono- and bis(indol-3-yl)hydrazineyl thiazole derivatives **48** and **49** (Scheme 18).[71] The products were evaluated for *in vitro* antibacterial activity against Gram-positive and Gram-negative bacteria. Some of the products have good antibacterial activity. The product **48** with OCH_3 as a donating group exhibited high activity against Gram-positive bacteria.

Shinde and Jeong developed the reaction between indole **1** and formaldehyde **3** with tertiary aromatic amines **42** in the presence of silica-supported tungstic acid (STA) as a heterogeneous acid catalyst under solvent-free conditions. The protocol was performed *via* the three component Mannich type Friedel–Crafts addition for the preparation of *N*,*N*-dialkyl amino arylated indole derivatives **50** (Scheme 19).[72] Application of sodium dodecyl sulfate (SDS) as surfactant in this reaction was also reported by Kumar *et al.* resulting in 78–94% yields of products.[73]

Mild aminoacylation of indoles **1** through a multicomponent process with ynol ethers **51** and sulfonyl azides **52** was established by Alford and Davies for the synthesis of oxo-tryptamines **53** (Scheme 20).[74] First, 4-alkoxy *N*-sulfonyltriazoles **A**[75] were generated from ynol ethers **51** and sulfonyl azides **52**, and treated with indoles **1**. Then, the obtained enol ethers **B** were converted to the amino ketones **53** for the α-aminoacylation of enols.[76]

N-Methyl indole **1** was reacted with diazooxindole **54** and nitrostyrene **55** in the presence of [Ru] and squaramide as catalysts *via* an asymmetric Michael addition[77] for the synthesis of 3,3′-bis(indole) derivatives **56** (Scheme 21).[78]

Novel spirooxindole-pyrrolidine compounds **61** and **62** were obtained through 1,3-dipolar cycloaddition of azomethine ylides generated from isatin **57** and sarcosine **59** or thioproline



Scheme 14

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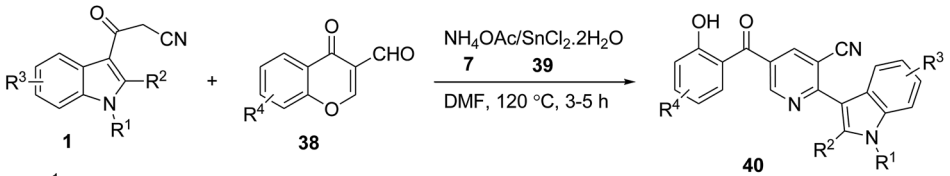
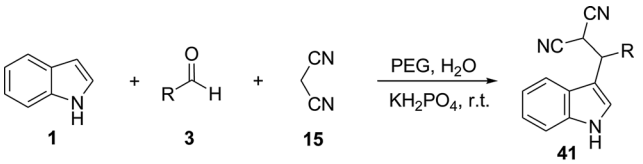


R^1= H, Me
R^2= H, Me, Ph
R^3= H, 5-OMe
R^4= H, 6-Me, 6-OMe, 6-Cl, 6-F, 7-F, 6,8-Cl_2

Scheme 15



R= H, *t*-Bu, 4-$OMeC_6H_4$, 3-$MeOC_6H_4$, 2-$MeOC_6H_4$, 4-MeC_6H_4
3-MeC_6H_4, 2-MeC_6H_4, 4-*i*-PrC_6H_4, 4-CNC_6H_4, 4-$COMeC_6H_4$
4-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 2-$NO_2C_6H_4$, 4-BrC_6H_4, 4-ClC_6H_4
3-ClC_6H_4, 2-ClC_6H_4, 2,4-$Cl_2C_6H_3$, 4-FC_6H_4, 4-$CF_3C_6H_4$

Scheme 16

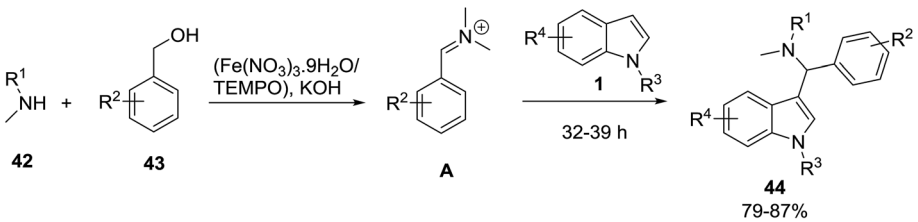
60 with the dipolarophile 3-(1*H*-imidazol-2-yl)-2-(1*H*-indole-3-carbonyl)acrylonitrile **58** (Scheme 22).[79] Anticancer activity studies were carried out for the synthesized compounds against A549 lung adenocarcinoma cancer cell line.[80] Several of the products showed very high activity against the cancer cell line. Reddy and co-workers also studied this reaction in MeOH as solvent under reflux conditions in 2–3 h giving 80–93% yields. The antimicrobial activity of all products were evaluated against several bacteria and fungi, and showed good activity.[81]

A one-pot four-component condensation strategy was employed by Naureen's group for the discovery of indole-based tetra-arylimidazoles **64**. This method involves the reaction of 2-arylindole-3-carbaldehydes **1**, substituted anilines **42**, benzil **63** and ammonium acetate **7** in acetic acid (Scheme 23).[82] The anti-urease activity of the synthesized compounds was evaluated and showed good results.

The same authors synthesized several new trisubstituted imidazoles, 3-(4,5-diaryl-1*H*-imidazol-2-yl)-2-phenyl-1*H*-indoles **65**, *via* the condensation of substituted indole aldehydes **1**, benzil **63** and ammonium acetate **7** in refluxing acetic acid (Scheme 24).[83] The products were evaluated for their α-glucosidase inhibition and showed significant α-glucosidase inhibitory activity.

Table 2 Comparison of different conditions for the synthesis of products **41**

Entry	Solvent	Catalyst	Temperature (°C)	Time (h)	Yield (%)
1	H_2O	PEG-200	r.t.	3	55–98 (ref. 54)
2	EtOH	L-Proline	r.t.	30–72	58–98 (ref. 55)
3	—	TBAF·$3H_2O$	60	2	55–97 (ref. 56)
4	DCM	Zn-salphen, DIPEA	r.t.	6	13–60 (ref. 57)
5	PEG-400	$Cu(OAc)_2$	70	15–40	48–98 (ref. 58)
6	H_2O	Cu(III)	30	12–24	70–96 (ref. 59)



R^1= Ph, Morpholyl, Pyrrolidyl
R^2= 4-Cl, 4-NO_2, Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 3-$MeOC_6H_4$
3,4,5-$(MeO)_3C_6H_2$, 4-*t*-Bu-C_6H_4, Cyclohexyl, Naphthalyl
R^3= H, Me
R^4= H, 5-OMe, 5-Br

Scheme 17

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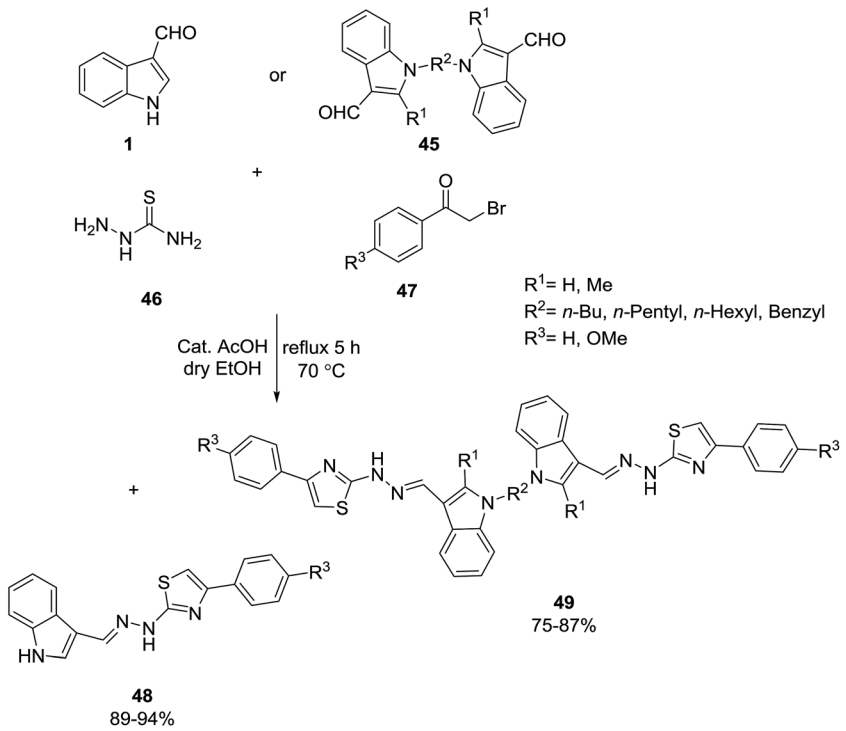
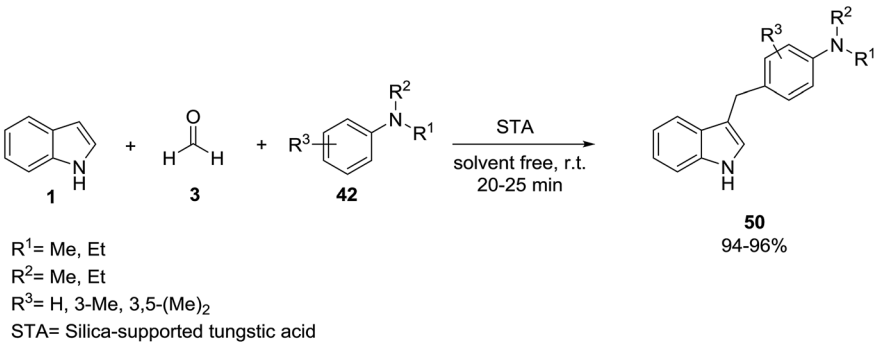
Table 3 Comparison of different conditions for the synthesis of product 44

Entry	Solvent	Catalyst	Temperature (°C)	Time (h)	Yield (%)
1	Toluene	($Fe(NO_3)_3 \cdot 9H_2O$/TEMPO)	r.t.	32–39	79–87 (ref. 62)
2	—	FHS	45	1–4	87–98 (ref. 63)
3	—	L-Proline	r.t.	5–18	68–89 (ref. 65)
4	MeOH	IRA-400 Cl resin	r.t.	1.5–3	70–85 (ref. 66)
5	H_2O	PANI-HBF_4	r.t.	30–50 min	88–97 (ref. 67)
6	MeOH	—	30	72	28–99 (ref. 68)



Scheme 18

Andreana and his group utilized the one-pot reaction of 4-nitroindolylacetaldehyde **1**, methylamine **32**, methyl isocyanide **66** and 3-hydroxyphenylpyruvic acid **67** for the synthesis of (±)-thaxtomin A (TA) **68** as a herbicidal natural product. First, the prerequisite dipeptide **A** was isolated which through a base-mediated keto-amide cyclization reaction afforded two diastereomeric compounds **B**. Then, compound **B** was treated with KOH under microwave irradiation to provide the intended product **68** (Scheme 25).[84] This natural product was synthesized previously by Zhang *et al.* and has



Scheme 19

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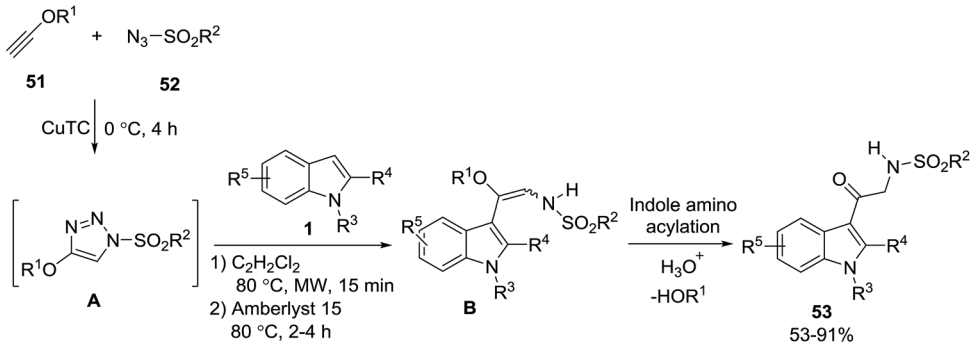


R^1= Et, Ph, Cyclohexyl, 2-Naphthyl
R^2= Ms, Ts, $(CH)_2TMS$
R^3= H, Me, Benzyl
R^4= Me, Ph
R^5= H, 5-Me, 5-OMe, 5-Br
CuTC = (copper(I) thiophene-2-carboxylate)

Scheme 20

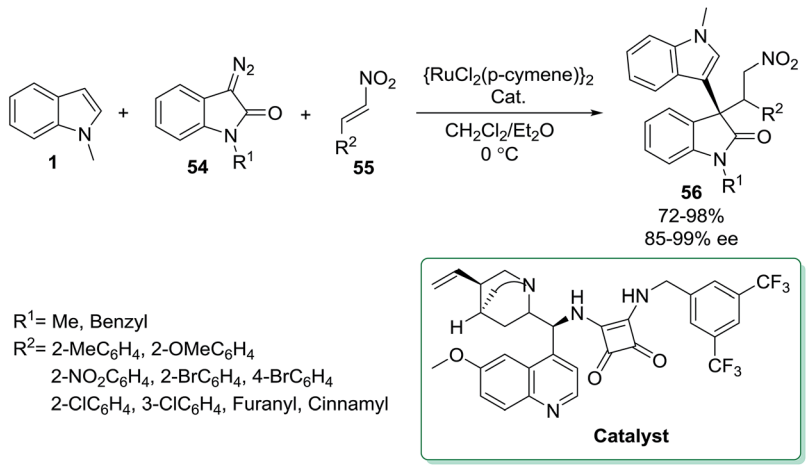
been demonstrated to possess activity against the tobacco mosaic virus.[85]

A one-pot three-component reaction of indole-3-aldehyde derivatives **1**, ethyl cyanoacetate **6**, and guanidine hydrochloride **69** under three different conditions, including microwave irradiation, grindstone technology and reflux, was developed to afford 2-amino-5-cyano-4-[(2-aryl)-1*H*-indol-3-yl]-6-hydroxypyrimidines **70** (Scheme 26)[86] The products **70** were evaluated for their antimicrobial activity against nine pathogenic bacteria and showed mild to moderate activity.

