

### 1H-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 1H-indole-3-carboxaldehyde chemistry *via* discussing different synthetic procedures developed for the preparation of its derivatives, as well sheds the light on the most common reactions of 1H-indole-3-carboxaldehyde derivatives and exploitation of these derivatives as the blocks of many biologically active compounds.

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

#### Introduction

1H-Indole-3-carboxaldehyde (I3C, 1) is a natural compound found in tomato seedling, pea seedling, barley, lupine, cabbage and cotton [1]. 1H-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 ( $\alpha$ -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 (cryptosanguinolentine 1) [12] and muscle relaxant ( $\alpha,\beta$ -cyclopiazonic acid)[13] activities (Fig. 1).

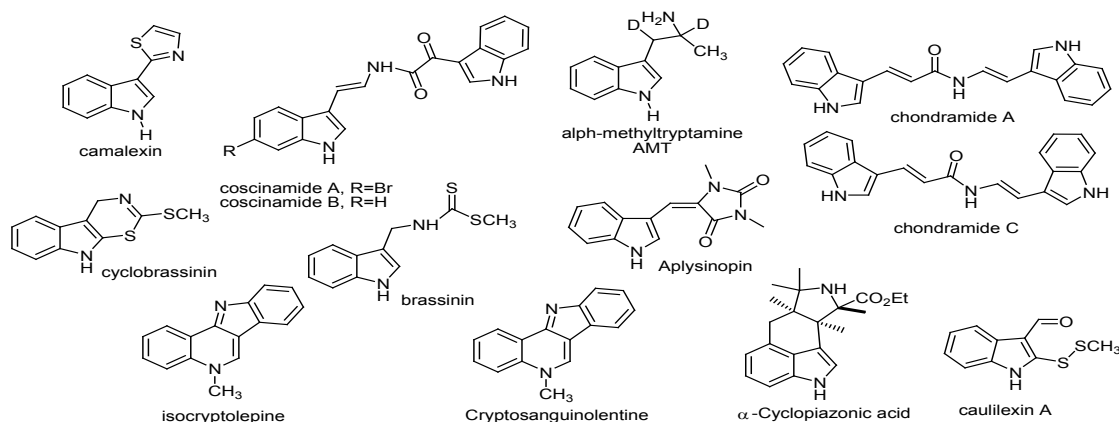


Figure 1. Bioactive natural compounds from 1H-indole-3-carboxaldehyde

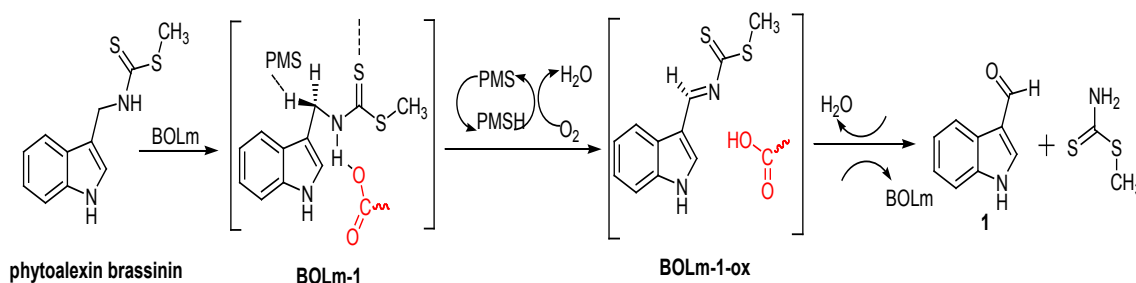
\*Corresponding author e-mail: eslamelsawy@gmail.com

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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).



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

1*H*-Indole-3-carboxaldehyde 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-carboxaldehyde and its derivatives.

#### *Synthetic methods of the preparation of 1H-Indole-3-carboxaldehyde*

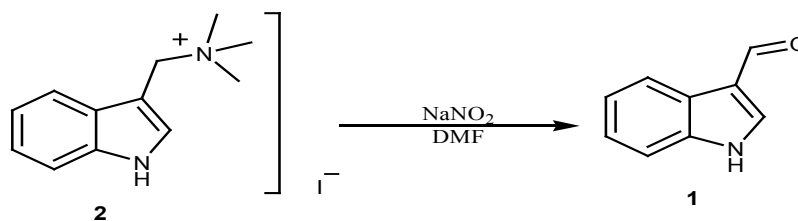
Previously, 1*H*-indole-3-carboxaldehyde (1) has been prepared synthetically either *via* direct formylation of indole using e.g., Reimer-Tiemann reaction (aq. KOH/CHCl<sub>3</sub>) [17], Grignard reaction [18], Vilsmeier Haack reaction (POCl<sub>3</sub>/DMF)

[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<sub>3</sub>·O(C<sub>2</sub>H<sub>5</sub>)<sub>2</sub> 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-carboxaldehyde (1), for an example:

