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Synthesis and characterisation of oxindole derivative from p- Toludene

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Abstract

The oxindole derivatives are synthesized and characterized by 5-methyl- 1,3-Dihydro-indol-2-one by preparation of 2-chloro-N-p-tolyl-acetamide and cyclisation of 2-chloro-N-p-tolyl-acetamide. The structures and characterisation of products were established by FT-IR and NMR techniques. The chemistry of oxindoles display a wide range of biological activities such as antiviral, antifungal, antibacterial, antiproliferative, anticancer, anti-inflammatory and the anticonvulsant activity. The oxindoles and their derivatives has made them very important in synthetic organic and medicinal chemistry.

Keywords: Oxindole, 5-methyl- 1, 3-Dihydro-indol-2-one, 2-chloro-N-p-tolyl-acetamide, p-toludene, dichloromethane, triethylamine, chloroacetyl chloride

Introduction

A cyclic organic compound containing all carbon atoms in ring formation is referred to as a carbocyclic compound. If at least one atom other than carbon forms a part of the ring system then it is designated as a heterocyclic compound. Nitrogen, oxygen and sulfur are the most common hetero atoms but heterocyclic rings containing other hetero atoms are also widely known.

Heterocyclic compounds may be classified into aliphatic and aromatic. The aliphatic heterocyclics are the cyclic analogues of amines, ethers, thioethers, amides, etc.

Their properties are particularly influenced by the presence of strain in the ring. These compounds generally consist of small (3- and 4- membered) and common (5 to7 membered) ring systems. The aromatic heterocyclic compounds, in contrast, are those which have a heteroatom in the ring and behave in a manner similar to benzene in some of their properties.

Furthermore, these compounds also comply with the general rule proposed by Hückel.

Heterocyclic compounds played a vital role in biological processes and are wide spread as natural products. They are widely found in nature particularly in nucleic acids, plant alkaloids, anthocyanin's and flavones as well as in haem and chlorophyll. Additionally some vitamins, proteins and hormones have aromatic heterocyclic system. Synthetically produced heterocyclic designed by organic chemists are used for instance as agrochemicals and pharmaceuticals which play an important role in human life.

Hetero cycles have enormous potential as the most promising molecules as lead structures for the design of new drugs. They play an indispensable role in the field of medicine.

Heterocyclic compounds are also finding an increasing use as intermediate in organic synthesis [1-4]. Very often this is because a relatively stable ring system can be carried through a number of synthetic steps and then cleaved at the required stage in a synthesis to reveal other functional groups

Oxindoles are endogenous aromatic organic compounds that are found in the tissues and body fluids of mammals, and in the natural products of some plants. They are aromatic heterocyclic organic compounds with a bicyclic structure. An oxindole molecule consists of a six membered benzene ring that is fused to a five-membered ring containing nitrogen. Oxindole's structure is based on the indoline structure but where a carbonyl is situated at the2-position of the 5 membered ring [5] (Fig.1) Molecular refraction studies and analytical data show that the molecular formula is C_8H_7NO and it is isomeric with indoxyl and obtainable by reduction of isatin. The systematic IUPAC name is 1,3-dihydro-indol-2-one and its molecular mass is given by 133.15g/mole, the melting point of oxindole is 128^{o}C.

Oxindole and its derivatives are used as a starting material in the synthesis of various organic compounds and drugs. The reactions can be performed on different reactive sites of oxindole which are the carbonyl group, C-3 site, nitrogen atom, and aromatic ring. In addition, they are also versatile substrates in one-pot and domino reactions. [6]

