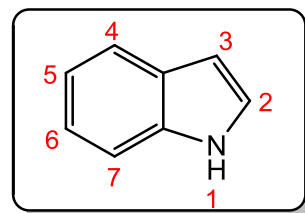
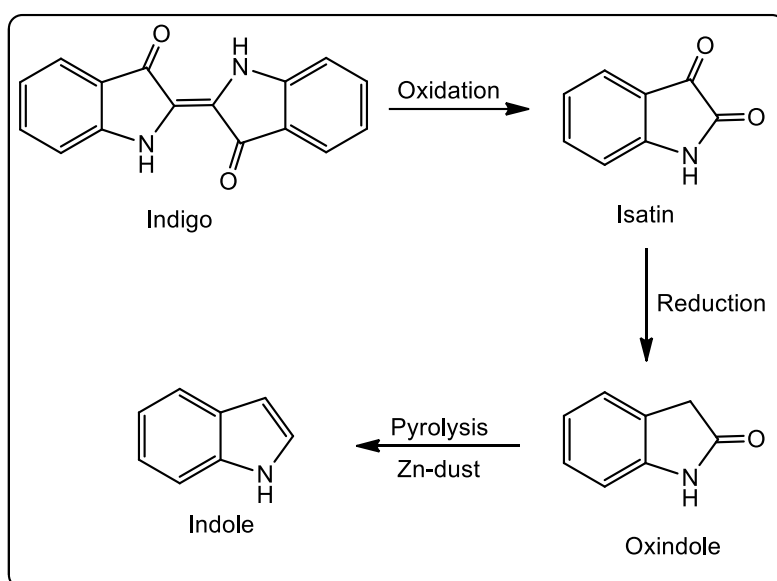


# Synthesis and Chemistry of Indole

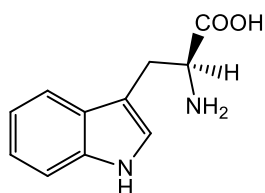


## 1. Introduction:

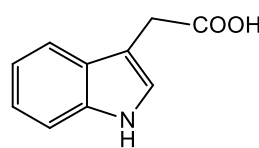
- Indole is a benzo[*b*]pyrrole formed by the fusion of benzene ring to the 2,3 positions of pyrrole nucleus.
- The word “Indole” is derived from the word India, as the heterocycle was first isolated from a blue dye “Indigo” produced in India during sixteenth century.
- In 1886, Adolf Baeyer isolated Indole by the pyrolysis of oxindole with Zn dust. Oxindole was originally obtained by the reduction of isatin, which in turn was isolated by the oxidation of Indigo.
- Commercially indole is produced from coal tar



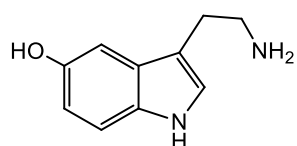
- Indole is the most widely distributed heterocycle
- Indole nucleus is an integral part of thousands of naturally occurring alkaloids, drugs and other compounds.



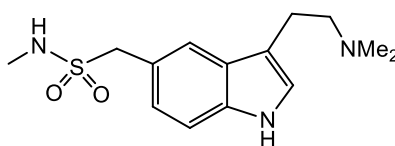
Tryptophan: Amino acid



Indol-3-ylacetic acid:  
Plant growth hormone



Serotonin: Neurotransmitter

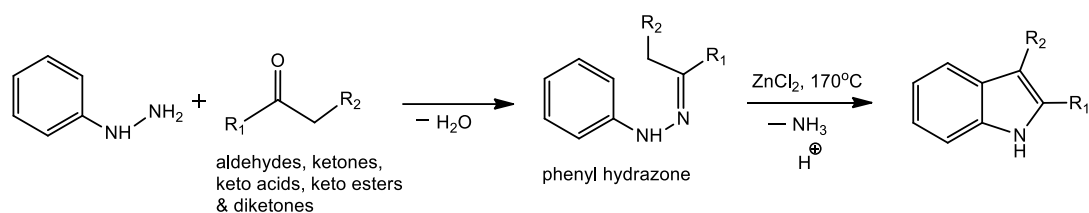


Sumatriptan: Medicine for migraine

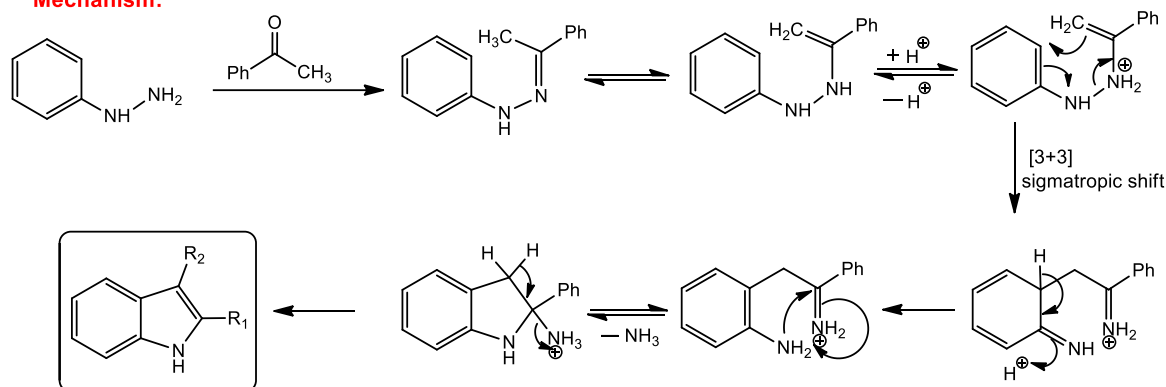
## 2. Synthesis of Indole

### 2.1. Fischer Indole Synthesis:

- This reaction was discovered in 1883 by Emil Fischer and so far remained the most extensively used method of preparation of indoles.
- The synthesis involves cyclization of arylhydrazones under heating conditions in presence of protic acid or lewis acids such as  $\text{ZnCl}_2$ ,  $\text{PCl}_3$ ,  $\text{FeCl}_3$ ,  $\text{TsOH}$ ,  $\text{HCl}$ ,  $\text{H}_2\text{SO}_4$ ,  $\text{PPA}$  etc.
- The starting material arylhydrazoles can be obtained from aldehydes, ketones, keto acids, keto esters and diketones etc.
- Reaction produces 2,3-disubstituted products. Unsymmetrical ketones can give a mixture of indoles.