#### *Oxidation of gramine methiodides*

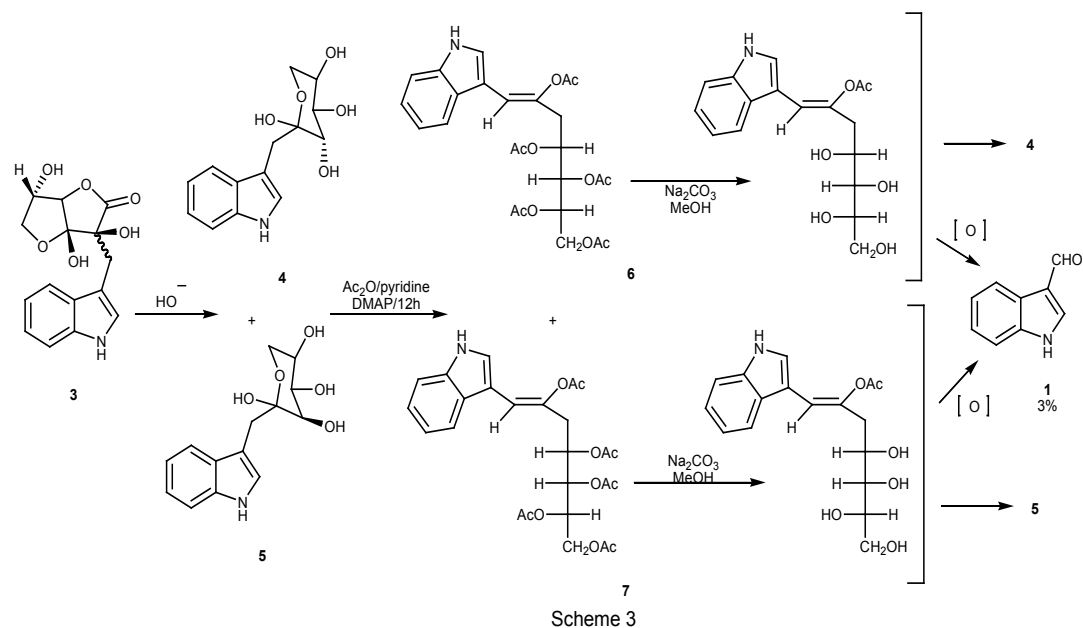
Unusual oxidation of graminemethiodide [1-(1*H*-indol-3-yl)-*N,N,N*-trimethylmethanaminium iodide] (2) using sodium nitrite in *N,N*-dimethylformamide (DMF) produces 1 in 68% yield [24] (Scheme 2).



#### *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

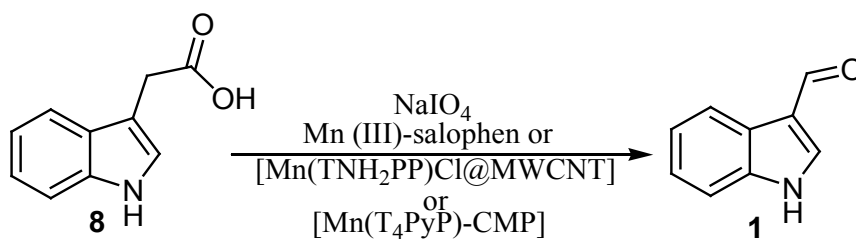
acetic anhydride in pyridine in the presence of 4-dimethylaminopyridine (DMAP) leads to a mixture of 6 and 7, which are separated by column chromatography. Deacetylations of compounds 6 and 7 have been accompanied by the formation of 1 with yield (3%) [25] (Scheme 3).



*Oxidative decarboxylation of indole-3-acetic acid*

Oxidative decarboxylation of indole-3-acetic acid (8) using sodium periodate catalyzed either with manganese(III)-salophen complex, tetrakis(4-aminophenyl) porphyrinato manganese

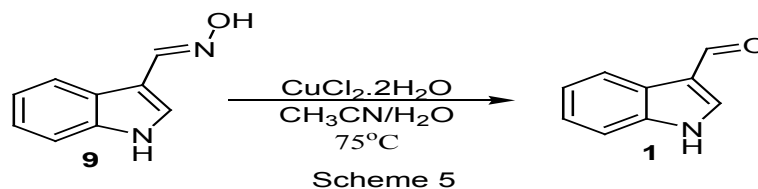
(III) chloride support on functionalized multi-wall carbon nano-tubes or with manganese (III) tetra (4-pyridyl)porphyrin support on cross-linked chloromethylated polystyrene, produces 1 in 78% yield [26] (Scheme 4).



*From oximes*

Treatment of (*E*)-1*H*-indole-3-carbaldehyde oxime (9) with 2 molar equivalents of cupric

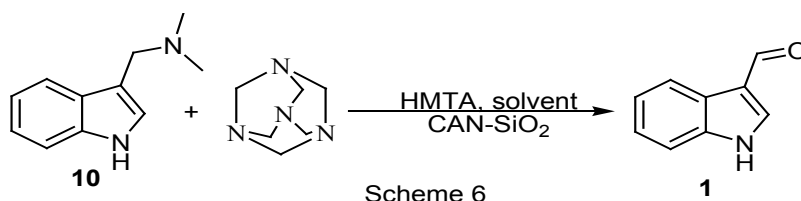
chloride dihydrate under reflux in acetonitrile and water (4:1) leads to the formation of 1 in 88 % yield [27] (Scheme 5).



*From gramine*

The reaction of gramine (10) with formulating species has been generated from hexamethylenetetramine (HMTA) and silica-

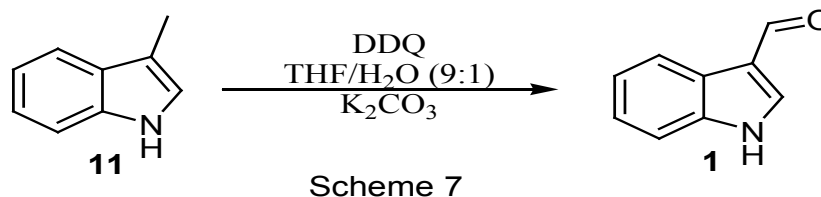
supported ceric ammonium nitrate (CAN-SiO<sub>2</sub>) yields 1 in 81% [28] (Scheme 6).