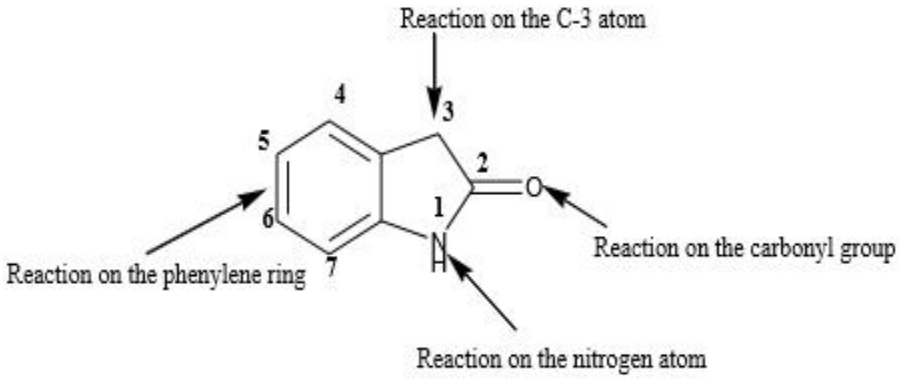
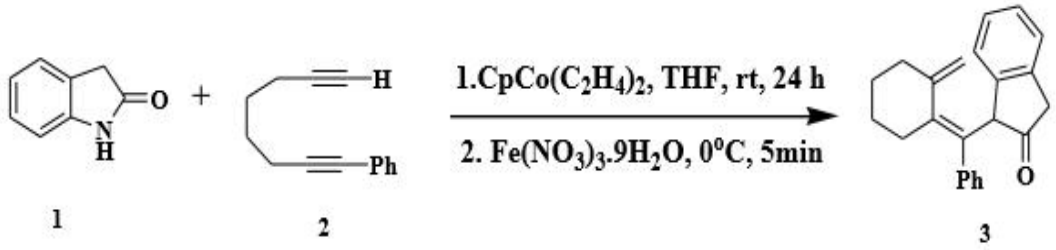


Fig.1: Oxindole structure

Reaction on the Nitrogen atom:

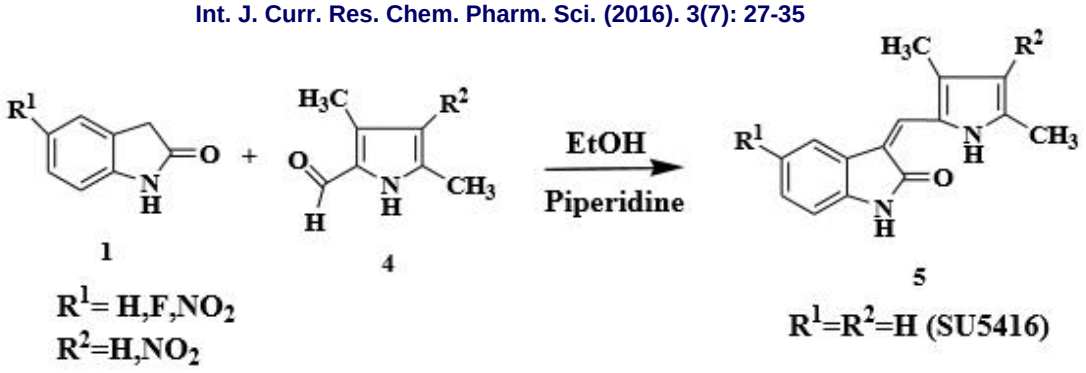
Oxindole**1** in the presence of a cobaltocyclopentadiene complex $CpCo(C_2H_4)_2$ reacts with α,-diynes**2** to give new dienamides**3** with control of region- and stereochemistry (**Scheme 1**). Dienamides are starting materials for the preparation of polycyclic systems [7].



Scheme -1

Reaction on the C-3 site:

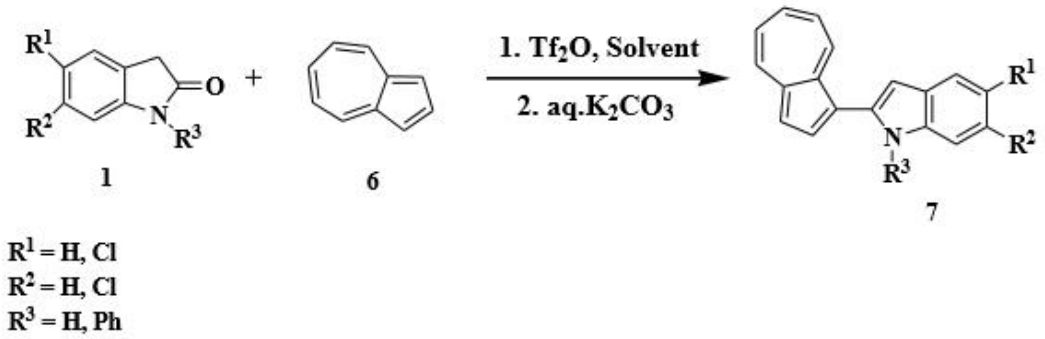
In oxindole, C-3 has two acidic hydrogen atoms that can be reacted separately or together. The reaction of various substituted oxindoles **1** with 3,5-dimethylpyrrol-2-carbaldehyde derivatives **4** under Knoevenagel condensations afforded an array of nitro-substituted derivatives of Semaxinib **5** (SU5416) in good yields (**Scheme2**). Semaxinib is a potent inhibitor of signaling activity of the Receptor Tyrosine Kinases (RTKs) for the vascular endothelial growth factor (VEGF)[8].



Scheme-2

Reaction on the carbonyl site:

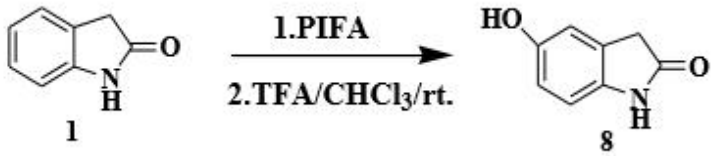
Reaction of azulene derivatives **6** with oxinoles**1** in the presence of Tf_2O and following hydrolysis with aq.K_2CO_3 afforded 2-(azulen-1-yl) indoles**7** in good yields (**Scheme 3**). This methodology is the first synthesis of such indole-substituted azulenes [8].



Scheme-3

Reactions on the aromatic ring:

Treatment of oxindole 1 with phenyliodine (III) bis (trifluoroacetate) (PIFA) in trifluoroacetic acid introduced a hydroxyl group at the aromatic ring of oxindole **8**. **(Scheme**- **4**)[9].



Scheme - 4

Oxindoles constitute an important structural motif in various natural products. For example there are two groups of oxindole alkaloids in the cat's claw plant *Uncariatomentosa* (Rubiaceae): pentacyclic oxindole alkaloids (POAs) and tetracyclic oxindole alkaloids (TOAs). POAs include pteropodine, isopteropodine, speciophylline, uncarine F, mitraphylline, and isomitraphylline, and TOAs include rhynchophylline, isorhynchophylline, corynoxeine, and isocorynoxeine (**Fig. 2**). Cat's claw is a woody, tropical vine indigenous to the Amazon rainforest and other tropical areas of South and Central America. It is used for the treatment of infection, cancer, gastric ulcers, arthritis and other inflammatory processes [10-14].

