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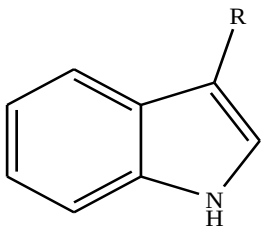
3-Substituted indole: A review

Nitish Kumar and Amrita Parle

Abstract
3-substituted indole is a heterocyclic compound having formula C_8H_6NR and has indole as parent moiety. Indole and its derivatives have vital role in medicinal chemistry. They are attaining considerable importance due to their wide range of pharmacological activities *viz*: antiviral, anti-HIV, antidepressant, antimicrobial, analgesic etc. Indoles can be obtained from natural sources and can also be synthesized chemically. This review deliberates on different synthetic methods of 3-substituted indole derivatives.

Keywords: Substituted indole, medicinal chemistry, antidepressant

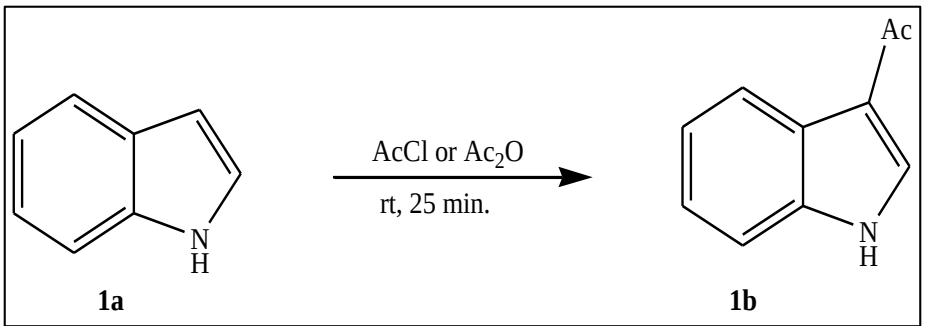
Introduction
Indole is nothing but benzpyrole. It has pyrrole and benzene ring fused at α, β-position. Indole is an important heterocyclic system as it is building block in proteins in the form of amino acid tryptophan. Indole is the parent moiety in drugs like indomethacin, zafirlukast as well as biologically active compounds from plants like strychnine and LSD (Lysergic acid diethylamide). Most indoles are quite stable in air, except 2-methylindoles which are auto oxidized easily even in a dark brown bottle [1].
3-Substituted indole is an aromatic heterocyclic compound having formula C_8H_6NR. It has indole as parent moiety with aromatic or aliphatic substitution at 3rd position. They are widely explored by scientists and found to contain various medicinal activities. The substitutions can be acetyl, methyl, phenyl, carboxy, carbonyl, ester, amido, amino, cyno etc. These indoles are synthesized by different methods and each method has its own advantages/disadvantage like improved yield, decreased time of synthesis, improved purity of product, less rigorous reaction conditions etc. This review covers on different synthetic methods, pharmacological activities, ongoing clinical trials and current marketed preparations of 3-substituted indole derivatives.



3-substituted indole

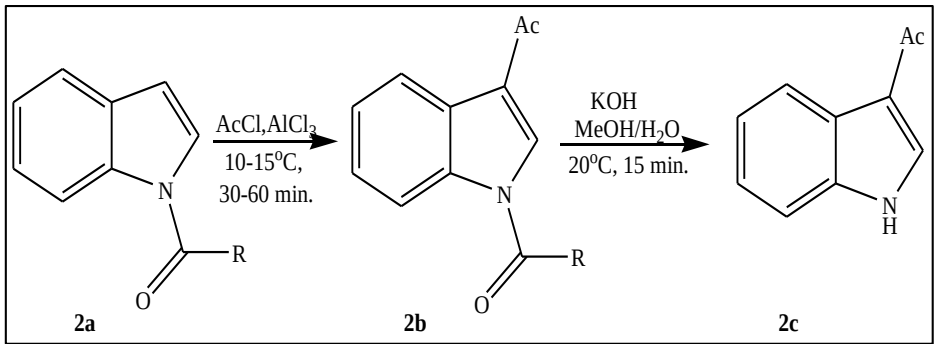
Synthesis
The synthesis of 3-substituted indole is covered under different headings:
- 3-Acetylindole
- 3-Substitueted acetyl indole
- 3-Methylindole

Acetylindole
Scheme 1
Indole (1a) undergoes Friedal-Crafts acetylation with acetyl chloride or acetic anhydride at room temperature and gives 3-acetylindole (1b) within 25 minute, in presensce of indium trichloride as catalyst in 65% yield. Various catalysts such as diethyl aluminium chloride, aluminium chloride, and indium triflate, tin tetrachloride, zinc chloride, vinyl acetate or styrene, perchloric acid, and silicon tetrachloride have been used for the acetylation of indole but the yields are very low [2].



