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Review article 51

1*H*-Indole-3-carboxaldehyde: Synthesis and Reactions

Eslam R. El-Sawy*, Heba M. Abo-Salem and Adel H. Mandour
Chemistry of Natural Compounds Department, National Research Centre, P.O. Box 12622 Dokki, Giza, Egypt .

1*H*-Indole-3-carboxaldehyde and its derivatives have represented the key intermediates for the preparation of biologically active compounds as well indole alkaloids. Also, they are important precursors for the synthesis of divers heterocyclic derivatives because their carbonyl groups facilely undergo C–C and C–N coupling reactions and reductions. This review highlights the recent advances in 1*H*-indole-3-carboxaldhyde chemistry *via* discussing different synthetic procedures developed for the preparation of its derivatives, as well sheds the light on the most common reactions of 1*H*-indole-3-carboxaldhyde derivatives and exploitation of these derivatives as the blocks of many biologically active compounds.

Keywords: 1*H*-Indole-3-carboxaldehyde, Synthesis, Reactions, Heterocycles.

Introduction

1*H*-Indole-3-carboxaldhyde (I3C, 1) is a natural compound found in tomato seedling, pea seedling, barley, lupine, cabbage and cotton [1]. 1*H*-Indole-3-carboxaldehyde (1) represents an important starting and intermediate compound for building many various synthetic and natural biologically active compounds especially with antitumor (camalexin [2] coscinamide) [3], anti-depressant (α-methyl-tryptamine)[4], antimicrobial (phytoalexins brassinin and cyclobrassinin) [5,6], antiviral (chondramide A) [7], anthelmintic (chondriamide C) [8], monoamine oxidase inhibitor (aplysinopin) [9], anti-plasmodial (isocryptolepine) [10], antifungal (phytoalexine caulilexins A-C) [11], inhibit DNA replication and transcription (cryptosanginolentine 1) [12] and muscle relaxant (α,β-cyclopiazonic acid)[13] activities (Fig. 1).

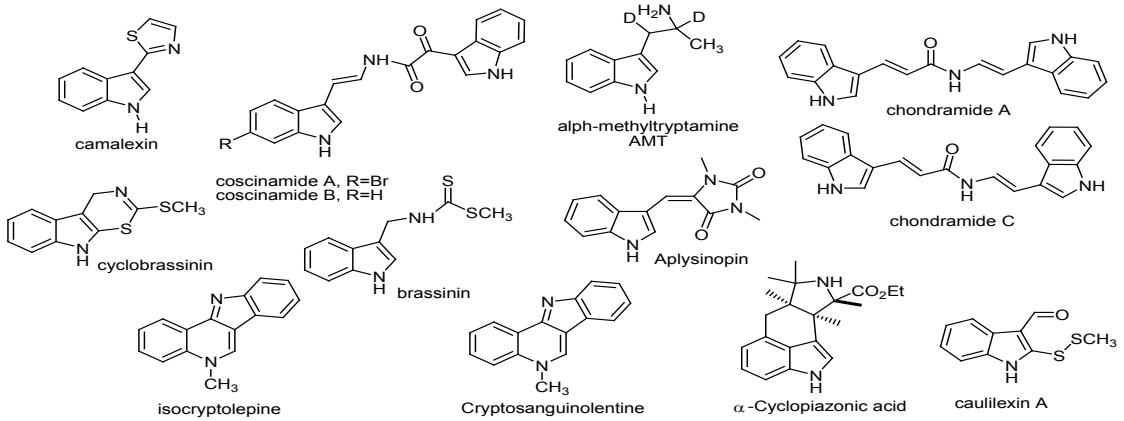

Figure 1. Bioactive natural compounds from 1*H*-indole-3-carboxaldhyde

*Corresponding author e-mail: eslamelsawy@gmail.com
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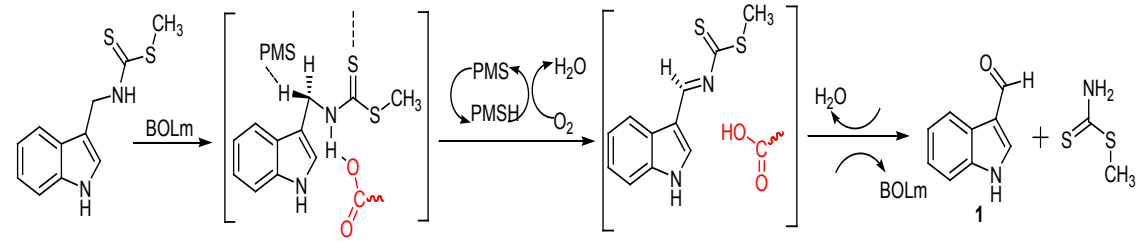
Biosynthesis of natural 1*H*-indole-3-carboxaldehyde (1) was first suggested by Tang and Bonner who reported that, aldehyde (1) was produced *via* biotransformation of indole-3-acetic acid (IAA) using crude enzyme which is prepared from etiolated pea seedlings [14]. On the other hand, brassinin oxidase (BOLm; a fungal detoxifying enzyme) mediates the conversion of the phytoalexin brassinin into 1*H*-indole-3-carboxaldehyde with equivalent ratio [15] (Scheme 1).



Scheme 1

Also, bacteria play an important role in the biosynthesis of 1 *via* biotransformation of L-tryptophan using *Escherichia coli* [16].

1*H*-Indole-3-carboxaldhyde and its derivatives are not only the key intermediates for the preparation of biologically active molecules as well indole alkaloids, but also they are important precursors for the synthesis of diverse heterocyclic derivatives. In this respect, this review point up the chemistry and the most common reactions of 1*H*-indole-3-carboxaldhyde and its derivatives.

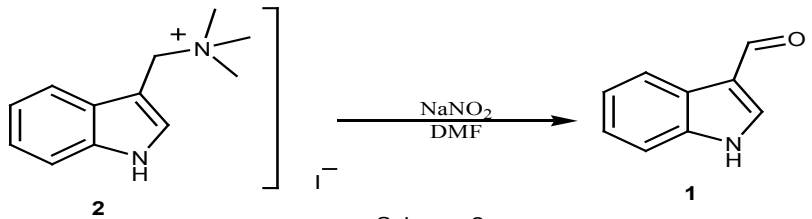
Synthetic methods of the preparation of 1H-Indole-3-carboxaldhyde

Previously, 1*H*-indole-3-carboxaldehyde (1) has been prepared synthetically either *via* direct formylation of indole using e.g., Reimer-Tiemann reaction (aq. KOH/CHC_{l3})[17], Grignard reaction [18], Vilsmeier Haack reaction ($POCl_3$/DMF) [19] or formylation of the potassium salt of indole using carbon monoxide under robust conditions of heat and pressure [20]. Sommelet reaction on gramine and on indole itself [21] oxidation of *N*-skatyl-*N*-phenyl-hydroxylamine [22] and/or by hydrolysis of 3-(1,3-dithiolan-2-yl)indole with boron trifluoride diethyl etherate $BF_3.O(C_2H_5)_2$ and mercury (II) oxide HgO [23].

Recently, the researchers developed general and simple approaches by the use of environmentally benign reagents in order to obtain 1*H*-indole-3-carboxaldyhde (1), for an example:

Oxidation of gramine methiodides

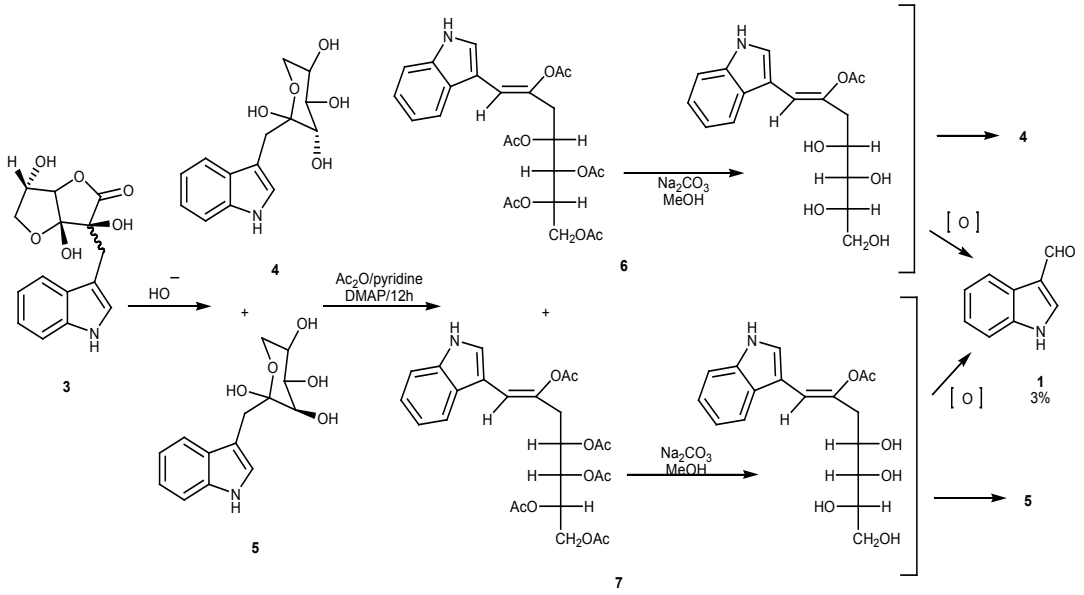
Unusual oxidation of graminemethiodide [1-(1H-indol-3-yl)-N,N,N-trimethylmethanaminium iodide] (2) using sodium nitrite in *N,N*-dimethylformamide (DMF) produces 1 in 68% yield [24] (Scheme 2).



Scheme 2

Alkaline degradation of ascorbigen

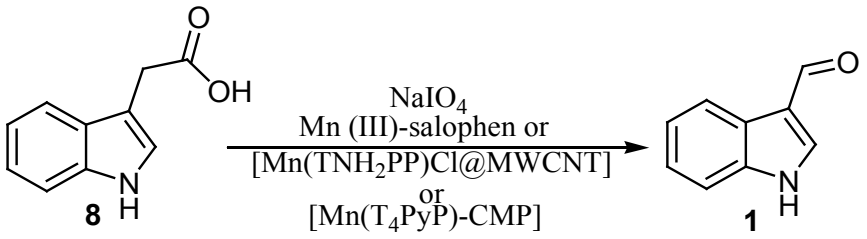
Alkaline degradation of ascorbigen 3 leads to a mixture of L-sorbose (4) and L-tagatose (5) derivatives. The later ketoses underwent acetylation and open ring of pyranose using acetic anhydride in pyridine in the presence of 4-dimethylaminopyridine (DMAP) leads to a mixture of 6 and 7, which are separated by column chromatography. Deacetylations of compounds 6 and 7 have been accompanied by the formation of 1 with yield (3%) [25] (Scheme 3).



Scheme 3

Oxidative decarboxylatoin of indole-3-acetic acid

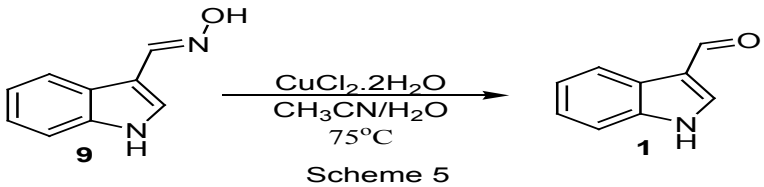
Oxidative decarboxylatoin of indole-3-acetic acid (8) using sodium periodate catalyzed either with manganese(III)-salophen complex, tetrakis(4-aminophenyl) porphyrinato manganese (III) chloride support on functionalized multi-wall carbon nano-tubes or with manganese (III) tetra (4-pyridyl)porphyrin support on cross-linked chloromethylated polystyrene, produces 1 in 78% yield [26] (Scheme 4).



