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Review article 51

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

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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).

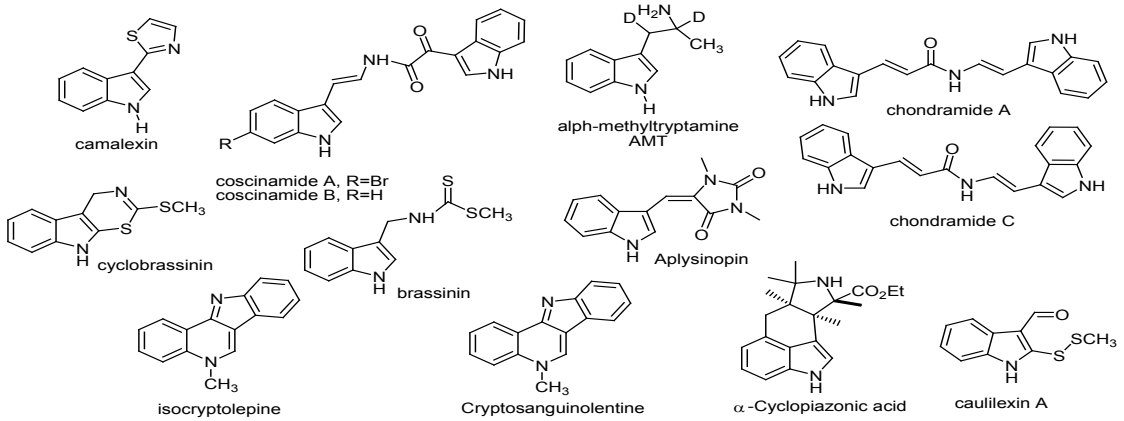

Figure 1. Bioactive natural compounds from 1*H*-indole-3-carboxaldhyde

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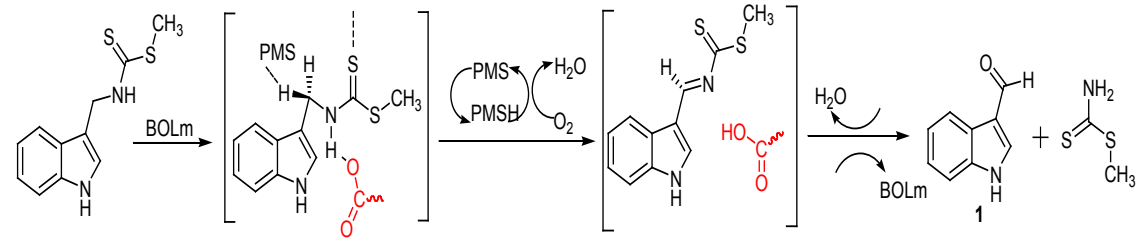
Biosynthesis of natural 1*H*-indole-3-carboxaldehyde (1) was first suggested by Tang and Bonner who reported that, aldehyde (1) was produced *via* biotransformation of indole-3-acetic acid (IAA) using crude enzyme which is prepared from etiolated pea seedlings [14]. On the other hand, brassinin oxidase (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.

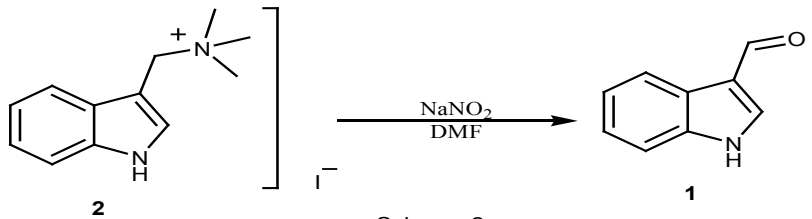
Synthetic methods of the preparation of 1H-Indole-3-carboxaldhyde

