

# Synthesis of Indole by Cyclization of Hydrazone Catalysed by Lewis Acid

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**Abstract:** *Experimental evidences have been shown that, stirring and grinding ( without solvent ) is good method instead of heating and it is time saving. The current studies have been revealed that prepared different indole derivatives have been shows exact melting point. Practical yield of obtained of 2-ethyl indole, 2-methyl indole, 2-(2-hydroxyphenyl)-indole, 2-acetyl indole, 2- (p-hydroxyl-phenyl)-indole, 3-ethyl-2- methyl)-indole, 2-ethyl-3-methyl)-indole were 75.00%, 79.48%, 85.10%, 62.22%, 56.54%, 68.56%, 72.30%, 67.42% respectively. Overall study revealed that excellent practical yield. 2-methyl indole have prepared in high yield by a Fischer indole synthesis of phenyl hydrazine with acetone. New one - pot version of the titled reaction involves string a mixture of  $\alpha$  - carbonyl compound, a phenyl hydrazine and the ethanol. A variety of ketones and several substituted phenylhydrazines could be thus converted to the corresponding indoles in excellent yields (approx. 70-88%). Reaction times were typically 1 hr, the resin being then filtered off and the product isolated after minimal workup.*

**Keywords:** 2-(p-hydroxyl-phenyl)-indole, Phenyl Hydrazine, one pot synthesis

## I. INTRODUCTION

Indole consists of a benzene ring fused to the Alpha and Beta positions of a pyrrole ring. Indole occurs in coal-tar and in the oils of jasmine and orange blossoms. It is also found as a part of the total structure of a number of alkaloids and amino acids e.g., serotonin, reserpine, and tryptophan.

The indole skeleton is famously present in a very large number of biologically-active molecules, both naturally-occurring and synthetically-engineered.[1-3] The essential amino acid tryptophan and an eponymous group of alkaloids come easily to mind,[4] but there also exists an expanding clutch of synthetic species covered by trade names that attest.

The skeleton has thus been the target of several synthetic strategies and approaches spread over the preceding century. The vast majority of these start from an aromatic precursor and fashion the fused pyrrole moiety by various tactics, whether ingenious or deliberate.


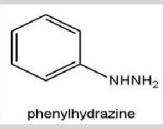
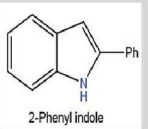
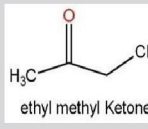
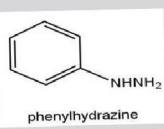
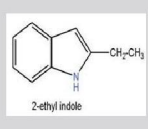
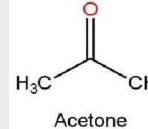
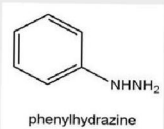

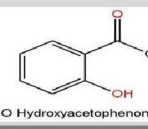
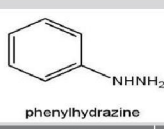

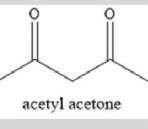
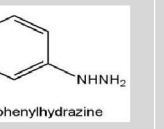
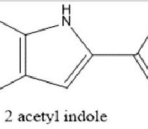
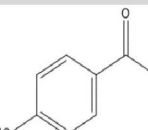
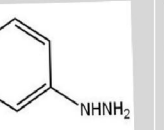
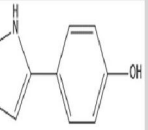
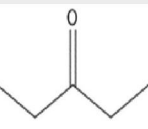
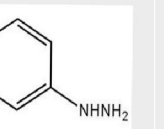
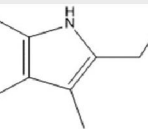
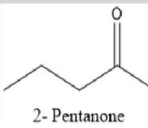
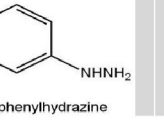
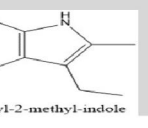
The acid catalyst is believed to facilitate the isomerisation of 1 to 2, a variety of Brønsted and Lewis acids having been employed to effect the transformation. Interestingly,  $ZnCl_2$ , one of the earliest catalysts thus employed, often continues to be the catalyst of choice. A problem with the reaction, however, is that the ammonia by-product neutralizes the acid catalyst, which thus must be employed at stoichiometric levels. An interesting variant of the Fischer indole synthesis involves the in situ formation of the phenylhydrazone from a carbonyl precursor and phenylhydrazine. This 'one-pot' reaction is feasible because hydrazone formation is also promoted by acid; under acidic conditions, an arylhydrazone tautomerizes to the enehydrazine, and undergoes a [3,3]-sigmatropic rearrangement that results in the functionalization of an unactivated aromatic C–H position. Further tautomerization and imine exchange give the desired indole, with ammonia eliminated as a side-product. Although maybe unfashionable, this celebrated reaction addresses all the requirements of a modern indole synthesis in its convenience and simplicity. The increasing importance of environmentally- friendly 'green' methodologies has led to use of aqueous media or solvent-free conditions, for effecting the Fischer indole synthesis<sup>[4]</sup>