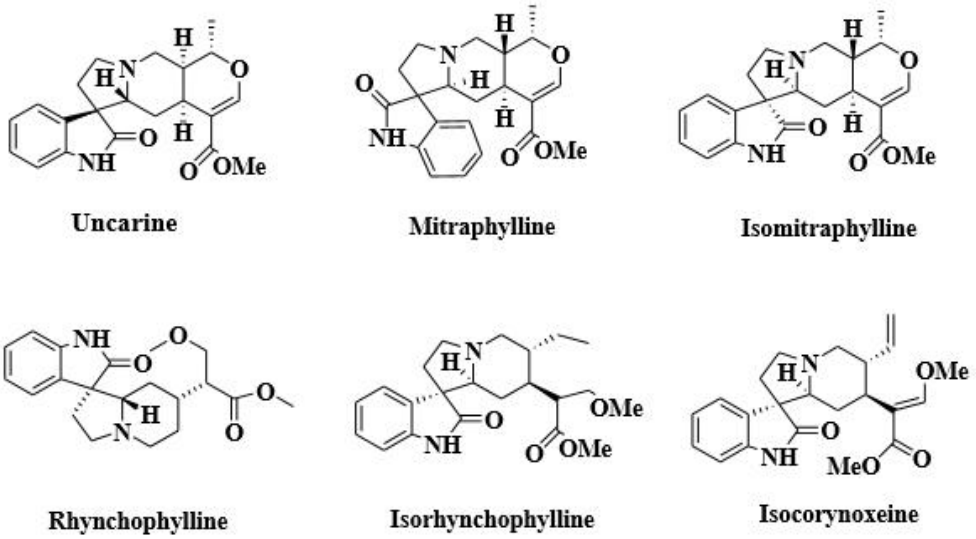


Fig. 2: Alkaloids having an oxindole nucleus

Oxindoles are credited to have a wide range of applications and are reported to exhibit an extensive range of biological effects. Indolin-2-one (Sunitinib) has been widely used in the treatment of gastrointestinalstromal tumors, and metastatic renal cell cancer. Oxindole-Schiff base copper (II) complexes have shown potentialantitumor activity towards different cells. Oxindole derivatives such as indolidan and adibendan are used for the treatment of congestiveheart failure as these have strong vasodilatory, positiveinotropic and inodilatory actions.

Amino methylene oxindole derivatives are useful as antihypertensive agents. 5-fluoro oxindole, 6-chloro oxindole, 6-fluoro oxindole, 7-chloro oxindole, 5-fluoro-1-methyl oxindole, 5-chloro-1-ethyl oxindole shows sleep inducing actions. Oxindole-oxazolidinone derivatives are the most important class of antimicrobials. Synthetic oxindoles moiety containing compounds exhibit useful pharmaceutical properties, including growth hormone secretagogues, analgesic,anti-inflammatory serotonergic. Most of these compounds contain a variety of substituents at the C-3 position of oxindole, and some of them are 3-spirooxindoleswhich possess P-glycoprotein multiple drug resistance inhibitors, antibacterial, and antiprotozoal properties [15-23].

Examples of some bioactive oxindoles are shown in **(Fig.3)**.

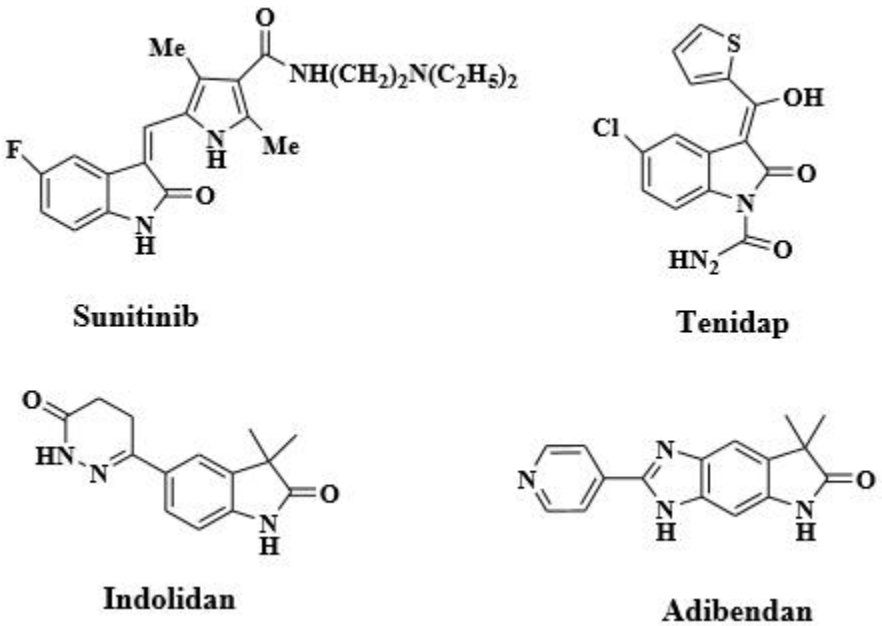


Fig.3: Examples of some bioactive oxindoles.