Bhattacharjee *et al.* employed ammonium chloride (NH_4Cl) as catalyst for the preparation of 9-(1*H*-indol-3-yl)-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-one **71** *via* the one-pot three-component reaction of indole **1** with salicylaldehyde **3** and dimedone **24** (Scheme 27).[87] In another study, Ganguly *et al.* developed this reaction in the presence of L-proline as catalyst in H_2O for 2 h in 86–96% yield.[88]

So and Mattson reported on the synthesis of glycine products **73** in the presence of chiral BINOL-based phosphoric-acid as catalyst. The process involves the multicomponent coupling reactions of indole derivatives **1**, nitrodiazoester **72** and anilines **42** in methyl *t*-butyl ether (MTBE) as solvent (Scheme 28).[89]

The three-component reaction of indoles **1**, α-oxoketene dithioacetals **74**, and aldehyde **3** or **75** was investigated for the synthesis of dihydrocoumarins **76** and quinolines **77** (Scheme 29).[90] The reaction mechanism was presented in Scheme 30. The electrophilic reaction of aldehyde **3** with two nucleophiles **1** and **74** resulted in the formation of intermediate **A** which was converted into a chromene-type intermediate **B** through an intramolecular substitution.[91] Finally, hydrolysis of intermediate **B** formed **77**. The reaction mechanism of aldehyde **75** is shown in Scheme 31. First, the condensation of **75** and indoles **1** produced the intermediate **D**. The NH_2 group of **75** attacked the C2 position of the indole ring, and formed the intermediate **E**.



R^1= Me, Benzyl
R^2= 2-MeC_6H_4, 2-$OMeC_6H_4$
2-$NO_2C_6H_4$, 2-BrC_6H_4, 4-BrC_6H_4
2-ClC_6H_4, 3-ClC_6H_4, Furanyl, Cinnamyl

Scheme 21

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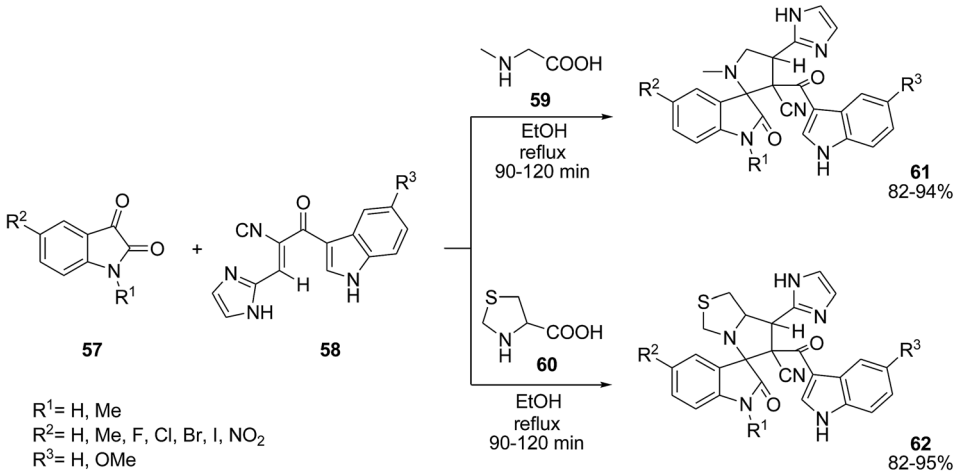
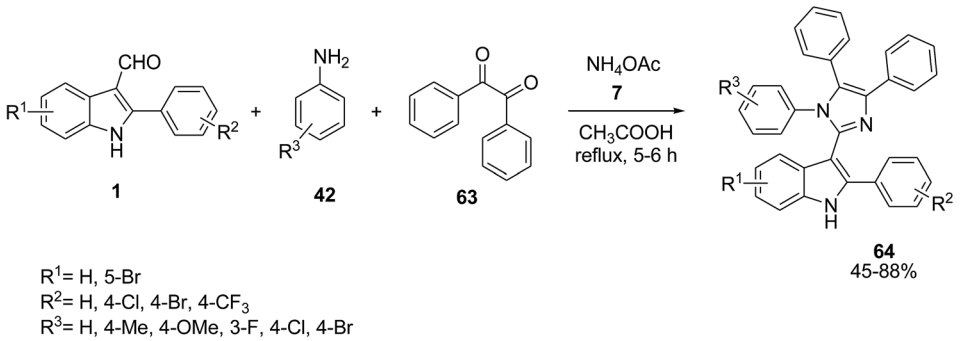


Scheme 22



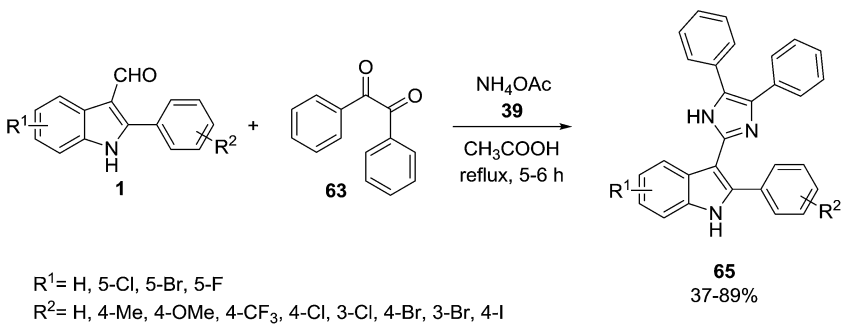
Scheme 23

Cleavage of an endocyclic C–N bond allowed the formation of a quinoline derivative **F**.[91] Then, compound **74** reacted with NH_2 group of quinoline **F** and final product **76** was obtained.

Borah *et al.* investigated the one-pot multicomponent reaction of 3-(cyanoacetyl)-indoles **1**, aromatic aldehydes **3** and ethyl acetoacetate **34** in the presence of $InCl_3$ under microwave irradiation to produce the functionalized 3-(pyranyl)-indole derivatives **78**. When ammonium acetate **7** was used as the source of ammonia in this reaction, the one-pot four-component reaction was carried out and 3-(dihydropyridinyl)-indole derivatives **79** were obtained (Scheme 32).[92] The results show that electron donating groups (EDG) in the aldehyde increase the product yield, whereas electron withdrawing groups (EWG) decrease the yield of products.

A sulfone-containing Brønsted acid ionic liquid was used in a one-pot reaction of indole **1**, salicylaldehydes **3** and 1,1-diphenylethylene **80** for the synthesis of substituted chromane derivatives **81** (Scheme 33).[93]

A series of indole incorporated thiazolylcoumarins **83** were synthesized from the reaction of indole derivatives **1**,



Scheme 24

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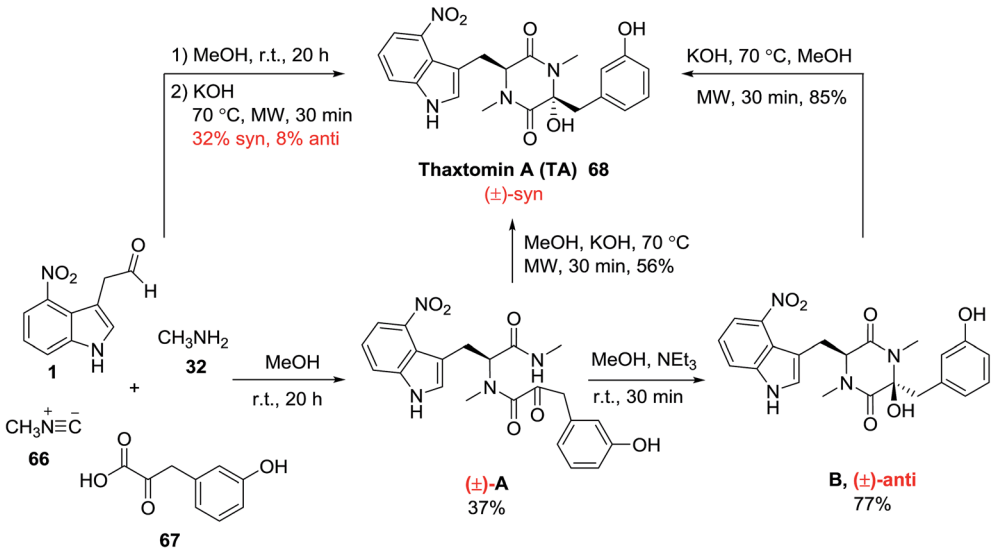
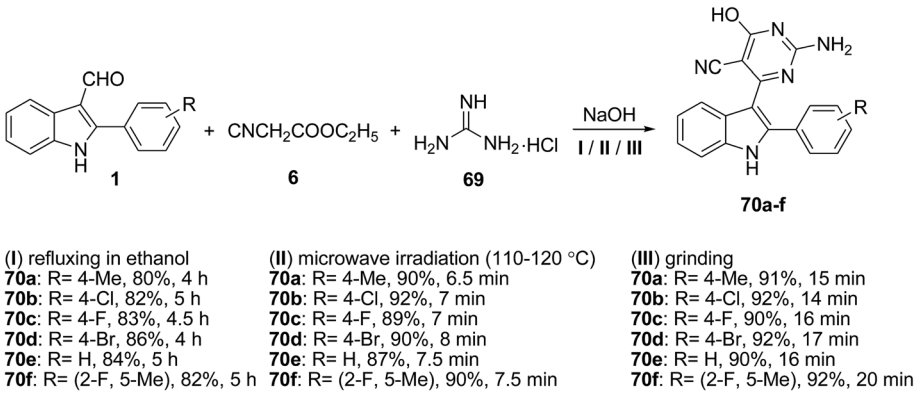


Scheme 25



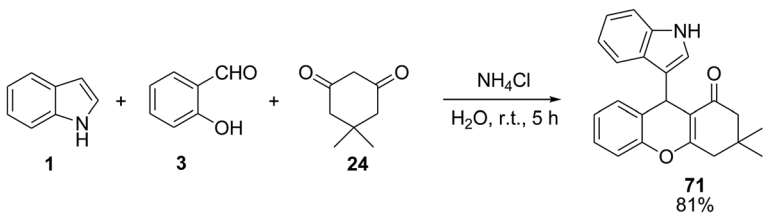
Scheme 26

thiosemicarbazide **46** and 3-(2-bromoacetyl)-2*H*-chromen-2-ones[94] **82** using a catalytic amount of acetic acid (Scheme 34).[95] The antibacterial, anticancer and DNA cleavage activities of products were evaluated. The results showed that all products have a good activity towards the screened bacterial strains.

Song *et al.* established the [3 + 3] cyclization of 3-(cyanoacetyl)-indoles **1** with dialkyl acetylenedicarboxylates (DMAD) **84** and isocyanides **2** for the preparation of 4-*H*-pyran derivatives **85** containing an indole scaffold (Scheme 35).[96]

Efficient synthesis of indol-3-yl substituted pyran derivatives **86** was investigated by Ji and co-workers *via* the one-pot multicomponent reaction of 3-cyanoacetyl indoles **1**, aldehydes **3** and malononitrile **15** in the present of piperidine as catalyst under ultrasonic irradiation (Scheme 36).[97] Thiamine hydrochloride (vitamin B_1) and cetyltrimethylammonium bromide (CTAB) were also utilized as catalysts in this reaction for 25 min giving 92–94% yield.[98]

A Knoevenagel[99] coupling of salicylaldehyde **3** and Meldrum's acid **87** followed by a Michael type reaction with indole **1**



Scheme 27

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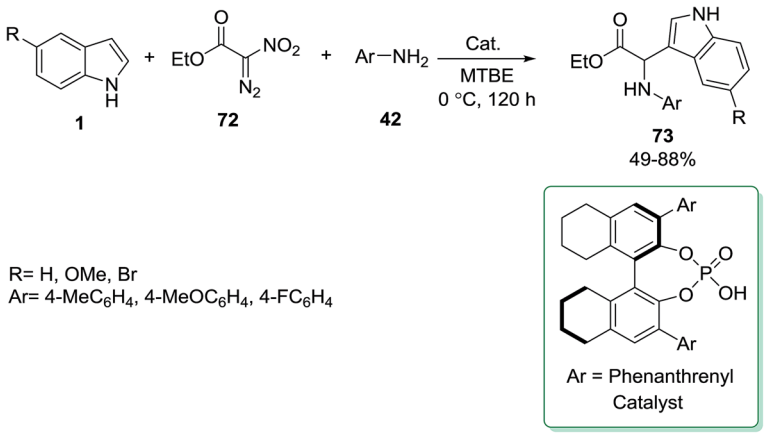
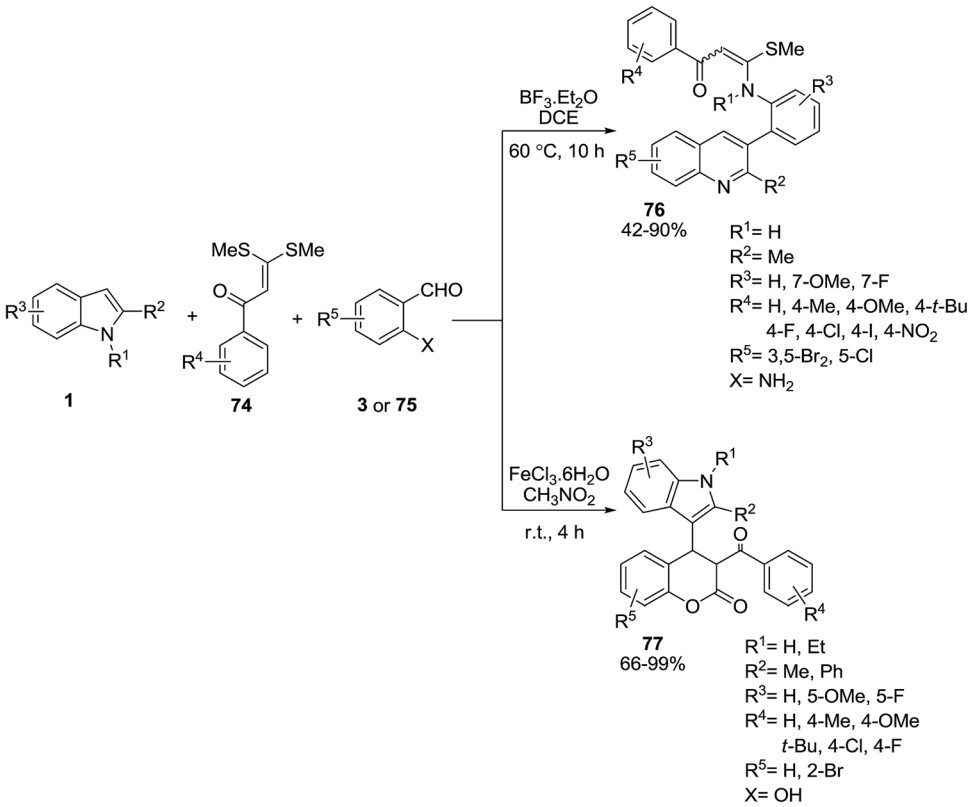


Scheme 28

in the presence of a (saccharin)-based functional ionic liquid (imidazolium saccharinate) was reported by Kumar *et al.* This multicomponent reaction was performed *via* lactonization decarboxylative elimination to functionalize the C-3 of indoles with dihydrocoumarin to yield indole-3-dihydro-coumarins **88** (Scheme 37).[100]

Biheterocycles containing indole and azole skeletons **90** and **91** were prepared from the multicomponent reaction of indoles **1**, 1,2-diaza-1,3-dienes **89** and aldehydes **3** or alkynes **13** (Scheme 38).[101] The synthesized compounds were screened for their *in vitro* biological studies. The results showed that some of them have anticancer activity against MCF7 and Caco-2 human tumor cell lines.