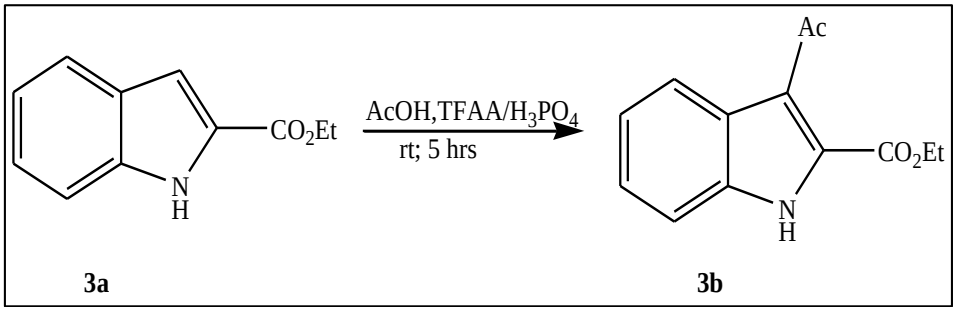
Scheme 2

1-acylindoles (2a) is stirred with acetyl chloride in presence of aluminium chloride as a catalyst at 10-15 ºC for 30-60 minutes to give 1-acyl-3-acetylindoles (2b) in 85% yield. Hydrolysis of 1-acyl-3-acetylindoles (R =Methyl) with potassium hydroxide (KOH) in aqueous methanol (MeOH) at 20 ºC gives 3-acetylindole (2c) in 15 minute. Good yield (83%) of **2c** in less time is the advantage of this method [3].



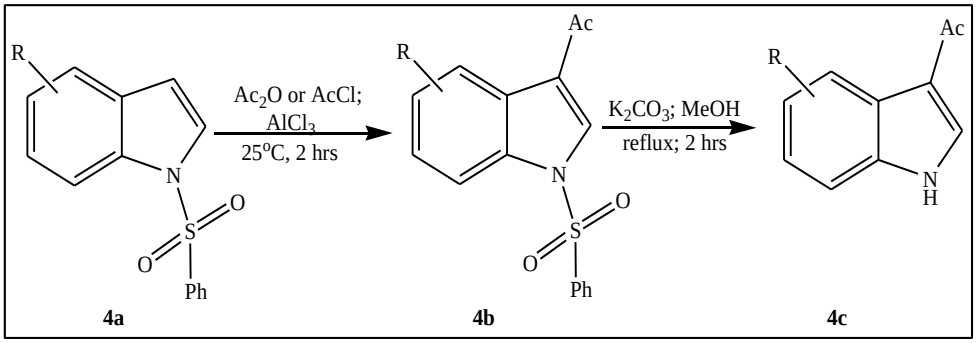
Scheme 3

Ethyl indole-2-carboxylates (3a) react with acetic acid in the presence of trifluoroacetic anhydride (TFAA) and phosphoric or polyphosphoric acid (PPA) at room temperature (rt) for 5 hours to give ethyl 3-acetylindole-2-carboxylates (**3b**). It is easy process with short reaction time and acceptable moderate yield [4].



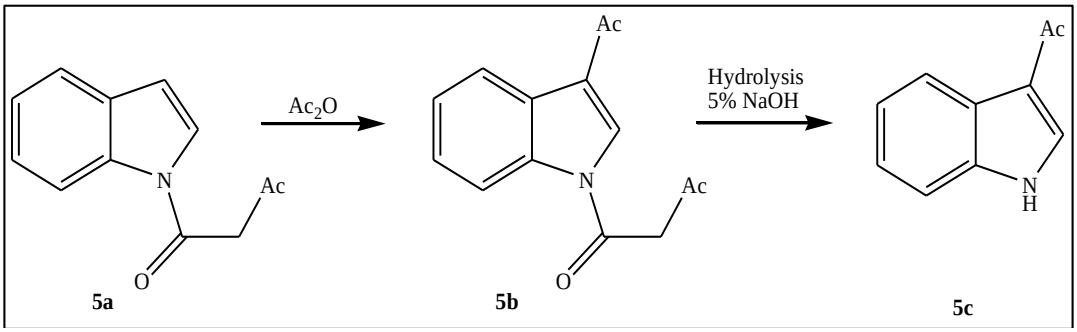
Scheme 4

1-(phenylsulfonyl) indoles (4a) undergo Friedel-Crafts acetylation with acetic anhydride or acetyl chloride in presence of aluminium chloride, at 25 ºC for 2 hours to give 3-acyl-1-(phenylsulfonyl) indoles (4b). Prepared 3-acyl-1-(phenylsulfonyl) indoles (4b) are subjected to base hydrolysis in presence of potassium carbonate & methanol and then refluxed under nitrogen for 2 hours to obtain 3-acylindoles (4c) in 79-96% yields. It is simple method with good yield [5].



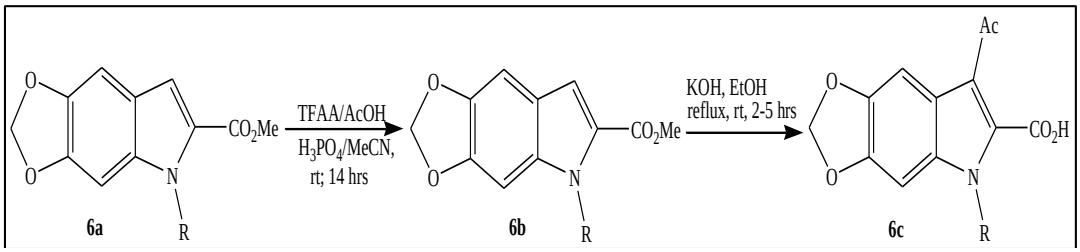
Scheme 5

N-acetoacetylindole (5a) is heated with acetic anhydride to give 1-acetoacetyl-3-acetylindole (5b) which on hydrolysis with 5% NaOH gives 3-acetylindole (5c) in 13% yield. Low yield is main disadvantage of this method [6].