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

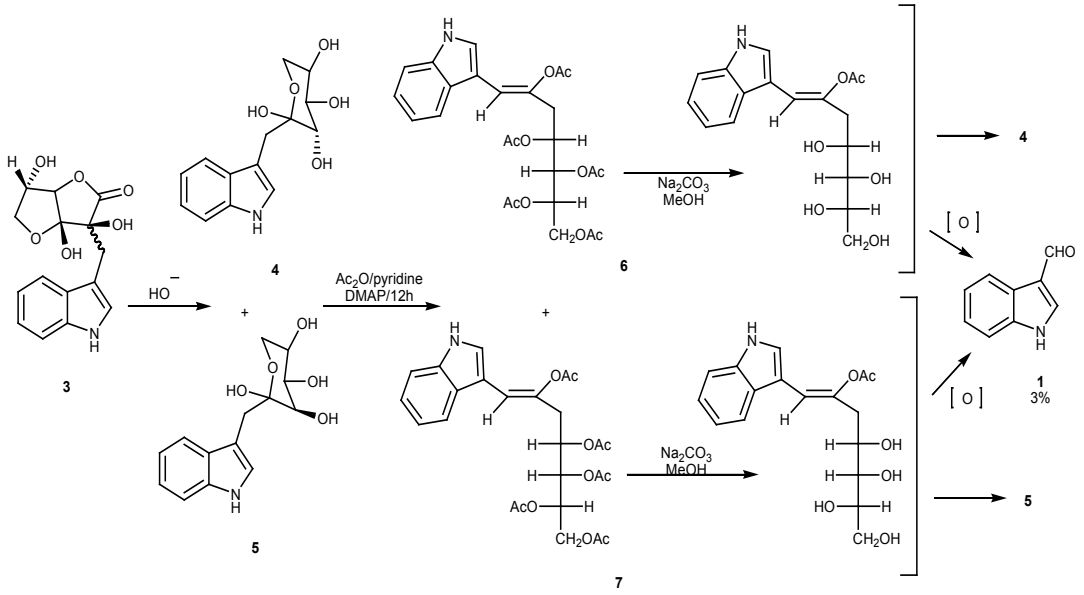
Unusual oxidation of graminemethiodide [1-(1H-indol-3-yl)-N,N,N-trimethylmethanaminium iodide] (2) using sodium nitrite in *N,N*-dimethylformamide (DMF) produces 1 in 68% yield [24] (Scheme 2).



Scheme 2

Alkaline degradation of ascorbigen

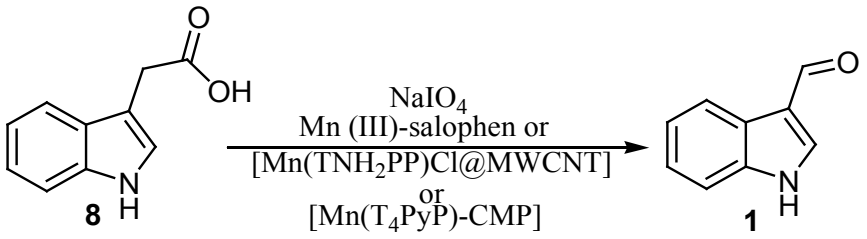
Alkaline degradation of ascorbigen 3 leads to a mixture of L-sorbose (4) and L-tagatose (5) derivatives. The later ketoses underwent acetylation and open ring of pyranose using acetic anhydride in pyridine in the presence of 4-dimethylaminopyridine (DMAP) leads to a mixture of 6 and 7, which are separated 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

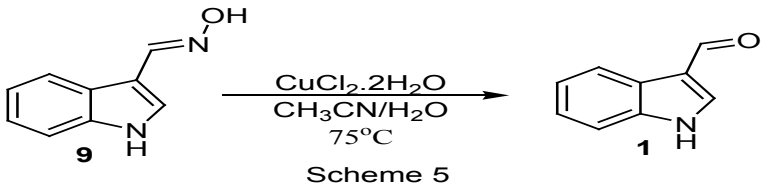
Oxidative decarboxylatoin of indole-3-acetic acid (8) using sodium periodate catalyzed either with manganese(III)-salophen complex, tetrakis(4-aminophenyl) porphyrinato manganese (III) chloride support on functionalized multi-wall carbon nano-tubes or with manganese (III) tetra (4-pyridyl)porphyrin support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



Scheme 4

From oximes

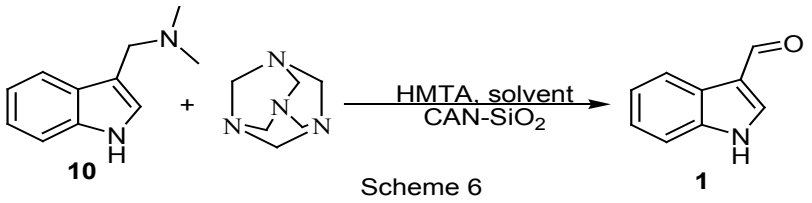
Treatment of (*E*)-1*H*-indole-3-carbaldehyde oxime (9) with 2 molar equivalents of cupric chloride dihydrate under reflux in acetonitrile and water (4:1) leads to the formation of 1 in 88 % yield [27] (Scheme 5).



Scheme 5

From gramine

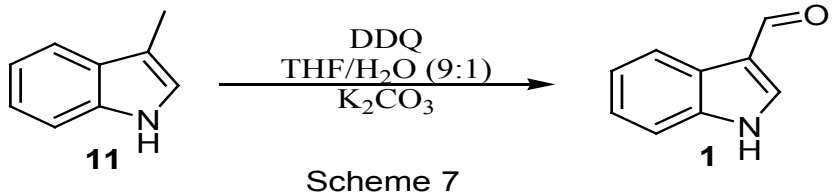
The reaction of gramine (10) with formulating species has been generated from hexamethylenetetramine (HMTA) and silica-supported ceric ammonium nitrate (CAN–SiO_2) yields 1 in 81% [28] (Scheme 6).