Stefani and co-workers utilized a mild approach for the synthesis of indole-3-glyoxyl derivatives **94** and indole-3-glyoxyl-1,2,3-triazoles **96**. For this purpose, the reaction of indole **1**, oxalyl chloride **92** and various nucleophiles **93** was carried out in *N*,*N*-diisopropylethylamine (DIPEA) to afford indole-3-glyoxyl derivatives **94** (Scheme 39). On the other hand, indole-3-glyoxyl-1,2,3-triazoles **96** were obtained from the one-pot



Scheme 29

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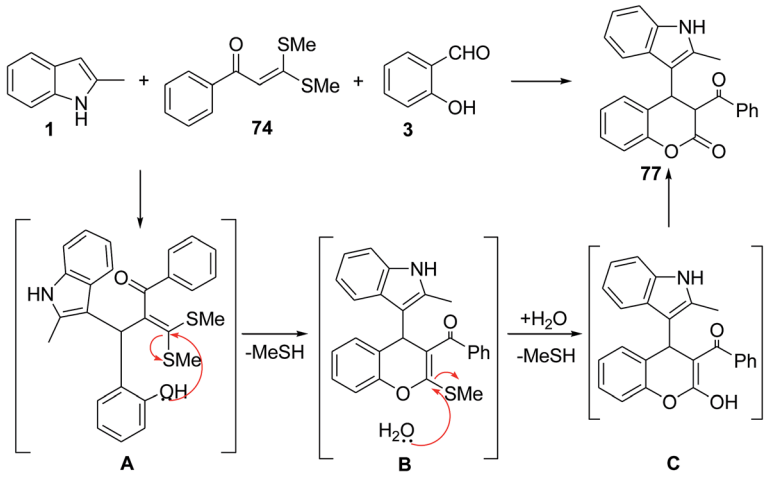
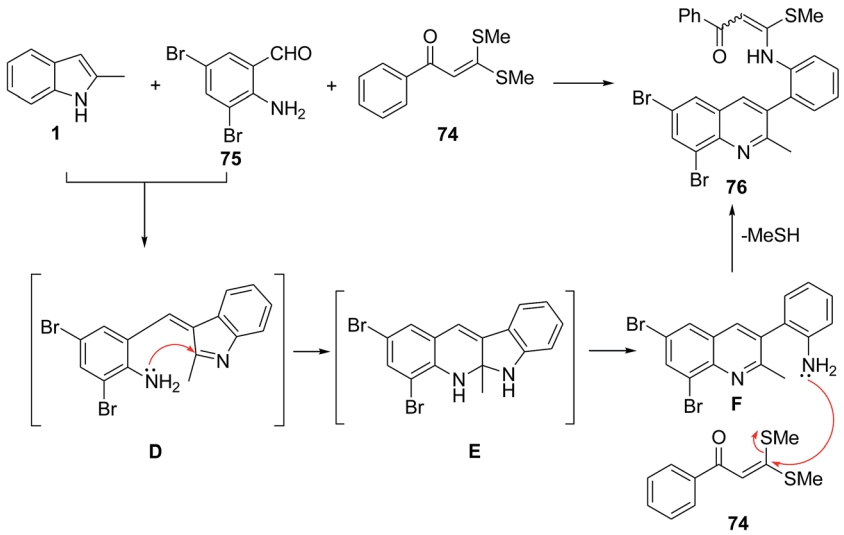


Scheme 30



Scheme 31

multicomponent reaction of these reactants and organic azides **95** *via* click[102] chemistry (Scheme 40).[103]

Indole **1** was reacted with anilines **42** and aldehydes **3** *via* an anhydrous $ZnCl_2$ catalyzed one-pot three-component reaction to afford diarylmethyl indoles **97** in toluene and 3-arylmethyl indoles **98** in MeOH. The reaction of indole **1** with benzaldehyde **3** in the presence of catalyst formed the azafulven **A** which reacted with another indole **1** to generate the kinetically stable bis(indolyl)methane **B**. In the presence of anilines, bis(indolyl) methane converted to the target products **97** (Schemes 41 and 42).[104]

A series of biologically important 3-(1-arylsulfonylalkyl) indoles **100** were prepared by Huang *et al.* This process was carried out using a catalyst-free three-component reaction of indoles **1**, carbonyl compounds **3**, and arenesulfinic acids **99** at room temperature (Scheme 43).[105] Bis(indolyl) methanes **A** were found as the key intermediates in this reaction.

The synthesis of bis(indolyl)methanes **101** was reported by Dhumaskar and Tilve *via* the reaction of two molecules of indole **1** with aldehydes **3** under solvent-free conditions without any catalyst (Scheme 44).[106] Two different methods were employed for this reaction. In method A, the mixture of aldehyde and indole was kept at ambient temperature in a test tube while in method B, the mixture was ground using a mortar and pestle. Method B resulted in the formation of products in shorter reaction times than method A. According to the results, anisaldehyde with an electron donating group at the *para* position and heptaldehyde failed to react completely. Mohammadi Ziarani and co-workers developed this reaction using the sulfonic acid functionalized silica (SiO_2-Pr-SO_3H) as catalyst and obtained the same products in short reaction times and good yields (5–20 min and 87–96% yields).[107]

Mohammadi Ziarani and coworkers synthesized a novel class of symmetrical 3,3-di(indolyl)indolin-2-ones **102** from the

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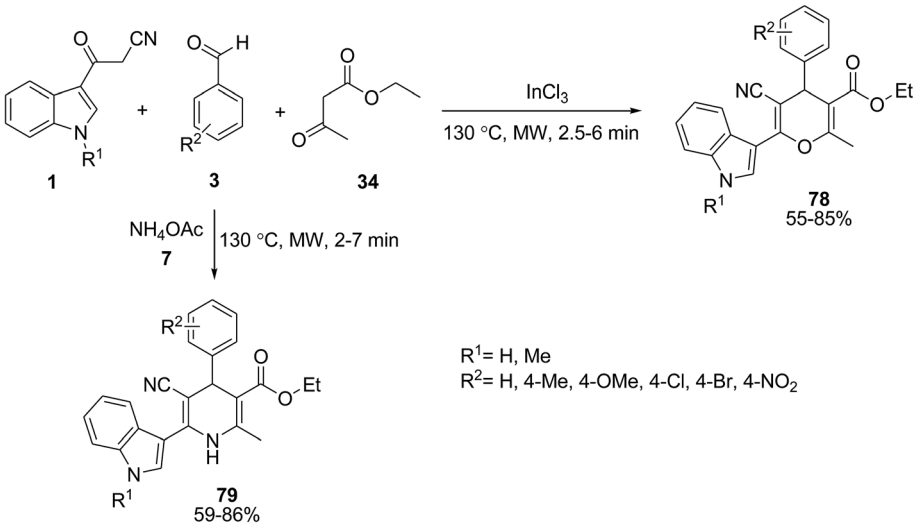
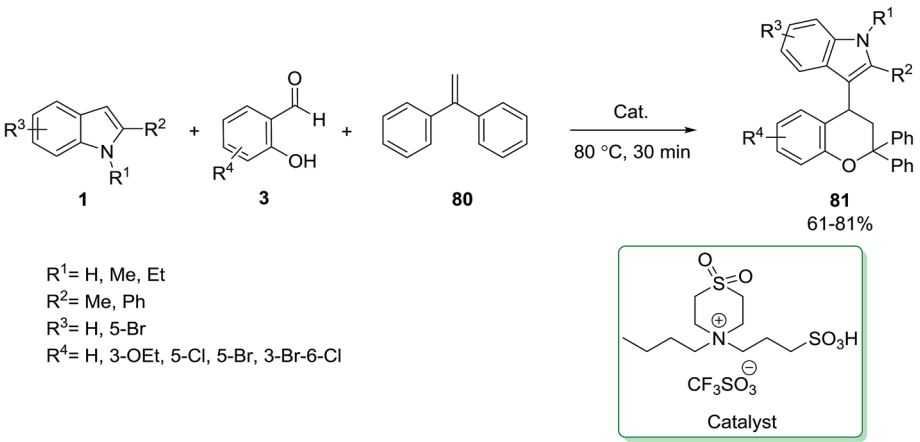
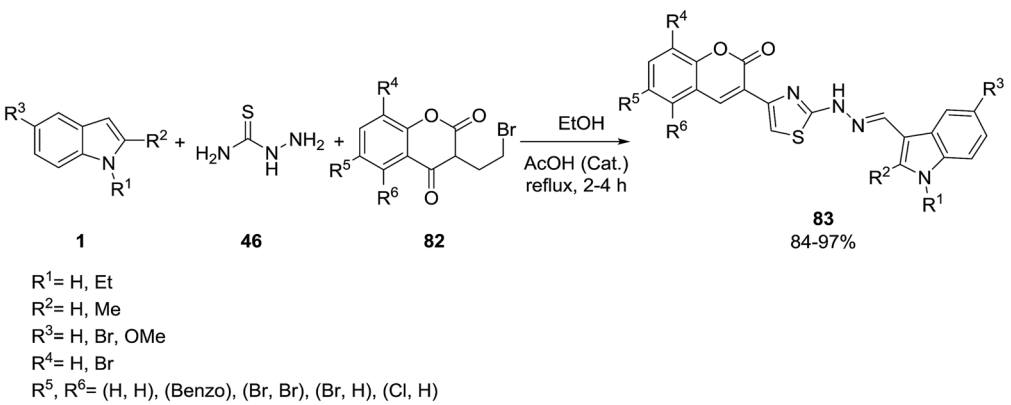


Scheme 32



Scheme 33

reaction of indoles **1** with isatins **57** in the presence of SBA-Pr-SO_3H as a solid acid catalyst under mild reaction conditions (Scheme 45).[108] The antimicrobial activities of the products were tested and the results demonstrated that the MIC value of one of the products ($R^1 = R^3 = H$, $R^2 = Bn$) against *B. subtilis* was equal to that of chloramphenicol.



Scheme 34

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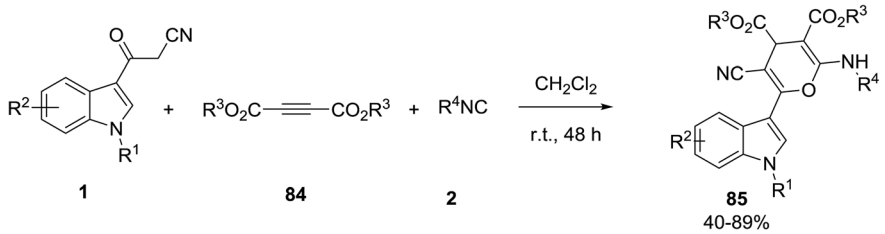
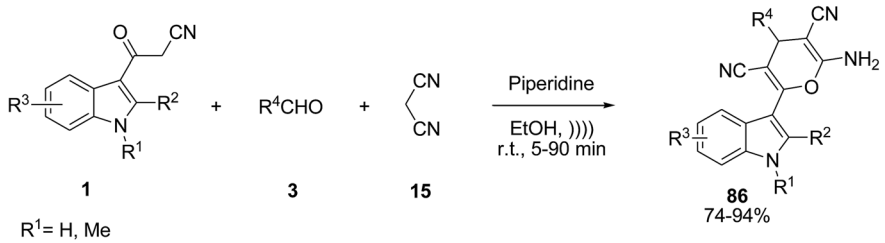


R^1= Me, *n*-Hexyl, 4-$MeOC_6H_4$, Benzyl, 4-Methoxybenzyl
4-Threefluorobenzyl, 3-Bromobenzyl
R^2= H, 5-OMe, 5-Br
R^3= Me, Et
R^4= *t*-Bu, Cyclohexyl

Scheme 35

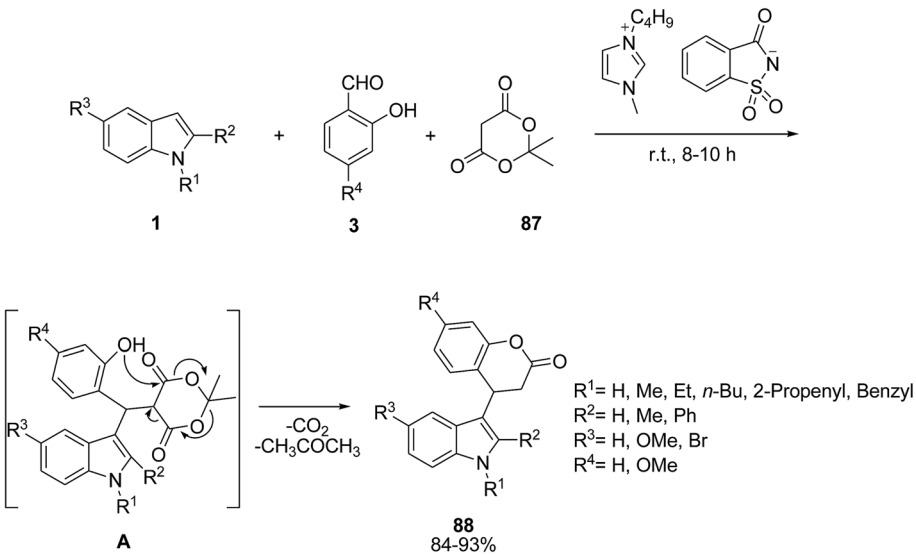


R^1= H, Me
R^2= H, Ph
R^3= 5-Br, 7-Me
R^4= Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2,4-$Cl_2C_6H_3$
2-BrC_6H_4, 4-BrC_6H_4, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 2-Naphthyl

Scheme 36

Geng's group developed the one-pot four component reaction of 3-(cyanoacetyl)indoles **1**, aromatic aldehydes **3**, 1-(9-butylcarbazol-3-yl)ethanone **103** and ammonium acetate **7** for the preparation of several 3-cyano-2-(1*H*-indol-3-yl)-6-(9-butylcarbazol-3-yl)pyridine derivatives **104**. The reaction was performed using AcOH and ethane-1,2-diol (glycol) under microwave irradiation (Scheme 46).[109]

Zn^{2+} supported on montmorillonite KSF (Zn^{2+}@KSF) as an efficient heterogeneous catalyst promoted the preparation of mono and bis-indolylimidazole derivatives **106** and **107**. This reaction was carried out from the condensation of indole-3-



R^1= H, Me, Et, *n*-Bu, 2-Propenyl, Benzyl
R^2= H, Me, Ph
R^3= H, OMe, Br
R^4= H, OMe