Scheme 6

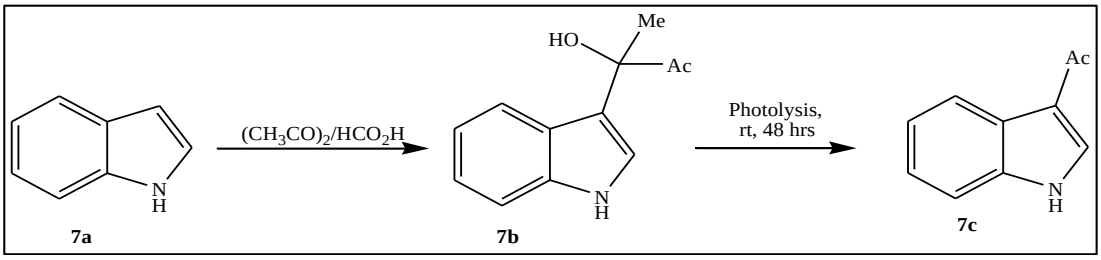
Methyl 5-alkyl-5H-[1,3] dioxolo [4,5-f] indole-6-carboxylates (6a) are treated with a mixture of trifluoroacetic anhydride(TFAA), glacial acetic acid and 85% phosphoric acid (H_3PO_4) in acetonitrile at room temperature for 14 hours to obtain the corresponding methyl 7-acetyl-5-alkyl-5H-[1,3] dioxolo [4,5-f] indole-6-carboxylate (6b) which on alkaline hydrolysis and reflux for 2-5 hours at room temperature gives 7-acetyl-5-alkyl-5H-[1,3] dioxolo[4,5-f]indole-6-carboxylic acid(6c). Lengthy process time is the disadvantage of this method [7].



R= Me, Et

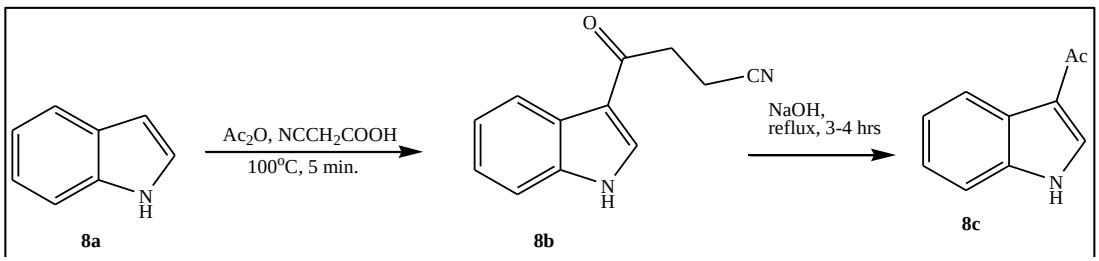
Scheme 7

When indole (7a) is treated with biacetyl in the presence of formic acid, it is converted into 3-(1-acetyl-1-hydroxyethyl) indole (7b). Photolysis of 3-(1-acetyl-1-hydroxyethyl) indole (7b) for 48 hours, at room temperature under nitrogen converts it into 3-acetyl indole (7c) in 77% yield. Long reaction time is the disadvantage of this method [8].



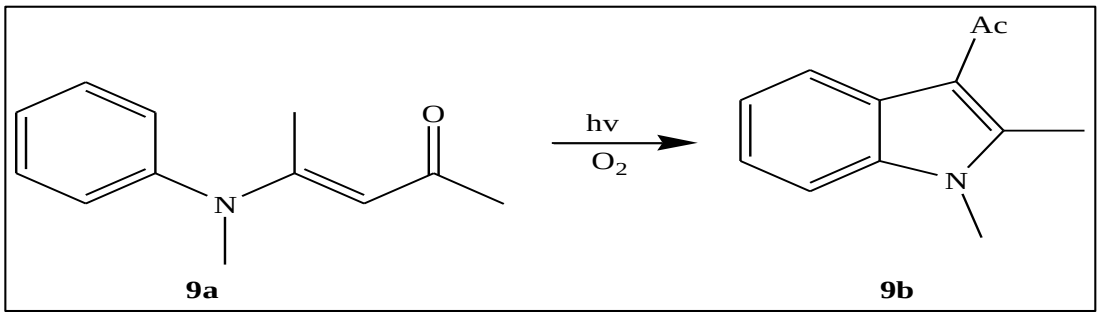
Scheme 8

Treatment of indole (8a) with cynoacetic acid in presence of acetic anhydride at 100 ºC for 5 min. gives 3-cynoacetylindole (8b). Prepared 8b is refluxed with aqueous sodium hydroxide (5%) for 3-4 hours to give 3-acetylindole (8c) in 96% yield. High yield and short reaction time is the advantage of this method [9].



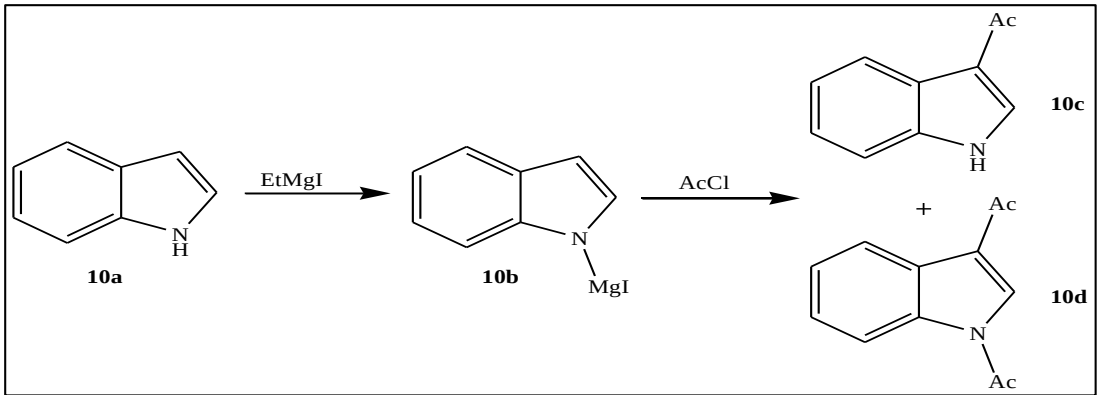
Scheme 9

Irradiation of 4-(N-methylanilino) pent-3-en-2-one (9a) with Pyrex-filtered light (cutoff - 280nm) in oxygen atmosphere leads to formation of 3-acetyl-1,2-dimethylindole (9b) in 35% yield. Low yield of 9b is the disadvantage [10].