Scheme 6

Oxidation of skatole

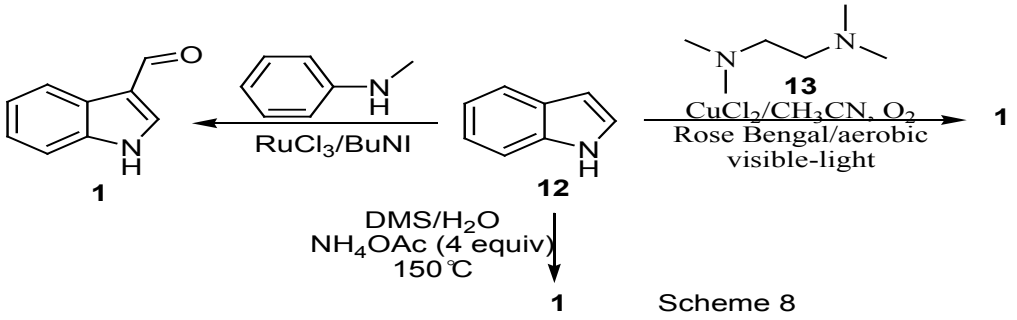
Oxidation of skatole (3-methylindole) (11) with 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ) in a mixture of tetrahydrofuran and water (9:l) at room temperature affords 1 in 30% yield [29] (Scheme 7).



Scheme 7

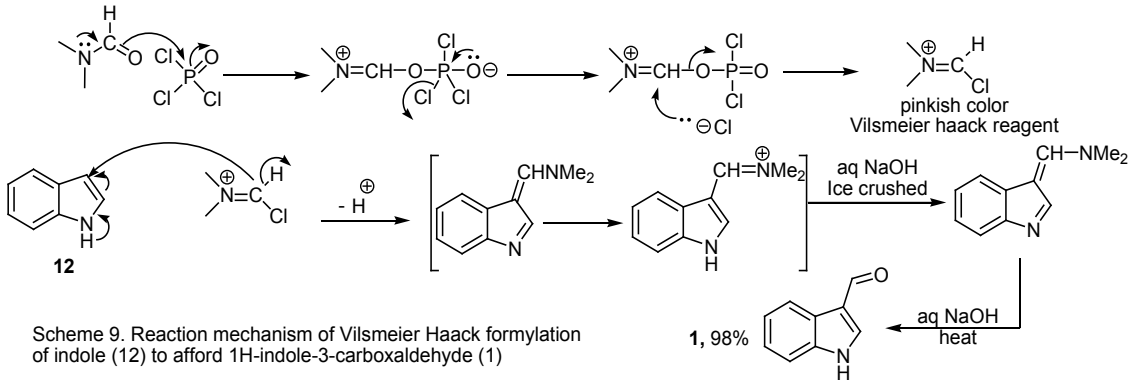
Formylation of indole

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).

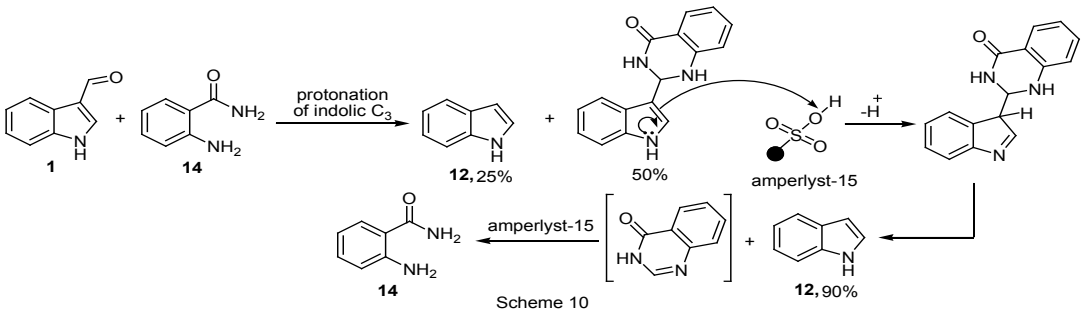


Scheme 9. Reaction mechanism of Vilsmeier Haack formylation of indole (12) to afford 1H-indole-3-carboxaldehyde (1)

Reactions of 1H-Indole-3-carboxaldehyde

Deformylation

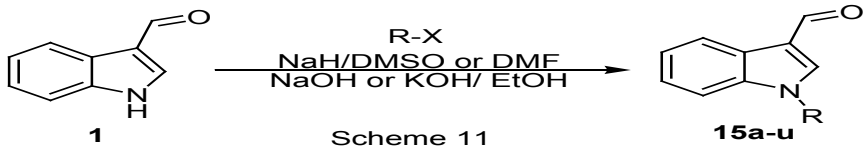
Deformylation of 1*H*-indole-3-carboxaldehyde (1) has been achieved by the use of anthranilamide (14) in the presence of solid acid heterogeneous catalyst. The reaction occurs through quinazolinone intermediate, which is exposed to acid catalyzed cleavage and forms deformylated product, indole (12) [34].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