Scheme 37

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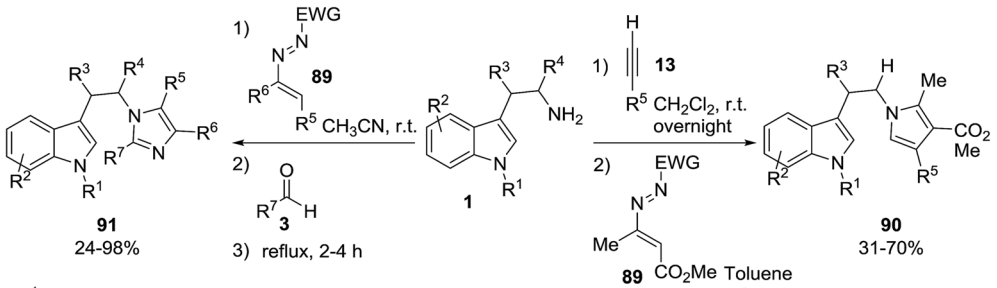
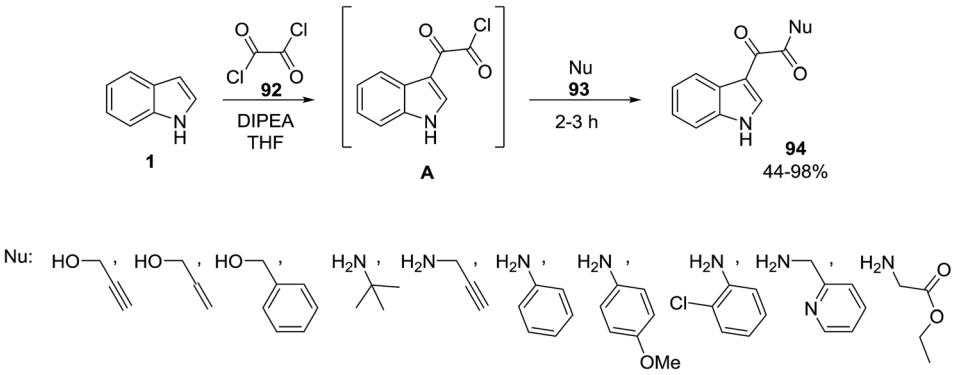


R^1= H, Me
R^2= H, 6-Br, 5-Me
R^3= H, 3-indolyl, 6-Br-3-indolyl, 1-Me-6-Br-3-indolyl
5-Me-3-indolyl, 1-Me-5-Me-3-indolyl
R^4= H, CO_2Me
R^5= CO_2Me, CO_2NMe_2
R^6= Me, Et, *n*-Propyl
R^7= H, Ph

R^1= H, Me
R^2= H, 6-Br, 5-Me
R^3= H, 1-Me-3-indolyl, 6-Br-3-indolyl
1-Me-6-Br-3-indolyl, 1-Me-5-Me-3-indolyl
R^5= CO_2Me, CO_2Et
EWG: Electron-withdrawing group

Scheme 38

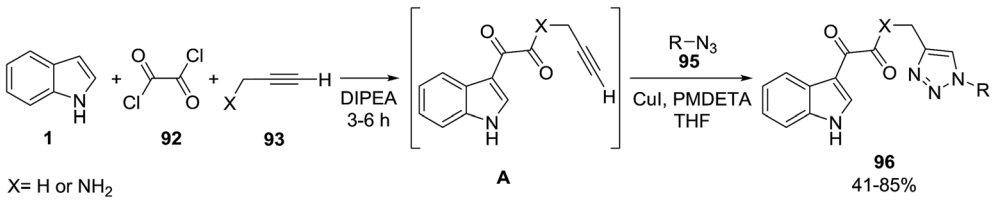


Scheme 39

carbaldehyde derivatives **1** or bis-aldehydes **105**,[110] aniline derivatives **42** and benzil **63** (Scheme 47).[111] The antibacterial activity of the synthesized compounds was examined and some of them exhibited promising activities.

Naidu *et al.* explored the one-pot three-component reaction of 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 **108**, aryl aldehydes **3** and 6-aminouracil derivatives **16** (obtained from the reaction of 3-(cyanoacetyl)-indoles **1** and nitrile **14**) for the synthesis of some hexahydropyrimido[4,5-*b*]-1,8-naphthyridine derivatives **109** and **110**. It was found that when the indole derivative **108** (R^1 = H; R^2 = CO_2Et) was treated with benzaldehyde (**4a**) and uracil **16** (R^4 = Me) the ester group participated in the cyclization process instead of the nitrile group, and the trioxo-nitrile compound **110** was obtained (Scheme 48).[112]

The three-component coupling reaction of indoles **1**, β-ketoesters **34** and arylboronicacids **111** *via* the regioselective palladium-catalyzed oxidative reaction was studied for the preparation of indole-based heterocycles **112** (Scheme 49).[113]



X= H or NH_2
R= Ph, 2-$MeOC_6H_4$, 3-$MeOC_6H_4$, 2-ClC_6H_4, 3-ClC_6H_4, Benzyl, *n*-Octyl-N_3

Scheme 40

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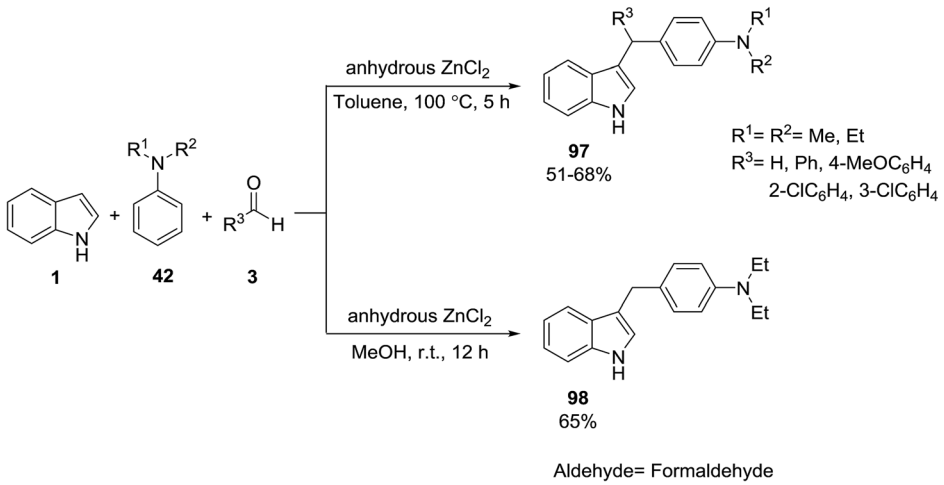
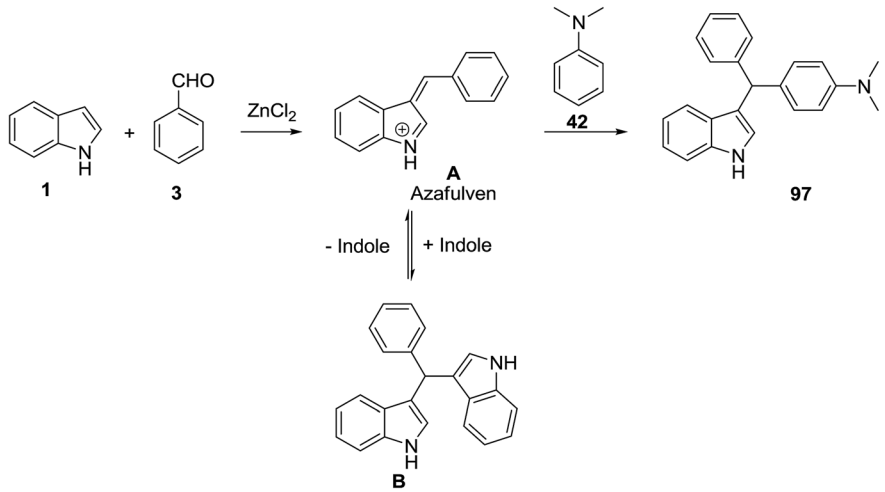


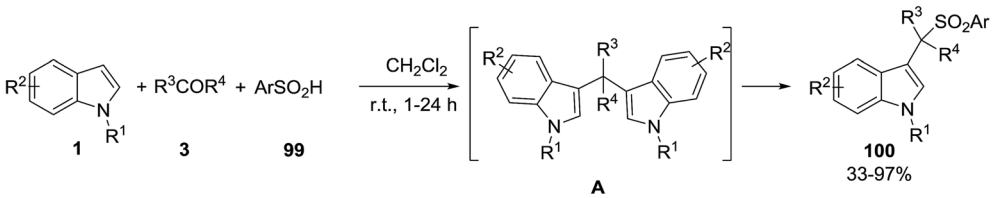
Scheme 41



Scheme 42

Indole coupled more rapidly than β-ketoester with the arylboronic acid, and this rate variation was important under the three-component reaction conditions, possibly because the coupling with β-ketoester involves an unstable enone intermediate.

Siddalingamurthy *et al.* described the synthesis of indole-3-propanamide derivatives **113** and **114** *via* the three-component reaction of *N*-methyl indole **1**, aromatic aldehydes **3** and Meldrum's acid **87** in the presence of choline chloride/urea ionic liquid as catalyst. At first, Meldrum's adduct **A** was generated,



R^1= H, Me, $SO_2C_6H_4$
R^2= H, 7-Me, 5-OMe, 7-CO_2Et, 6-Cl, 5-Br, 5-NO_2, 2-Ph
R^3, R^4= (H, H) (H, Ph), (H, 4-MeC_6H_4), (H, 4-$MeOC_6H_4$), (H, 3,4-$(MeO)_2C_6H_3$)
(H, 2-ClC_6H_4), (H, 4-ClC_6H_4), (H, 4-BrC_6H_4), (H, 4-$NO_2C_6H_4$), (H, 2-Thienyl), Cyclohexyl
Ar= Ph, 4-MeC_6H_4, 4-ClC_6H_4

Scheme 43

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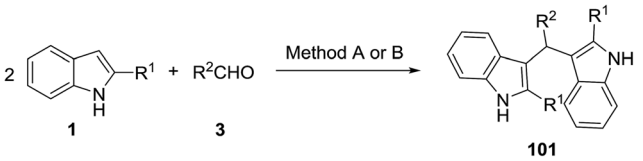


Method A: r.t., 3 min to 6 days, 51-96%
Method B: Grounding, r.t., 2 min to 2 days, 60-98%

R^1= H, Me
R^2= Ph, 3-$MeOC_6H_4$, 4-$MeOC_6H_4$, 2-ClC_6H_4
4-ClC_6H_4, 2-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 2-Furyl, 2-Pyridyl

Scheme 44

which then reacted with various amines, and the indole-3-propanamide derivatives **113** were formed. On the other hand, when Meldrum's adduct was treated with H_2O, corresponding acid products **114** were obtained (Scheme 50).[114]

A one-pot four-component reaction of 3-(cyanoacetyl)indole **1**, benzaldehyde derivatives **3**, 3-acetylpyridine **114**, and NH_4OAc **7** was explored for the preparation of 2-(indol-3-yl) pyridine derivatives **115** (Scheme 51). In the same paper, 4-aryl-2-(1*H*-indol-3-yl)-6-arylnicotinonitriles **117** were also obtained based on this process, from the reaction of 3-(cyanoacetyl)indole **1**, aromatic aldehydes **3**, aromatic ketones **116**, and NH_4OAc **7** under two different conditions (Scheme 52).[115]

Deb *et al.* reported a base-promoted three-component one-pot approach for the synthesis of 3-(α,α-diarylmethyl) indoles **119** *via* arylation of *in situ* generated 3-indolylalcohols **A** in an EtOH–H_2O solvent system. Substituted indoles **1**, benzaldehydes **3** and electron-rich aromatics **118** were used as starting materials in this reaction (Scheme 53).[116]

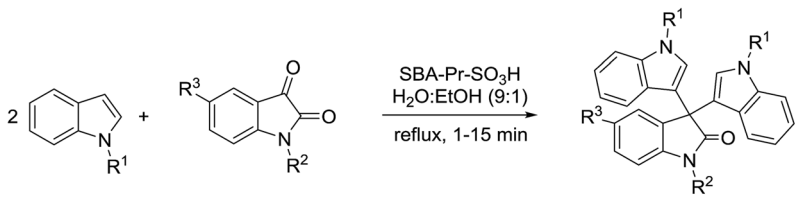
2.2. The N position reactions of indoles

Martinez-Ariza *et al.* reported a two-step one-pot procedure for the synthesis of *N*-1-quinoxaline-indoles **123** from the reaction of indoles **1**, amines **120** and glyoxaldehydes **121**. In the first step, α-iminoketones **A** were formed from the reaction of amines **120** and glyoxaldehydes **121**, which were then treated with indole **1** for the preparation of compounds **122**. The deprotection-cyclization of **122** was performed for the synthesis of target products **123** (Scheme 54).[117]

Hulme and co-workers reported a one-pot two-step multi-component reaction of indole **1**, arylglyoxaldehyes **121** and amines **42** for the synthesis of α-oxo-acetamidines **125** under microwave conditions. The main reaction step was the N-1 addition of indole to α-iminoketones **A** (obtained from the reaction of arylglyoxaldehyes **121** and amines **42**), followed by an air- or oxygen-mediated oxidation (Scheme 55).[118]

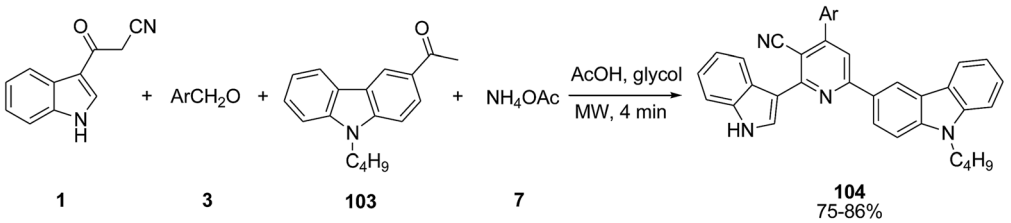
2.3. The cycloaddition reactions of indoles

2.3.1. The cycloaddition reactions of indoles at the C2–C3 π-bond. The tetracyclic tetrazole scaffold compounds **128** were constructed *via* a one-pot four-component Ugi–Pictet–Spengler reaction[119] of indole **1**, carbonyl compounds **3**, isocyanoacetaldehyde (dimethylacetal) **126** and trimethylsilyl azide ($TMSN_3$) **2**. The reaction was carried out using methanesulfonic acid without any solvent at room temperature. First, the Ugi reaction was performed to obtain compounds **127**, which was



R^1= H, Me
R^2= H, Allyl, Benzyl
R^3= H, Cl, Br, NO_2

Scheme 45



Ar= Ph, 4-MeC_6H_4, 3-$MeOC_6H_4$, 4-$MeOC_6H_4$, 4-*i*-PrC_6H_4, 4-*t*-BuC_6H_4
4-$(CH_3)_2NC_6H_4$, 4-OHC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, Naphthyl