The presence of complex molecular architectures coupled with impressive pharmacological properties prompted several research groups to contribute significantly to the construction of oxindole derivatives. However, the quest for the development of a simple and efficient method to access this class of compounds from readily available starting materials still remains an area of active research.

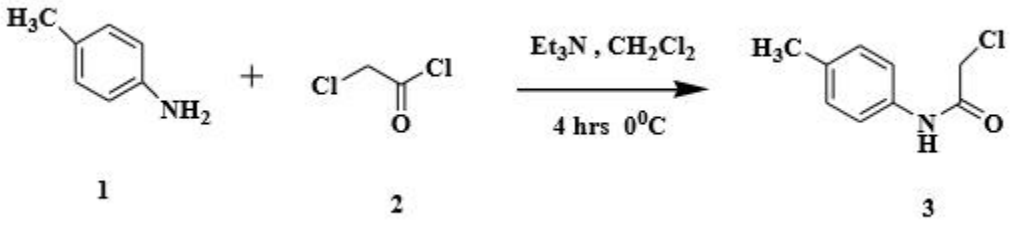
Experimental work

Synthesis of 5-methyl-1,3-Dihydro-indol-2-one

i) Preparation of 2-chloro-N-p-tolyl-acetamide(3):

To a solution of p-toludene (1) (10g, 109.52 mmole) in dichloromethane (250ml) was added triethylamine (30 ml, 215.23 mmol) and then the reaction mixture was cooled 0^0C.

Then chloroacetyl chloride (2) (13 ml, 163.44 mmol) was added drop wise and the reaction mixture was stirred at room temperature for four hour. The reaction mixture was diluted with dichloromethane, washed with water and dried over sodium sulphate and the solvent was evaporated under reduced pressure to obtained crude product as brown viscus oil. The crude product was titrated with diethyl ether and solid obtained was collected by filtration, washed with diethyl ether and dried to obtain 2-chloro-N-p-tolyl-acetamide (3).

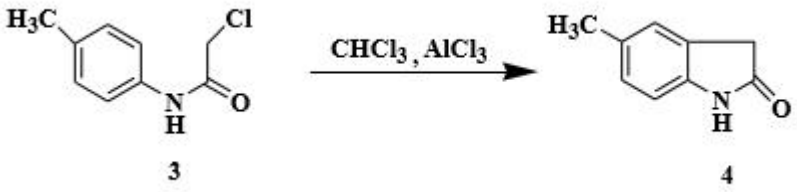


1 2 3

Colour : Brown solid
Melting Point : 158^{o}C
Yield : 76 %

ii) Cyclisation of 2-chloro-N-p-tolyl-acetamide:

2-chloro-N-p-tolyl-acetamide **(3)** (15g, 88.43 mmol) dissolved in chloroform (40 ml) at atmospheric temperature. To this solution aluminum chloride (90 g) was added portion wise. The contents were refluxed on an oil bath preheated to 120^0C to 130^0C. The reaction monitored through thin layer chromatography. After the completion of the reaction the contents were then cooled and poured into ice-cold water with stirring. The layer that separated was extracted with ethyl acetate, the organic layer was washed twice with water and dried over anhydrous sodium sulphate. After the removal of the solvent under reduced pressure to give 5-methyl-1,3-Dihydro-indol-2-one **(4)**.



3 4

Colour : Brown solid
Melting point : 144^{0}C
Yield : 63 %

Thin Layer Chromatography:

Thin layer chromatography was done by using dichloromethane as solvent and a mixture of petether and ethylacetate as elutent (4:1).

FT-IR:

FT-IR spectra of the products were recorded using shimadzu spectrophotometer in the range of 500 – 4000 cm^{-1}.

NMR:

^{1}H NMR and ^{13}C NMR were registered using $CDCl_3$ as solvent chemical shift were expressed in δ units (ppm) and quoted downfield from TMS as internal standard by the instrument Brucker. W.M.