#### Oxidation of skatole

Oxidation of skatole (3-methylindole) (11) with 2,3-dichloro-5,6-dicyano-p-benzoquinone

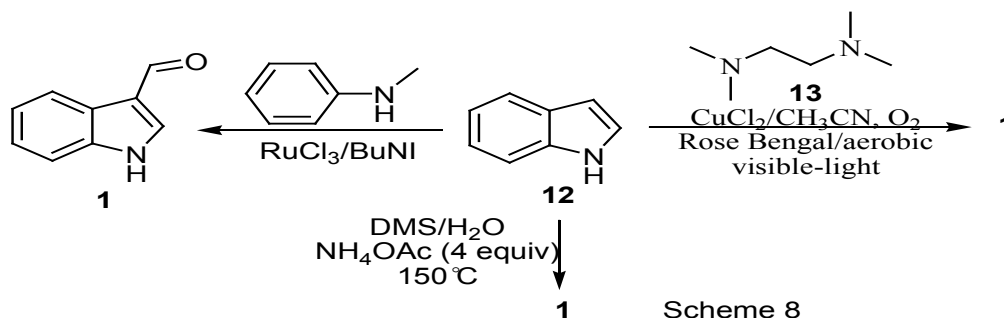
(DDQ) in a mixture of tetrahydrofuran and water (9:1) at room temperature affords 1 in 30% yield [29] (Scheme 7).



#### Formylation of indole

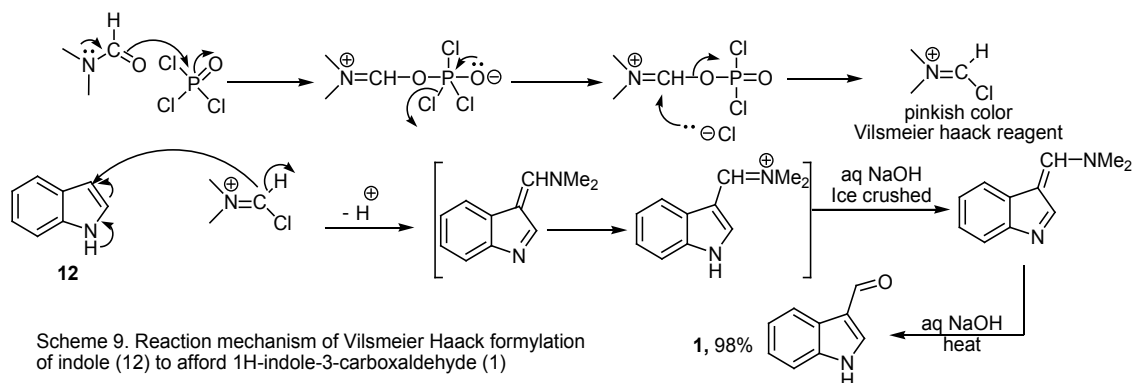
C3-selective formylation of indole (12) has been achieved either by the use of, a) N-methyl aniline in the presence of ruthenium (III) chloride as oxidative catalyst [30]; b) ammonium acetate in dimethylsulfoxide as a source of carbon with water

[31] or ; c) using tetramethylethylene-diamine (TMEDA) (13) as a carbon source catalyzed either by  $\text{CuCl}_2$  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).



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

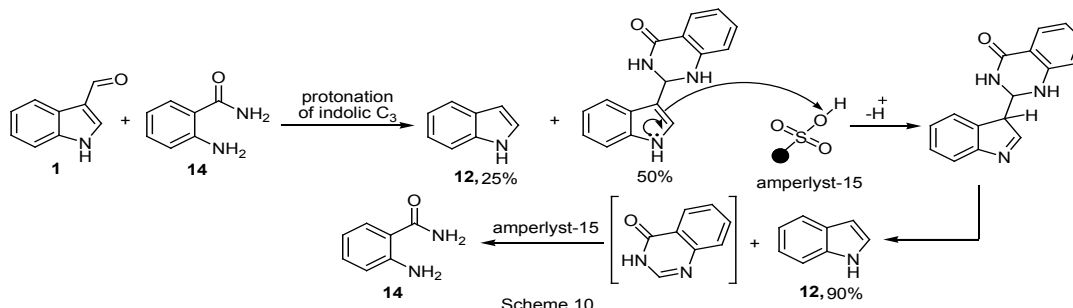
for the preparation of 1 due to it is considerably simple, the yield is almost quantitative, and the aldehyde product is obtained in a state of high purity [19] (Scheme 9).



## Reactions of 1H-Indole-3-carboxaldehyde

## Deformylation

Deformylation of 1H-indole-3-carboxaldehyde (1) has been achieved by the use of anthranilamide (14) in the presence of solid acid heterogeneous



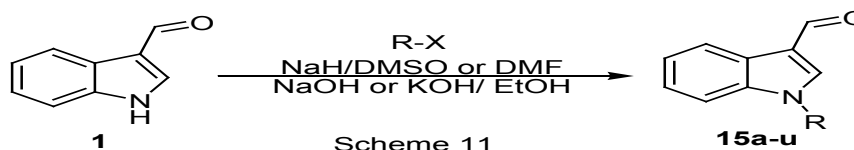
Scheme 10

*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

catalyst. The reaction occurs through quinazolinone intermediate, which is exposed to acid catalyzed cleavage and forms deformylated product, indole (12) [34]. (Scheme 10).

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<sub>3</sub> 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-1H-indole-3-carboxaldehydes.