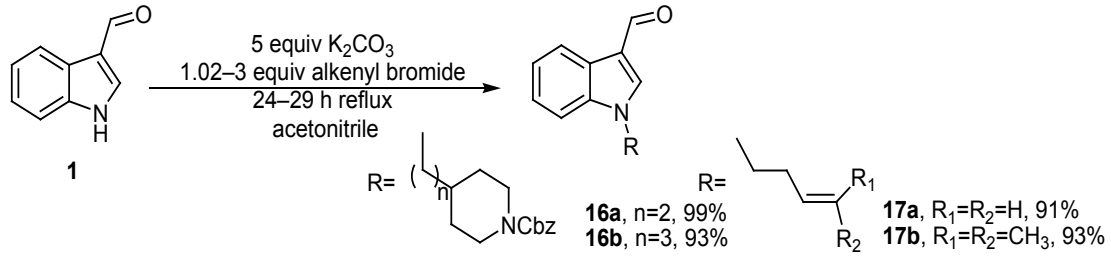
Scheme 11

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]

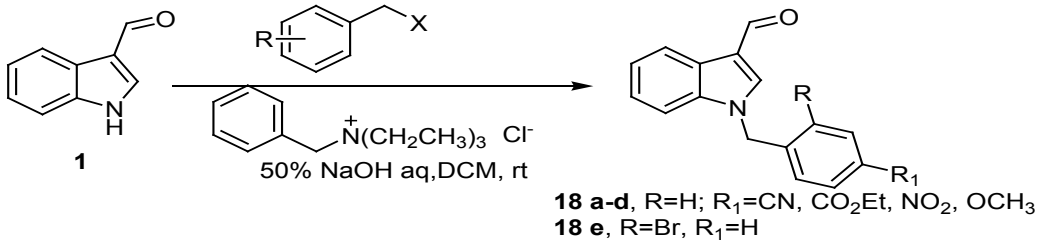
(p): powder; (o): oil; (c): crystals
(-): This experiment was not carried out.

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

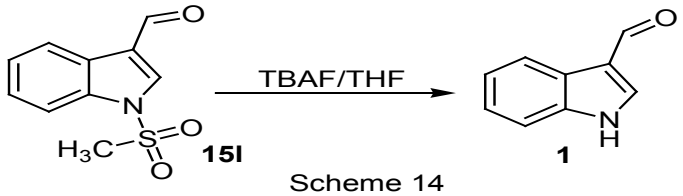
On the other hand, the desired N-(substituted) benzylindole-3-carboxaldehydes 18a-e have been prepared in 85–90% yield *via* the reaction of 1 with different substituted benzyl halides under phase-transfer catalytic (PTC) conditions utilizing triethylbenzyl-ammonium chloride and 50% w/v aqueous NaOH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



Scheme 13

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

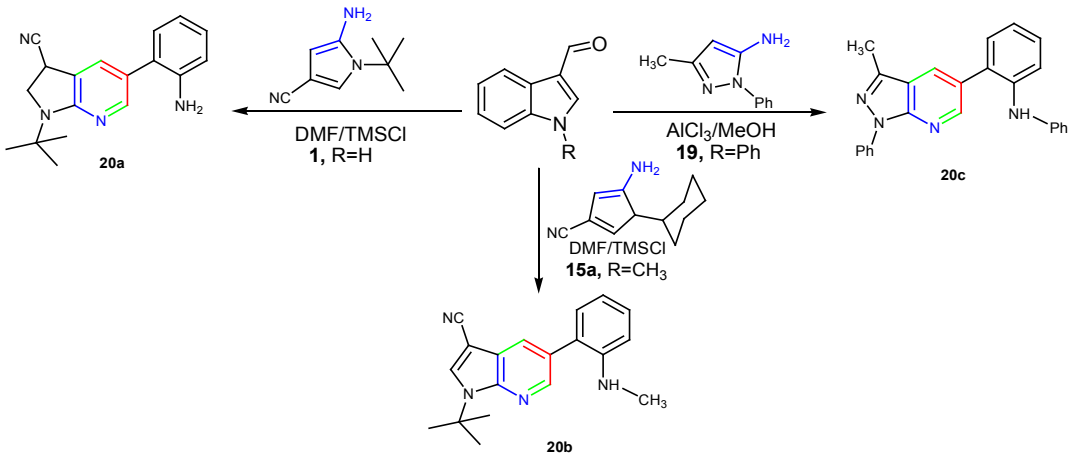
Sulfonyl groups are often used as protecting groups for nitrogen of 1 [35,43,45]. Removable of sulfonyl group was achieved *via* hydrolysis of 1 by KOH (or NaOH) in MeOH under harsh conditions (long time, strongly basic medium) [53]. A new mild and neutral deprotection of N-methylsulfonyl-indole-3-carboxaldehyde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