Results and Discussion

Spectral Analysis of 2-Chloro-N-p-tolyl-Acetamide (3):

FT-IR Spectral data:

FT-IR spectrum of compound 2-chloro-N-p-tolyl-acetamide, is depicted in the **Fig. 4.**

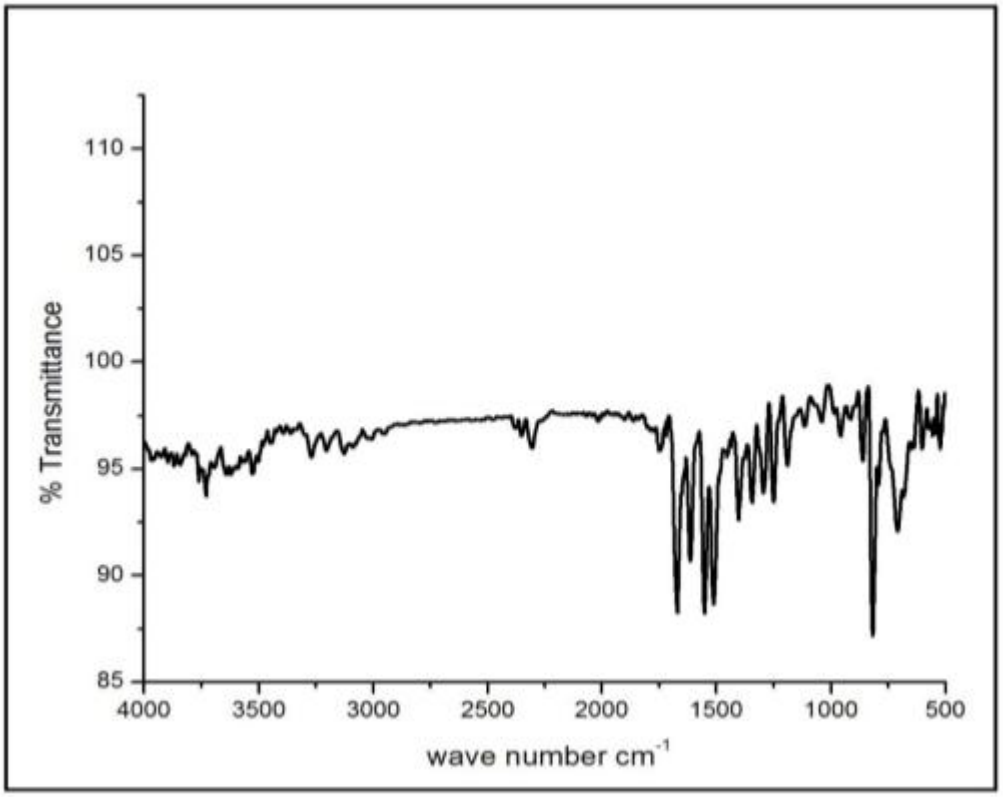


Fig.4. FT-IR Spectrum of 2-chloro-N-p-tolyl-acetamide

The band at 3733 cm^{-1} is due to NH stretching. C=O stretching is found at the range 1671 cm^{-1}.The aromatic the band at 1540 cm^{-1} is due to C=C stretching. The aromatic C-N stretching observed at 1279 cm^{-1}. A band is found at the range at 817 cm^{-1} is due to the C-Cl stretching.

NMR Spectra:

^{1}H NMR Spectral data:

The ^{1}H NMR in ($CDCl_3$) of the compound 2-chloro-N-p-tolyl-acetamide is depicted in **Fig. 5.** A peaks atδ 2.47ppm appeared as singlet for methyl group, The two protons at C_2,carbon appear as singlet at δ 3.99 ppm. The four aromatic protons at C_2, C_3, C_5, C_6, stand responsible for the multiplet appeared between δ 7.05 – 7.43 ppm. Another peak appears as a broad singlet at δ 10.20 ppm indicates the presence of N-H proton.