Scheme 4

From oximes

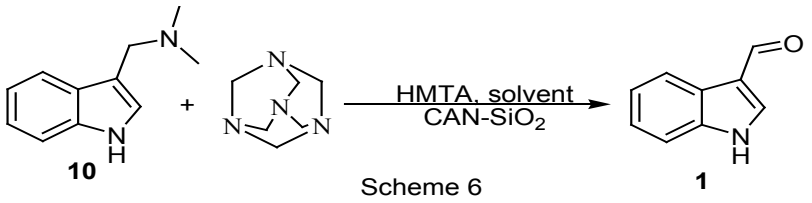
Treatment of (*E*)-1*H*-indole-3-carbaldehyde oxime (9) with 2 molar equivalents of cupric chloride dihydrate under reflux in acetonitrile and water (4:1) leads to the formation of 1 in 88 % yield [27] (Scheme 5).



Scheme 5

From gramine

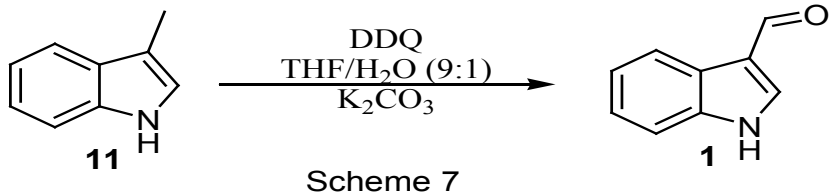
The reaction of gramine (10) with formulating species has been generated from hexamethylenetetramine (HMTA) and silica-supported ceric ammonium nitrate (CAN–SiO_2) yields 1 in 81% [28] (Scheme 6).



Scheme 6

Oxidation of skatole

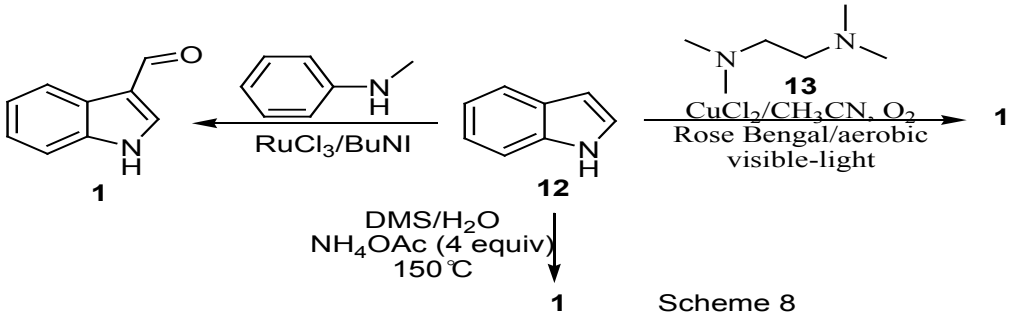
Oxidation of skatole (3-methylindole) (11) with 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ) in a mixture of tetrahydrofuran and water (9:l) at room temperature affords 1 in 30% yield [29] (Scheme 7).



Scheme 7

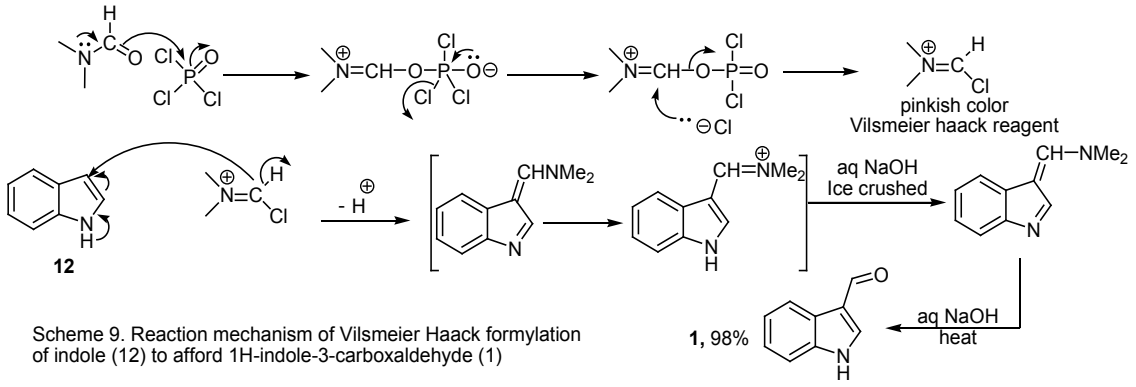
Formylation of indole

C3-selective formylation of indole (12) has been achieved either by the use of, a) N-methyl aniline in the presence of ruthenium (III) chloride as oxidative catalyst [30]; b) ammonium acetate in dimethylsulfoxide as a source of carbon with water [31] or ; c) using tetramethylethylene-diamine (TMEDA) (13) as a carbon source catalyzed either by $CuCl_2$ in acetonitrile with atmospheric oxygen as oxidant, [32] or catalyzed by Rose Bengal in the presence of an aerobic visible-light and oxygen to afford 1 [33] (Scheme 8) .



Scheme 8

In spite of the development in the methods for the preparation of 1*H*-indole-3-carboxaldehyde (1), it remains to be seen Vilsmeier Haack formylation reaction is the convenient method for the preparation of 1 due to it is considerably simple, the yield is almost quantitative, and the aldehyde product is obtained in a state of high purity [19] (Scheme 9).

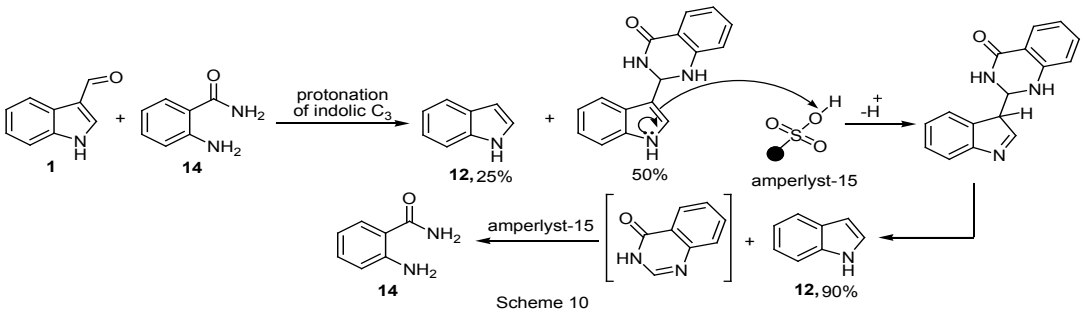


Scheme 9. Reaction mechanism of Vilsmeier Haack formylation of indole (12) to afford 1H-indole-3-carboxaldehyde (1)

Reactions of 1H-Indole-3-carboxaldehyde

Deformylation

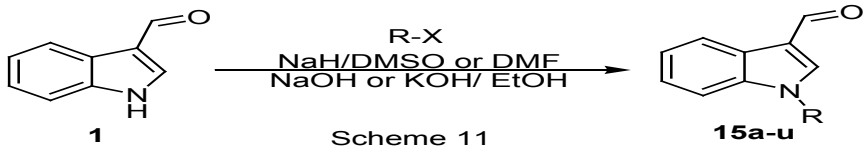
Deformylation of 1*H*-indole-3-carboxaldehyde (1) has been achieved by the use of anthranilamide (14) in the presence of solid acid heterogeneous catalyst. The reaction occurs through quinazolinone intermediate, which is exposed to acid catalyzed cleavage and forms deformylated product, indole (12) [34]. (Scheme 10).



Scheme 10

N-Alkylation, N-acylation and N-sulfonation

The importance and the necessity of protecting nitrogen of indole-3-carboxaldehyde (1) are well established [35]. There are two different kinds of protecting groups used on the free N-H of 1; a) electron releasing groups (commonly); and b) electron withdrawing groups [35]. As a matter of fact, most of the methods have been used to introduce the protect groups require strong bases such as NaH in order to generate the indole anion, which reacts as a nucleophile with alkyl, acyl and sulfonyl halides in DMSO or DMF. In 1998 Ottoni et al., [35] have reported new weaker bases than the traditional NaH, such as NaOH, KOH and NE_{t3} in ethanol to form *N*-substituted indole-3-carboxaldehyds derivatives 15a-u with 80-100% yields (Scheme 11, Table 1).



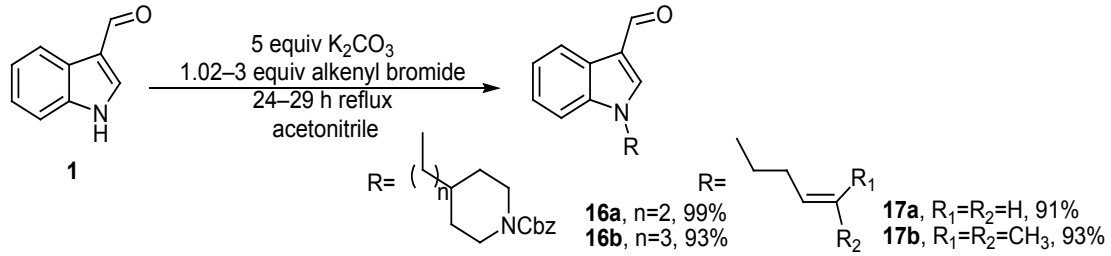
Scheme 11

TABLE 1. ***N*-Substituted-1*H*-indole-3-carboxaldhydes.**

Compd.	R	X	Yield % NaOH	KOH	NaH	M.p. [°C]/color [ref]
15a	CH_3	I	64	-	-	91-5/ red (p)[36]
15b	CH_2CH_3	I	-	-	55	84-6/buff (p)[37]
15c	CH_2Ph	Cl	-	93	97	102-4/orange (c)[35,38]
15d	$CH_2PhCl_{(4)}$	Cl	-	-	89	117-9/brown (p)[39]
15e	$CH_2Ph\ F_{(3)}$	Br	-	39	-	127-9 [40,41]
15f	$CH_2Ph\ F_{(4)}$	Cl	-	-	76	116-8/brown (p)[39]
15g	$CH_2PhCl_{2\ (2,4)}$	Cl	-	-	87	121-3/brown (p)[39]
15h	$CH_2Ph\ F_{2\ (2,4)}$	Cl	-	-	84	120-2/brown (p)[39]
15i	COPh	Cl	-	84	76	177-9/purple (p)[35,42]
15j	$COPh\text{-}Cl_{(2)}$	Cl	-	-	68	162-4/purple (p)[43]
15k	$COPh\text{-}Cl_{(4)}$	Cl	65	-	73	154-6/purple (p)[42, 44]
15l	SO_2CH_3	Cl	-	85	-	127-9/purple (p)[35]
15m	SO_2Ph	Cl	94	95	97	156-8/purple (p)[35,45]
15n	$SO_2Ph\ Br_{(4)}$	Cl	-	75	-	112-4/purple (p)[43]
15o	$SO_2PhCl_{(4)}$	Cl	-	76	-	113-5/purple (p)[43]
15p	$COCH_3$	Br	75	68	-	162-4[35]
15q	$COOCH_2CH_3$	Br	92	-	-	61-3[46]
15r	CH_2CH_2Cl	Cl	-	-	80	188-190[47]
15s	$CH_2(CH_2)_2N_3$	Cl	-	-	53	165-7[47]
15t	$CH_2(CH_2)_3Br$	Br	-	-	62	pale yellow (o)[48]
15u	$CH_2CH{=}C(CH_3)_2$	Br	-	-	92	80-2/pale yellow (c)[49]

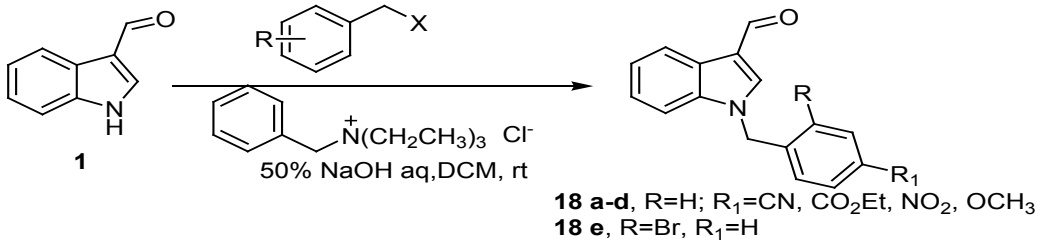
(p): powder; (o): oil; (c): crystals
(-): This experiment was not carried out.