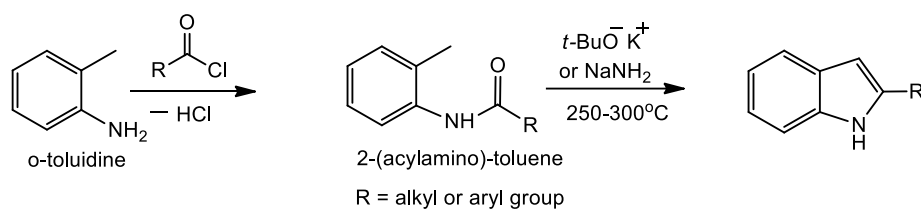


#### Mechanism:

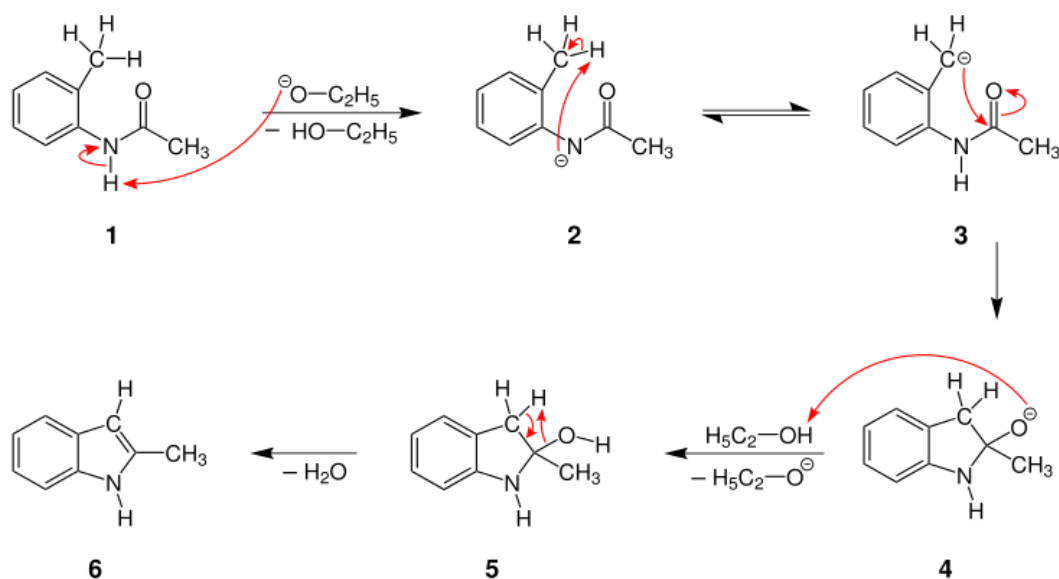


### 2.2 Madelung Synthesis:

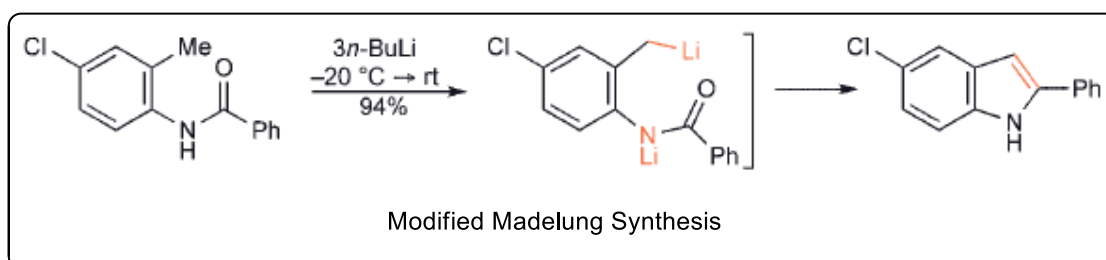
- Base catalyzed cyclization of 2-(acylamino)-toluenes under very harsh conditions (typically sodium amide or potassium *t*-butoxide at  $250\text{-}300^\circ\text{C}$ ).
- Limited to the synthesis of simple indoles such as 2-methyl indoles without having any sensitive groups.



### Mechanism:



- A modern variant of madelung reaction is performed under milder conditions by the use of alkylolithiums as bases.
- 2-Substituted indoles bearing sensitive groups can be synthesized using this method



### 2.3 Reissert Synthesis:

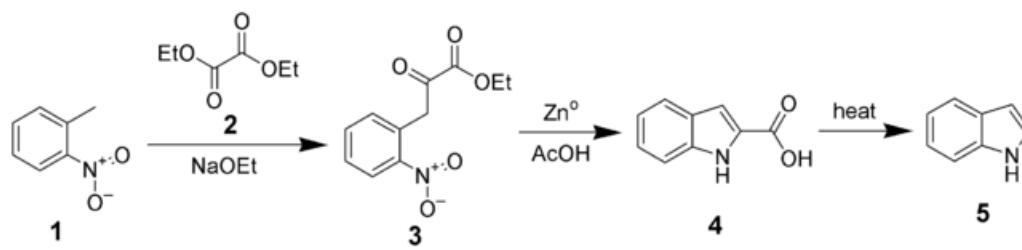
Reissert indole synthesis is a multistep reaction:

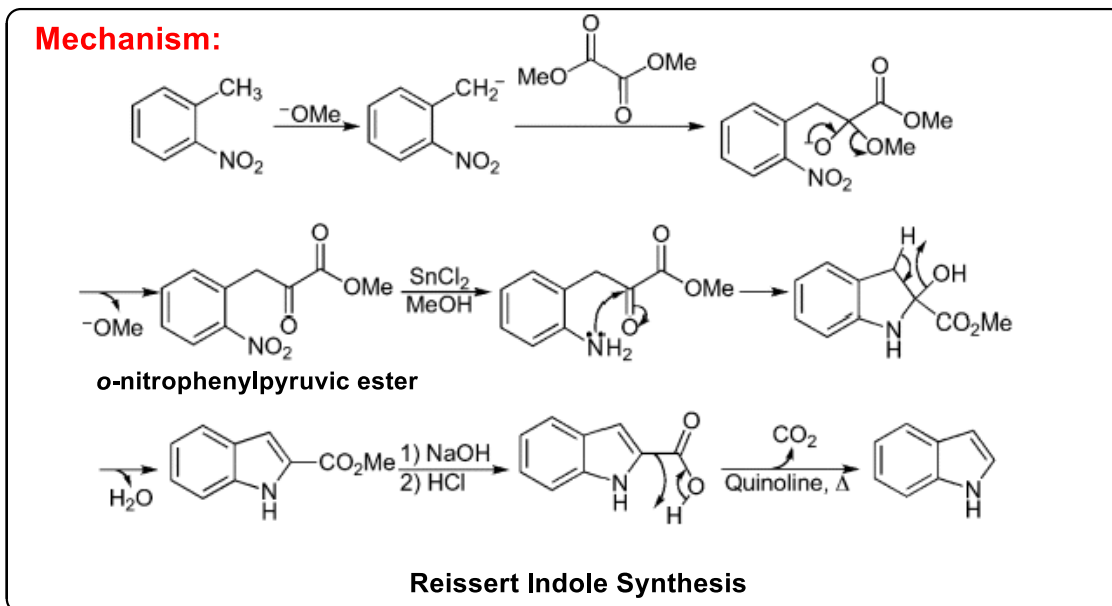
Step 1: Base catalysed condensation of *o*-nitrotoluene with oxalic ester (methyl oxalate) to give *o*-nitrophenylpyruvic ester