Scheme 14

Ring opening

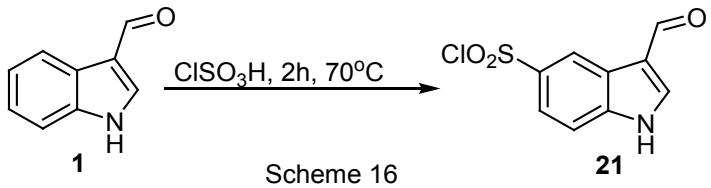
Reaction of electron-rich aminoheterocycles with *N*-substituted-1-*H*-indole-3-carboxaldehydes 1, 15a and 19 resulted in the indole ring opening and subsequent cyclocondensation to give heteroannulated pyridines 20a-c, which can be regarded as purine isosteres [55] (Scheme 15).



Scheme 15

Chlorosulfonation

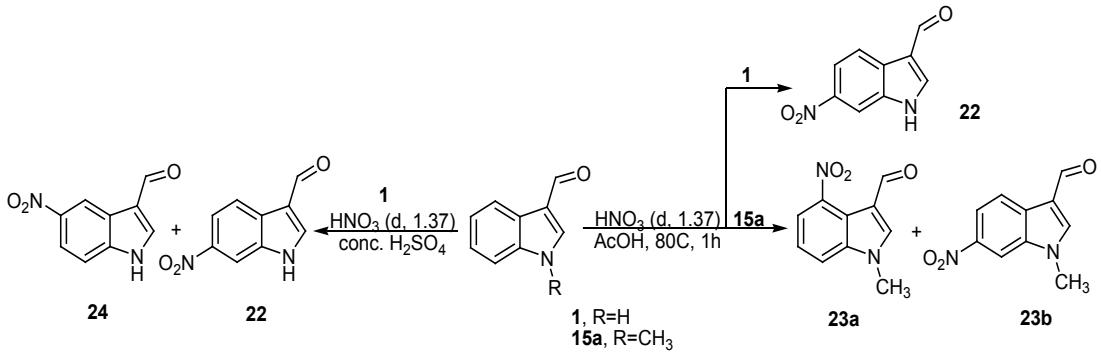
Chlorosulfonation of 1 using chlorosulfonic acid yields 5-chlorosulfonyl-1*H*-indole-3-carboxaldehyde (21) [56] (Scheme 16).



Scheme 16

Nitration

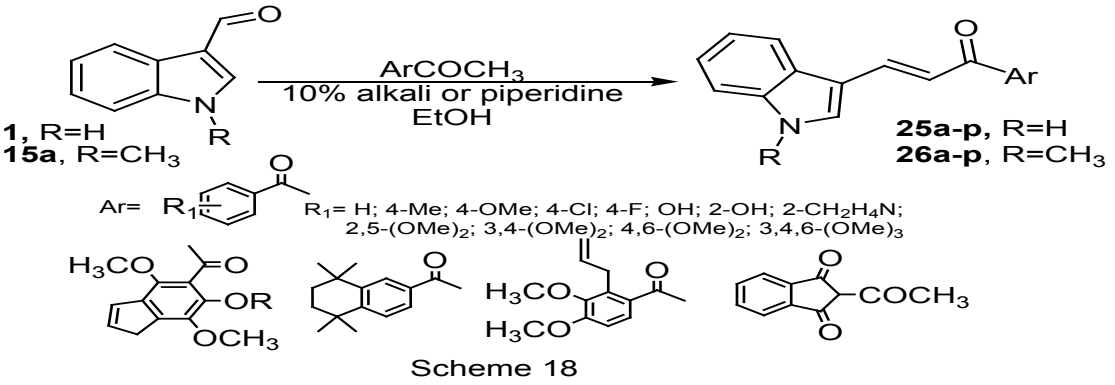
Nitration of 1 using a mixture of nitric acid (d, 1.37) and acetic acid (1: 80 ml) at 80 ºC for 1h affords 6-nitro-1*H*-indole-3-carboxaldehyde (22) [57]. Whereas, nitration of *N*-methyl-1*H*-indole-3-carboxaldehyde (15a) under the above mentioned reaction conditions give a mixture of 4-nitro (23a) 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)