Scheme 46

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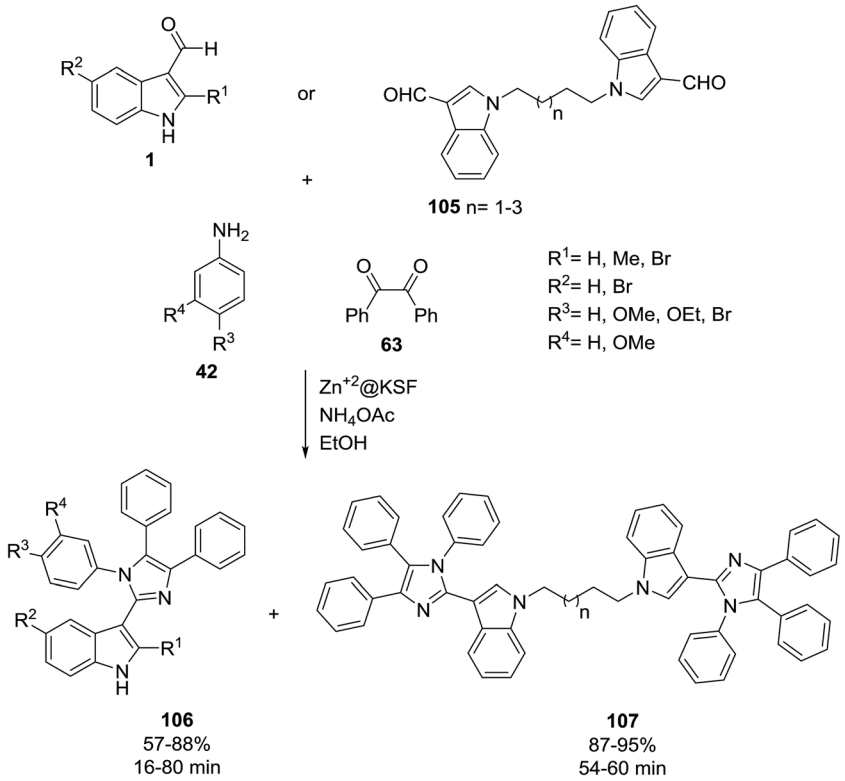
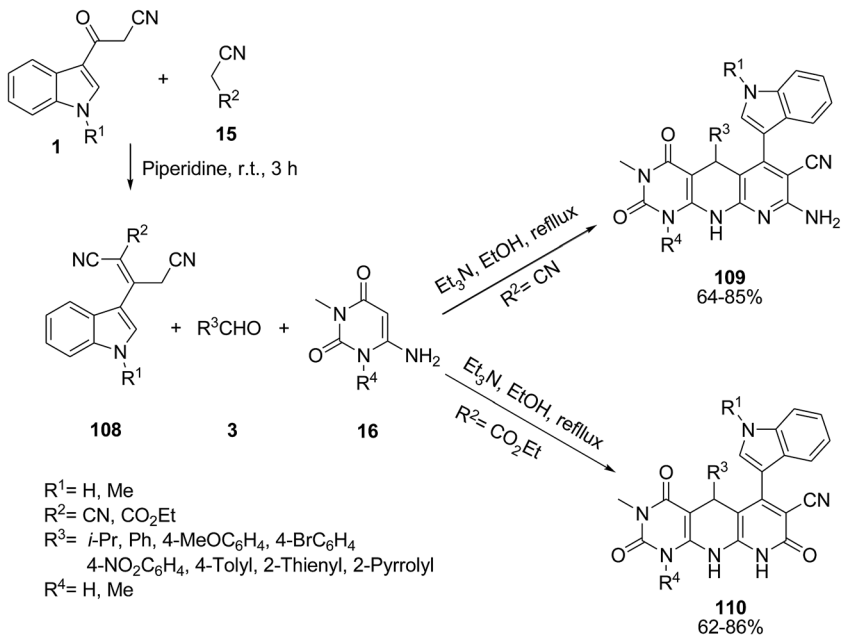


Scheme 47

then followed immediately by the Pictet–Spengler reaction for the preparation of final products **128** (Scheme 56).[120]

Jiang *et al.* described an aerobic dehydrogenative coupling interaction between indole derivatives **1**, diazoacetates **129** and conjugated α-keto esters **130** in the presence of sequential $Rh_2(OAc)_4$ and $CuCl_2$ as catalysts for the synthesis of polyfunctional cyclopenta[*b*]indoles **131** (Scheme 57).[121]

A acid-catalyzed multicomponent tandem cyclization protocol was applied by Cai *et al.* for the preparation of polyfunctional dihydroindolizino[8,7-*b*]indoles **134** and **135**. The



Scheme 48

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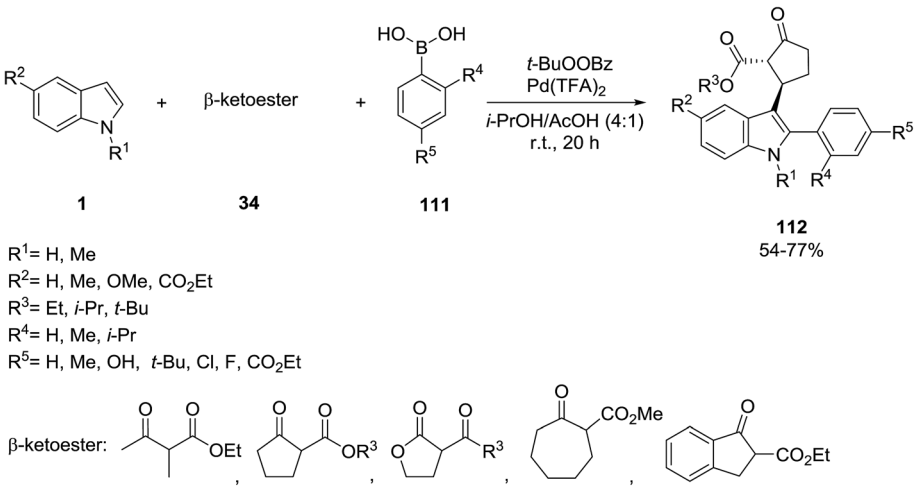
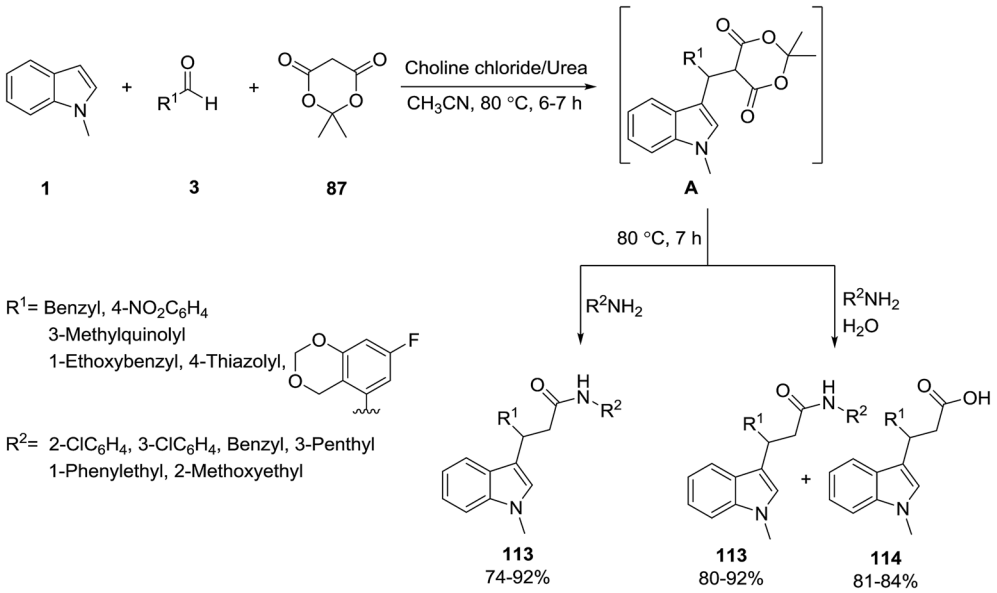


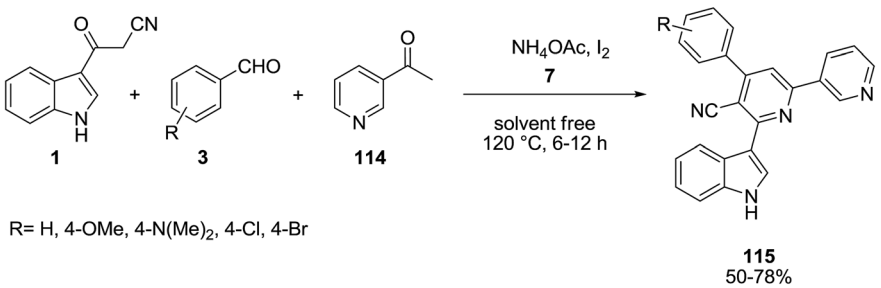
Scheme 49



Scheme 50

process involves the reaction of indole derivatives **1**, arylglyoxal monohydrates **132** and *trans*-β-nitrostyrenes **133** or malononitrile **15** under mild, metal-free conditions (Scheme 58).[122]

The silica supported ionic liquid of [pmim]HSO_4SiO_2 (silica supported 1-methyl-3-(triethoxysilylpropyl)imidazolium hydrogen sulfate) was used as an efficient catalyst for the



Scheme 51

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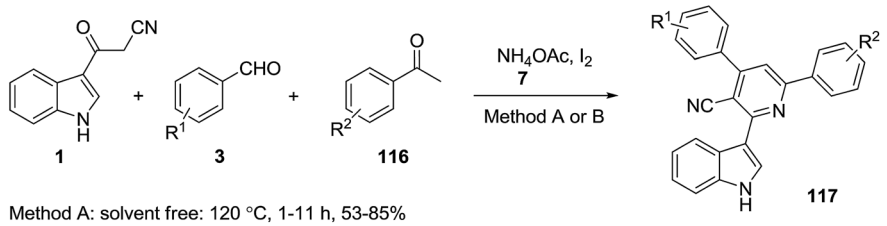
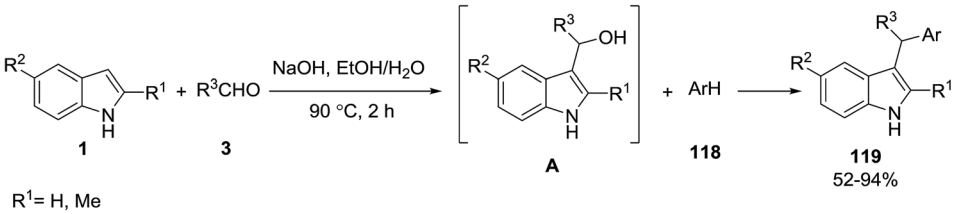


Method A: solvent free: 120 °C, 1-11 h, 53-85%
Method B: reflux: AcOH, 1.5-10 h, 43-87%

R^1= H, 4-OMe, 4-N(Me)$_2$, 2-Cl, 4-Cl, 4-Br
R^2= H, 4-OMe, 4-Cl

Scheme 52

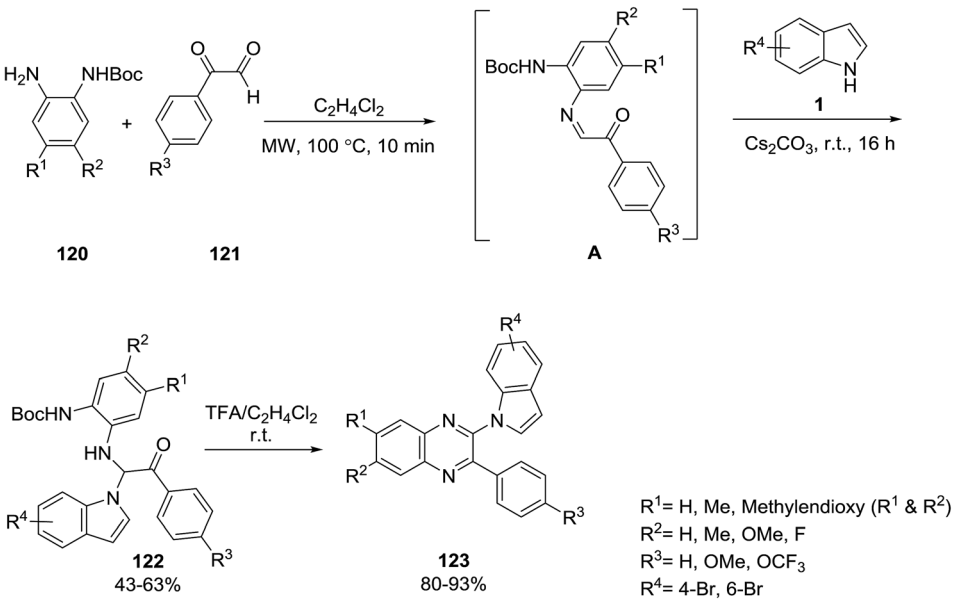


R^1= H, Me
R^2= H, Br
R^3= Ph, 4-MeC_6H_4, 4-OMeC_6H_4, 2-ClC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 2-Thiophenyl, 2-Pyridyl
Ar= 4-Methylphenol, 4-Methoxyphenol,4-(*t*-Butyl)phenol, 2-Naphthyl, 6-OMe-2-Naphthyl, 6-Br-2-Naphthyl

Scheme 53

synthesis of 2-amino-4,5-dihydro-4-arylpyrano[3,2-*b*]indole-3-carbonitrile derivatives **136**. The reaction was carried out *via* the three-component condensation of indoles **1**, aromatic aldehydes **3** and malononitrile **15** (Scheme 59).[123] Other catalysts such as $KHPO_4$ under ultrasonic irradiation[124] and triphenylphosphine (PPh_3)[125] were also used in this reaction as demonstrated in Table 4.