Step 2: Reduction of the nitro group to an amino group,

Step 3: Cyclization to indole-2-carboxylic acid

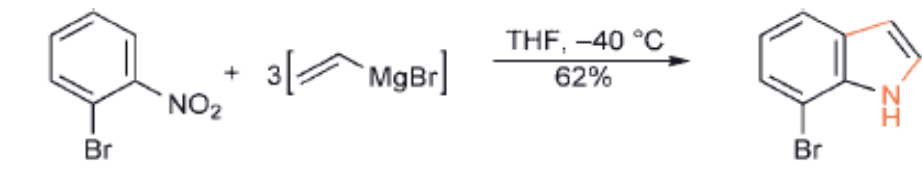
Step 4: Decarboxylation





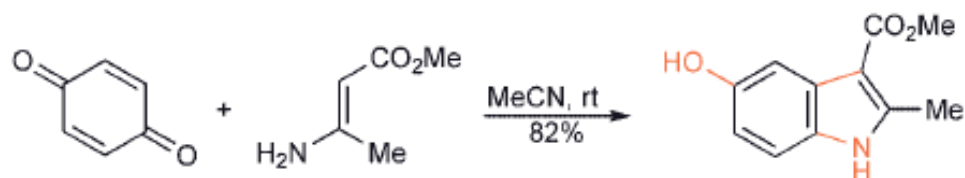
## 2.4 Bartoli Indole Synthesis:

- Efficient and extremely practical approach for indole synthesis
- Ortho-substituted nitrobenzenes react with three mole equivalents of vinyl magnesium bromide (Grignard reagent) to give 7-substituted indoles.



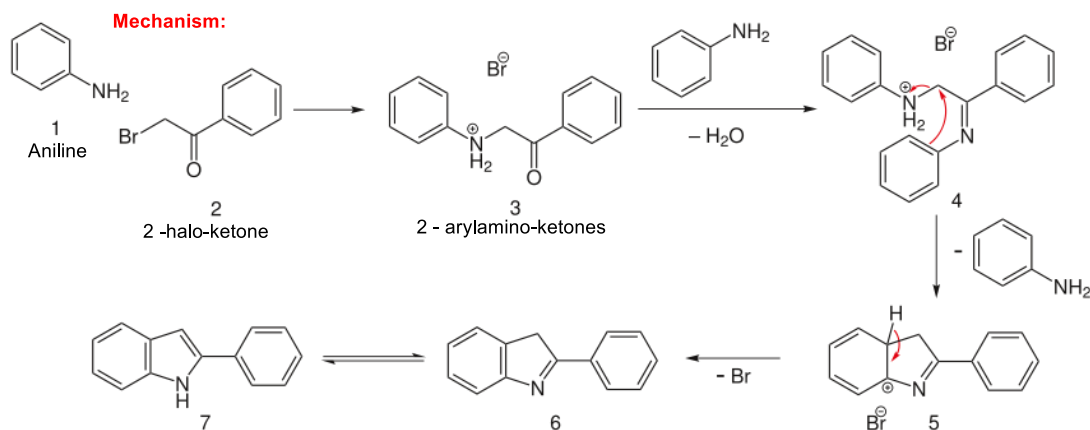
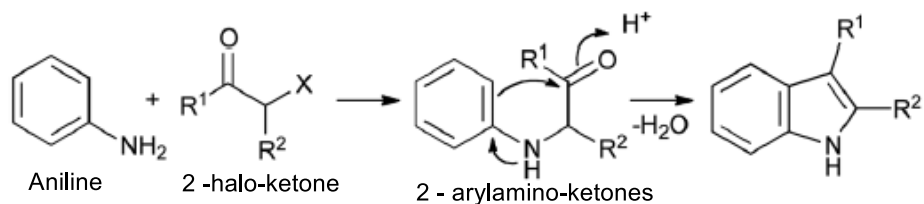
## 2.5 Nenitzescu Synthesis:

- Reaction provides direct route for the synthesis of 5-hydroxyindoles.
- Condensation of substituted 1,4-benzoquinone with a  $\beta$ -amino-substituted  $\alpha$ ,  $\beta$ -unsaturated carbonyl compounds with ring closure to a 5-hydroxyindole.

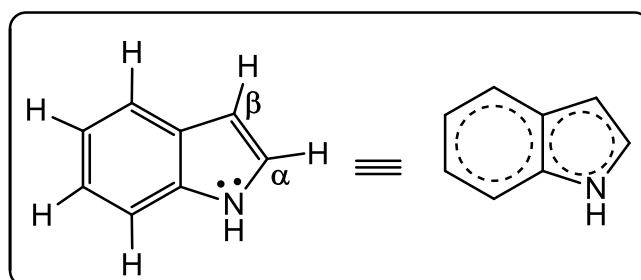


## 2.6 Bischler Indole Synthesis:

- Reaction involves acidic treatment of 2-arylamino-ketones (produced from a 2-halo-ketone and an arylamine) to bring about electrophilic cyclisation onto the aromatic ring
- Often result in mixtures of products *via rearrangements*.



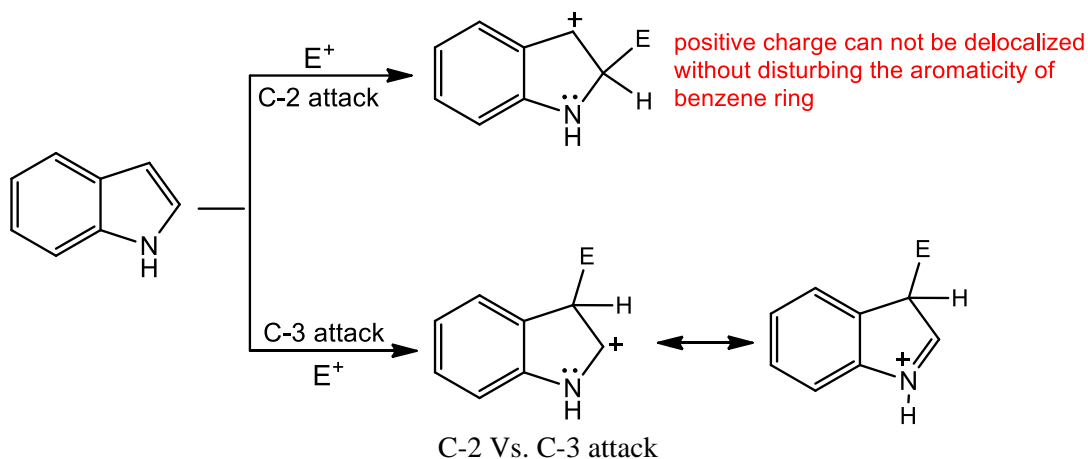
### 3. Reactions of Indole:



- The fusion of a benzene ring to the 2,3-positions of a pyrrole generates one of the most important heterocyclic ring systems – indole.
- **Aromatic:** Indole is a planar molecule and follows Huckel's rule  $[(4n+2) \pi \text{ electrons}]$ . All atoms in indole are  $sp^2$  hybridized and each of them possesses one unhybridized  $p$ -orbital. These  $p$ -orbitals overlap to generate  $\pi$ -molecular orbital containing 10 electrons (eight electrons from eight carbons and two lone pair electrons from N).
- It is resonance hybrid of several canonical structures.
- Indole is a  $\pi$ -excessive (electron rich) heterocycle, so their chemistry is mostly dominated by electrophilic substitution reactions.
- Indole is markedly less reactive than corresponding monocyclic heterocycles.

#### 3.1 Electrophilic Substitution Reactions:

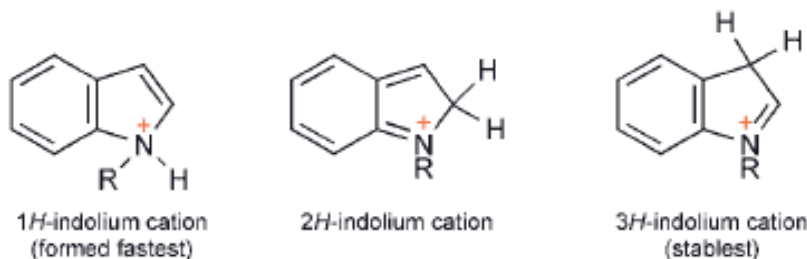
- The pyrrole ring in indole is very electron rich, in comparison to the benzene ring, therefore, electrophile's attack always takes place in the five-membered ring, except in special circumstances.



- The preferred site of electrophilic substitution is C-3, because the cation formed by the C-3 attack of electrophile is more stable than that of the C-2 attack. In case of C-3 attack, transition intermediate formed has positive charge adjacent to N atom that can be stabilized by the delocalization of lone pair of electrons of nitrogen. Whereas, the positive charge of transition intermediate formed by the C-2 attack, cannot be stabilized without disturbing aromaticity of benzene ring. If C-3 position is occupied, then electrophilic substitution takes place at C-2 and if both of them are occupied then electrophile attacks at C-6 position.

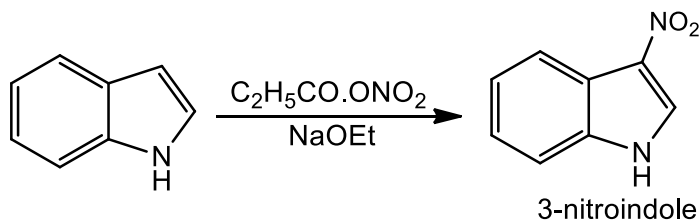
3.1.1 **Protonation:** Indole is a very weak base  $pK_a -3.5$ . The nitrogen atom of indole gets easily protonated even in water (at  $pH = 7$ ) giving 1*H*-indolium cation. However, thermodynamically most stable cation is formed by the protonation of C-3 rather than N.

3-protonated cation (3 *H*-indolium cation) retains full benzene aromaticity (in contrast to the 2 - protonated cation) with delocalisation of charge over the nitrogen and  $\alpha$  carbon.



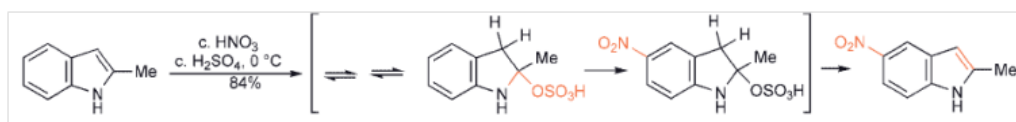
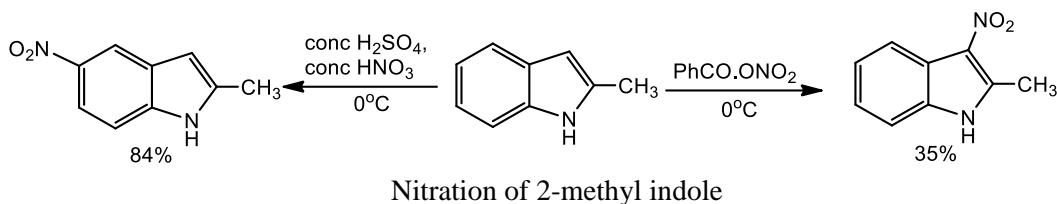
### 3.1.2 Nitration:

- Common nitrating reagent, mixture of acids ( $H_2SO_4 + HNO_3$ ) leads to acid-catalysed polymerisation of indole.
- Therefore, nitration of indole is carried out using non-acidic nitrating agent such as benzoyl nitrate and ethyl nitrate.



Nitration of indole

- Nitration of **2-Methylindole** with benzoyl nitrate gives a 3-nitro derivative however, nitration under acidic conditions using nitric/sulfuric acids gives C-5 -NO<sub>2</sub> substituted product.

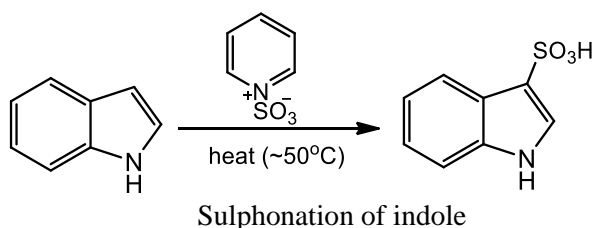


Possible explanation for the formation of C-5-nitro substitution

- The absence of attack on the heterocyclic ring can be explained: 2-methylindole undergoes protonation at C-3 under strongly acidic condition and this leads to deactivation of pyrrole ring for further electrophilic attack. The regioselectivity of attack, para to the nitrogen, may mean that the actual moiety attacked is a hydrogen sulfate adduct of the initial 3*H*-indolium cation.