Some N-alkylation reactions of aldehyde 1 have not been completed under the above mentioned conditions, so the researchers revealed promising alternative bases and conditions [50,51]. For an example, N-alkylation of 1 by benzyl-4-(2-iodoethyl)-1-piperidine carboxylate, benzyl-4-(2-iodopropyl)-1-piperidine carboxylate, 4-bromo-but-1-ene or 5-bromo-2-methyl-pent-2-ene have been first attempted using sodium hydride in THF, but the reaction wasn't completed [50,51]. Grumel et al., [50] and Stevens et al., [51] discovered a promising alternative method by the use of a 3–5M excess of potassium carbonate in acetonitrile and a similar excess of alkenyl bromide under reflux for 24-29hr, to give 16a,b and 17a,b, respectively (Scheme 12).



Scheme 12

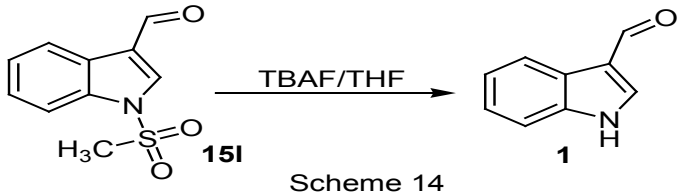
On the other hand, the desired N-(substituted) benzylindole-3-carboxaldehydes 18a-e have been prepared in 85–90% yield *via* the reaction of 1 with different substituted benzyl halides under phase-transfer catalytic (PTC) conditions utilizing triethylbenzyl-ammonium chloride and 50% w/v aqueous NaOH solution in dichloromethane [52] (Scheme 13).



Scheme 13

Deprotection of nitrogen of 1-H-indole-3-carboxaldehyde

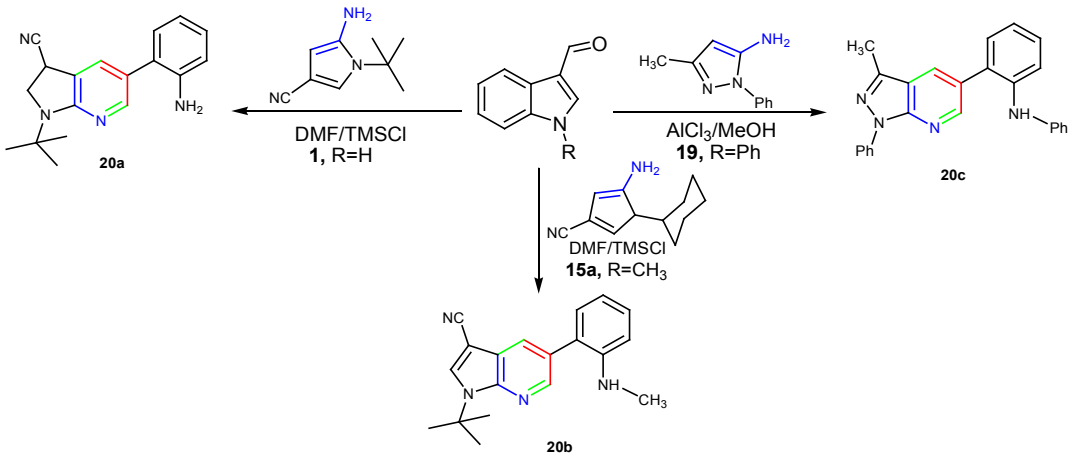
Sulfonyl groups are often used as protecting groups for nitrogen of 1 [35,43,45]. Removable of sulfonyl group was achieved *via* hydrolysis of 1 by KOH (or NaOH) in MeOH under harsh conditions (long time, strongly basic medium) [53]. A new mild and neutral deprotection of N-methylsulfonyl-indole-3-carboxaldehyde (15l) using tetrabutylammonium fluoride (TBAF) in THF has been reported [54] (Scheme 14).



Scheme 14

Ring opening

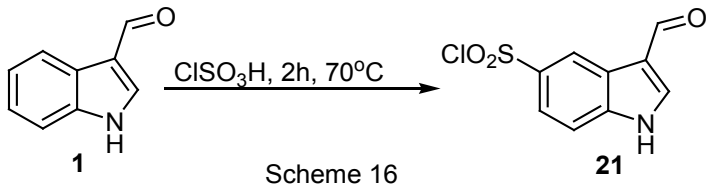
Reaction of electron-rich aminoheterocycles with *N*-substituted-1-*H*-indole-3-carboxaldehydes 1, 15a and 19 resulted in the indole ring opening and subsequent cyclocondensation to give heteroannulated pyridines 20a-c, which can be regarded as purine isosteres [55] (Scheme 15).



Scheme 15

Chlorosulfonation

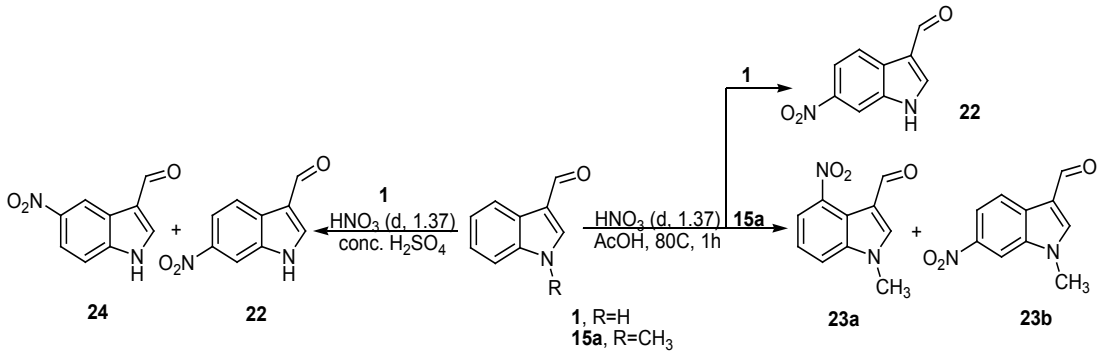
Chlorosulfonation of 1 using chlorosulfonic acid yields 5-chlorosulfonyl-1*H*-indole-3-carboxaldehyde (21) [56] (Scheme 16).



Scheme 16

Nitration

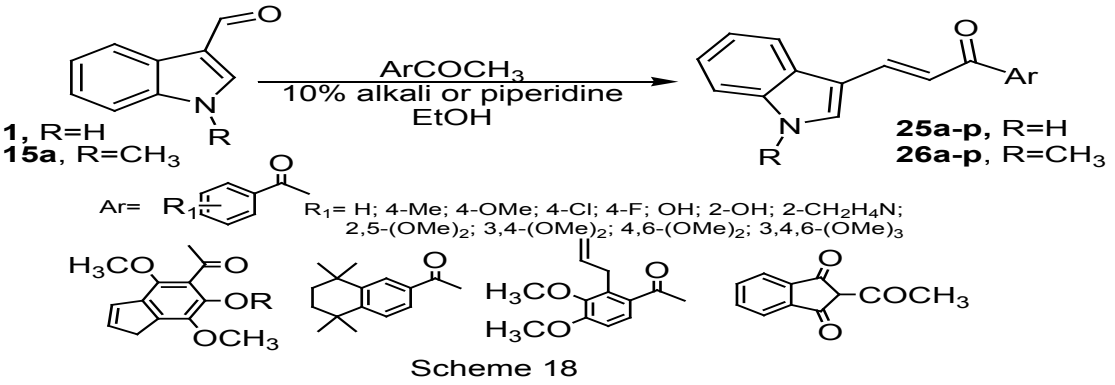
Nitration of 1 using a mixture of nitric acid (d, 1.37) and acetic acid (1: 80 ml) at 80 ºC for 1h affords 6-nitro-1*H*-indole-3-carboxaldehyde (22) [57]. Whereas, nitration of *N*-methyl-1*H*-indole-3-carboxaldehyde (15a) under the above mentioned reaction conditions give a mixture of 4-nitro (23a) and 6-nitro-*N*-methyl-1*H*-indole-3-carboxaldehydes (23b) [57]. On the other hand, nitration of 1 by the use of nitric acid and sulfuric acid give a mixture of 5-nitro (24) and 6-nitro-1*H*-indole-3-carboxaldehydes (22)[58] (Scheme 17).



Scheme 17

Claisen-Schmidt reaction (α,β-unsaturated ketones)

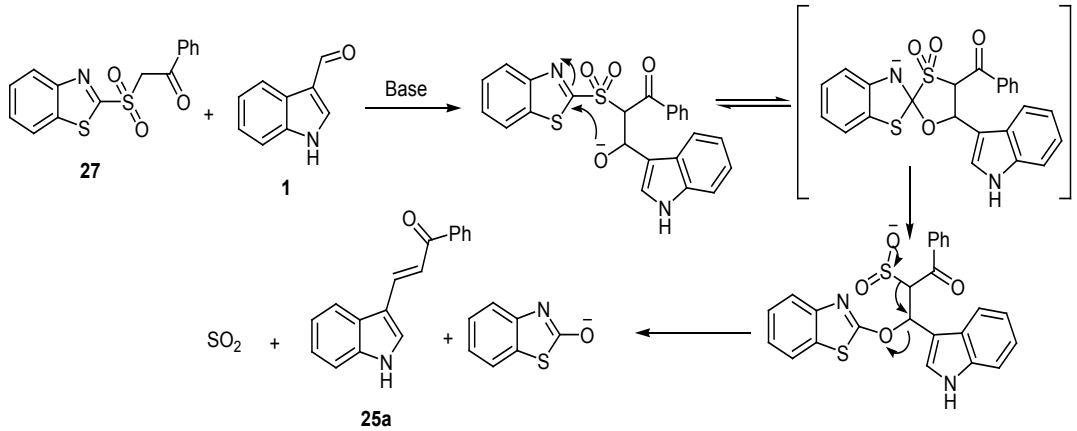
Reaction of 1 and 15a with various aryl methyl ketones in alcohol in the presence of aqueous alkaline medium and/or piperidine leads to the formation of the corresponding α,β-unsaturated ketones 25a-p and 26a-p (Scheme 18), which act as key precursors in the synthesis of many biologically important heterocycles such as pyrimidine, pyridine, benzothiazepine, pyrazolines, isoxazole, 1,4-diketones and flavones [59-66].