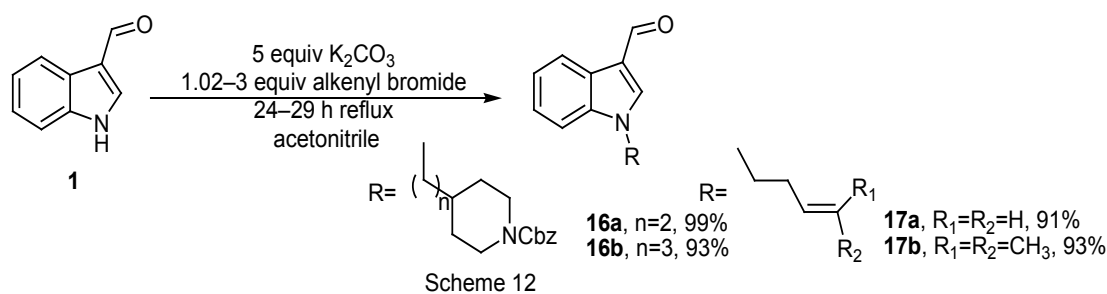
Compd.	R	X	Yield %			M.p. [°C]/color <sup>ref</sup>
			NaOH	KOH	NaH	
15a	CH <sub>3</sub>	I	64	-	-	91-5/ red (p)[36]
15b	CH <sub>2</sub> CH <sub>3</sub>	I	-	-	55	84-6/buff (p)[37]
15c	CH <sub>2</sub> Ph	Cl	-	93	97	102-4/orange (o)[35,38]
15d	CH <sub>2</sub> PhCl <sub>(4)</sub>	Cl	-	-	89	117-9/brown (p)[39]
15e	CH <sub>2</sub> Ph F <sub>(3)</sub>	Br	-	39	-	127-9 [40,41]
15f	CH <sub>2</sub> Ph F <sub>(4)</sub>	Cl	-	-	76	116-8/brown (p)[39]
15g	CH <sub>2</sub> PhCl <sub>2(2,4)</sub>	Cl	-	-	87	121-3/brown (p)[39]
15h	CH <sub>2</sub> Ph F <sub>2(2,4)</sub>	Cl	-	-	84	120-2/brown (p)[39]
15i	COPh	Cl	-	84	76	177-9/purple (p)[35,42]
15j	COPh-Cl <sub>(2)</sub>	Cl	-	-	68	162-4/purple (p)[43]
15k	COPh-Cl <sub>(4)</sub>	Cl	65	-	73	154-6/purple (p)[42, 44]
15l	SO <sub>2</sub> CH <sub>3</sub>	Cl	-	85	-	127-9/purple (p)[35]
15m	SO <sub>2</sub> Ph	Cl	94	95	97	156-8/purple (p)[35,45]
15n	SO <sub>2</sub> Ph Br <sub>(4)</sub>	Cl	-	75	-	112-4/purple (p)[43]
15o	SO <sub>2</sub> PhCl <sub>(4)</sub>	Cl	-	76	-	113-5/purple (p)[43]
15p	COCH <sub>3</sub>	Br	75	68	-	162-4[35]
15q	COOCH <sub>2</sub> CH <sub>3</sub>	Br	92	-	-	61-3[46]
15r	CH <sub>2</sub> CH <sub>2</sub> Cl	Cl	-	-	80	188-190[47]
15s	CH <sub>2</sub> (CH <sub>2</sub> ) <sub>2</sub> N <sub>3</sub>	Cl	-	-	53	165-7[47]
15t	CH <sub>2</sub> (CH <sub>2</sub> ) <sub>3</sub> Br	Br	-	-	62	pale yellow (o)[48]
15u	CH <sub>2</sub> CH=C(CH <sub>3</sub> ) <sub>2</sub>	Br	-	-	92	80-2/pale yellow (c)[49]

(p): powder; (o): oil; (c): crystals

(-): This experiment was not carried out.

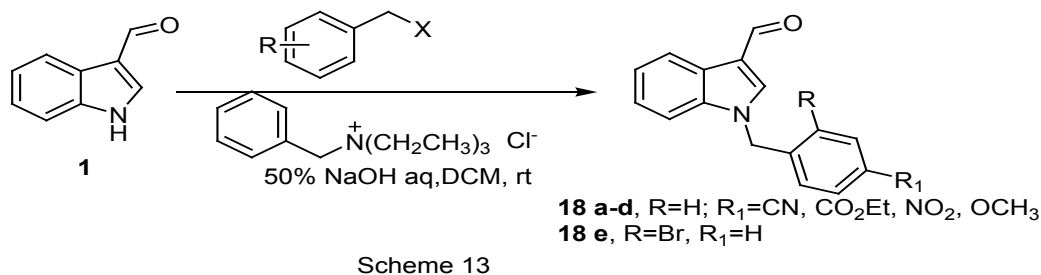
Some N-alkylation reactions of aldehyde **1** have not been completed under the above mentioned conditions, so the researchers revealed promising alternative bases and conditions [50,51]. For an example, N-alkylation of **1** by benzyl-4-(2-iodoethyl)-1-piperidine carboxylate, benzyl-4-(2-iodopropyl)-1-piperidine 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).



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

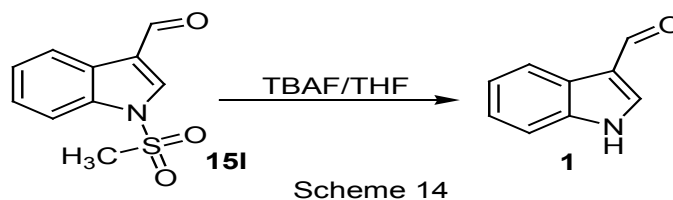
phase-transfer catalytic (PTC) conditions utilizing triethylbenzyl-ammonium chloride and 50% w/v aqueous NaOH solution in dichloromethane [52] (Scheme 13).