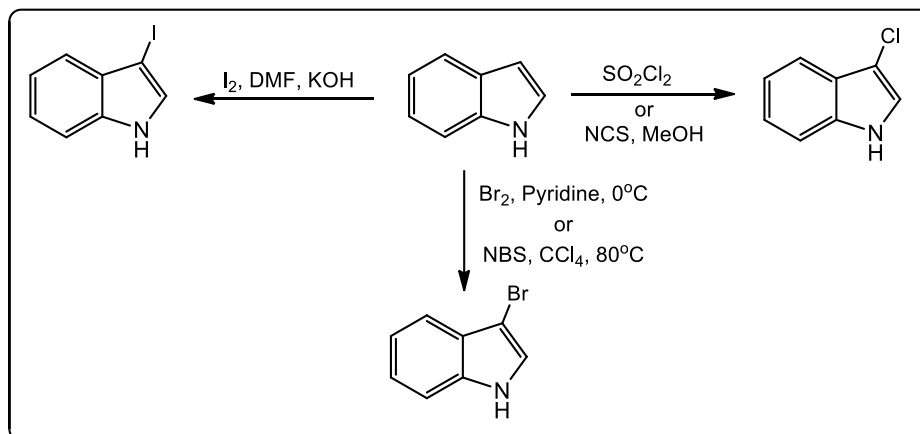
### 3.1.3 Sulphonation:

Sulfonation of indole, at C-3, is performed using the pyridine-sulfur trioxide complex in hot pyridine.



### 3.1.4 Halogenation:

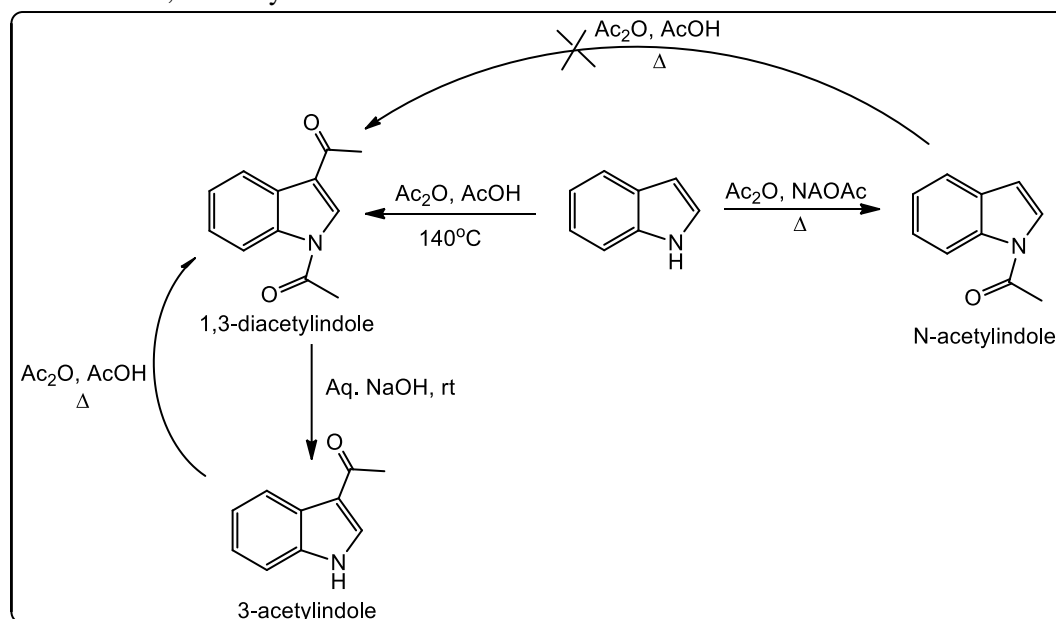
3-Halo- and 2-halo-indoles are unstable therefore, must be utilised immediately after their preparation.



Halogenation of indole

### 3.1.5 Acylation:

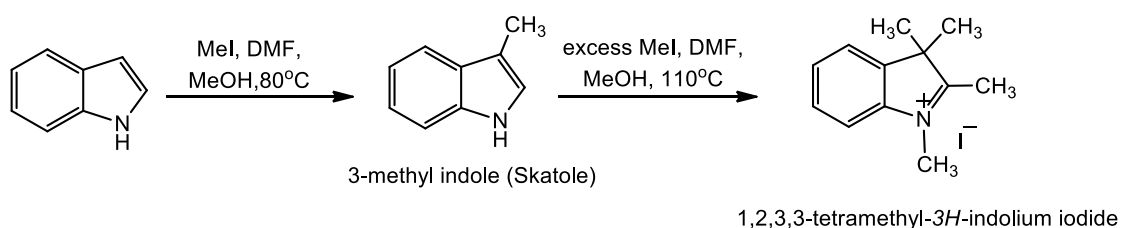
- Indoles react with acetic anhydride in acetic acid above 140°C to afford 1,3-diacetylindole predominantly.
- On the other hand, acetylation in the presence of sodium acetate or 4-dimethylaminopyridine, affords exclusively 1-acetylindole.
- Acylation occurs at C-3 position before N in 1,3-diacetylindole as, N-acylated product showed resistance to conversion to 1,3-diacetylindole but 3-acetylindole showed easy conversion to 1,3-diacetylindole.



Acylation of indole

### 3.1.6 Alkylation:

Indoles do not react with alkyl halides at room temperature. Indole itself begins to react with methyl iodide in dimethylformamide at about 80°C, to give main product 3-methyl indole (skatole). As the temperature is increased, further methylation takes place resulting in 1,2,3,3-tetramethyl-3*H*-indolium iodide.