Scheme 18

Juliae-Kocienski olefination reaction

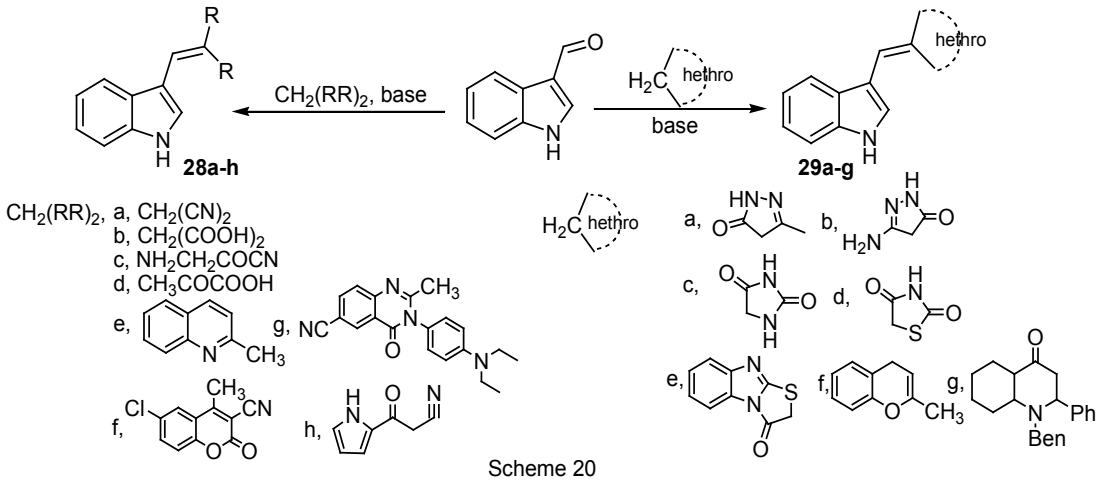
2-(Benzo[d]thiazol-2-ylsulfonyl)-1-phenylethanone (27) has been developed as new reagent for direct Juliae-Kocienski olefination of 1 in the presence of a base to afford α,β-unsaturated ketone 25a [67] (Scheme 19).



Scheme 19. Plausible mechanism for Juliae-Kocienski olefination reaction

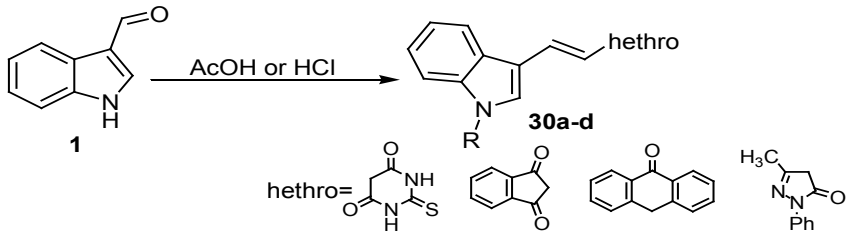
Knoevenagel reaction

Base catalyzed reaction of 1 either with the active methylene groups of aliphatic or heterocycle compounds (Knoevenagel reaction) leads to the formation of the corresponding Knoevenagel products 28a-h and 29a-g, respectively [40, 43, 68-81] (Scheme 20).



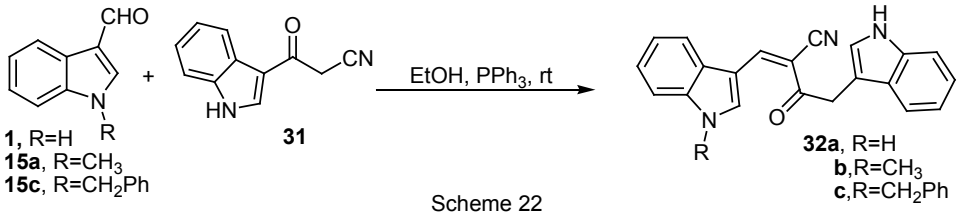
Scheme 20

However, some cases of Knoevenagel condensation of 1 have been carried out in the presence of acid such as hydrochloric acid and/or acetic acid, for example, reaction of 1 with 2-thioxo-dihydro-pyrimidine-4,6-dione,82 indan-1,3-dione, 10H-anthracen-9-one [83] and/or 3-methyl-1-phenyl-1H-pyrazol-5(4H)-one [84] yield Knoevenagel products 30a-d. (Scheme 21).



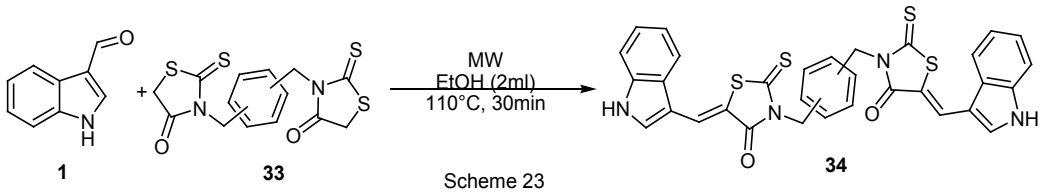
Scheme 21

Triphenylphosphine (TPP) has been found to be an efficient catalyst for the Knoevenagel condensation of 1, 15a, 15c with 3-cyanoacetylindole (31) to give 3-(1-substituted-1H-indol-3-yl)-2-(1H-indole-3-carbonyl) acrylonitriles 32a-c [85] (Scheme 22).



Scheme 22

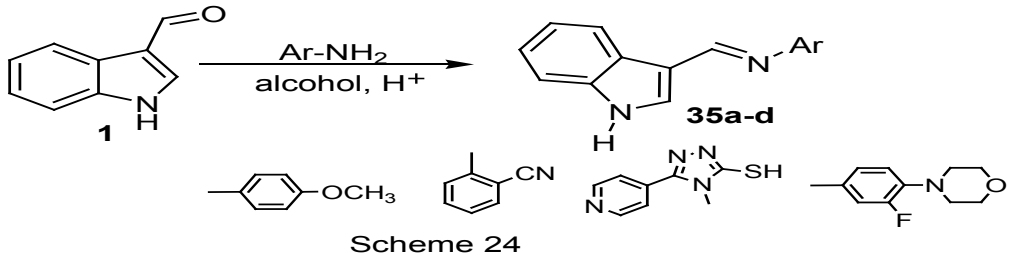
Application of microwave assisted the Knoevenagel condensation of 3,3'-(1,4- or 1,3-phenylenebis (methylene)- bis(2-thioxothiazolidin - 4-ones 33 with 1 to afford the novel bis-(2-thioxo-thiazolidin-4-one) derivatives 34 [86] (Scheme 23).



Scheme 23

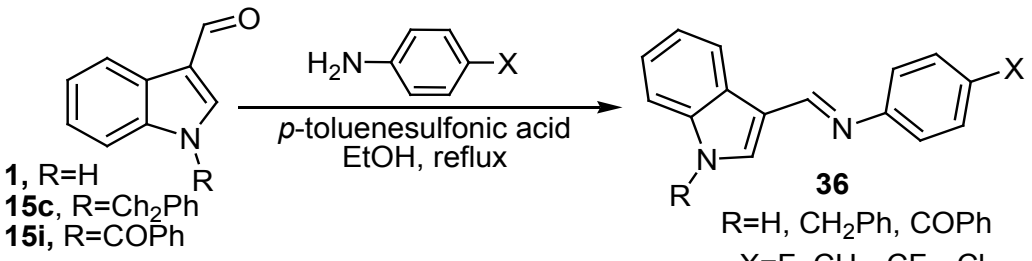
Schiff's bases reaction

Condensation of 1*H*-indole-3-carboxaldhyd with primary amine in the presence of an electrophilic catalyst leads to the formation of aldimines =CH=N- (Schiff's bases). For example, the reaction of 1 with amino compounds, namely anisidine, [87] 2-cyanoaniline, [88] 4-amino-5-pyridin-4-yl-4H-[1,2,4]triazole-3-thiol [89] and 3-fluoro-4-morpholin-4-yl-phenylamine [90] afforded the corresponding aldimines derivatives 35a-d (Scheme 24).



Scheme 24

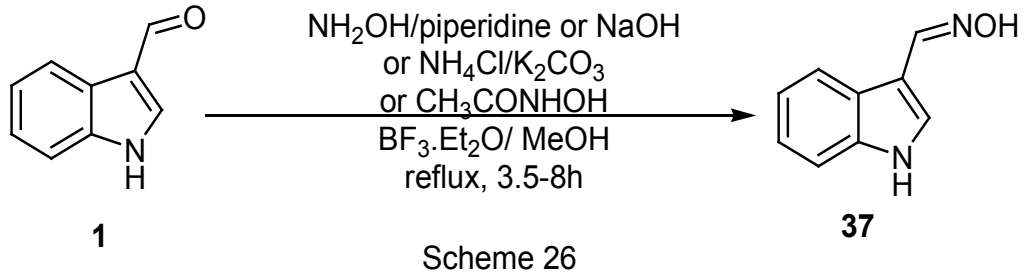
On the other hand, indole Schiff's bases 36 bearing a substituent at N-1 (R= H, CH_2Ph, COPh) in conjunction with $CH{=}N{-}C_6H_4X(p)$ (X= F, Me, CF_3, Cl) at C-3 have been synthesized *via* acid catalyzed reaction of aldehydes 1, 15c, 15i with primary aromatic amines [91]. (Scheme 25).



Scheme 25

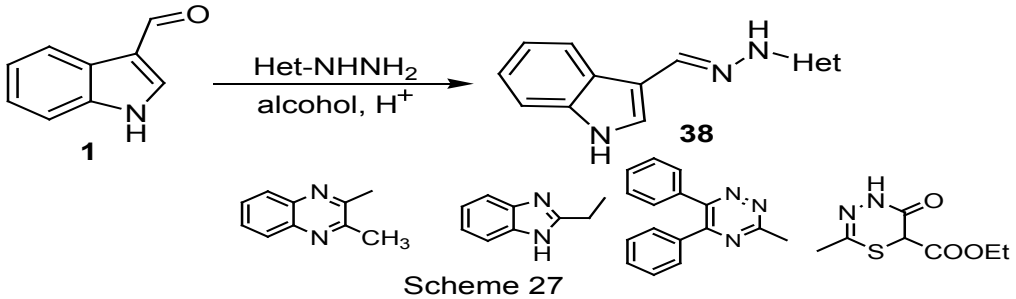
A host of ammonia derivatives other than amines also form similar condensation products with indole aldehydes. Included in this group are hydroxyl amine, hydrazine, carbohdrazide, acetic acid hydrazide, semicarbazide hydrochloride and thiosemicarbazide derivatives. The products of these groups are called oxime, hydrazone, hydrazide, semicarbazone and thiosemicarbazone derivatives, respectively.

Oxime : Oxime 37 has been prepared for the first time *via* condensation of 1 with hydroxyl amine hydrochloride in alcohol and in the presence of piperidine [92] or sodium hydroxide [93]. Whereas, Mahboobi et al., [94] have demonstrated an alternative method for the preparation of oxime 37 *via* reaction of 1 with ammonium chloride in the presence of potassium carbonate. On the other hand, Sridhar et al., reported an efficient synthesis of 37 *via* reaction of 1 with acetohydroxamic acid using $BF_3.OEt_2$ as a catalyst [95] (Scheme 26).



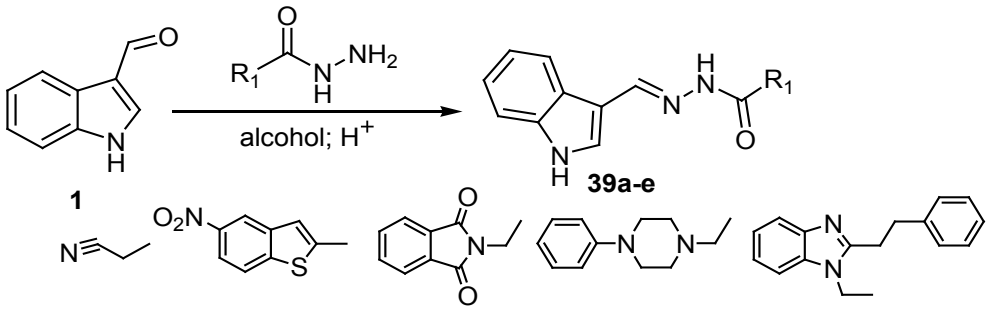
Scheme 26

Hydrazones (Hydrazine derivatives) : Acid catalyzed reaction of 1 with hydrazine hydrate, [96,97] and also with some hetero-hydrazine derivatives, namely (3-methyl-quinoxalin-2-yl)-hydrazine, [98] (1H-benzoimidazol-2-ylmethyl)- hydrazine, [99] (5,6-diphenyl-[1,2,4] triazin-3-yl)-hydrazine [100] and ethyl 2-hydrazinyl-5,6-dihydro-5-oxo-4H-1,3,4-thiadiazine-6-carboxylate, [101] yields the corresponding hydrazones 38a-d (Scheme 27).