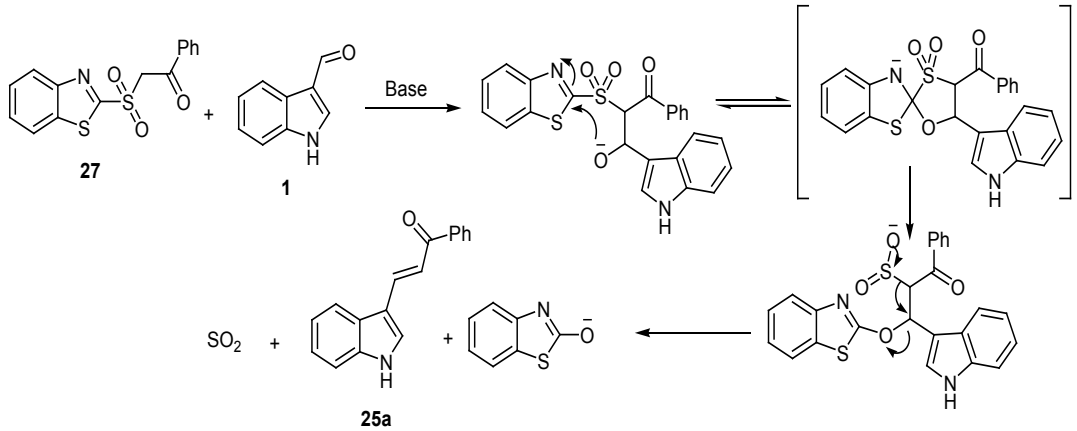
Reaction of 1 and 15a with various aryl methyl ketones in alcohol in the presence of aqueous alkaline medium and/or piperidine leads to the formation of the corresponding α,β-unsaturated ketones 25a-p and 26a-p (Scheme 18), which act as key precursors in the synthesis of many biologically important heterocycles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



Scheme 18

Juliae-Kocienski olefination reaction

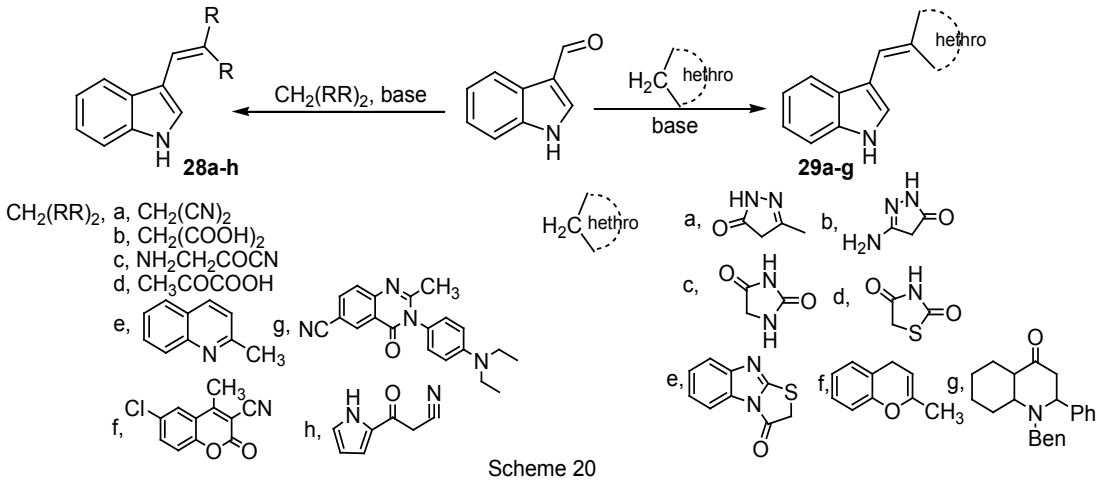
2-(Benzo[d]thiazol-2-ylsulfonyl)-1-phenylethanone (27) has been developed as new reagent for direct Juliae-Kocienski olefination of 1 in the presence of a base to afford α,β-unsaturated ketone 25a [67] (Scheme 19).



Scheme 19. Plausible mechanism for Juliae-Kocienski olefination reaction

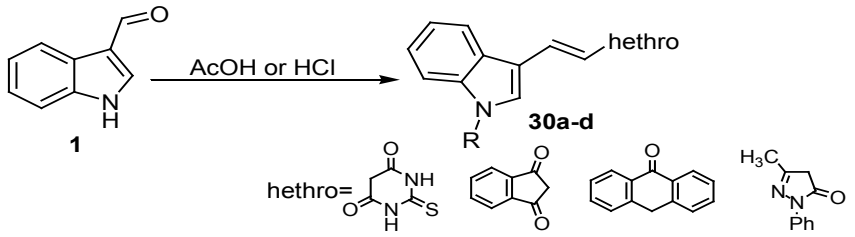
Knoevenagel reaction

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).



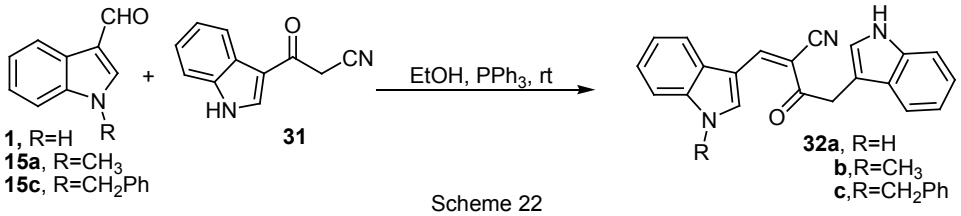
Scheme 20

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).