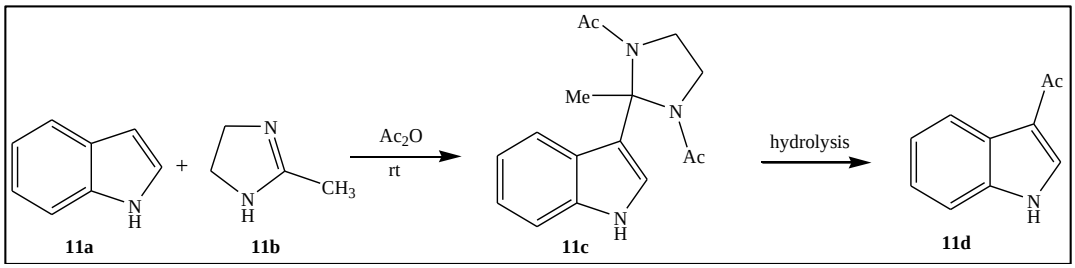
Scheme 10

Indole (10a) reacts with Ethylmagnesium iodide in dry ether to form indolylmagnesium iodide (10b) which further reacts with acetyl chloride to produce a mixture of 3-acetylindole (10c) and 1,3-diacetylindole (10d). Separation of product mixture of 10c and 10d is quite difficult [11].



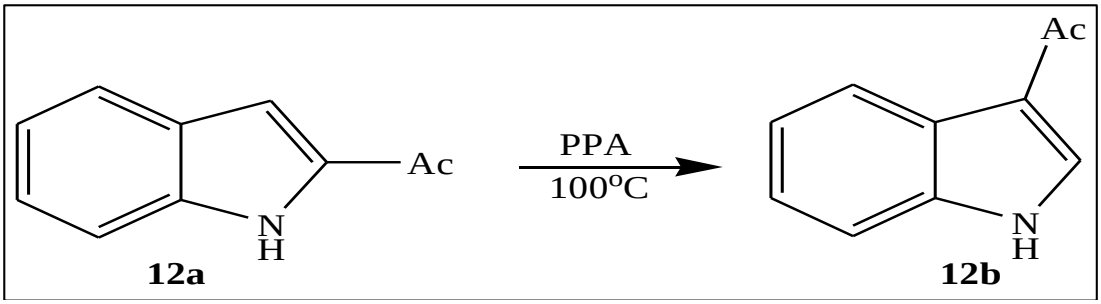
Scheme 11

Treatment of indole (11a) with 2-methyl-4,5-dihydroimidazole (11b) in presence of acetic anhydride at room temperature (rt) gives *N*,*N'*-diacetyl-2-methyl-2-(3-indolyl)-imidazolidine (11c) in 85-95% yeild, which is readily hydrolyzed to 3-acetylindole (11d) in presence of 5% sodium hydroxide in ethanol/water. It is simple method for the preparation of 11d [12].



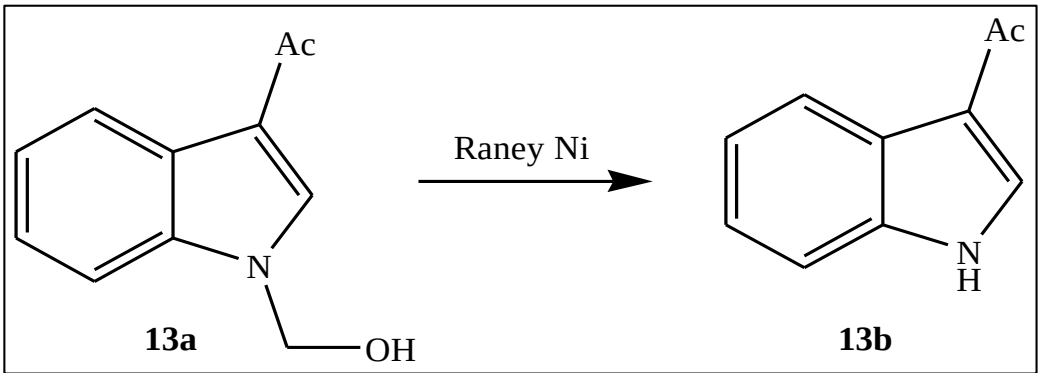
Scheme 12

3-Acetylindole (12b) is produced by rearrangement of 2-acetylindole (12a) in presence of polyphosphoric acid (PPA) at 100 °C. The main disadvantage is very low yield [13].