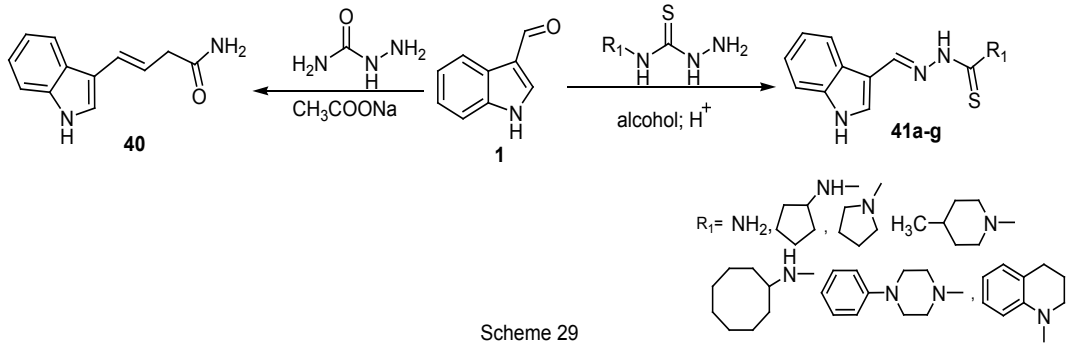
Scheme 27

Hydrazide derivatives : The reaction of aldehydes 1, 15a, 15c, 15i and 58 with carbohdrazide or acetic acid hydrazides derivatives, namely 2-cyanoacetic acide hydrazide, [102] 5-nitro-benzo-[b]thiophene-2-carboxylic acid hydrazide, [103] 2-(1,3-dioxoisoindolin-2-yl) acetohydrazide, [104](2-phenyl-sulfanylmethyl-benzoimidazol-1-yl)-acetic acid hydrazide [105] and (4-phenyl-piperazin-1-yl) acetic acid hydrazide [106] has been carried out in alcohol and in the presence of acid as a catalyst to yield the corresponding hydrazide derivatives (39a-e) (Scheme 28).



Scheme 28

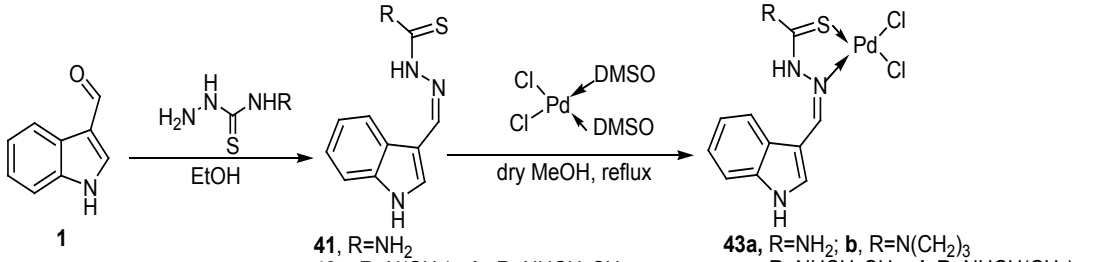
Semicarbazone and thiosemicarbazone derivatives : Reaction of 1 with semicarbazide hydrochloride in the presence of sodium acetate yields the corresponding 1H-indole-3-semicarbazone (40) [107,108]. Whereas, reaction of 1 with thiosemicarbazide or different hetero-thiosemicarbazide derivatives in methanol in the presence of acetic acid 30% afforded thiosemi-carbazone derivatives 41a-g [109-111] (Scheme 29).



Scheme 29

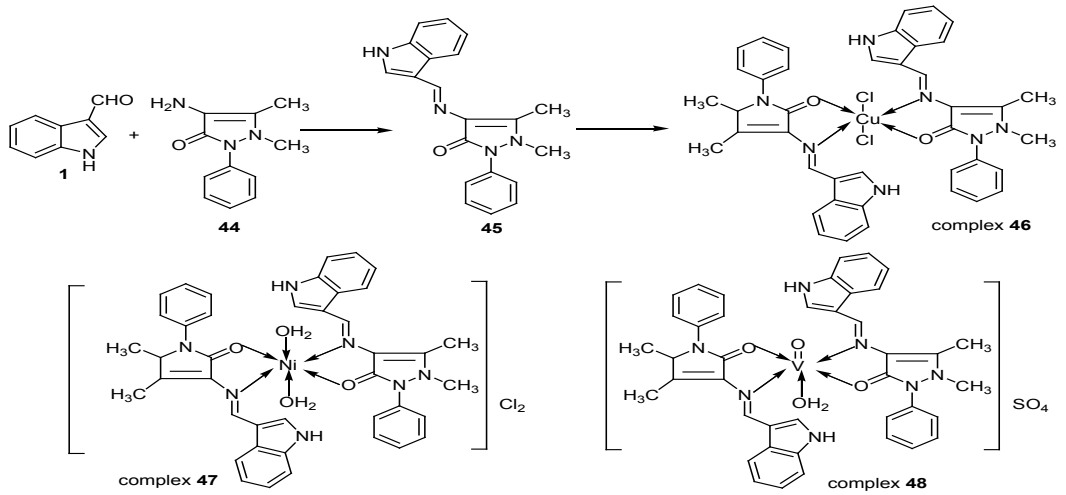
Complex formation

Thiosemicarbazones 41, 42a-f obtained *via* the reaction of 1 with some thiosemicarbazides have been used as ligands to the formation of [Pd(TSC) Cl_2] complexes 43a-g [112] (Scheme 30).



Scheme 30

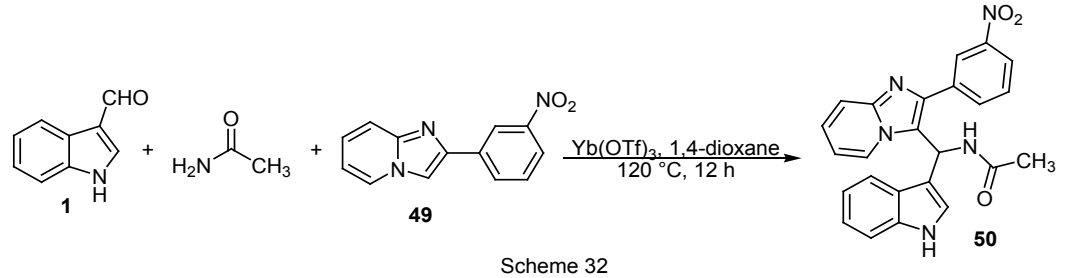
Some new Cu (II) (46), VO (II) (47), and Ni (II) (48) complexes based on indole-Schiff base have been synthesized using the metal salts: $CuCl_2$. $2H_2O$, $VOSO_4$. $_2H_2O$, $NiCl_2$. $6H_2O$, respectively [113] (Scheme 31).



Scheme 31

Mannish reaction

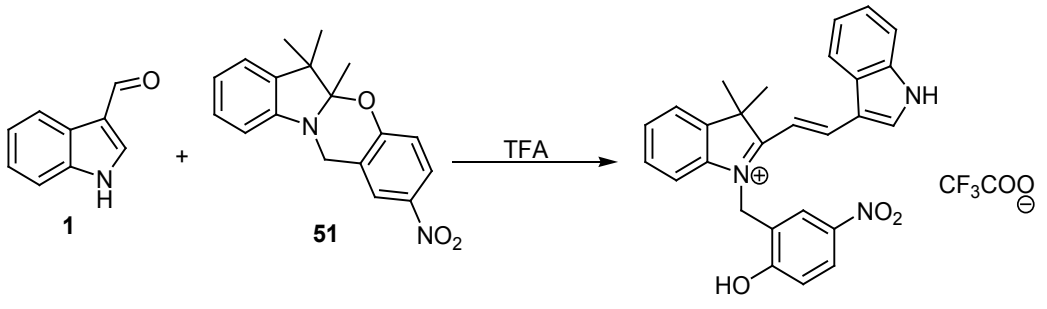
Ytterbium triflate [Yb(OTf)3] catalyzes one pot three-components reaction of 1, acetamide and 2-(3-nitrophenyl)H-imidazo[1,2-a]pyridine (49) to give the corresponding Mannish product 50 [114] (Scheme 32).



Scheme 32

Dyes formation

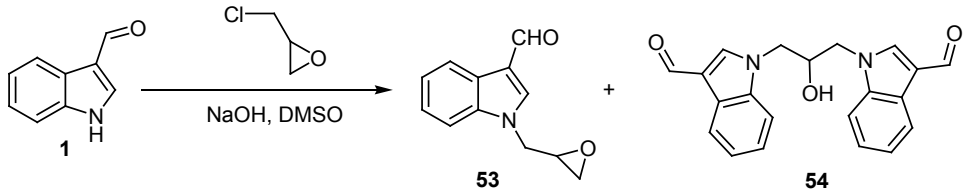
Acid catalized reaction of 1 with 2-methyl-benzo[1,3]oxazine (51) afforded directly polymethine dye 52. This dye has the structure of a cationic thermally stable colored open form of a photochromic benzo[1,3]oxazine [115] (Scheme 33)



Scheme 33

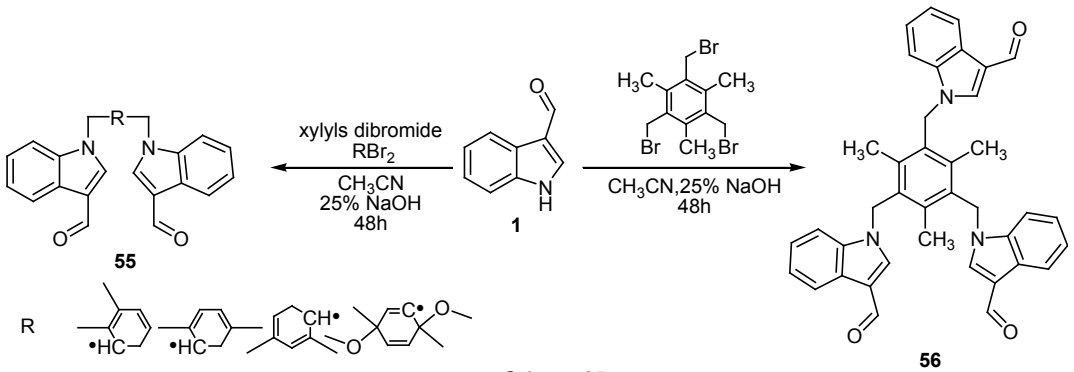
Bi and tri-(1H-indole-3-carbaldehyde)

The reaction of 1 with epichlorohydrin in DMSO in the presence of NaOH gives bi-1H-indole -3-carbaldehyde (54) on cooling [116] (Scheme 34).