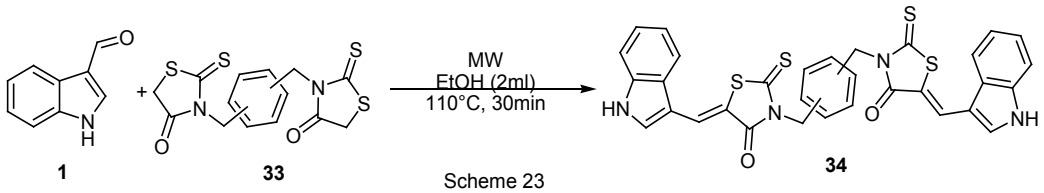
Scheme 21

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

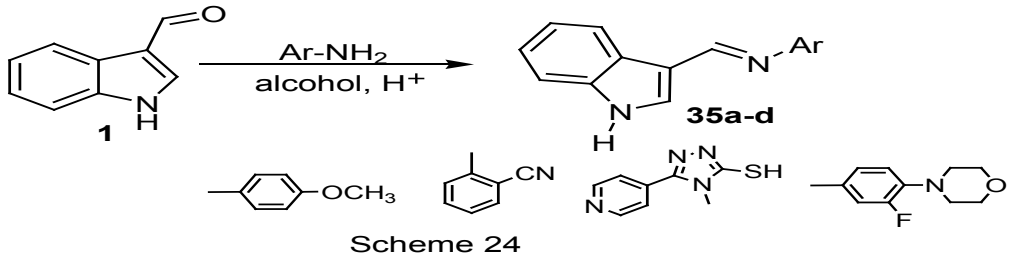
Application of microwave assisted the Knoevenagel condensation of 3,3'-(1,4- or 1,3-phenylenebis (methylene)- bis(2-thioxothiazolidin - 4-ones 33 with 1 to afford the novel bis-(2-thioxo-thiazolidin-4-one) derivatives 34 [86] (Scheme 23).



Scheme 23

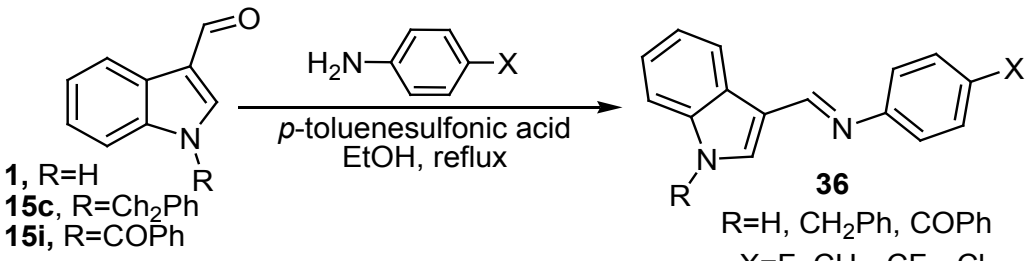
Schiff's bases reaction

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

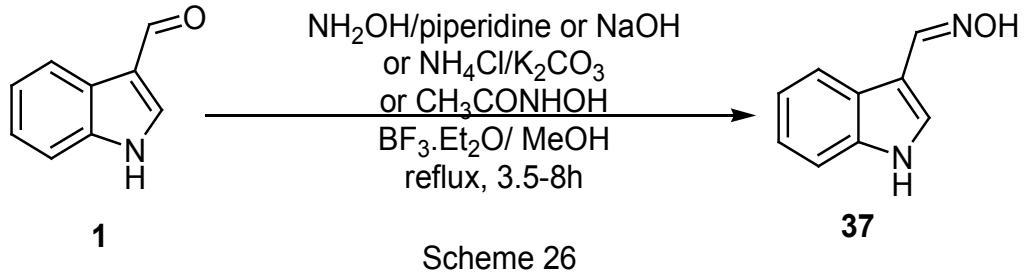
On the other hand, indole Schiff's bases 36 bearing a substituent at N-1 (R= H, CH_2Ph, COPh) in conjunction with $CH{=}N{-}C_6H_4X(p)$ (X= F, Me, CF_3, Cl) at C-3 have been synthesized *via* acid catalyzed reaction of aldehydes 1, 15c, 15i with primary aromatic amines [91]. (Scheme 25).