Galvan *et al.* accomplished the reaction of indole-2-aldehydes **1**, imines **137** and alkenes **138** *via* stereoselective [3 + 2] carbocyclization to achieve cyclopenta[*b*]indoles **139** or tetrahydroquinolines **140**. It was found that the model coupling reaction could be changed to give related products **139** or **140** in the presence of different acid catalysts (Schemes 60 and 61).[126]



R^1= H, Me, Methylendioxy (R^1 & R^2)
R^2= H, Me, OMe, F
R^3= H, OMe, OCF_3
R^4= 4-Br, 6-Br

Scheme 54

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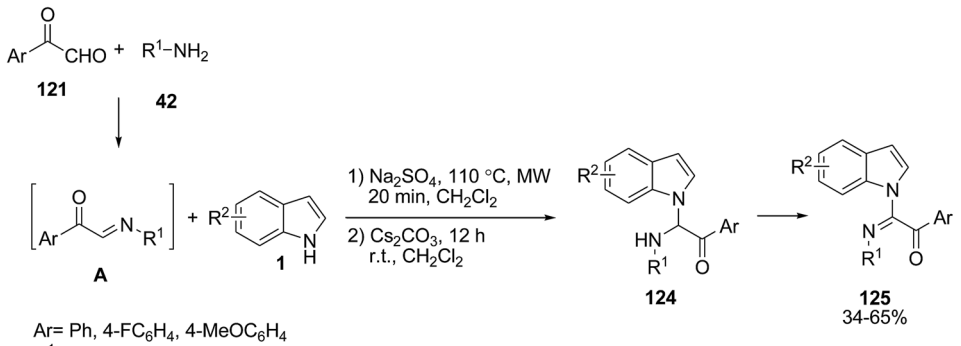
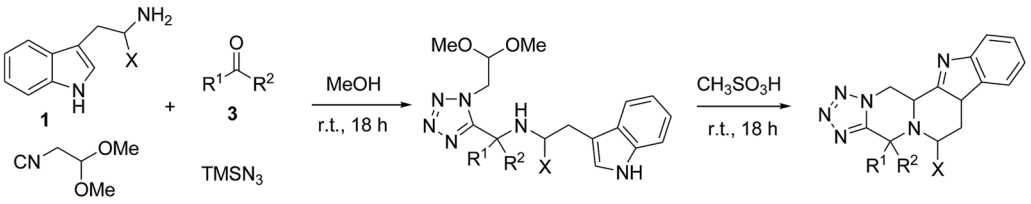


Ar= Ph, 4-FC$_6$H$_4$, 4-MeOC$_6$H$_4$
R^1= Ph, 3-ClC$_6$H$_4$, 4-MeOC$_6$H$_4$, (CH$_2$)$_2$C$_6$H$_5$, Indolinyl
R^2= H, 5-CN, 4-Br, 4-OMe

Scheme 55



R^1, R^2= (H, Et), (H, *i*-Pr), (Me, Et), (H, 4-ClC$_6$H$_4$), (H, 4-NO$_2$C$_6$H$_4$), (H, 3,4,5-MeOC$_6$H$_2$)
(H, (CH$_2$)$_2$C$_6$H$_5$), (H, Ph), (H, 4-FC$_6$H$_4$), (H, (CH$_2$)$_2$SMe), Cyclohexyl, 1-Benzylpyridinyl
X= H, CO$_2$Me

Scheme 56

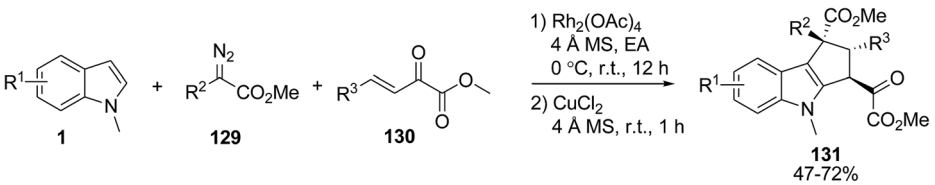
Kundu and co-workers established a new synthetic protocol for the preparation of pyrido- and pyrimido-indoles **141** and **142** employing ethyl 2-amino-1*H*-indole-3-carboxylates **1**, aromatic aldehydes **3**, and terminal alkynes **13** in the presence of a Brønsted acid such as trifluoroacetic acid (TFA) (Scheme 62).[127] When the reaction catalyzed by Yb(OTf)$_3$ as a Lewis acid, pyrimidoindoles **142** were prepared as the single products in 58–75% yield.

Tron's group have prepared heteroarylogous 1*H*-indole-3-carboxamidines **143** utilizing a three-component interrupted Ugi reaction of *N*-alkyl-*N*-(1*H*-indol-2-ylmethyl)amines **1**,[128] isocyanides **2** and carbonyl compounds **3** (Scheme 63).[129]

Silvani *et al.* reported an impressive method to prepare dihydroimidazo[1′,5′:1,2]pyrido[3,4-*b*]indol-2-ium salts **145** utilizing a Ugi/Bischler-Napieralski/heterocyclization MCR. The Ugi reaction was carried out following a general procedure, consisting of the sequential addition of aldehydes **3**, amines **42**, acids **28** and, finally, indole **1** for the synthesis of compounds **144**. Treatment of intermediate compounds **144** in MeOH under the Bischler–Napieralski and heterocyclization gave the intended products **145** (Scheme 64).[130]

A gold-catalyzed multicomponent reaction of vinyl indoles **1** with two *N*-allenamides **146** and **147** was investigated by Pirovano *et al.* to prepare tetrahydrocarbazole **148** in 78% yield (Scheme 65).[131]

Chiral phosphoric acid was used as the catalyst in the asymmetric aza-Diels–Alder reaction[132] of indole derivatives **1** with 2-azadiene generated *in situ* from oxetane **149**[133] and 3,5-



R^1= H, 4-Cl, 4-F, 4-MeO, 5-Me, 6-Me
R^2= Ph, 4-OMeC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-FC$_6$H$_4$, 3-OMeC$_6$H$_4$
R^3= Ph, 4-OMeC$_6$H$_4$, 4-MeC$_6$H$_4$, 3-MeC$_6$H$_4$, 4-BrC$_6$H$_4$, 3-BrC$_6$H$_4$, 4-FC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, Thienyl

Scheme 57

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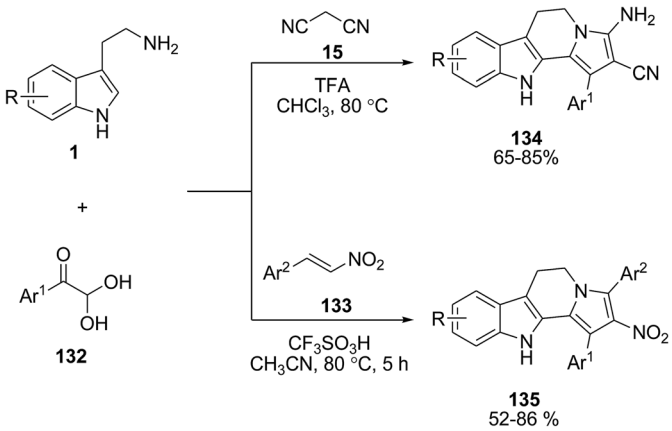
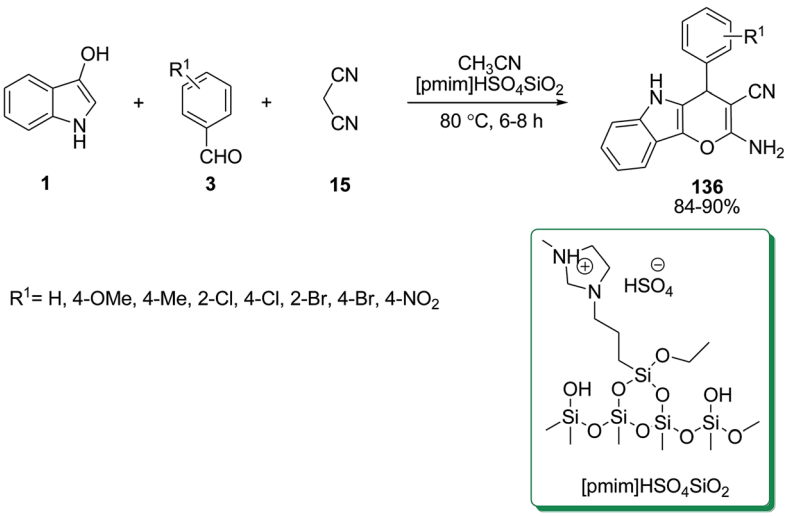


R= H, 7-Me, 5-OMe
Ar^1= Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 3-$MeOC_6H_4$, benzo[1,3]dioxyl
4-$NO_2C_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 2-BrC_6H_4, 1-Naphthyl, 3-Thienyl, 2-Benzofuryl
Ar^2= Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-OHC_6H_4, 4-ClC_6H_4, 2-ClC_6H_4, 2-BrC_6H_4
1-Naphthyl, 2-Thienyl

Scheme 58



R^1= H, 4-OMe, 4-Me, 2-Cl, 4-Cl, 2-Br, 4-Br, 4-NO_2

Scheme 59

dimethoxyaniline **42** to obtain a series of indole-alkaloid-type polycycles **150** (Scheme 66).[134] The authors hypothesized that the introduction of a hydrogen-bond acceptor on the aldehyde moiety may help to orient the transition state and lower the activation barrier for the desired process. Thus, they employed substrates with a simple ether group in proximity to the aldehyde moiety, and encouragingly, the desired aza-Diels–Alder reaction proceeded cleanly to form the desired products with good yields and diastereoselectivities. The biological activity evaluation of the products showed that the cytotoxicities of products in human lung carcinoma and human cervical carcinoma cells exhibited inhibitory effects against cell proliferation with IC_{50} values in the range of 15.0–27.5 μM.

Table 4 Comparison of different conditions for the synthesis of product **136**

Entry	Solvent	Catalyst	Temperature (°C)	Time (min)	Yield (%)
1	CH_3CN	[pmim]HSO_4SiO_2	80	6–8 h	84–90 (ref. 123)
2	EtOH	$KHPO_4$	60	30	85–92 (ref. 124)
3	H_2O–EtOH	PPh_3	60	30–50	85–92 (ref. 125)

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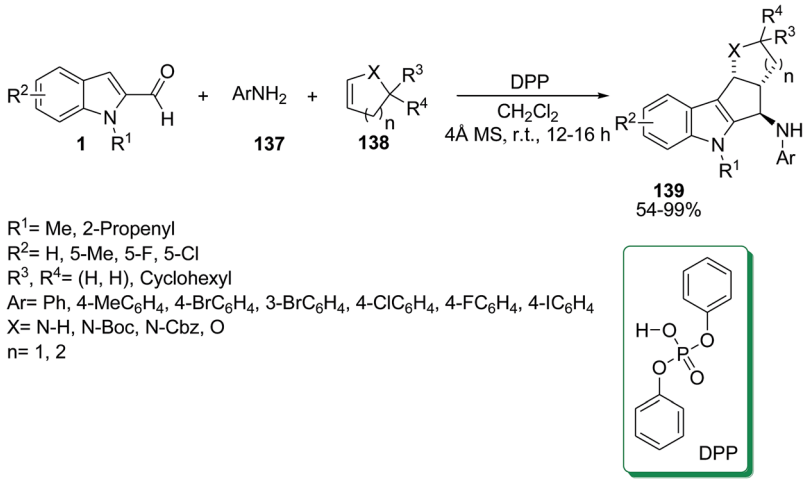
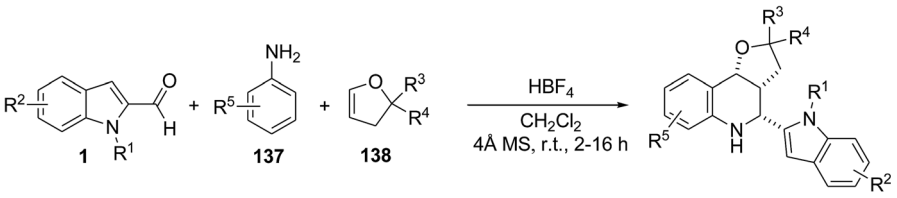


R^1= Me, 2-Propenyl
R^2= H, 5-Me, 5-F, 5-Cl
R^3, R^4= (H, H), Cyclohexyl
Ar= Ph, 4-MeC_6H_4, 4-BrC_6H_4, 3-BrC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-IC_6H_4
X= N-H, N-Boc, N-Cbz, O
n= 1, 2

Scheme 60



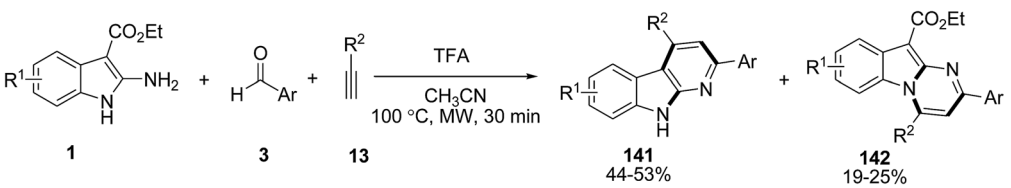
R^1= H, Me, Boc
R^2= H, 5-Me, 5-F
R^3, R^4= (H, H), Cyclopentyl, Cyclohexyl, 4-Tetrahydropyryl
R^5= H, 4-Me, 4-F, 4-Cl, 3,5-Cl_2, 4-Br, 4-I

Scheme 61

The annulation of indoles **1**, 2-amino benzyl alcohols **42** and benzaldehydes **3** in a two step three-component tandem reaction was used to form benzazepinoindoles **151**. In the first step, indoles were C-3 alkylated and the intermediates **A** were obtained. Then in the second step, intermediates **A** underwent a 7-*endo*-trig cyclization (the modified Pictet–Spengler cyclization reaction) to obtain the intended products **151** (Scheme 67).[135]

A stereoselective Povarov reaction[136,137] catalyzed by iodine was developed by Wang and co-workers for the preparation of *exo*-tetrahydroindolo[3,2-*c*]quinoline derivatives **153**. The procedure involved a reaction between indoles **1**, aldehydes **3** and amines **152** in toluene (Scheme 68).[138] The results showed that only reactive amines could be included in this reaction to give the desired products **153** with high stereoselectivity.