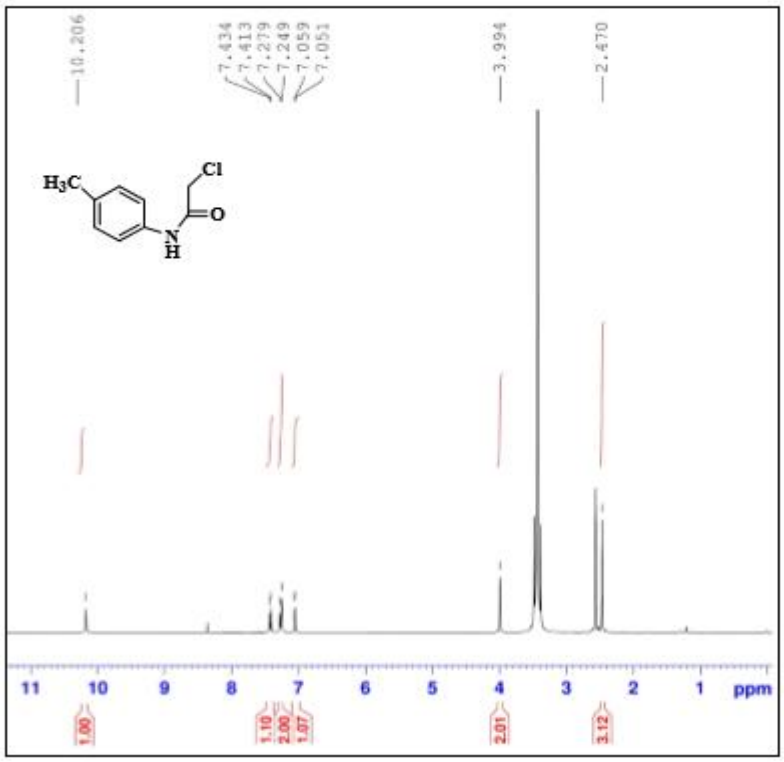


Fig.5.^{1}H NMR spectrum of 2-chloro-N-p-tolyl-acetamide

Spectral Analysis of 5-methyl-1,3-Dihydro-Indol-2-One (4):

FT-IR Spectral data:

FT-IR spectrum of compound 5-methyl- 1,3-Dihydro-indol-2-one is depicted in the **Fig.6.** The band at 3186 cm^{-1}is due to NH stretching. The aromatic C-H stretching observed at3055 cm^{-1} and 2924 cm^{-1}. C=O stretching is found at the range 1638 cm^{-1}. The band at 1475 cm^{-1} is due to C=C stretching. A band is found at the range at 1300 cm^{-1} is due to the C-N stretching.