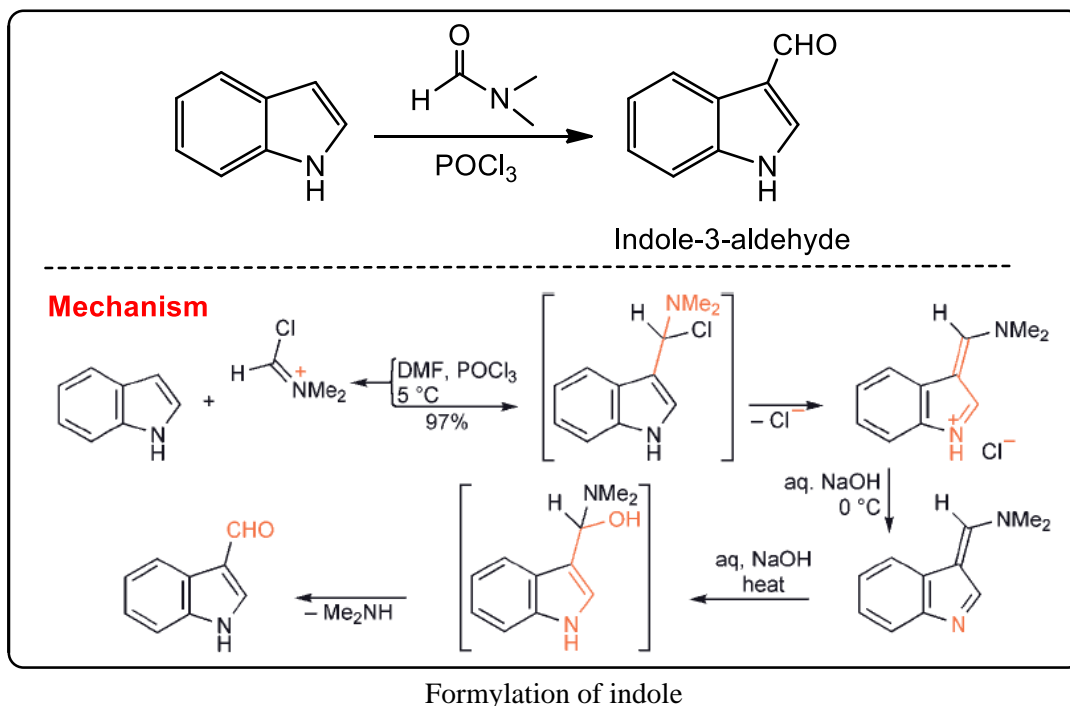


Alkylation of indole

### 3.1.7 The Vilsmeier Haack reaction:

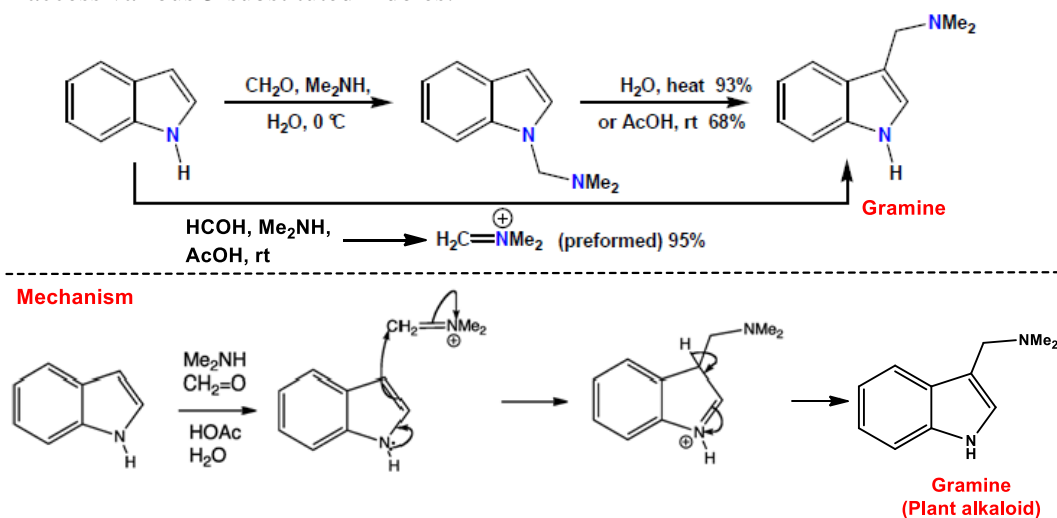
The Vilsmeier reaction is a very efficient method for the formylation of electron rich aromatic rings by the use of acid chloride (POCl<sub>3</sub>) and DMF. Indoles can be readily formylated to 3-formyl-indoles via Vilsmeier reaction. Even indoles carrying an electron-withdrawing group at the 2-position, for example ethyl indole-2-carboxylate, undergo smooth Vilsmeier 3-formylation.





### 3.1.8 Mannich reaction (reaction with iminium ions):

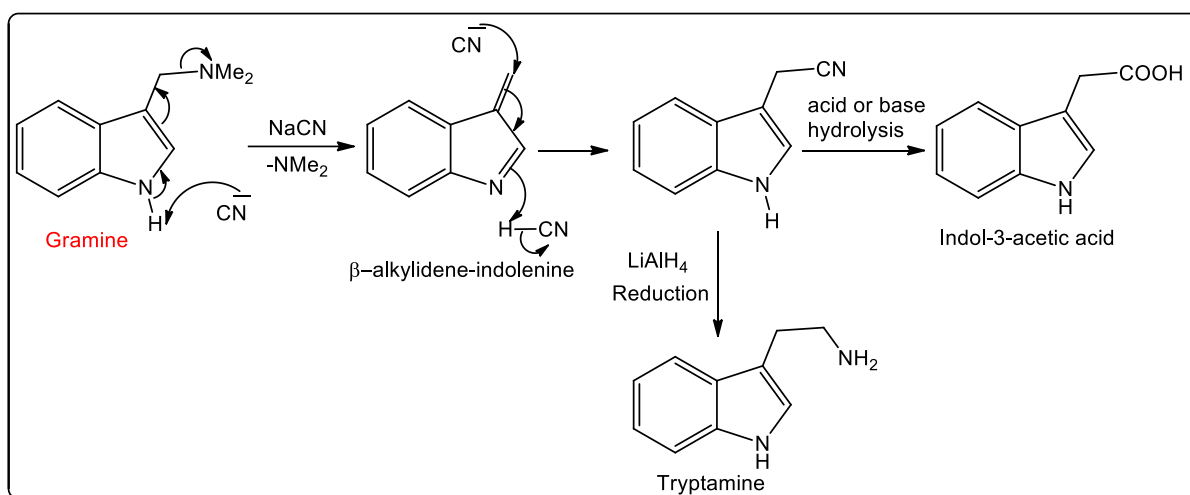
- Indole reacts with a mixture of formaldehyde and dimethylamine at  $0^\circ\text{C}$  in neutral conditions to give *N*-substituted dimethylaminomethyl indole.
- Under neutral conditions at higher temperature or in acidic medium acetic acid, *N*-substituted dimethylaminomethyl indole gets transformed into thermodynamically more stable 3-(dimethylaminomethyl)indole, gramine.
- Gramine can be directly prepared in high yield, by reaction of indole with formaldehyde and dimethylamine in acetic acid.
- The Mannich reaction is useful because the product gramine can be used as intermediates to access various 3-substituted indoles.