Scheme 34

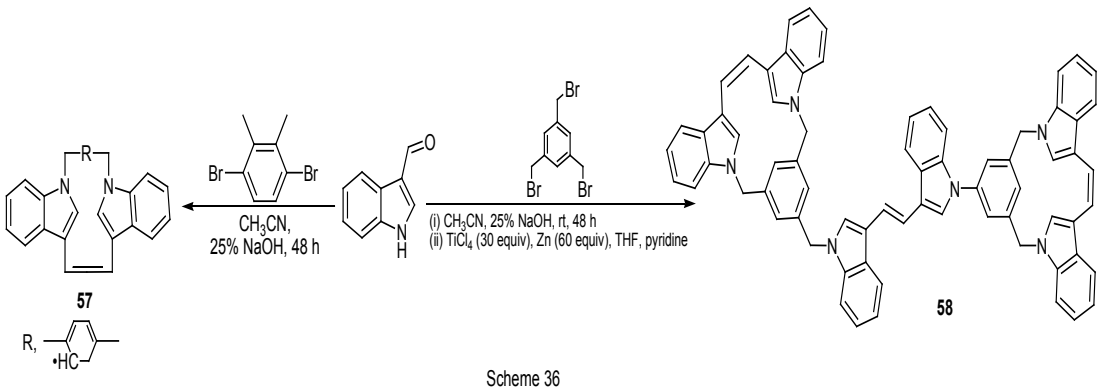
1*H*-indole-3-carboxaldehyde (1) on reaction with xylyl dibromides or 1,3,5-trimethyl-tris-(bromomethyl)benzene in CH_3CN and 25% NaOH for 2 days gave bi-indole aldehyde (55) and tri-indole aldehyde (56), respectively [117,118] (Scheme 35).



Scheme 35

Indolophanes and bisindolostilbenophanes

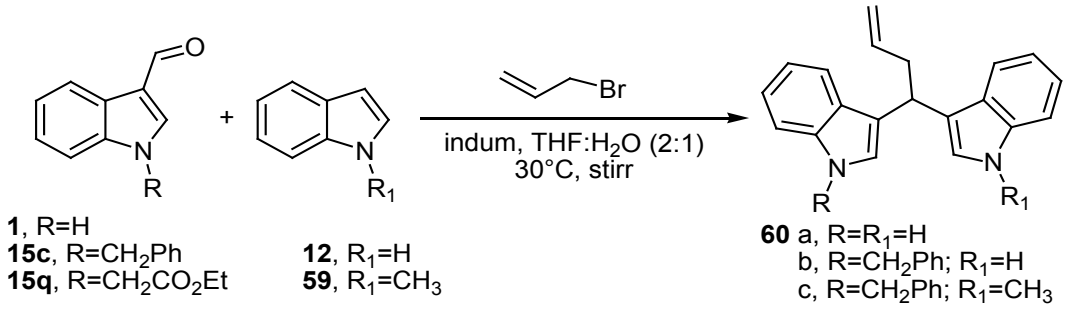
Divers types of indolophanes (57) and bisindolostilbenophanes (58a,b) have been synthesized by intra-, inter- and tandem intra-molecular McMurry coupling [117] (Scheme 36).



Scheme 36

Bis- and triindole derivatives

Bisindolyl alkanes and their derivatives constitute an important group of bioactive metabolites of terrestrial and marine origin. Aldehydes 1, 15c, 15q undergo indium-mediated ternary reactions with allyl bromide and indoles 12,59 provided symmetrical and unsymmetrical bisindolyl alkanes 60a-c [119] (Scheme 37).



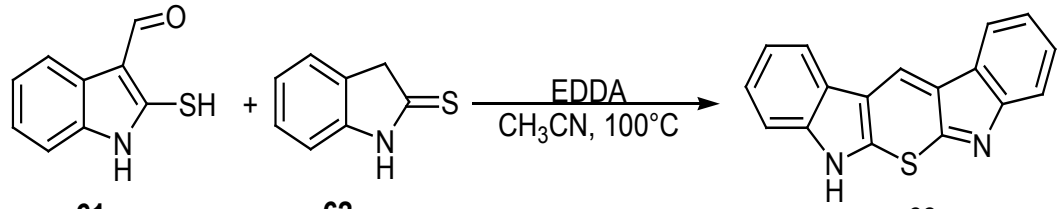
1, R=H
15c, R=CH_2Ph
15q, R=CH_2CO_2Et

12, R_1=H
59, R_1=CH_3

60 a, R=R_1=H
b, R=CH_2Ph; R_1=H
c, R=CH_2Ph; R_1=CH_3

Scheme 37

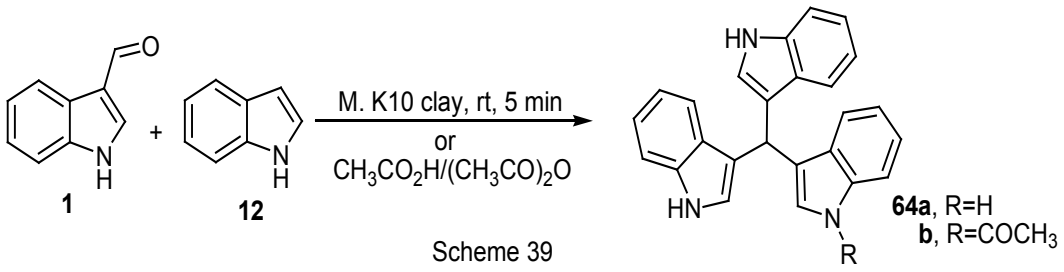
Synthesis of the fused 5H-thiopyrano[2,3-b:6,5-b'] diindole (63) has been achieved *via* condensation of 2-(alkylthio)-indole-3-carbaldehyde (61) with indole-2,3-dihydro-2-thione (62) in EDDA in acetonitrile in a Q-Tube™ pressure reactor [120] (Scheme 38).



61 **62** **63**

Scheme 38

Tri(indol-3-yl)methanes 64a and 64b are produced in a few minutes *via* dry reaction of 1 with indole (12) either on Montmorillonite K10 clay at room temperature [121] or by a mixture of acetic acid and acetic anhydride [122] (Scheme 39).



1 **12**

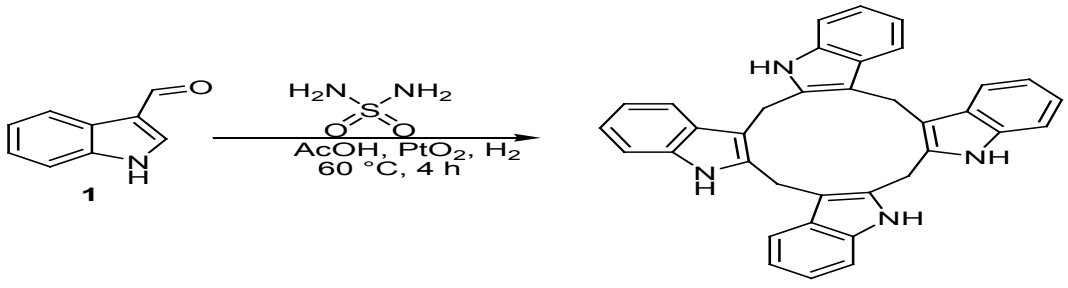
64a, R=H
b, R=$COCH_3$

Scheme 39

Cyclic tetraindole (65) has been synthesized via reaction of 1 with sulfamide and platinum oxide in catalytic amounts [123] (Scheme 40).

Indolenyl sulfonamides

Various indolenyl sulfonamides 66a-k, have been synthesized *via* condensation of 1 with

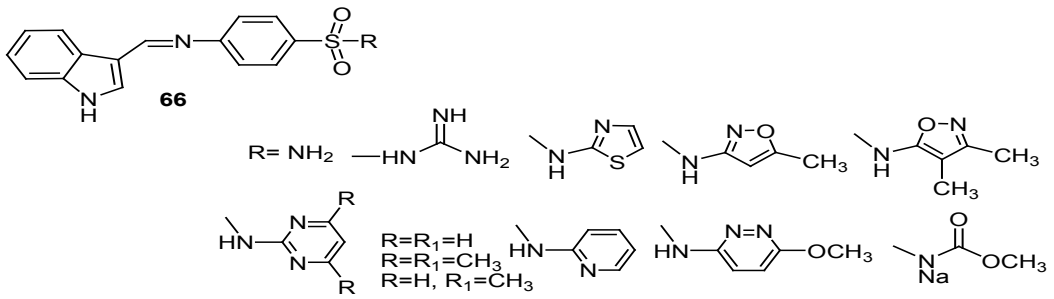


1

65

Scheme 40

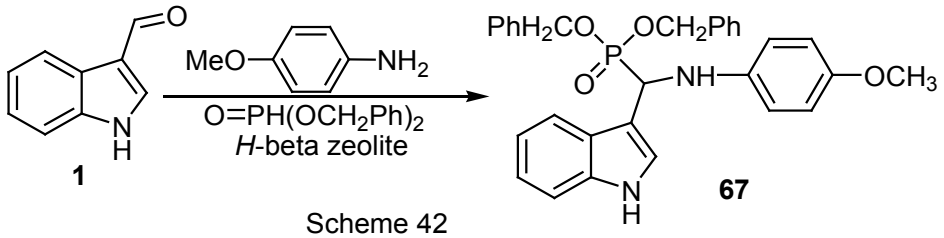
different sulfonamides, namely sulfanilamide, sulfaguanidine, sulfathiazole, sulfamethoxazole, sulfaisoxazole, sulfadiazine, sulfamethazine, sulfapyridine, sulfadiazine, sulfamerazine, sulfamethoxy-pyridazine and sulfacetamide sodium in ethanol (1:1) [124,125] (Scheme 41).



Scheme 41

Kabachnik–Fields reaction (Synthesis of α-amino-phosphonate)

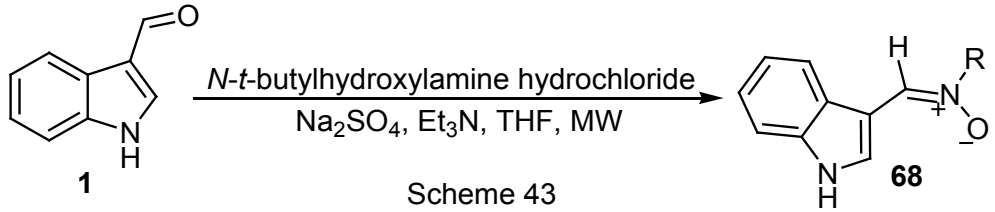
α-Aminophosphonate, the key substrate in the synthesis of α-amino-phosphonic acid, shows a number of interesting activities, such as peptidomimetics, enzyme inhibitors, pharmacogenic agents, herbicides, inhibitors of serine hydrolysis, inhibitors of UDP-galactopyranose mutate and anti-tumor agents [126]. Tillu et al., [126] reported one-pot three-component reaction of 1, primary amine (p-anizidine) and dibenzyl phosphite using H-beta zeolite as a catalyst to afford α-aminophosphonate 67 (Scheme 42).



Scheme 42

Synthesis of nitrone derivative

For years, the ability of nitrones to act as a good radical traps has been in the origin of a number of basic and clinical studies that aiming at the investigation of their potential therapeutical applications for the treatment of cerebral ischemia, or neurodegenerative diseases where reactive oxygen species (ROS) are implicated [127]. Samadi et al., reported the preparation of nitrone, namely (Z)-α-(1H-3-indolyl) -N-tertbutylnitrone (68) *via* reaction of 1 with N-t-butyl-hydroxyl-amine hydrochloride in THF in the presence of Na_2SO_4 and Et3N [127]. (Scheme 43) .