#### 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

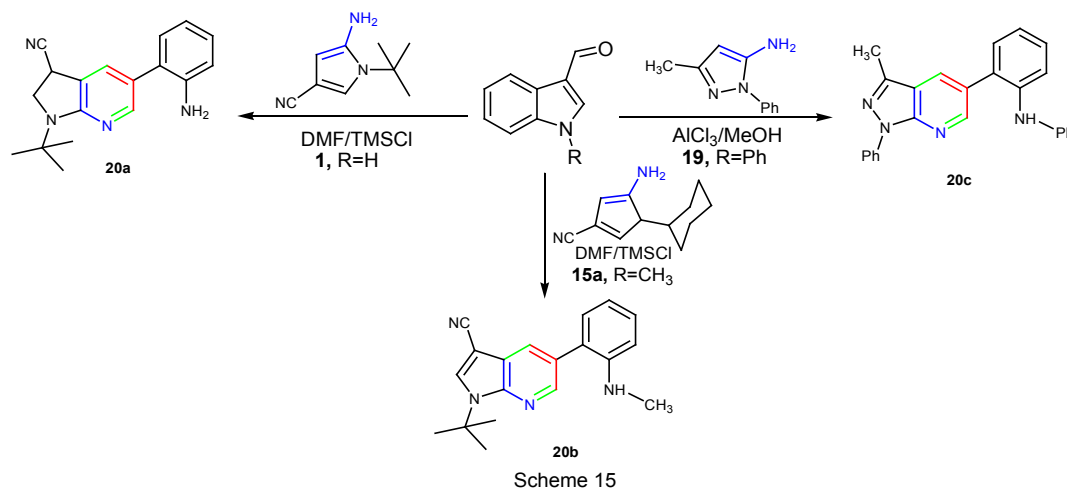
conditions (long time, strongly basic medium) [53]. A new mild and neutral deprotection of N-methylsulfonyl-indole-3-carboxaldehyde (**15I**) using tetrabutylammonium fluoride (TBAF) in THF has been reported [54] (Scheme 14).



#### 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

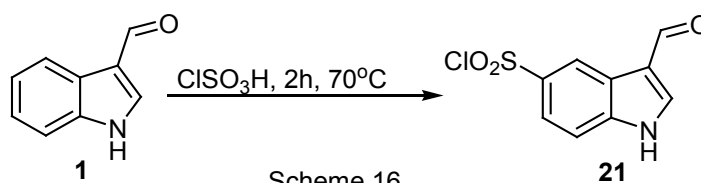
and subsequent cyclocondensation to give heteroannulated pyridines **20a-c**, which can be regarded as purine isosteres [55] (Scheme 15).



### Chlorosulfonation

Chlorosulfonation of 1 using chlorosulfonic

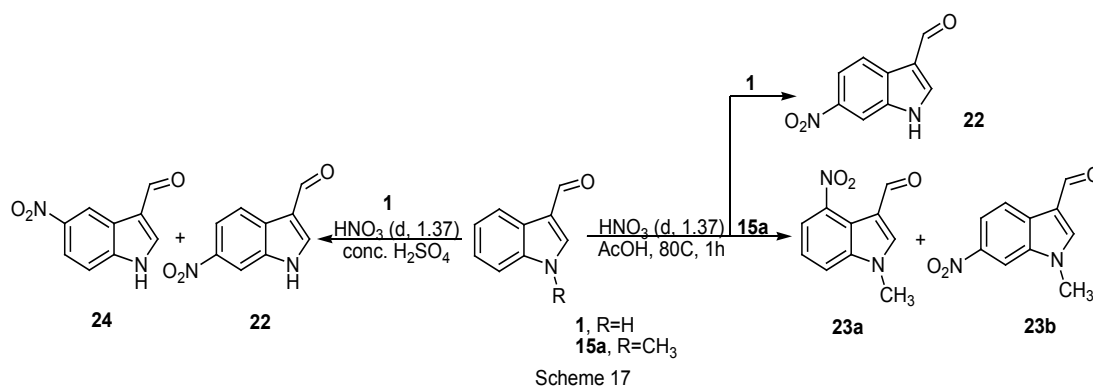
acid yields 5-chlorosulfonyl-1*H*-indole-3-carboxaldehyde (21) [56] (Scheme 16).



### Nitration

Nitration of 1 using a mixture of nitric acid (d, 1.37) and acetic acid (1: 80 ml) at 80 °C 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

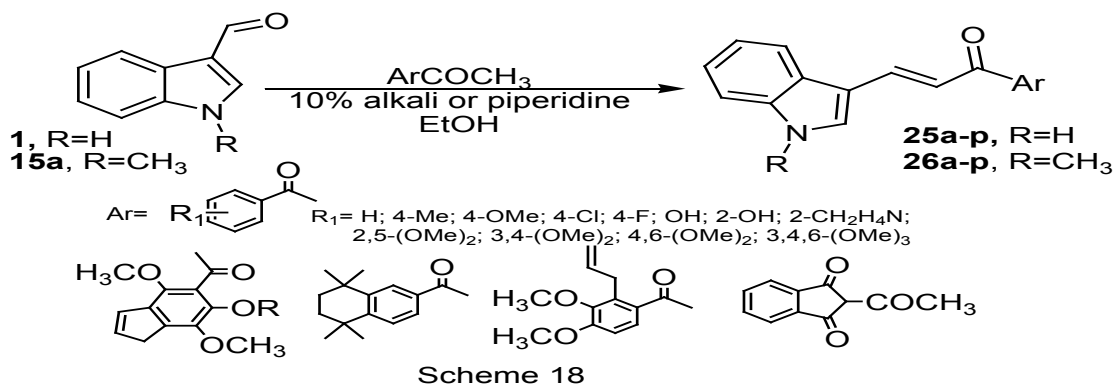
mentioned reaction conditions give a mixture of 4-nitro (23a) and 6-nitro-*N*-methyl-1*H*-indole-3-carboxaldehydes (23b) [57]. On the other hand, nitration of 1 by the use of nitric acid and sulfuric acid give a mixture of 5-nitro (24) and 6-nitro-1*H*-indole-3-carboxaldehydes (22) [58] (Scheme 17).