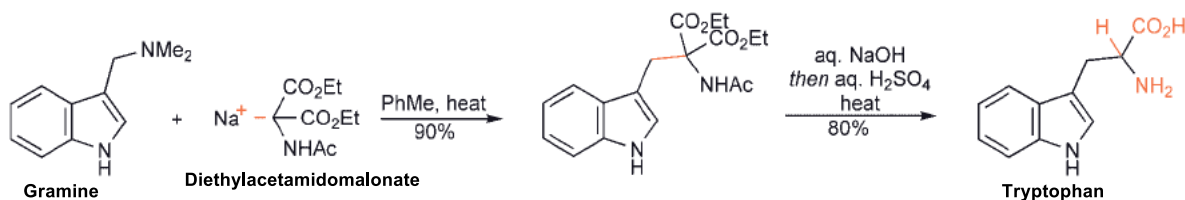
Mannich reaction of indole

### Synthetic Application of Gramine:

- Gramine and, especially, its quaternary salts are useful synthetic intermediates as they are easily prepared and the dimethylamino group is easily displaced by nucleophiles for example – reactions with cyanide and acetamidomalonnate anions.
- The electron donating power of is never better demonstrated than in case of mannich bases. For the removal of dimethylamino group, normal mannich bases require alkylation to convert them to its quaternary salts before elimination by heating. However, in case of indole derived mannich bases no alkylation is needed and nitrogen of indole itself can expel the  $\text{Me}_2\text{N}$ -group in presence of  $\text{CN}^-$  ions. The reaction is slow but gives high yield.

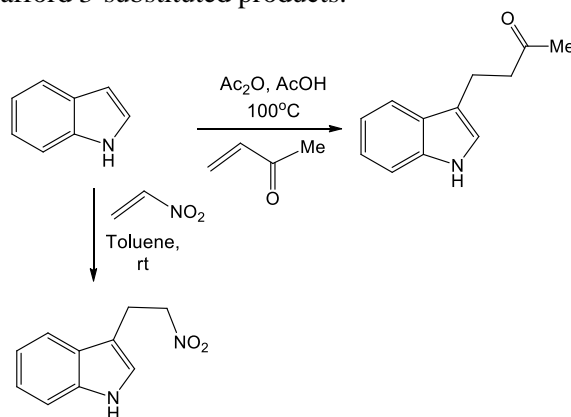


### Synthesis of Tryptophan from Gramine:

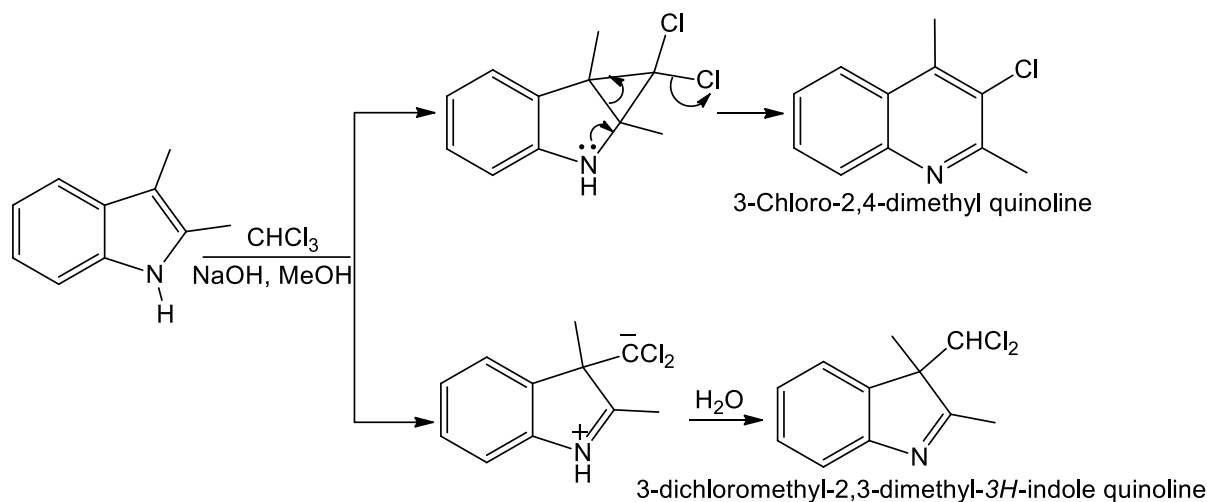


#### 3.1.9 Reaction with Michael acceptors:

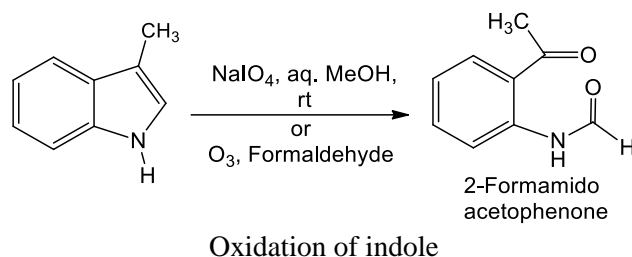
Indole reacts with electrophilic  $\alpha,\beta$ -unsaturated ketones, nitriles and nitro compounds under acidic conditions to afford 3-substituted products.



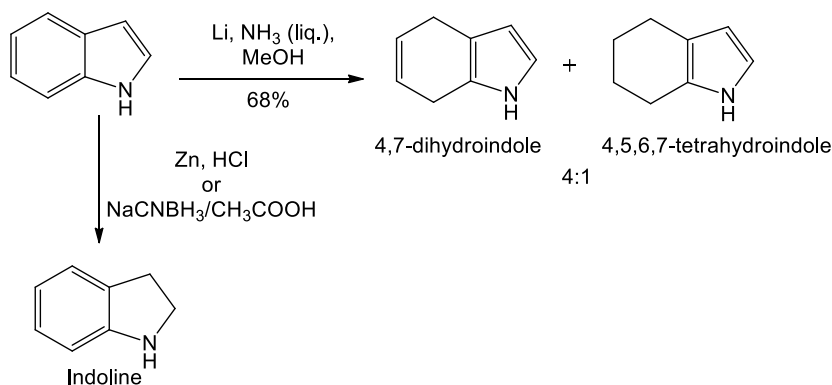
**3.2 Reaction with carbene:** Halocarbenes react with indole to add onto 2,3 C-C double bond to give a mixture of two products as given below.



**3.3 Oxidation Reaction of Indole:** C2-C3 double bond of indole is oxidatively cleaved by the use of reagents such as ozone, sodium periodate, potassium superoxide or  $\text{CuCl}_2$  in  $\text{O}_2$  atmosphere.

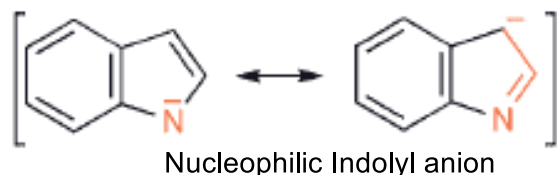


**3.4 Reduction Reaction of Indole:** The indole ring can be reduced selectively in carbocyclic or the heterocyclic ring. Nucleophilic reducing agents such as  $\text{LiAlH}_4$  or  $\text{NaBH}_4$  does not affect indole nucleus. However, lithium/liquid ammonia reduces the benzene ring to 4,7-dihydroindole as major product. The heterocyclic ring can be reduced in acidic reagents such as  $\text{Zn}/\text{HCl}$  or  $\text{NaCNBH}_3/\text{CH}_3\text{COOH}$  to give indoline.