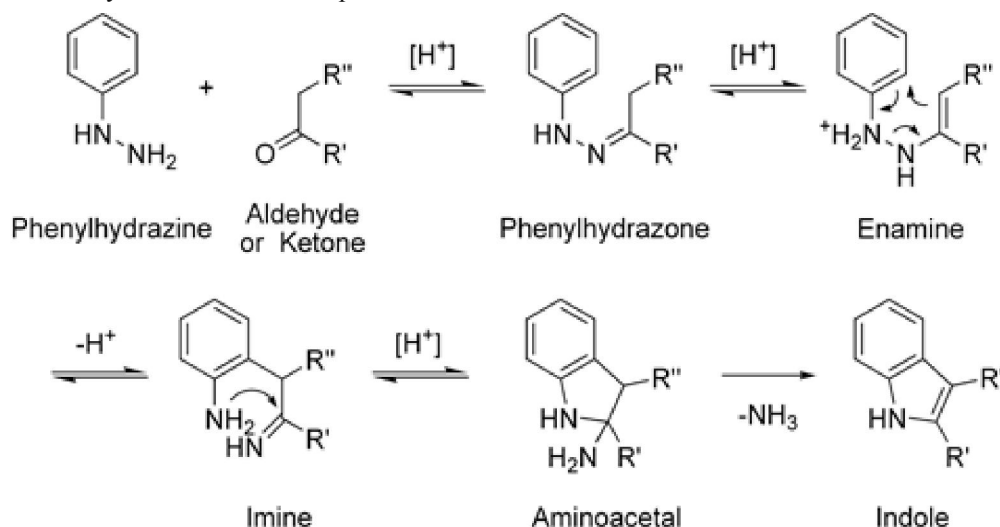
## II. METHODOLOGY/PROCEDURE

A mixture of the carbonyl compound (5, 1.0 mmol), arylhydrazine (6, 1.2 mmol) and the solid acid was stirred and grinding (solvent free Condition) in absolute ethanol (10 ml) for 1 h. The reaction was monitored by tlc, and upon completion the mixture was cooled to room temperature, the catalyst filtered off and washed thoroughly with ethyl acetate (30 ml). The combined organics were washed with water, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo. to obtain the purified indole.

Table 1. Conditions and yields for the Fischer indole synthesis ;

Reactant A	Reactant B	Product	Time			Colour
			Heating	Stirring	Grinding	
 Acetophenone	 phenylhydrazine	 2-Phenyl indole	3hr	1hr	50 min	white
 ethyl methyl Ketone	 phenylhydrazine	 2-ethyl indole	2.15 hr	50min	45 min	Yellow crystal
 Acetone	 phenylhydrazine	 2-Methyl indole	3.30 hr	45min	30min	White solid turns Brown
 O Hydroxyacetophenone	 phenylhydrazine	 2-(2-hydroxyphenyl)-indole	3 hr	1hr	50 min	Brown
Reactant A	Reactant B	Product	Time			Colour
 acetyl acetone	 phenylhydrazine	 2 acetyl indole	3.15 hr	45min	1 hr	Brown
 P-hydroxy acetophenone	 phenylhydrazine	 2-(P-hydroxy Phenyl) indole	2.30 hr	50 min	45 min	White solid turn Brown
 3- Pentanone	 phenylhydrazine	 2-Ethyl-3-methyl-indole	3.30 hr	1 hr	55 min	Brown
 2- Pentanone	 phenylhydrazine	 3-Ethyl-2-methyl-indole	3 hr	40 min	50 min	Brown

