

The Fischer Indole Synthesis

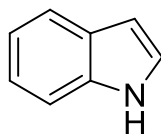
Nicole Fisher CHM 254

Abstract:

The Fischer indole synthesis is considered one of the best methods for preparing indoles. Named after the famous chemist Emil Fischer, it converts arylhydrazones into indoles in the presence of an acid catalyst.¹ This reaction has proven very useful for the pharmaceutical synthesis of antimigrane drugs.²

Introduction:

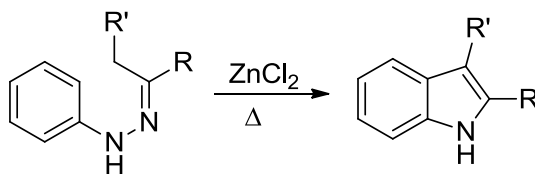
An indole is characterized as a benzene ring fused to a nitrogen-containing five-membered heterocyclic ring. The structure of the most basic indole is shown below:¹



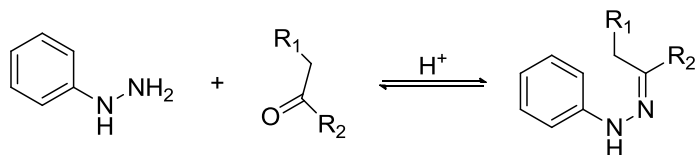
Substituents may be added anywhere on the above molecule to create an indole derivative. Several thousand indole derivatives appear annually in chemical literature.³ The Fischer indole synthesis is the most widely used and versatile method for indole synthesis.

Reaction Mechanism:

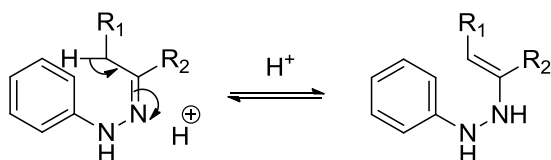
The Fischer indole synthesis converts arylhydrazones of aldehydes or ketones into indoles in the presence of an acid catalyst.³ Below is the overall reaction:



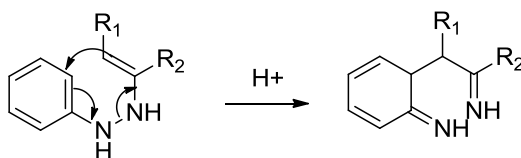
Arylhydrazones are formed from a condensation reaction between an arylhydrazine and an aldehyde or ketone:⁴



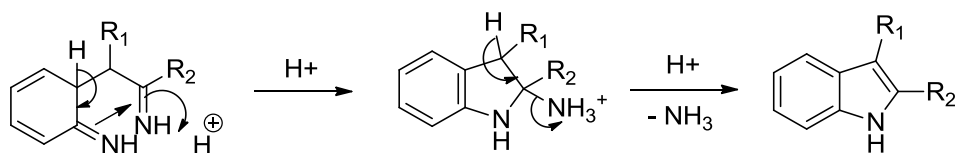
The arylhydrazone then rearranges by the mechanism below:



This intermediate rearranges once again to form a new C-C bond. This type of rearrangement is called a [3,3] sigmatropic shift.¹



A final rearrangement occurs so as to restore the benzene ring and simultaneously close the five member ring. The double bond in the five member ring is formed with the loss of ammonia to give the final indole product.¹



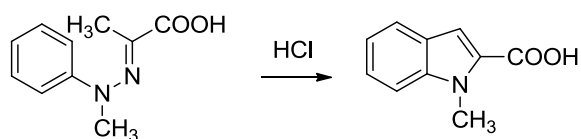
Acid Catalysis

The Fischer indole synthesis is accelerated in an acidic environment. Both protic and Lewis acids have been shown to help break the nitrogen-nitrogen bond in the sigmatropic shift. Hydrochloric or sulfuric acids are frequently used, and zinc chloride is the most effective Lewis acid. However, the synthesis is not completely dependent on an acid. Indolization can also

occur under thermal conditions without a catalyst in solvents such as ethylene glycol, diethylene glycol, sulfolane or pyridine.³

History of the Reaction

This reaction was first completed by Emil Fischer and Friedrich Jourdan in 1883. They treated pyruvic acid 1-methylphenylhydrazone with alcoholic hydrogen chloride to form 1-methylindole-2-carboxylic acid.⁴