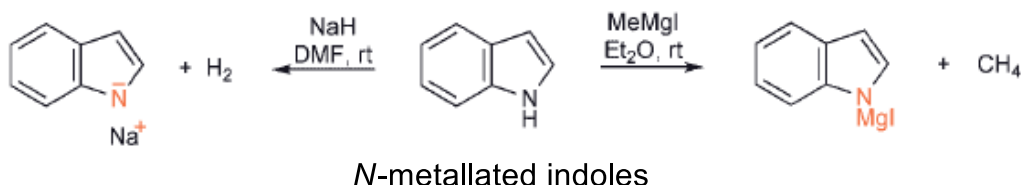


Reduction of indole

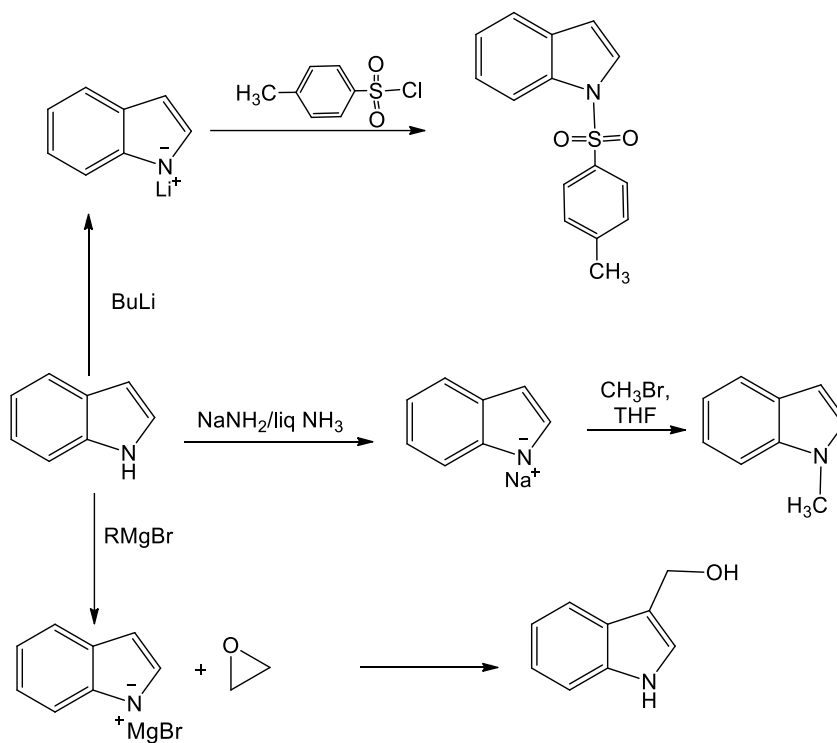
**3.5 Reaction of N-metallated Indoles:** In presence of very strong bases, indoles behave as weak acid, thus; it can be deprotonated with strong bases to obtain its N-metallated derivatives. N-metallated indoles are nucleophiles that can react with suitable electrophiles either at N or at C-3.



These *N*-sodio derivatives can be prepared by reaction with sodamide in liquid ammonia, or by the use of sodium hydride in organic solvent. Salts of other metals can be prepared by using various bases such as potassium *t*-butoxide, Grignard reagent or butyl lithium.



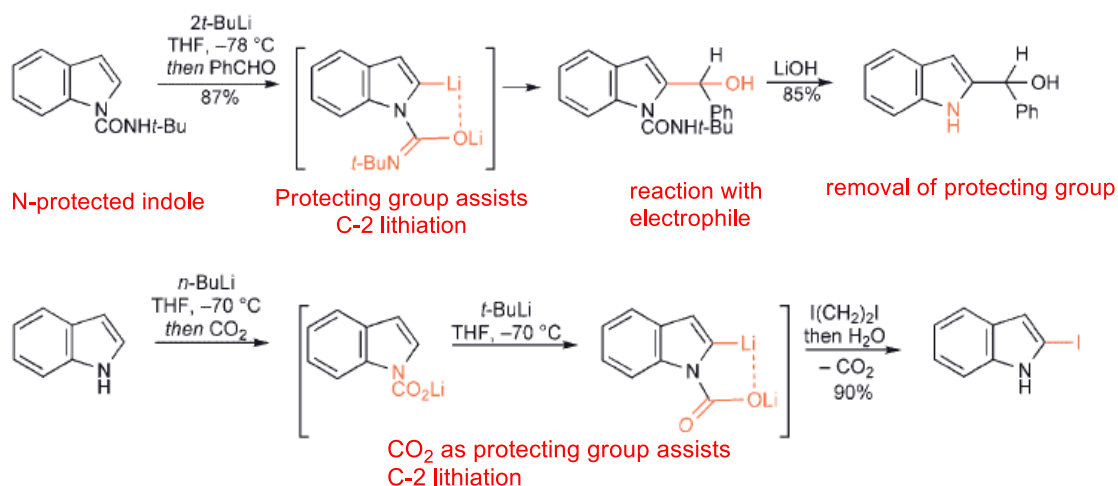
The more ionic sodium and potassium salts tend to react at *N*, especially with hard electrophiles. In contrast to 1-indolyl magnesium halides are alkylated and acylated at C-3.



Reaction of *N*-metallated Indoles with electrophiles

### 3.6 Reaction of C-metallated Indoles:

C-Metallation of indoles can be brought about only in absence of the much more acidic *N*-hydrogen. *N*-hydrogen can be removed by the *N*-substitution of indole with methyl, ethyl etc. or by the use of a protecting group such as phenylsulfonyl, lithium carboxylate and *t*-butoxycarbonyl, that can be easily removed after the desired product formation. Each of these removable substituents assists lithiation at C-2 position of indole by intramolecular chelation. This way obtained lithiated indoles can be converted into 2-substituted indoles by reaction with appropriate electrophiles.



- CO<sub>2</sub> is one of the most convenient *N*-protecting groups in indole  $\alpha$ -lithiations because the *N*-protecting group is installed *in situ* and, further, falls off during normal work-up.
- This technique has been used to prepared 2-halo-indoles and to introduce a variety of substituents by reaction with appropriate electrophiles—aldehydes, ketones, chloroformates, etc.

## References:

Heterocyclic Chemistry, 5th Edition John A. Joule, Keith Mills.  
 Heterocyclic Chemistry (3rd Edition) 3rd Edition by Thomas L. Gilchrist.  
 Heterocyclic Chemistry by Raj K. Bansal  
 Wikipedia.