### Claisen-Schmidt reaction ( $\alpha,\beta$ -unsaturated ketones)

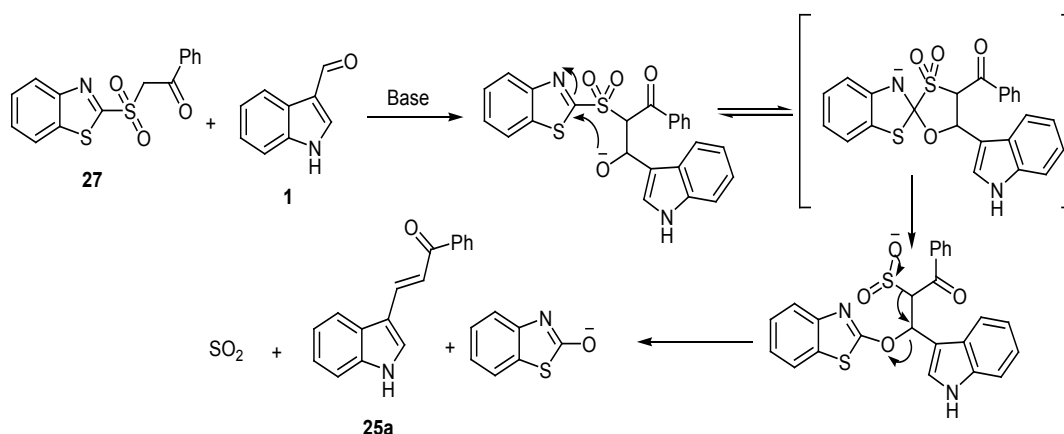
Reaction of 1 and 15a with various aryl methyl ketones in alcohol in the presence of aqueous alkaline medium and/or piperidine leads to the formation of the corresponding  $\alpha,\beta$ -

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].



*Julia-Kocienski olefination reaction*  
2-(Benzo[d]thiazol-2-ylsulfonyl)-1-phenylethanone (**27**) has been developed as new

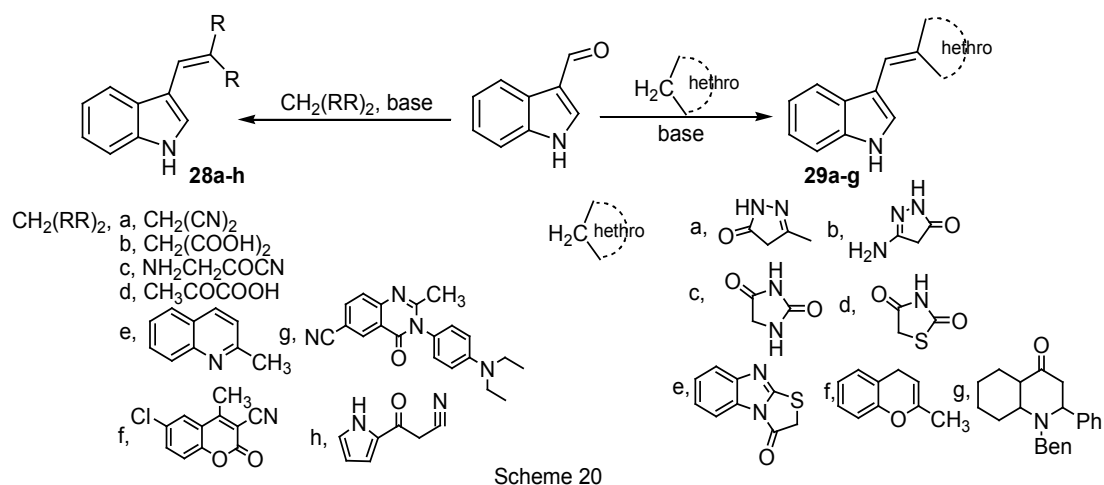
reagent for direct Julia-Kocienski olefination of **1** in the presence of a base to afford  $\alpha,\beta$ -unsaturated ketone **25a** [67] (Scheme 19).



*Knoevenagel reaction*

Base catalyzed reaction of **1** either with the active methylene groups of aliphatic or heterocycle compounds (Knoevenagel reaction) leads to the

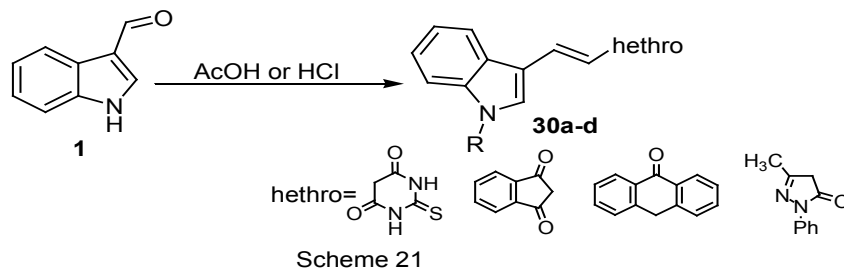
formation of the corresponding Knoevenagel products **28a-h** and **29a-g**, respectively [40, 43, 68-81] (Scheme 20).





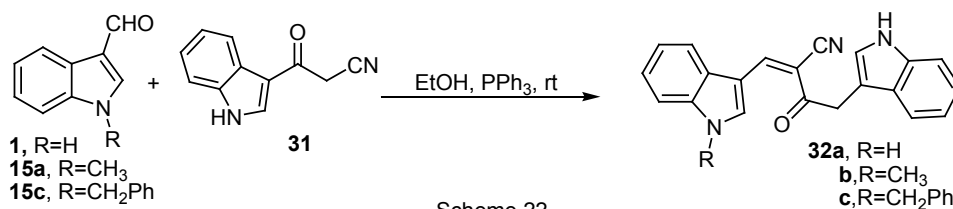
However, some cases of Knoevenagel condensation of **1** have been carried out in the presence of acid such as hydrochloric acid and/or acetic acid, for example, reaction of **1** with

2-thioxo-dihydro-pyrimidine-4,6-dione, 8,2 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).