Fischer realized the complexity of this reaction. He wrote, “Its behavior towards acids is quite remarkable. If the same is warmed in 10% hydrochloric acid it turns reddish-yellow and goes into solution. On stronger heating the coloration disappears and fine, colorless needles separate... A noticeable amount of ammonia is present in the acid liquid... This process is so remarkable that for the time being we dare not venture an explanation for the reaction.”⁵

Emil Fischer

Emil Fischer is perhaps one of the most notable and successful chemists of all time. He was born on October 9, 1852 in Euskirchen, Germany. He attended a private school in his youth and then attended the University of Bonn to study physics. After a year at Bonn, he transferred to the University of Strasbourg where he met his most influential mentor Adof von Baeyer. Under Baeyer, he received his PhD in chemistry from Strasbourg in 1874 with a dissertation on the phthalein dyes fluorescein and orcin-phthalein. From there, he served as a professor at the University of Erlangen, the University of Wurzburg, and the University of Berlin. He was appointed chairman of the chemistry department at Berlin, where he served until his death in 1919.⁶

Fischer made his first great discovery in 1875 when he was first to successfully synthesize phenylhydrazine by reaction of aniline with potassium hydrogen sulfite. This opened the door to much research on phenylhydrazines, which eventually led to the Fischer indole synthesis. Besides his research in organic chemistry, Fischer is also known for his work on amino acid and enzymes. He is considered a founder of peptide chemistry and a pioneer in biochemistry.⁵ In 1894, he proposed the well-known lock and key model for enzyme action. This idea states that enzymes are unique asymmetric molecules, and their orientation must be compatible to other molecules in order to catalyze a reaction.⁷

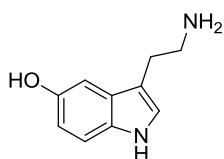
Fischer went on to study sugars and purines in depth. He synthesized over 130 purines and was the first chemist to successfully synthesize a nucleotide. He synthesized the purines barbital and phenobarbital, which are used as sedative and hypnotic drugs.⁶ Between 1891 and 1894, he established the stereochemical configuration of all the known sugars and identified their possible isomers. In addition, he structurally characterized and synthesized glucose, fructose, and mannose from glycerol. For these advances, Emil Fischer received the Nobel Prize in 1902.⁸

Application:

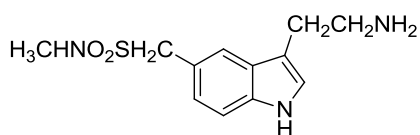
There are many naturally occurring indole derivatives that are of significant interest to chemists. The ancient dye indigo, the amino acid tryptophan, the plant hormone heteroauxin, and the neurotransmitter serotonin are all indole derivatives. An indole called skatole is also found naturally in jasmine and citrus oils and is widely used in fragrances.⁹

Tryptophan metabolites are important to the biological chemistry of plants and animals. The search for specific agonists and antagonists of these compounds has been a large pursuit of pharmaceutical chemistry for many years.⁹ Perhaps the most impressive application of

the Fischer indole synthesis is its use to synthesize agonists for the neurotransmitter serotonin. Serotonin is known to exhibit antimigrane activity, so serotonin-like compounds have been synthesized as receptor agonists for the treatment of migraine headaches. The first drug of this kind to be commercialized was Sumatriptan. The structures of serotonin and Sumatriptan are compared below.²

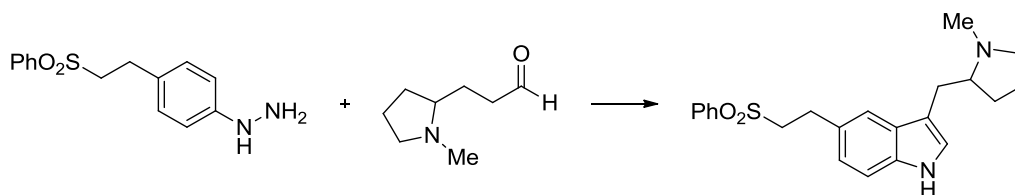


Serotonin



Sumatriptan

Today chemists are still using the Fischer indole synthesis to create new drugs. For example, in a paper published in 2011 researchers proposed using a Fischer indole synthesis method to help commercialize a newer antimigrane drug called Eletriptan. They claimed that the Fischer indole synthesis led to improve manufacturing and consequently increased output. The reaction they proposed is shown below:¹⁰



Conclusion:

Since its discovery over one hundred years ago, the Fischer indole synthesis has grown to be a well-respected and widely used reaction in organic chemistry. It provides an effective and versatile method for synthesizing indoles, a class of compounds with much importance in biological chemistry. The reaction's greatest application lies in pharmaceutical chemistry and the production of commercialized antimigrane drugs.

References:

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