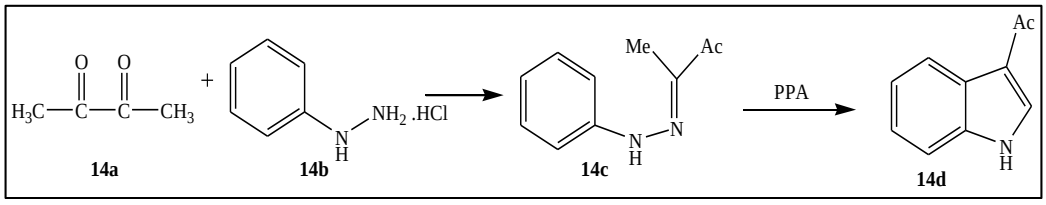
Scheme 13

Hydrogenation of 1-hydroxymethyl-3-acetylindole (13a) in presence of Raney Ni in ethanol (EtOH) gives 3-acetylindole (13b) in 82% yield. It is simple method to synthesize 13b with good yield [14].



Scheme 14

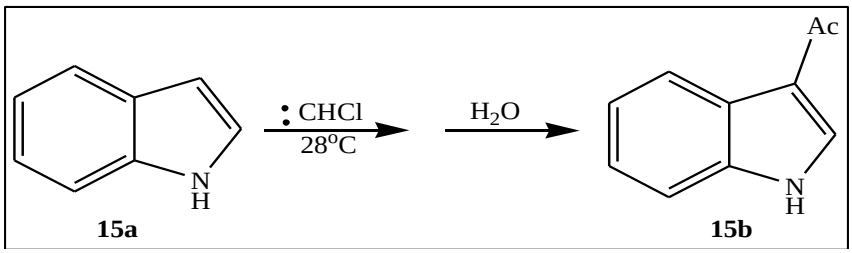
Diacetyl (14a) and phenyl hydrazine hydrochloride (14b) react to give 3-(2-phenylhydrazono) butan-2-one (14c) which on heating with polyphosphoric acid affords 3-acetylindole (14d) in 52% yield [15].



Scheme 15

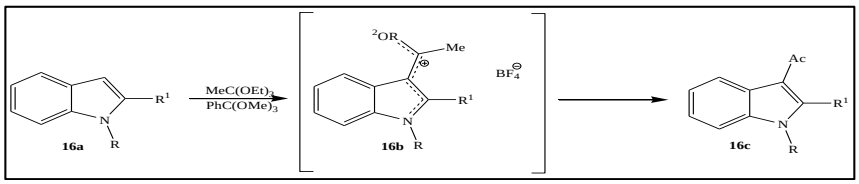
Monochlorocarbene forms in situ by reaction of indium trichloride and dichloromethane. Indole (15a) in presence of Monochlorocarbene undergoes several rearrangements at 28 °C to form 1-chloro-1-(3-indolyl) ethane and this on hydrolysis gives 3-acetylindole (15b). Low yield is obtained [16].

$InCl_3 + CH_2Cl_2 \longrightarrow$: CHCl



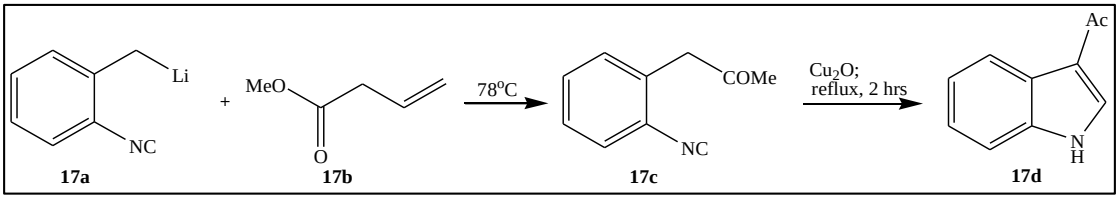
Scheme 16

Acylation of 1,2-disubstituted indoles (16a) with 1,1,1-triethoxyethane 1-(trimethoxymethyl) benzene in presence of fluoroboric acid(HBF_4) proceeds with high regioselectivity to give acylindoletetrafluoroborates (16b) in 45-95% yields. Hydrolysis of 16b gives 3-acetylindoles (16c) in the yield of 95-98%. 16c is synthesized with high regiocontrol in high yield [17].



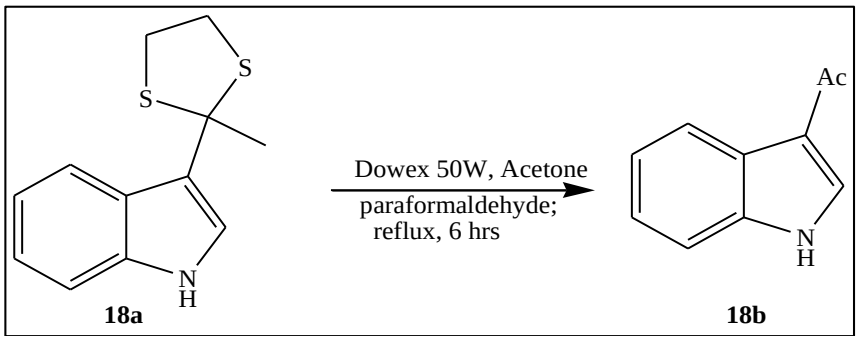
Scheme 17

Reaction of (2-isocyanobenzyl) lithium (17a) with methyl but-3-enoate (17b) at 78 °C produces 1-(2-isocyanophenyl) propan-2-one (17c), which is followed by reaction with cuprous oxide and reflux for 2 hours under nitrogen to obtain 3-acetylindole (17d). Less reaction time with acceptable yield is main advantage of this process [18].