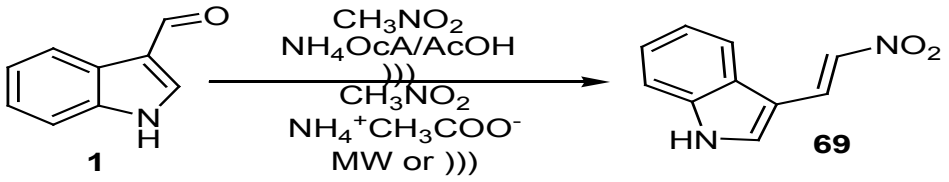


Scheme 43

Reaction with nitromethane (Henary reaction)

Henary reaction involves condensation of nitroalkane with aromatic aldehyde in the presence of a mixture of acetic acid and ammonium acetate to give nitroalkene [128]. McNulty et al., have demonstrated the synthesis of 3-(2-nitro-vinyl)-

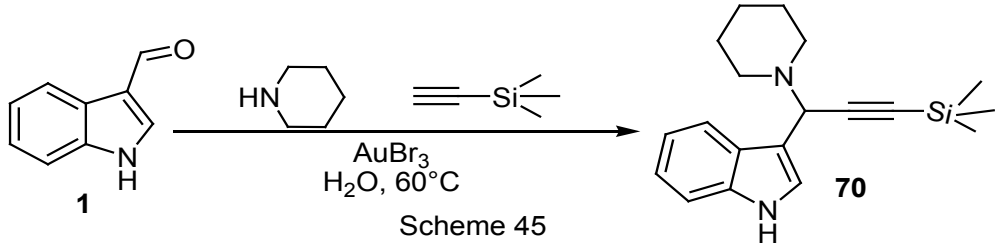
1*H*-indole 69 *via* reaction of 1 with nitromethan under ultrasound assisted Henery reaction.[128]. Whereas, Rodriguez and Pujol, reported a new modification by using microwave irradiation or ultra sound assisted Henery reaction as the energy source [129] (Scheme 44).



Scheme 44

Preparation of propargylamines

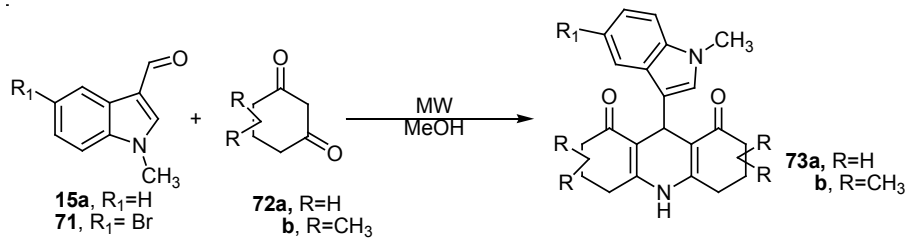
Propargylamines are considered important intermediates for the synthesis of many natural products [130]. Srinivas and Koketsu, have reported a simple and efficient route for the preparation of 3-substituted propargylamine 70 by three component coupling of 1 with terminal alkyne (silyl acetylene), and secondary amine (piperidine) in the presence of AuBr3 as a catalyst [130] (Scheme 45).



Scheme 45

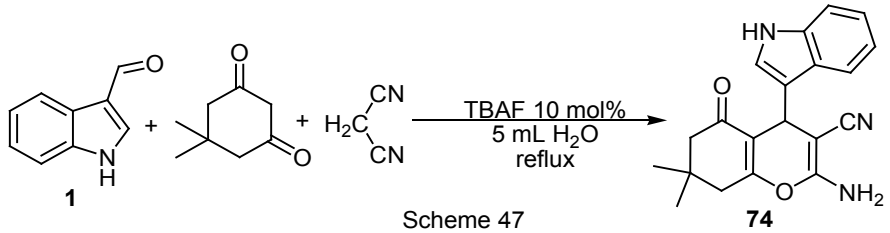
Synthesis of heterocycles

Acridine : A microwave-assisted synthesis has been applied for the synthesis of novel 3,4,6,7-tetr ahydroacridines73a,b, using substituted aldehydes 15a, 71 and 1,3-cyclic dicarbonyls, namely 4,4-(72a) or 5,5-dimethyl-1,3-cyclo-hexanediones (72b) in the presence of ammonium acetate [131] (Scheme 46).



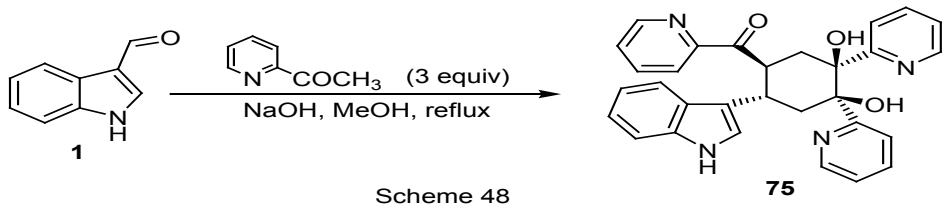
Scheme 46

Chromene : Multi-component reaction of 1, malononitrile and cyclic 1,3-diketones utilizing tetrabutyl ammonium fluoride (TBAF) as a catalyst, yielded the 4H-chromene derivative (74) [132] (Scheme 47).



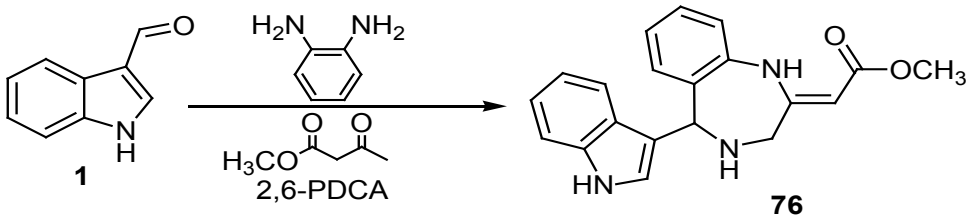
Scheme 47

Cyclohexanone : One-pot reaction of (1 equiv) of 1 with (3 equiv) of 2-acetylpyridine under Claisen-Schmidt condensation, Michael addition, followed by double aldol condensation afforded cyclohexanone (75) [60]. (Scheme 48) .



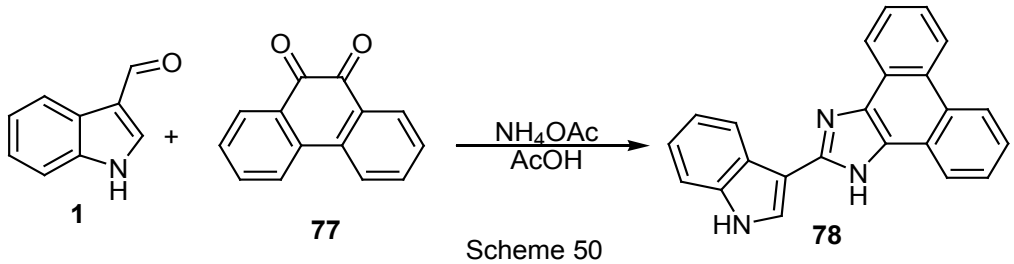
Scheme 48

Diazepine : One pot three component reaction of 1, o-phenylenediamine and 3-oxo-butyric acid methyl ester in the presence of 2,6-pyridine dicarboxylic acid (2,6-PDCA) leads to the formation of 1,5-benzodiazepine derivative 76 [133] (Scheme 49).



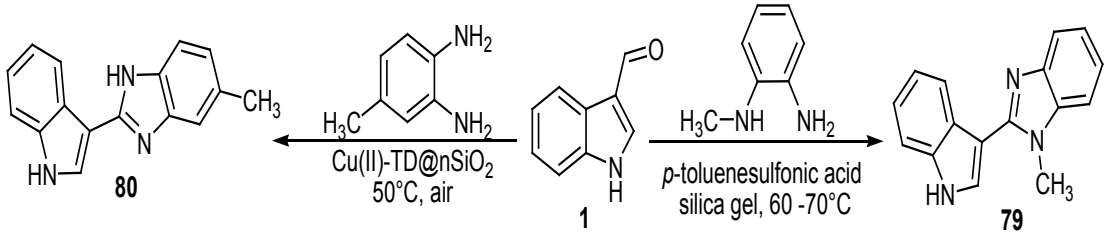
Scheme 49

Imidazole : Condensation of 1 with phenanthrene-9,10-dione (77) in the presence of ammonium acetate and acetic acid leads to the formation of imidazole derivative 78 [134] (Scheme 50).



Scheme 50

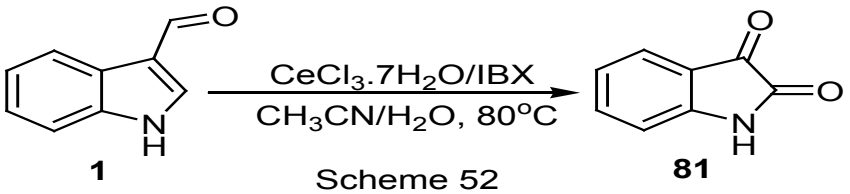
A cheap and eco-friendly catalyst, namely p-toluenesulphonic acid on-silica gel, has been used for a convenient one-pot synthesis of benzimidazole 79 from 1 and N-methylbenzene-1,2-diamine 78 [135]. On the other hand Nasr-Esfahani et al., have demonstrated an efficient method for the synthesis benzoimidazole 80 *via* condensation of 1 with 4-methyl-o-phenelynendiamine in the presence of catalytic amount of Cu(II) containing nanosilica triazine dendrimer (Cu(II)-TD@nSiO2) [136] (Scheme 51).



Scheme 51

Isatin

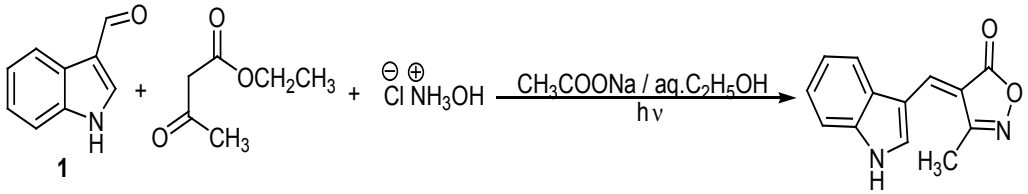
Oxidation of 1 using iodoxy-benzoic acid (IBX) in the presence of $CeCl_3$. $7H_2O$ in aqueous acetonitrile at ambient temperature afforded isatin (81) [137] (Scheme 52).



Scheme 52

Isoxazole

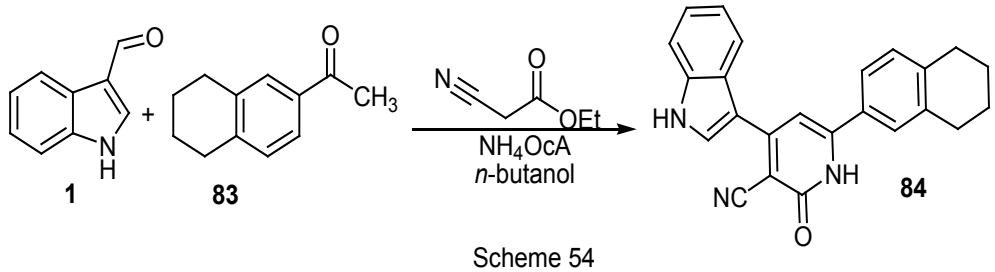
Saikh et al., reported an efficient methodology for the synthesis of isoxazole (82) *via* visible light induced multi component reaction of 1, ethyl acetoacetate, hydroxylamine hydrochloride, and sodium acetate [138] (Scheme 53).



Scheme 53

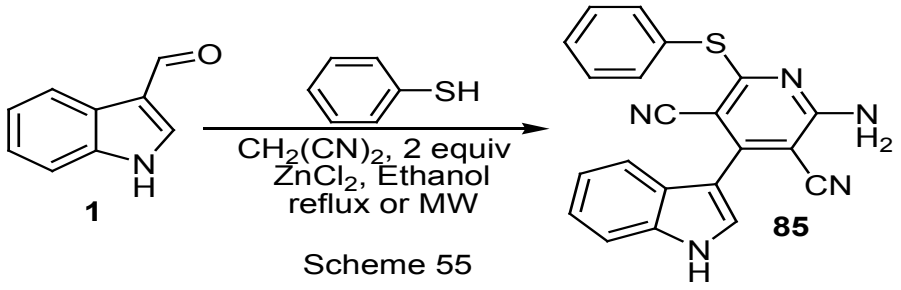
Pyridine

One pot three component reaction of 1, 2-acetyl-5,6,7,8-tetrahydronaphthalene (83) and ethyl cyanoacetate in n-butanol in the presence of excess ammonium acetate gives the corresponding cyanopyridone derivative 84 [139] (Scheme 54).