Scheme 25

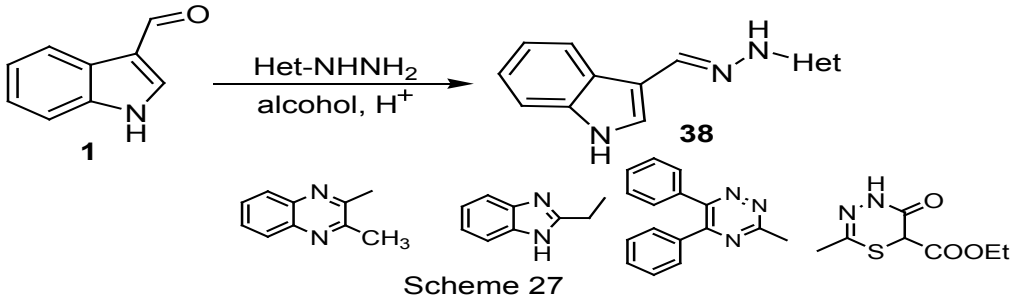
A host of ammonia derivatives other than amines also form similar condensation products with indole aldehydes. Included in this group are hydroxyl amine, hydrazine, carbohdrazide, acetic acid hydrazide, semicarbazide hydrochloride and thiosemicarbazide derivatives. The products of these groups are called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



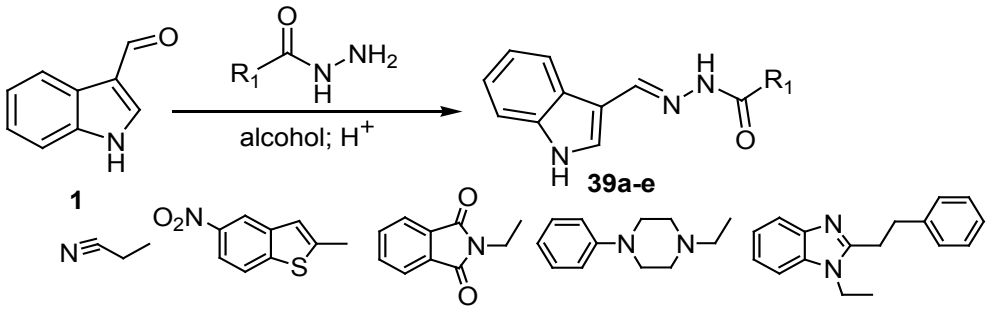
Scheme 26

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).



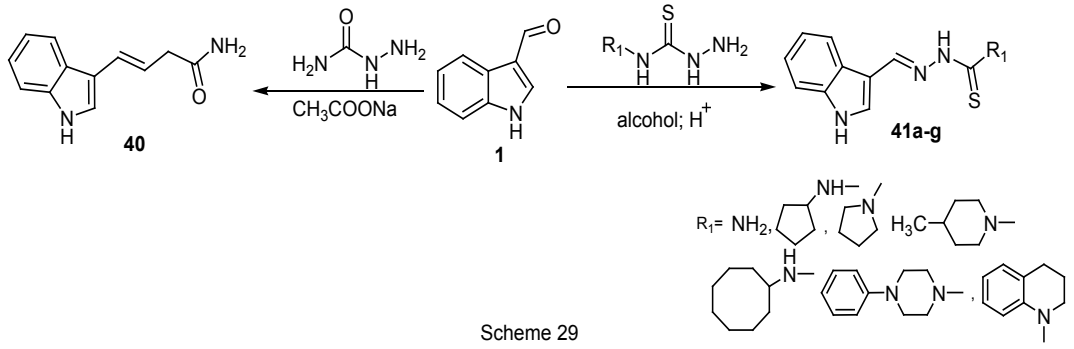
Scheme 27

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

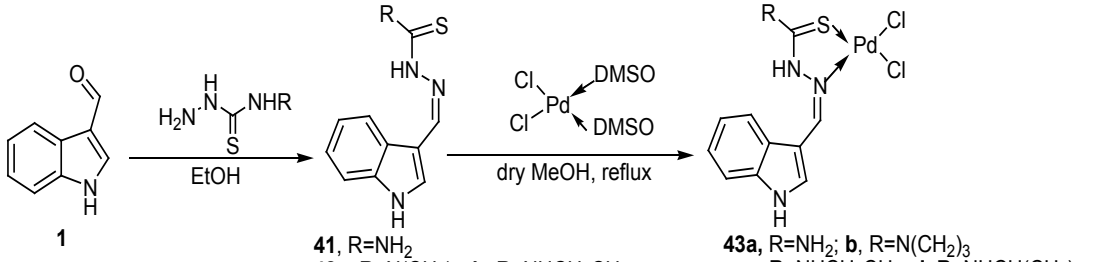
Semicarbazone and thiosemicarbazone derivatives : Reaction of 1 with semicarbazide hydrochloride in the presence of sodium acetate yields the corresponding 1H-indole-3-semicarbazone (40) [107,108]. Whereas, reaction of 1 with thiosemicarbazide or different hetero-thiosemicarbazide derivatives in methanol 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