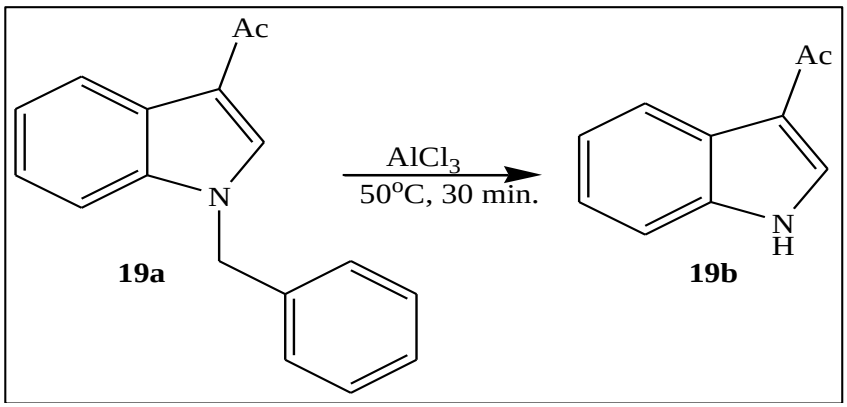
Scheme 18

Thioketals {3-(α,α-Ethylenedithioethyl) indole}(18a) are gently refluxed with the mixture of Dowex 50W (an acidic catalyst) and paraformaldehyde in acetone for 6 hours to give 3-acetylindole (18b) in 65% yield. Affordable yield of 18b is obtained [19].



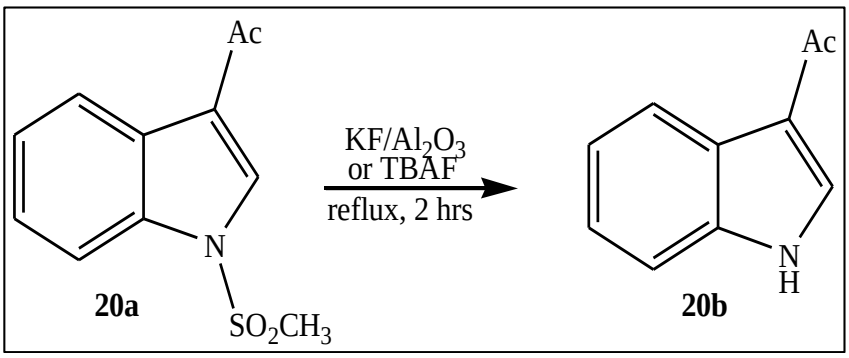
Scheme 19

1-Benzyl-3-acetylindole (19a) when heated in presence of aluminium chloride in benzene or anisole at 50 ^{0}C, for 30 minute it undergoes debenzylation to give 3-acetylindole (19b). The advantage of this method is short process time with affordable yield of 19b [20].



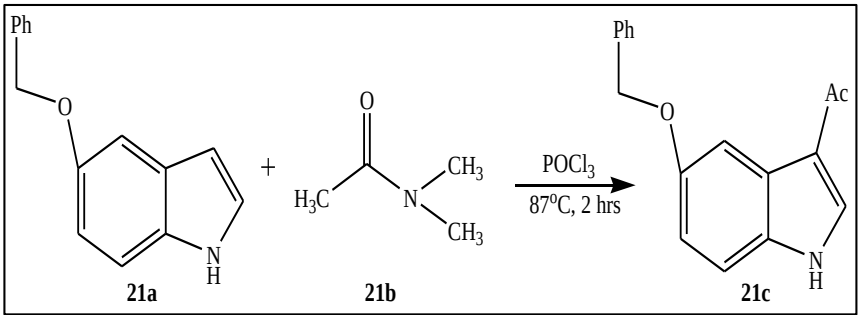
Scheme 20

Desulfonylation of 1-[1-(methylsulfonyl)-1*H*-indol-3-yl]ethanone (20a) proceeds using potassium fluoride/aluminium oxide or tetra-*n*-butylammonium fluoride(TBAF) in tetrahydrofuran (THF) under reflux conditions for 2 hours to give 3-acetylindole (20b) in 91% yield [21].



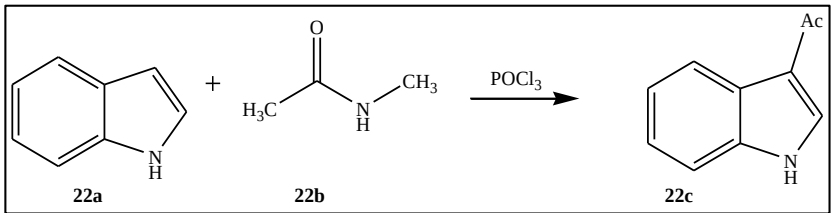
Scheme 21

5-Benzyloxy-3-acetylindole (21c) is obtained from reaction of 5-benzyloxyindole (21a) with a mixture of N,N-dimethylacetamide (21b) and phosphorus oxychloride, at 87^{o}C for 2 hours, in 71% yield. It is simple acetylation process and good yield of 21c is obtained in short time [22].