Gallium(III) ($GaBr_3$) catalyzed a three component [4 + 3] cycloaddition reaction of indoles **1**, aldehyde/ketone/ketal derivatives **3** and dienes **154** to furnish cyclohepta[*b*]indoles **155**. The authors have proposed the mechanism of formation of the product *via* nucleophilic addition of the C3 of indole to electrophile **3** to give the alcohol **A**, which in the presence of a Lewis acid generated the indolyl cation **B**. The treatment of **B** with diene component **154** afforded the corresponding products (Scheme 69).[139]



R^1= H, 5-Me, 6-F
R^2= Ph, 4-MeC_6H_4, 4-*t*-BuC_6H_4, C_6H_9
Ar= 4-MeC_6H_4, 4-ClC_6H_4, 4-FC_6H_4

Scheme 62

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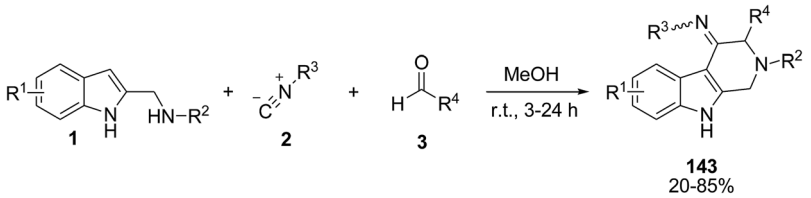
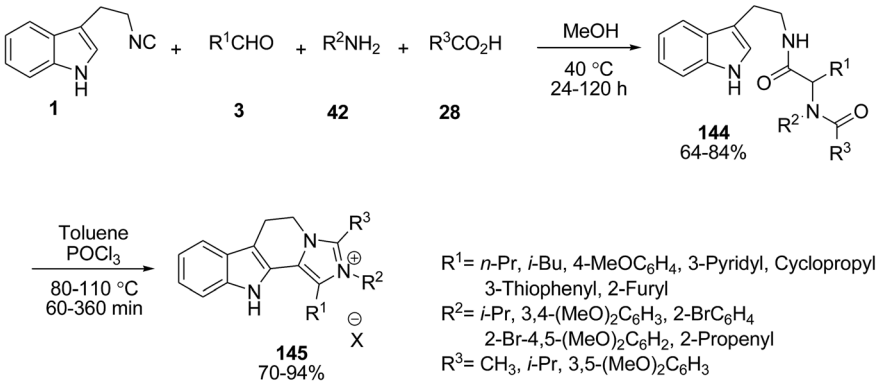


R^1= H, 5-Cl, 5,6-$(OMe)_2$
R^2= Me, *n*-Bu, Benzyl, EtC_6H_4
R^3= Benzyl, Naphthyl, Cyclohexyl, *n*-Penthyl, MeOAc
R^4= H, *i*-Pr, Ph, 4-ClC_6H_4, *n*-Hexyl, Cyclohexyl

Scheme 63



R^1= *n*-Pr, *i*-Bu, 4-$MeOC_6H_4$, 3-Pyridyl, Cyclopropyl
3-Thiophenyl, 2-Furyl
R^2= *i*-Pr, 3,4-$(MeO)_2C_6H_3$, 2-BrC_6H_4
2-Br-4,5-$(MeO)_2C_6H_2$, 2-Propenyl
R^3= CH_3, *i*-Pr, 3,5-$(MeO)_2C_6H_3$

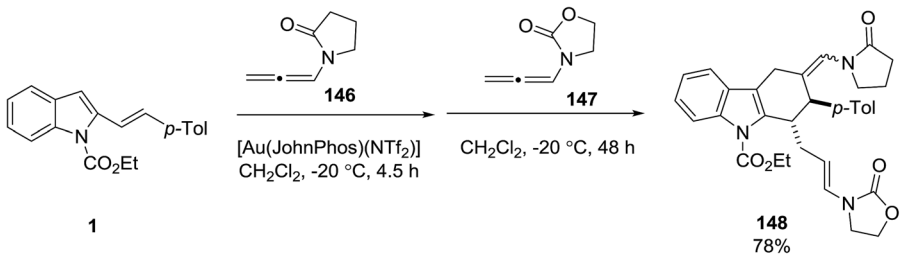
Scheme 64

Damavandi and Sandaroos have synthesized 2,9-dihydro-2-oxo-4-aryl-1*H*-pyrido[2,3-*b*]indole-3-carbonitriles **158** by the one-pot multicomponent cyclocondensation reaction of 1-methyl-1*H*-indol-2-ol **1**, substituted (triethoxymethyl) arenes **156** and cyanoacetamide **157** in the presence of silica supported ionic liquid [pmim]HSO_4SiO_2 as a catalyst (Scheme 70).[140]

A new series of diketopiperazine-fused tetrahydro-β-carboline ring systems **160** were obtained *via* the Pictet–Spengler/Ugi-4CR/deprotection-cyclization reactions. According to the proposed mechanism, the Pictet–Spengler cyclization of indole **1** and ethyl glyoxalate **159** followed by a deesterification reaction produced 2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-1-carboxylic acid **B**. The reaction of acid **B**, amines **42**, isocyanides **2** and aldehyde **3** *via* the Ugi reaction gave the intermediate products **C**. The deprotection cyclization reaction of this intermediate generated the target products **160** (Scheme 71).[141]

A stereoselective catalyst-free three-component reaction of 2-isocyanoethylindole **1**, malononitrile **15** and aldehyde **3** was developed for the construction of polycyclic spiroindolines **161** in high yields (up to 90%) with excellent levels of diastereoselectivity (Scheme 72).[142] The presence of an electron-withdrawing group on the aldehyde led to a decrease in yields of the products.

John and co-workers developed a multicomponent reaction involving *N*-protected 3-nitroindole **1** a primary amine **162** and an enolizable ketone **163** for the preparation of a series of functionalized pyrrolo[3,2-*b*]indoles **164** (Scheme 73).[143] It was found that the yield of product **164** decreased to 45% with 1-phenylethylamine. With cyclohexylamine, the product **164** was obtained in moderate yield (53%) and with adamantylamine the MCR failed, proving that the reactivity decreases with an increase in the steric bulk of the amine component.



Scheme 65

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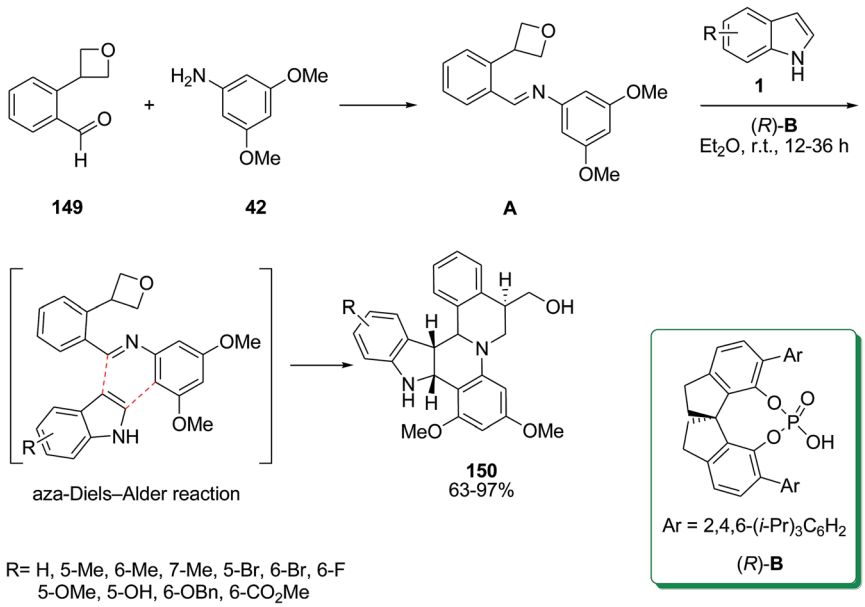
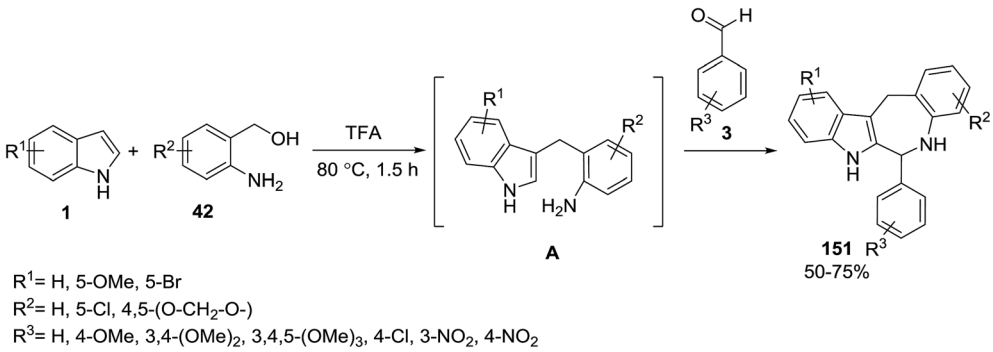
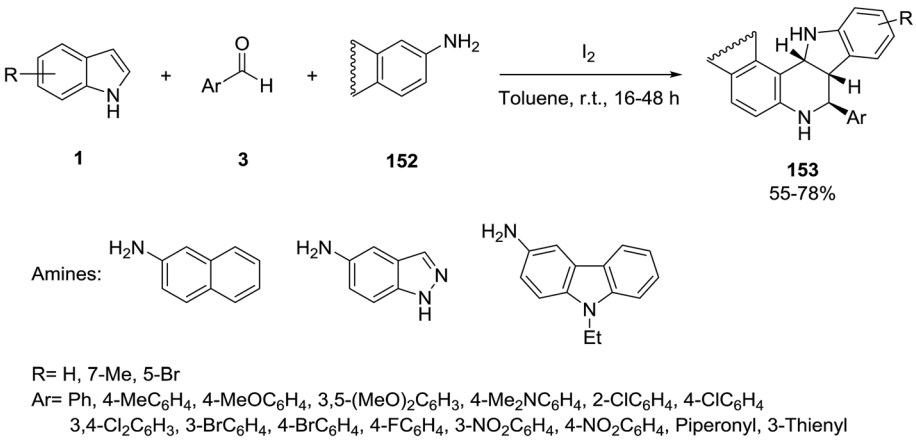


Scheme 66



Scheme 67

The Lewis acid catalyzed three-component [3 + 2] cycloaddition reaction of pentafulvene **165** with *in situ* generated indolylmethanol **A** has been developed for the construction of pentaleno[1,2-*b*]indoles **166** (Scheme 74).[144] It was found that aromatic aldehydes bearing electron-withdrawing groups (R^3 = Cl, Br, F) were tolerated well under the reaction conditions and



Scheme 68

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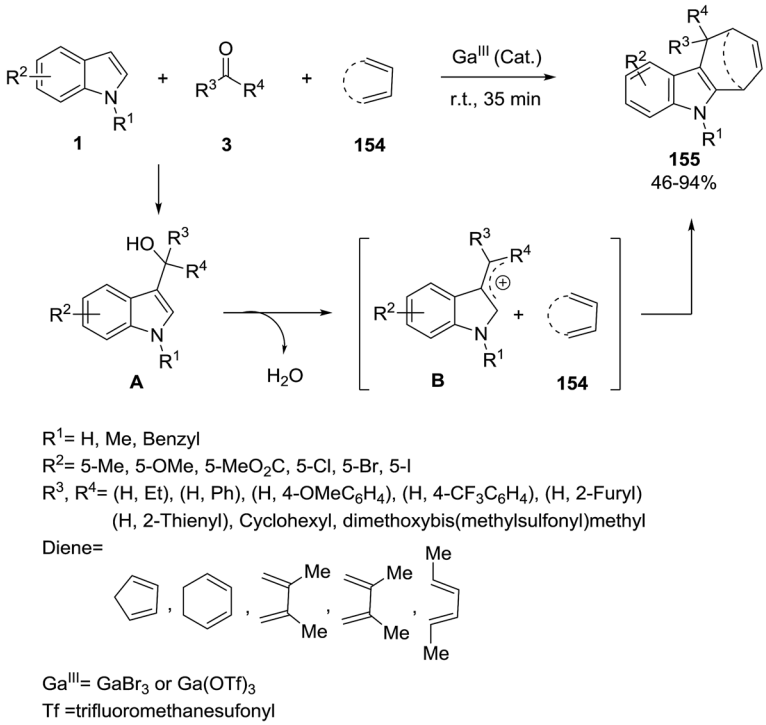
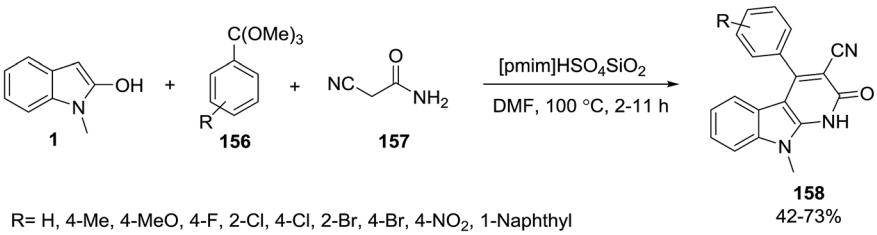


Scheme 69



Scheme 70

afforded the cycloaddition products in moderate to good yields. However, aldehydes with electron-rich substituents (R^3 = 2,4-OMe, Me) were unable to take part in the cycloaddition reaction.

Alpers *et al.* developed a photoinduced three-component radical [4 + 2]-cyclization–allylation reaction between 3-(2-iodoethyl)indoles **1**, acceptor-substituted alkenes **167**, and allyl zirconocenes of the structure Cp ZrCl(σ-allyl) **168** for the synthesis of hexahydrocarbazoles **169** (Scheme 75).[145]

A copper(I)-catalyzed cascade multicomponent reaction strategy was performed for the construction of 5-hydroxy-1*H*-pyrrol-2(5*H*)-ones **171** bearing an indole moiety. The reaction was carried out using substituted indole **1**, (*Z*)-3-iodoacrylic acids **170** and terminal alkynes **13** (Scheme 76).[146]

2.3.2. The cycloaddition reactions of indoles at the C–N sigma bond. An enantioselective multicomponent coupling reaction for the synthesis of pyrrolo[1,2-*a*]indoles **173** was reported using a chiral disulfonimide as catalyst. The [3 + 2] cyclization reaction between the imine **A** (generated *in situ* from indole-2-aldehyde derivatives **1** and anilines **42**) and 2,3-dihydrofuran **172** led to products **173** (Scheme 77).[147] It was observed that the yields of products synthesized from substituted anilines at the 3- and 5-positions with halogen atoms groups were lower than those synthesized from 3,5-bis(-trifluoromethyl)aniline.