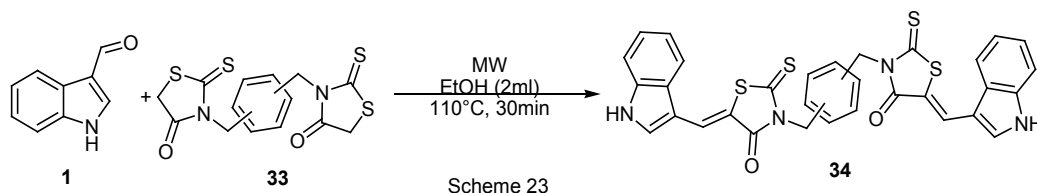
Triphenylphosphine (TPP) has been found to be an efficient catalyst for the Knoevenagel condensation of **1**, **15a**, **15c** with

3-cyanoacetylintole (31) to give 3-(1-substituted-1H-indol-3-yl)-2-(1H-indole-3-carbonyl) acrylonitriles **32a-c** [85] (Scheme 22).



Application of microwave assisted the Knoevenagel condensation of 3,3'-(1,4- or 1,3-phenylenebis (methylene)- bis(2-

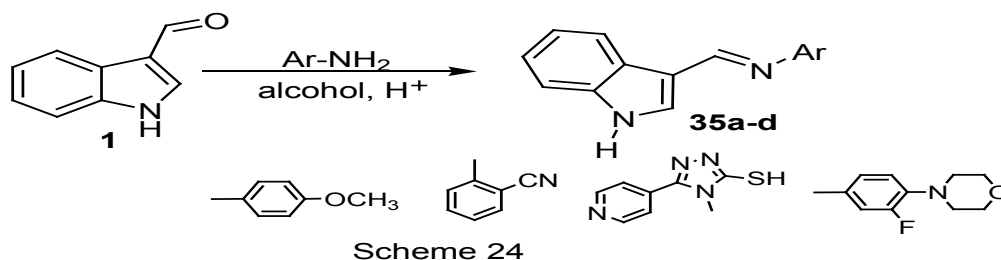
thioxothiazolidin - 4-ones **33** with **1** to afford the novel bis-(2-thioxo-thiazolidin-4-one) derivatives **34** [86] (Scheme 23).



#### Schiff's bases reaction

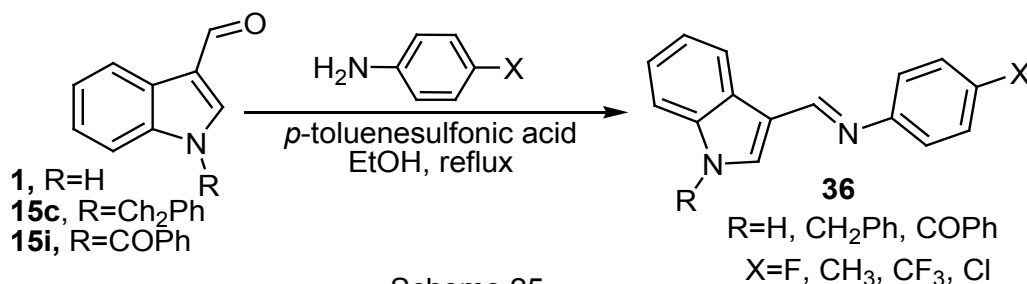
Condensation of 1H-indole-3-carboxaldehyde with primary amine in the presence of an electrophilic catalyst leads to the formation of aldimines =CH=N- (Schiff's bases). For example, the reaction of **1** with amino compounds, namely

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).



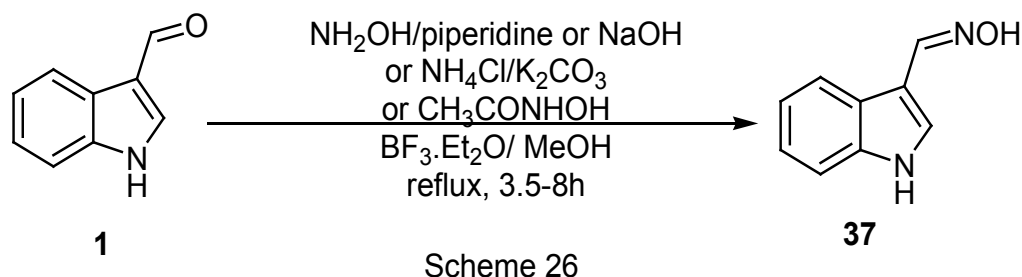
On the other hand, indole Schiff's bases 36 bearing a substituent at N-1 (R= H, CH<sub>2</sub>Ph, COPh) in conjunction with CH=N-C<sub>6</sub>H<sub>4</sub>X(p) (X= F, Me,

CF<sub>3</sub>, Cl) at C-3 have been synthesized *via* acid catalyzed reaction of aldehydes 1, 15c, 15i with primary aromatic amines [91]. (Scheme 25).