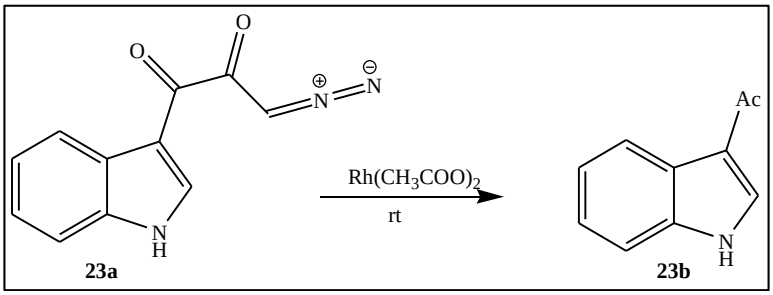


Scheme 22

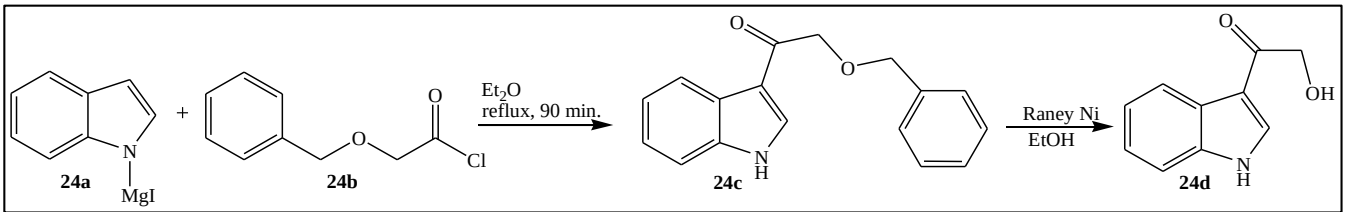
3-Acetyl indole (22c) is obtained by reaction of indole (22a) with *N*-methylacetamide (22b) in presence of phosphorus oxychloride, in 22.4% yield. Low yield is the drawback of this process [23].



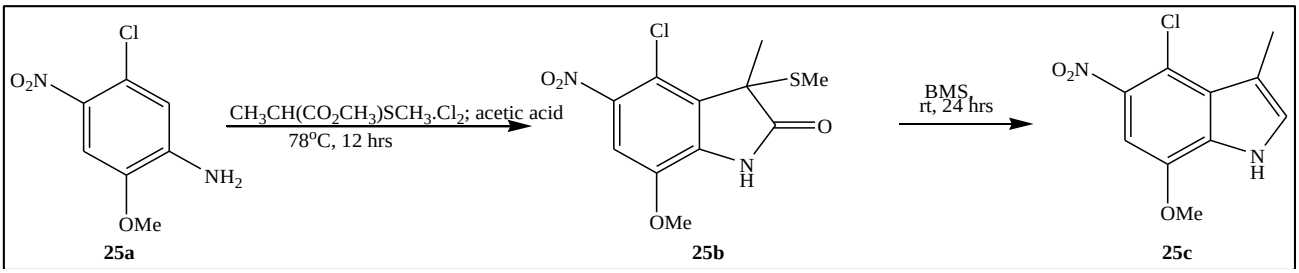
Scheme 23:
Diazoketone {3-diazo-1-(indol-3-yl) propane-1,2-dione}(23a) in the presence of rhadium(II) acetate in catalytic amount at room temperature gives 3-acetylindole (**23b**) in 70% yield. The reaction involves a Wolff rearrangement [24].



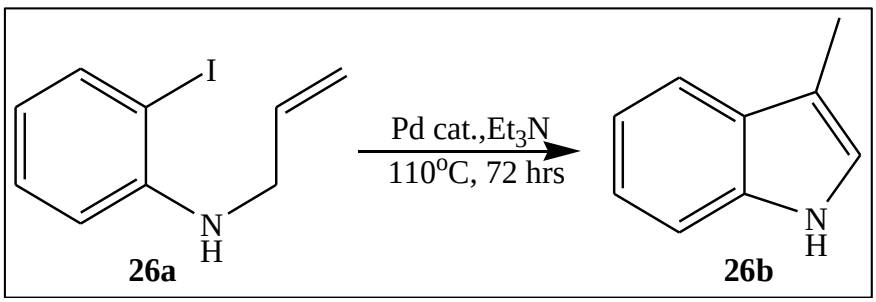
3-Substitueted acetyl indole
Scheme 24:
Mixture of 2-(benzyloxy)acetyl chloride (24b) and indolylmagnesium iodide (24a) is refluxed for 90 minutes in presence of diethyl ether, to give 3-benzyloxyacetylindole (24c) which on reduction with Raney Ni in absolute ethanol gives 2-hydroxy-1-(1*H*-indol-3-yl)ethanone (24d) in 68% yield. In this process affordable yield is obtained in short time [25].



3-Methylindole
Scheme 25
Respective 5-chloro-2-methoxy-4-nitrobenzenamine (25a) converts into corresponding oxindole (25b) in presence of acetic acid and $CH_3CH(CO_2CH_3)SCH_3.Cl_2$ after heating for 12 hours at 78 ºC. Prepared 25b is subjected for reduction in presence of borane dimethylsulfide under the atmosphere of nitrogen at room temperature for 24 hours to give 4-chloro-7-methoxy-3-methyl-5-nitro-1*H*-indole (25c) in 95% yield. It is lengthy process but high yield of 25c is obtained [26].

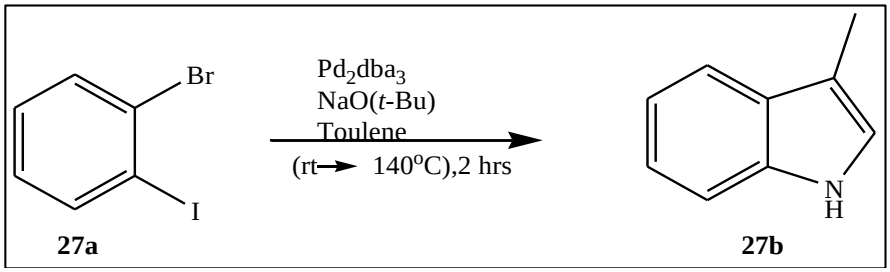


Scheme 26
When *N*-allyl-2-iodoaniline (26a) is heated in presence of palladium at 110ºC for 72 hours, it is converted into 3-methylindole (26b). High yield of 82% is the advantage but the process is very lengthy [27].