The Fischer indole synthesis with the accepted mechanism :



### III. RESULTS AND DISCUSSION

A mixture of phenylhydrazine, a ketone and a was Stirred in a solvent (MeOH, EtOH, MeCN,  $CHCl_3$ , EtOAc and ) over 1 hours. The reaction was monitored by thin layer chromatography, which also indicated the formation of the expected indole product. Reaction conditions were then optimized in terms of catalyst, solvent and the time taken for completion of the reaction. The replacement of the normally employed soluble acid catalysts by a solid acid herein is a significant improvement, as the catalyst is generally employed at stoichiometric levels (often in large excess) in the Fischer indole synthesis.[11] This is because of the liberation of ammonia as a by-product, which neutralizes a large part of the acid catalyst. The advantages of a solid acid catalyst are clearly greater on larger scales, thus leading to environmentally sustainable ('green') processes.

The optimized conditions and yields are shown in Table ;

Starting material	Reagent	Product	Melting point	% Prctical Yield		
				Heating	Stirring	Grinding
Acetophenone	ZnCl <sub>2</sub>	2-phenyl indole	112 °C			
				50%	75 %	76.4%
Ethyl methyl ketone	ZnCl <sub>2</sub>	2-ethyl indole	120 °C	66.54%	79.48%	79.38%
Acetone	ZnCl <sub>2</sub>	2-methyl indole	224 °C	45.55%	85.10%	80.42%
O-hydrony-acetophenone	ZnCl <sub>2</sub>	2-(2-hydroxyphenyl)-indole	116 °C	54.74%	72.22%	69.52%
Acetyl acetone	ZnCl <sub>2</sub>	2-acetyl indole	142 °C	38.84%	56.54%	58.72%
P-hydroxy acetophenone	ZnCl <sub>2</sub>	2-(p-hydroxy-phenyl)-indole	242 °C	42.92%	68.56%	69.72%
3-Pentanone	ZnCl <sub>2</sub>	3-ethyl-2-methyl)-indole	68 °C	48.39%	72.30%	80.30%

#### IV. APPLICATIONS

Indoles constitute extensively explored heterocyclic ring systems with wide range of applications in pathophysiological conditions that is, cancer, microbial and viral infections, inflammation, depression, migraine, emesis, hypertension, *etc.* Presence of indole nucleus in amino acid tryptophan makes it prominent in phytoconstituents such as perfumes, neurotransmitters, auxins (plant hormones), indole alkaloids *etc.* The interesting molecular architecture of indole makes them suitable for the drug development.



Indole are Some of the most versatile and Common Nitrogen based compound Frequently used in synthesis of various organic compounds. Indole acts as therapeutic agent in medicinal chemistry including Anti-microbial and Anti-viral infections, Anti-inflammation, Anti- depression, Anti- hypertension, and so on.<sup>[1]</sup> The indoles are also used as dyes, pigments, fungicides, vitamin supplements, flavor enhancers, and perfumes<sup>[5]</sup>

#### V. CONCLUSION

A convenient modification of the conventional Fischer indole synthesis has been developed, essentially work-up. These derive from the fact that the normally employed soluble acid catalyst has been replaced by a solid acid . Excellent yields have been realized with a wide range of reactants, with reasonable reaction times. Additional benefits, particularly on large scales, involve environmental concerns, as the acid catalyst is normally employed in excess in the Fischer indole synthesis. Experimental evidences have been shown that, stirring and grinding (without solvent ) is good method instead of heating and it is time saving. The current study have been revealed that , prepared different indole derivatives have been shows exact melting point. Stirring and grinding are simple and efficient method For synthesis of indole. Easy to handle and Less time are required

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