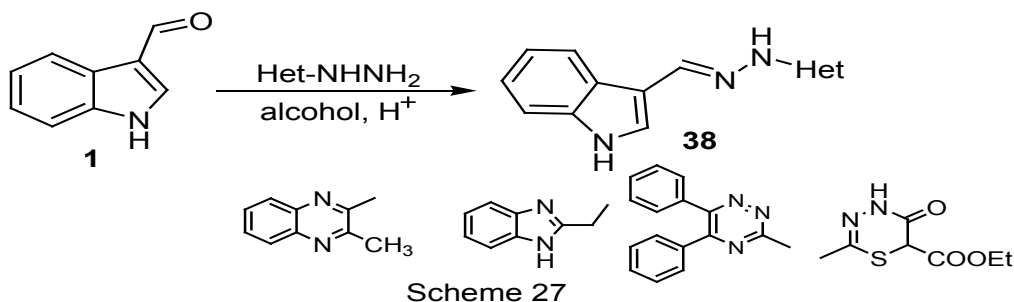
A host of ammonia derivatives other than amines also form similar condensation products with indole aldehydes. Included in this group are hydroxyl amine, hydrazine, carbodrazide, acetic acid hydrazide, semicarbazide hydrochloride and thiosemicarbazide derivatives. The products of these groups are called 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<sub>3</sub>·OEt<sub>2</sub> as a catalyst [95] (Scheme 26).



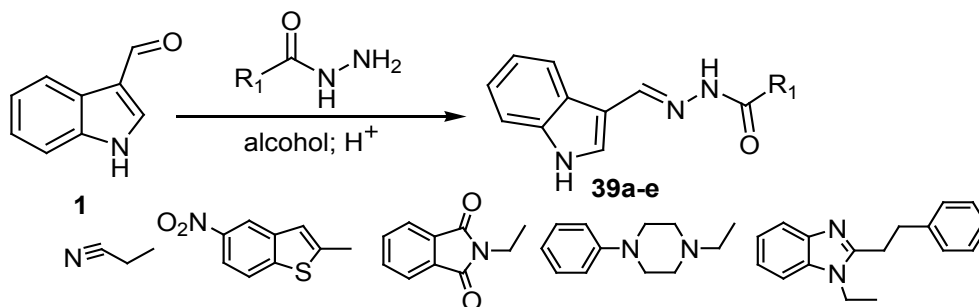
*Hydrazones (Hydrazine derivatives)* : Acid catalyzed reaction of 1 with hydrazine hydrate, [96,97] and also with some hetero-hydrazine derivatives, namely (3-methyl-quinoxalin-2-yl)-hydrazine, [98] (1H-benzoimidazol-2-

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).



**Hydrazone derivatives** : The reaction of aldehydes 1, 15a, 15c, 15i and 58 with carbohydrazide or acetic acid hydrazides derivatives, namely 2-cyanoacetic acid hydrazone, [102] 5-nitro-benzo-[b]thiophene-2-carboxylic acid hydrazone, [103] 2-(1,3-dioxoisindolin-2-yl)

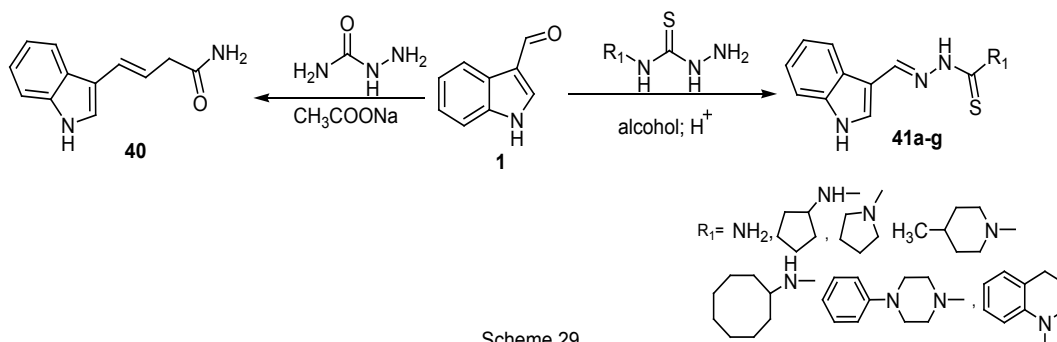
acetohydrazone, [104] (2-phenyl-sulfanylmethyl-benzoimidazol-1-yl)-acetic acid hydrazone [105] and (4-phenyl-piperazin-1-yl) acetic acid hydrazone [106] has been carried out in alcohol and in the presence of acid as a catalyst to yield the corresponding hydrazone derivatives (39a-e) (Scheme 28).



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 thiosemicarbazone derivatives 41a-g [109-111] (Scheme 29).

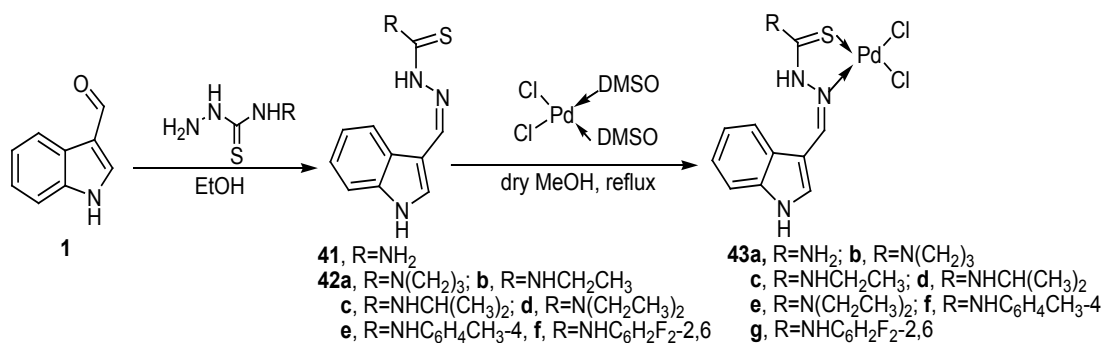


Scheme 29

#### 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<sub>2</sub>] complexes 43a-g [112] (Scheme 30).



Scheme 30







