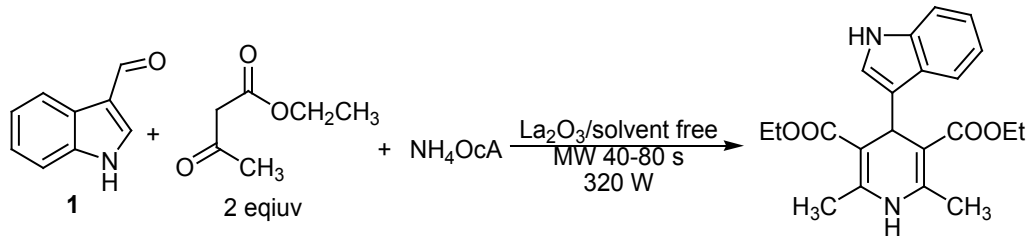
Scheme 54

$ZnCl_2$-catalyzes one-pot multi-component reaction of 1, malononitrile and thiophenol under microwave and conventional methods to yield thiopyridine derivative (85) [140] (Scheme 55).



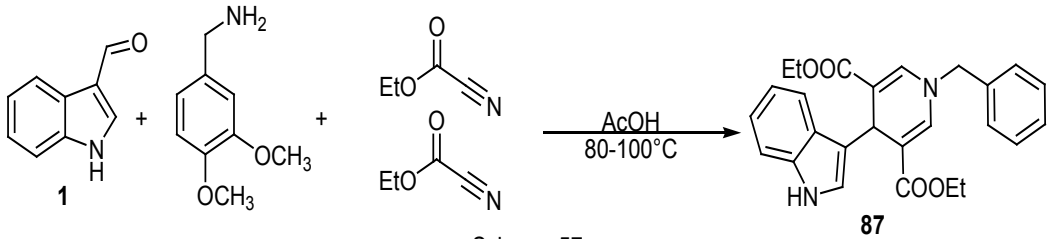
Scheme 55

Cyclocondensation of 1, ethyl acetoacetate and ammonium acetate under microwave irradiation using La_2O_3 as a catalyst, leads to the formation of the corresponding 1,4-dihydropyridine (86) [141] (Scheme 56).



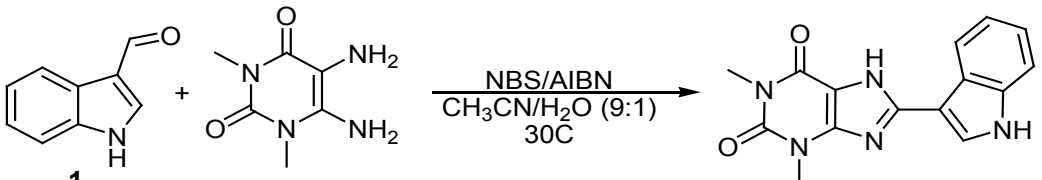
Scheme 56

Also, cyclocondensation of three-component of 1, ethyl propiolate and 3,4-dimethoxybenzyl amine, under heating at 80°C in glacial acetic acid afforded 1,4-dihydropyridine derivative(87) [142] (Scheme 57).



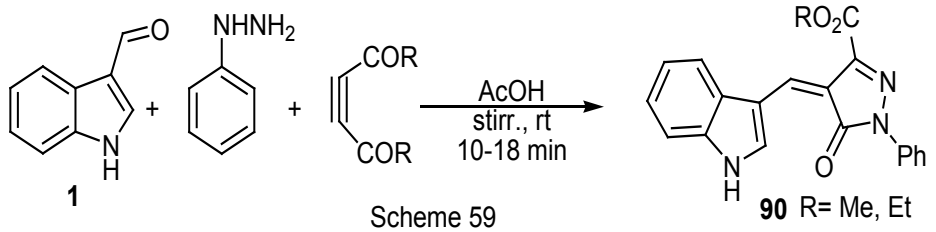
Scheme 57

Purine : One pot reaction of 1 and 5,6-diamino-1,3-dimethyluracil (88), in acetonitrile and in the presence of catalytic amount of N-bromosuccinimide (NBS) and azo bis-isobutyronitrile (AIBN) yields the corresponding purine derivative (89) [143] (Scheme 58).



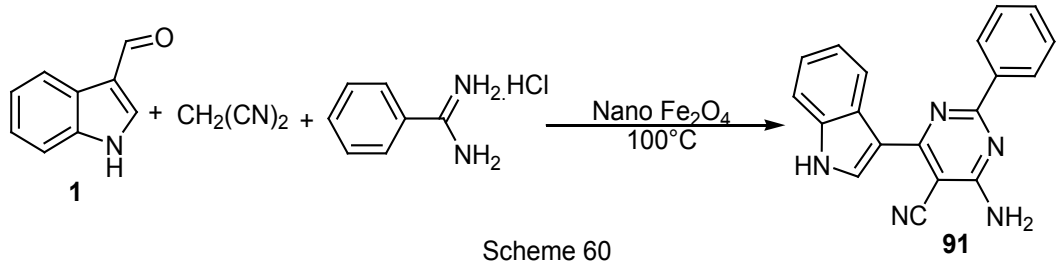
Scheme 58

Pyrazole : Multi component reaction of acetylene dicarboxylates, phenylhydrazine and 1 under stirring in acetic acid leads to the formation of pyrazolones 90 [144] (Scheme 59).



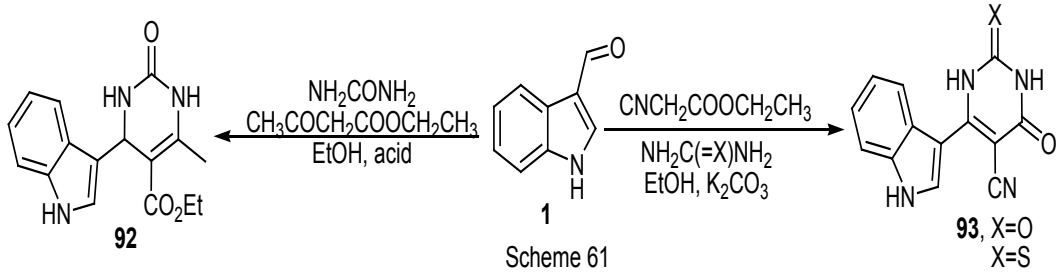
Scheme 59

Pyrimidine : One-pot three component reaction of 1, malononitrile and benzamidine hydrochloride in the presence of magnetic nano Fe_3O_4 particles as a catalyst under solvent-free conditions yields pyrimidine derivative 91 [145]. (Scheme 60).



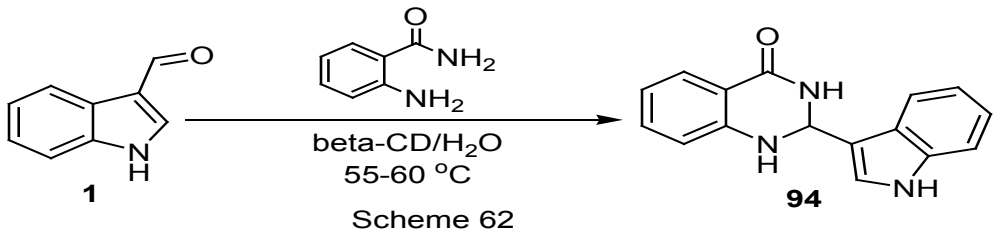
Scheme 60

On the other hand, condensation of 1 with urea and ethyl acetoacetate in the presence of acid as a catalyst [Biginelli reaction] gives 3,4-dihydropyrimidine-2 (1H)-one (92) [146]. Also, reaction of 1 with ethyl cyanoacetate and urea or thiourea in ethanol in the presence of potassium carbonate leads to the formation of pyrimidine derivative 93a,b [68] (Scheme 61).



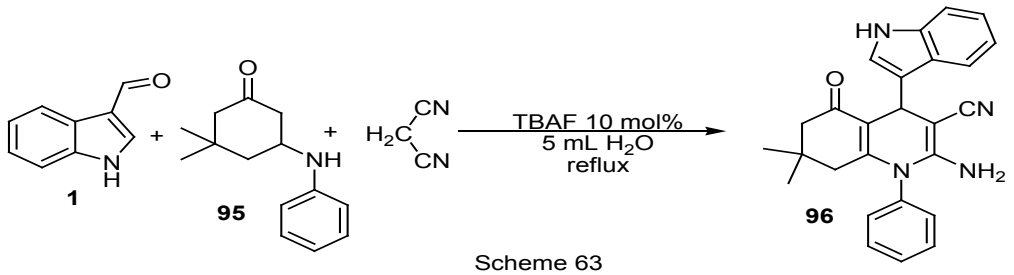
Scheme 61

Quinazoline: Reaction of 1 with anthranilamide in the presence of β-cyclodextrin as a catalyst leads to the formation of 2,3-dihydroquinazoline 94 [147] (Scheme 62).



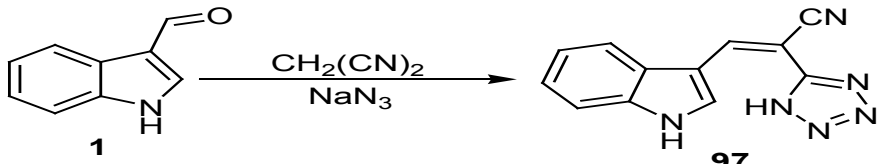
Scheme 62

Quinoline : One-pot reaction of 1, malononitrile and 3,3-dimethyl-5-(phenylamino) cyclohexanone (95) using tetrabutylammonium fluoride (TBAF) as a catalyst yields the corresponding 4H-quinoline derivative 96 [132] (Scheme 63).



Scheme 63

Tetrazole : Multi-component of 1, malononitrile and sodium azide in water under Knoevenagel condensation followed by 1,3 dipolar cycloaddition afforded (E)-3-(1H-indol-3-yl)-2-(1H-tetrazole-5-yl)acrylonitrile (97) [148] (Scheme 64).



Scheme 64

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إندول -٣- كاربوكسالدهيد : تخليقه و تفاعلاته

إسلام رضا الصاوى ، هبة محمد شحاته أبو سالم وعادل حامد مندور
قسم كيمياء المركبات الطبيعية - المركز القومى للبحوث - ص.ب. ١٢٦٢٢ دقى - الجيزة - مصر .

الاندول-٣-كاربوكسالدهيد و مشتقاته يمثلوا الوسيط الرئيسى لإعداد المركبات النشطة بيولوجياً كما انها تمثل الوسيط فى تحضير القلويدات المحتوية على حلقة الاندول. أيضا يمثل الاندول-٣-كاربوكسالدهيد و مشتقاته الأساس فى تحضير عديد من مشتقات الحلقات الغير متجانسة و يرجع ذلك إلى مجموعة الكاربونيل و التى تخضع لتفاعلات الإقتران و الإختزال.

هذا المرجع يسلط الضوء على التطورات الكيميائية الاخيرة و الخاصة بالاندول-٣-كاربوكسالدهيد من خلال مناقشة الطرق المختلفة و المتطوره لتخليقه و تخليق مشتقاته , كما أنها تسلط الضوء على التفاعلات الهامة و المشهورة الخاصة به و إستخدام هذه المشتقات فى تحضير العديد من المركبات النشطة بيولوجياً.