The Ugi four-component condensation of indole-2-aldehyde derivatives **1**, acids **28**, anilines **42** and isocyanides **2** in the presence of orthogonal copper and palladium catalysts under microwave heating was accomplished for the synthesis of two important indole-fused heterocycles **174** and **175**. First, the Ugi adduct **A** was obtained *via* the intramolecular cyclization conditions and served as a precursor in subsequent selective post-transformations. 5,6-Dihydroindolo[1,2-*a*]quinoxalines **174** were prepared by a copper catalyzed N–H arylation pathway, while 6,7-dihydroindolo[2,3-*c*]quinolones **175** were formed by palladium catalyzed C–H arylations without the protection of the indole N1 moiety (Scheme 78).[148] In another approach to synthesize these compounds, no catalyst has been employed in this reaction and the products were obtained in good yields.[149]

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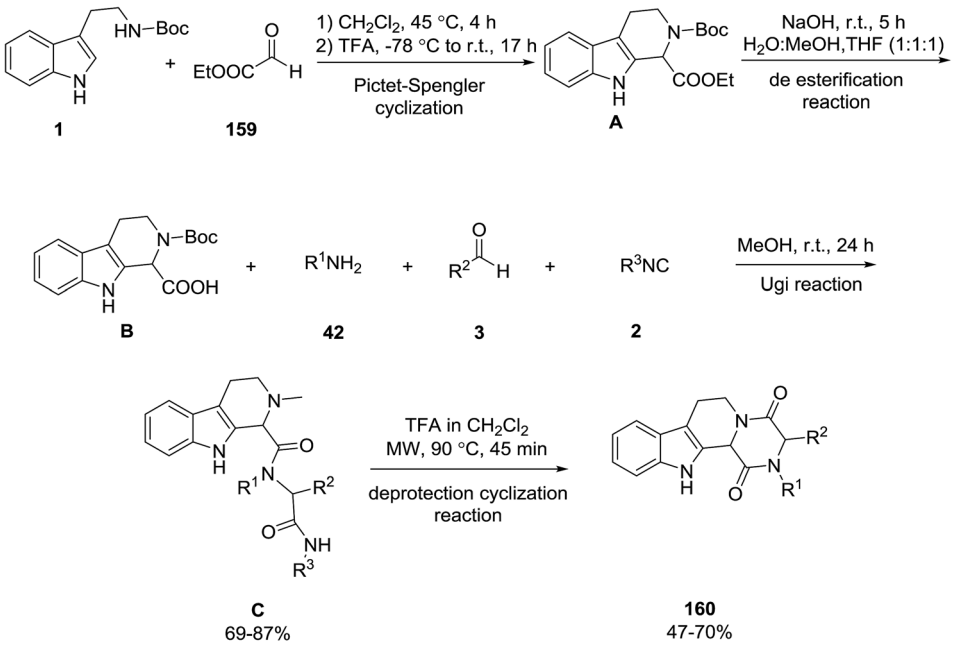
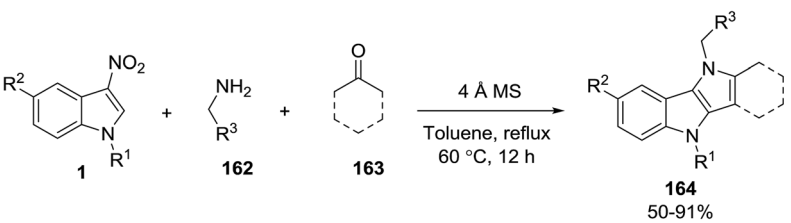


R^1 = *t*-Bu, Cyclopropyl, 4-Methylbenzyl, 4-Methoxybenzyl, 2-Chlorobenzyl, 4-Fluorobenzyl
R^2 = H, Ph, 3,5-$(MeO)_2C_6H_3$, 4-ClC_6H_4, 3-Methylbuthanal
R^3 = *t*-Bu, *n*-Bu

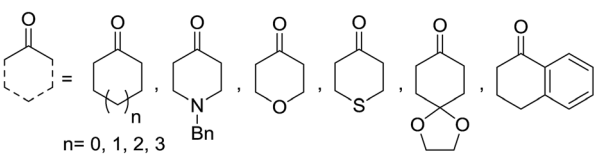
Scheme 71

Ar= Ph, 3-MeC_6H_4, 4-MeC_6H_4, 4-FC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 3,4-$Cl_2C_6H_3$, 3-BrC_6H_4
4-BrC_6H_4, 2-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 4-CNC_6H_4, 4-$SO_2MeC_6H_4$, 2-Naphthyl

Scheme 72



R^1= Ts, Boc, CO_2Et
R^2= H, Cl, Br
R^3= *n*-Pentyl, *n*-Hexyl, Ph, 4-MeC_6H_4, 4-$OMeC_6H_4$, 4-ClC_6H_4, Benzyl



Scheme 73

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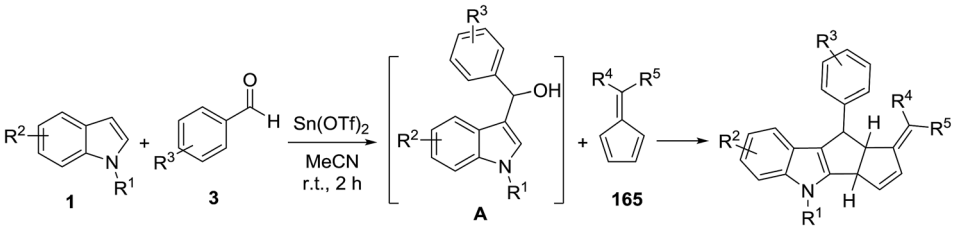
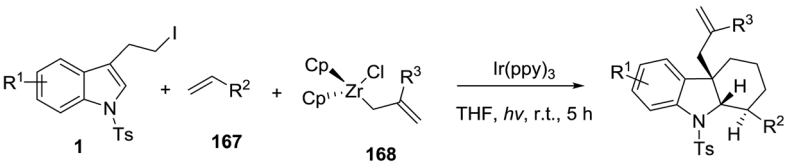


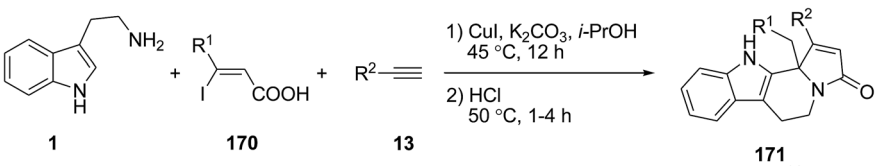
R^1= H, Me
R^2= H, 6-Me, 7-F
R^3= H, 4-OMe, 4-Cl, 1-Br, 4-Br, 4-F, 3,4-Cl_2
R^4, R^5= (Ph, Ph), (4-MeC_6H_4, 4-MeC_6H_4)

Scheme 74



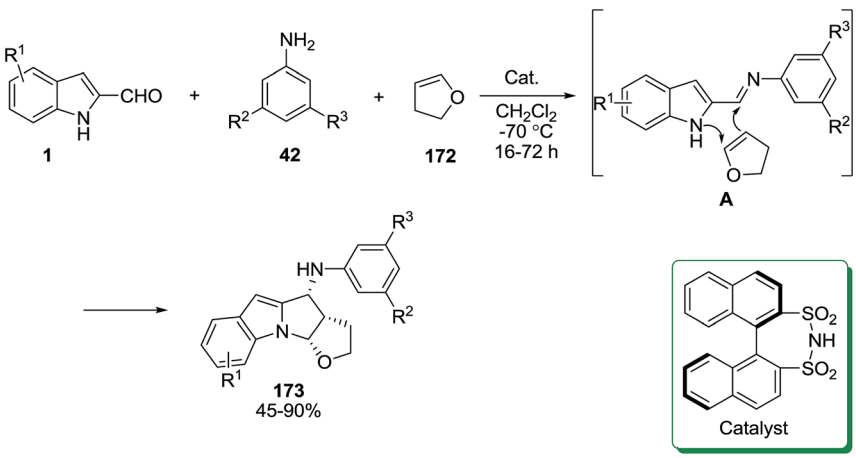
R^1= H, 5-Me
R^2= CO_2Me, $CONMe_2$
R^3= H, Me
$Ir(ppy)_3$: Tris[2-phenylpyridinato-C^2,*N*]iriddium(III)

Scheme 75



R^1= Me, Bu, CH_2OCH_3, Ph
R^2= Ph, $(CH_2OCH_2)C_6H_5$, $CH(OEt)_2$

Scheme 76



R^1= 4-Me, 5-Me, 5-Cl, 6-Cl, 6-Br, 4-F, 5-F, 6-F, 5-CF_3
R^2, R^3= 3,5-$(CF_3)_2$, 3,5-$(Cl)_2$, (3F, 5-CF_3), (3-Cl, 5-F)

Scheme 77

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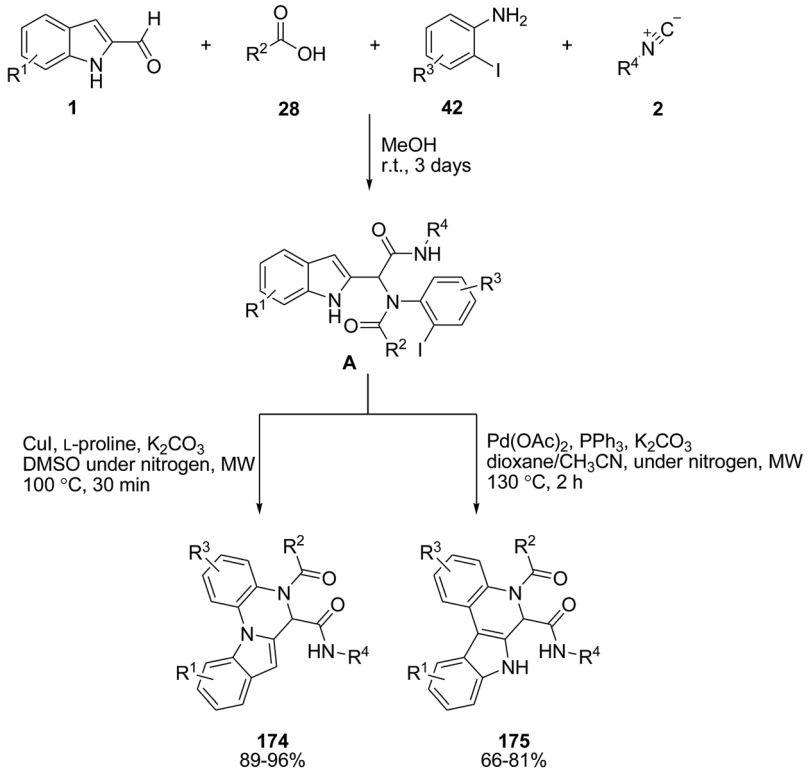
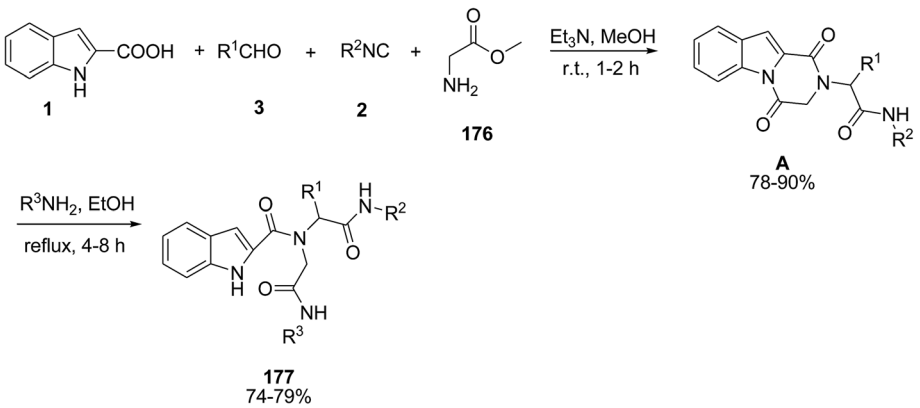


R^1= H, 5-OMe, 5-Cl
R^2= *i*-Bu, CH_2NHBoc, Ph, 3-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 3,4-$Cl_2C_6H_3$
R^3= H, 5-Cl
R^4= Cyclohexyl, *n*-Bu, *t*-Bu

Scheme 78

2.4. Miscellaneous reactions of indoles

Pandey *et al.* have published their results on the synthesis of diverse indole-2-carboxamides **177** *via* a two-step multicomponent reactions. Initially, Et_3N was added to amino ester hydrochloride **176** and after 10 minutes, 1*H*-indole-2-carboxylic acid **1**, aldehyde **3**, and isocyanide **2** were



R^1= 3,4,5-$(MeO)_3C_6H_2$, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4
R^2= *t*-Bu, 2,4,4-trimethylpentanyl
R^3= EtOH, Benzyl, 4-Methoxybenzyl, 4-Chlorobenzyl, 3,4-Dichlorobenzyl
3-Methoxybenzyl, 3-Propyl morpholine, 4-Methyl pyridine

Scheme 79

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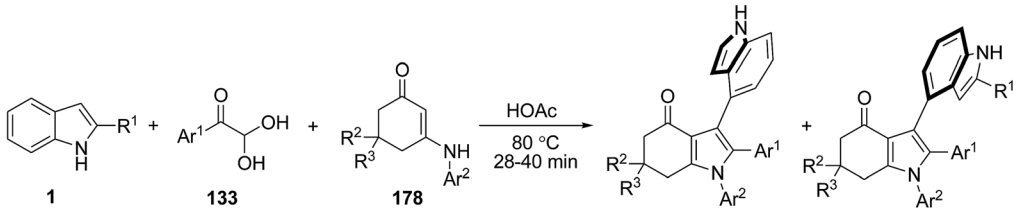

R^1= H, Me, Ph
R^2, R^3= (H, H), (Me, Me)
Ar^1= Ph, 4-MeC_6H_4, 4-$OMeC_6H_4$, 4ClC_6H_4, 4-BrC_6H_4, 4-FC_6H_4, 4-$NO_2C_6H_4$
Ar^2= Ph, 4-MeC_6H_4, 4-$OMeC_6H_4$, 4ClC_6H_4, 4-BrC_6H_4, 4-FC_6H_4

Scheme 80

successively added to the mixture to produce corresponding indole-fused diketopiperazines **A**.[150] Then, compound **A** in the presence of amines formed the functionalized carboxamides **177** (Scheme 79).[151] The biological activities of products were evaluated and showed that most products have anti-leishmanial activity against intracellular amastigotes form of *Leishmania donovani*.

Fu and co-workers designed a strategy for the preparation of 3,2′- **179** and 3,3′-bis-indoles **180** through the microwave-assisted regioselective reaction of indoles **1**, arylglyoxal monohydrate **133** and diverse *N*-aryl enaminones **178** in HOAc (Scheme 80).[152] The 2-unsubstituted indoles resulted in 3,2′-bis-indole frameworks **179**, while indoles bearing a methyl or phenyl group at C2 led to the 3,3′-bis-indoles **180** with simultaneous formation of three sigma-bonds.

3. Conclusion and outlook

This review summarizes recent studies on the application of indoles in multicomponent reactions for the synthesis of a variety of heterocyclic compounds during the period of 2012 to 2017. Indole is a significant nitrogen-based heterocycle with particular importance in the synthesis of complex heterocyclic scaffolds. Indole fragments have been recently attracting much attention due to their biological and pharmaceutical activities. Diversely multisubstituted indole substances are useful building blocks in pharmaceutical and organic syntheses. Consequently, the novel methodologies for the synthesis of complex heterocyclic frameworks involving indole are expected to receive further increasing attention in the future.

4. Conflicts of interest

There are no conflicts to declare.

5. Abbreviations

CTAB	Cetyltrimethylammonium bromide
DCE	1,2-Dichloroethylene
DIPEA	*N*,*N*-Diisopropylethylamine
DMAD	Dialkyl acetylenedicarboxylate
DMF	Dimethylformamide
DPP	Diketopyrrolopyrrole
EA	Ethyl acetate
FHS	Ferric hydrogen sulfate
MTBE	Methyl *tert*-butyl ether
mpCuO	Macroporous copper oxide
MW	Microwave
NHC	*N*-Heterocyclic carbene
NPs	Nanoparticles
PEG	Polyethylene glycol
PMDETA	Pentamethyldiethylenetriamine
PTS	Polyoxyethanyl-α-tocopheryl sebacate
SDS	Sodium dodecyl sulfate
STA	Silica-supported tungstic acid
TBAF	Tetra-*n*-butylammonium fluoride
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran

6. Acknowledgements

We are grateful for financial support from the Research Council of Alzahra University and support of National Elites Foundation of Iran, Tehran.

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