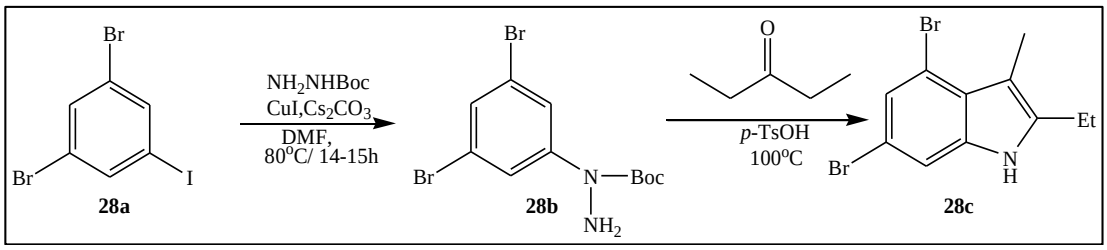
Scheme 27

When 2-bromoiodobenzene (27a) is heated in presence tris (dibenzylideneacetone) dipalladium (Pd_2dba_3) at 140 °C for 2 hours, it is converted into 3-methylindole (27b) in 85% yield. Less reaction time is to synthesize 27b in good yield [28].



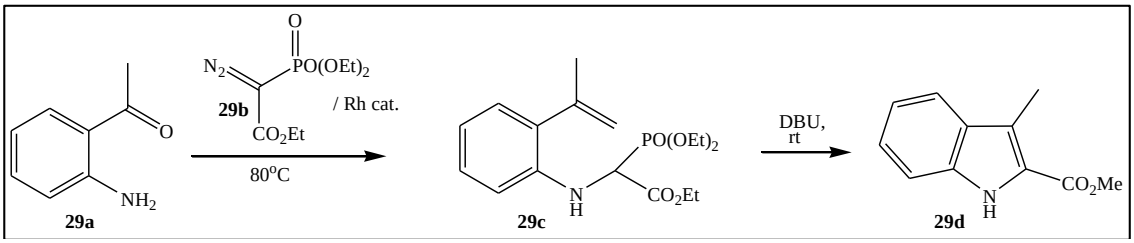
Scheme 28

When dibromoaryl iodide (28a) is heated in presence of *tert*-butyloxycarbonyl hydrazine at 80 °C for 14-15 hours, it undergoes animation to give butyloxycarbonyl (Boc)-protected dibromoaryl hydrazine (28b). Prepared 28b is further condensed with ketone at 100 °C until 28b is comsumed to give 2-ethyl-3-methyl-4,6-dibromoindole (28c) in 60% yield. The condensation reaction proceeds with high regioselectivity [29].



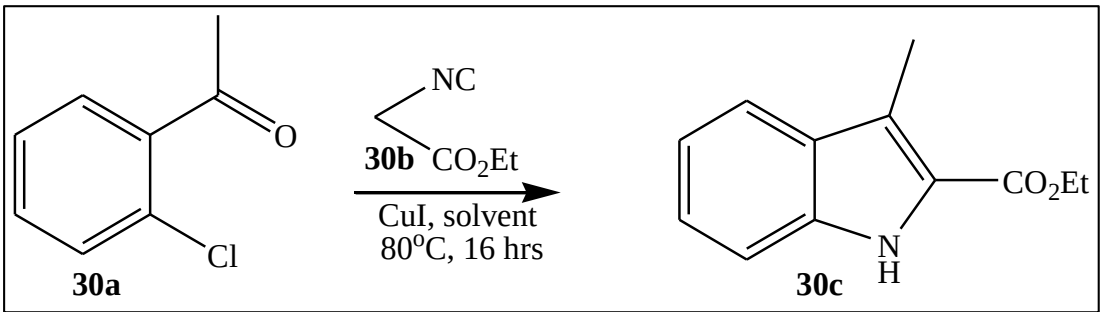
Scheme 29

When 2-aminoacetophenone (29a) is treated with triethyl diazophosphonoacetate (29b) in presence of rhodium(II) acetate catalyst at 80 °C, it gives ethyl 2-(diethoxyphosphoryl)-2-(2-(prop-1-en-2-yl)phenylamino)acetate (29c). Prepared 29c is further treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at room temperature in toluene to give Methyl 3-methyl-1*H*-indole-2-carboxylate (29d) in 84% yield [30].



Scheme 30

When 2-chlorobenzene aldehyde (30a) is heated with ethyl isocyanoacetate (30b) in presence of copper salt (CuI) and dimethyl sulfoxide as solvent at 80 °C for 16 hours, it gives ethyl 3-methyl-1*H*-indole-2-carboxylate (30c) in 45% yield. Low yield and long reaction time are the drawbacks [31].



Conclusion

This review contains 81 schemes for synthesis of 3-substituted indoles which covers Freidal-Craft acetylation, Bartoli indole synthesis, Bischler indole synthesis, Fischer indole synthesis, Hemetsberger indole synthesis, Julia indole synthesis, Larock indole synthesis, Leimgruber–Batcho indole synthesis, Madelung indole synthesis, Nenitzescu indole synthesis, Reissert indole synthesis and Sundberg indole synthesis.

3-substituted indoles have wide range of pharmacological acvities like antimicrobial, antifungal, antioxidant, antitumor, anti-inflammatory, analgesic, anticonvulsant, antihypertensive and antiviral activity. Thus we can say that 3-substituted indole is a moiety which has exhibited versatility in

pharmacological action and has further potential for exploring its unexplored pharmacological activities.

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