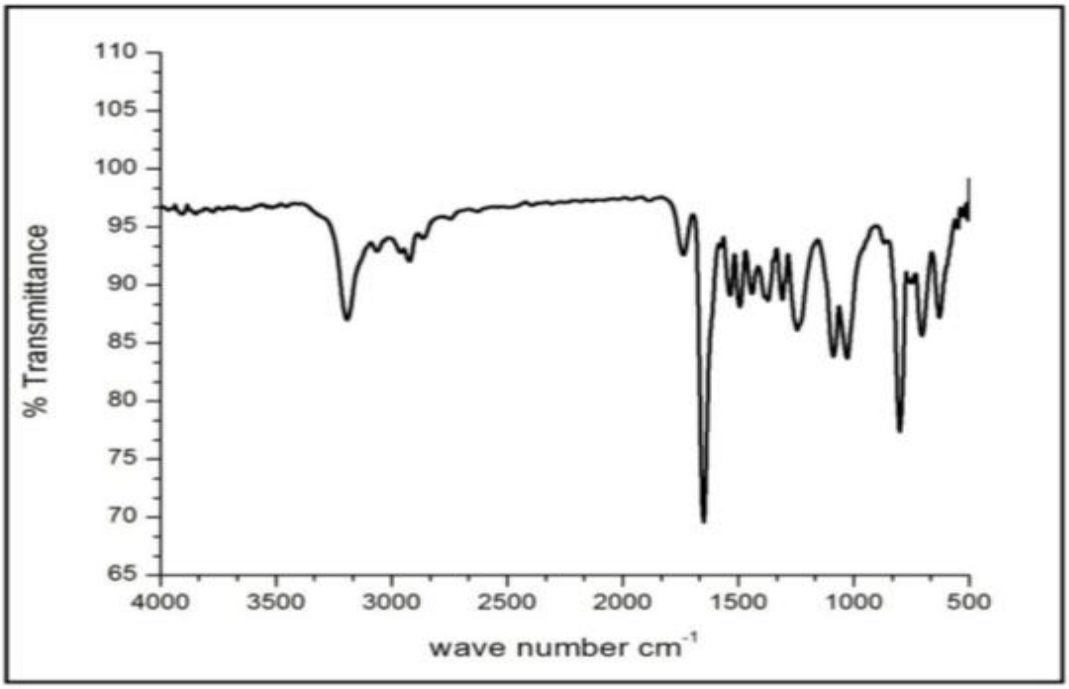


Fig.6. FT-IR spectrum of 5-methyl-1,3-Dihydro-indol-2-one

^{1}H NMR Spectral data:

The ^{1}H NMR in ($CDCl_3$) of the compound 5-methyl-1,3-Dihydro-indol-2-one is depicted in **Fig7.** A peaks at δ 1.24 ppm appeared as singlet for methyl group, The two protons at C_3 carbon appear at singlet at δ 2.57 ppm. The three aromatic protons at C_4, C_6, C_7, stand responsible for the multiplet appeared between δ 7.17 – 7.75 ppm. Another peak appears as a broad singlet at δ 10.08 ppm indicates the presence of N-H proton.

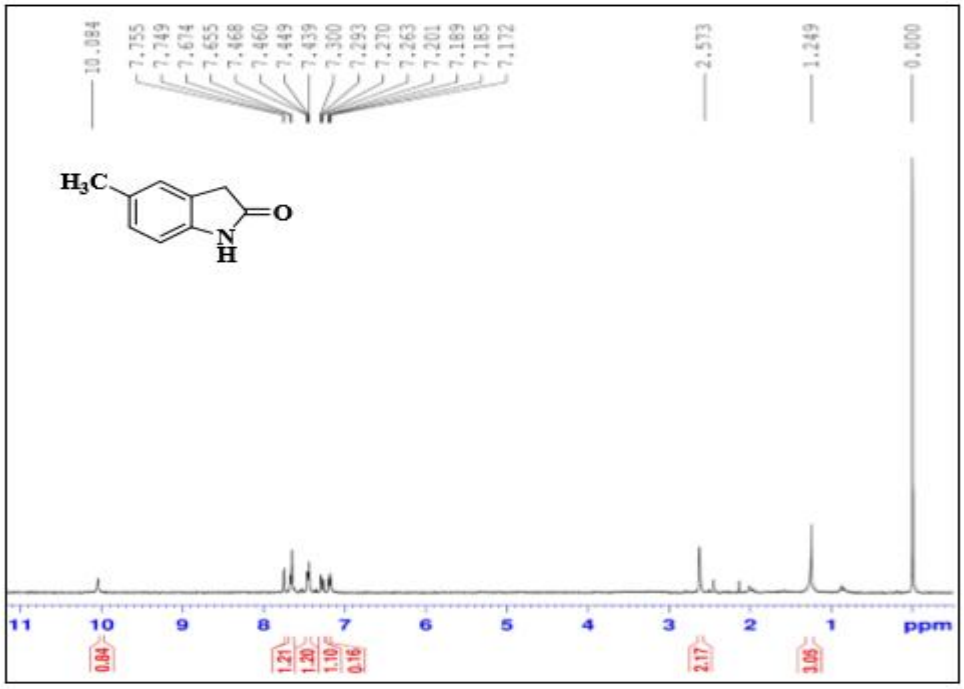


Fig.7.^{1}H NMR spectrum of 5-methyl-1,3-Dihydro-indol-2-one

^{13}C NMR Spectral data:

The appearance of 9 distinct peaks in the ^{13}C-NMR spectrum (in $CDCl_3$) confirms the molecular structure of 5-methyl-1,3-Dihydro-indol-2-one (4) **Fig.8.** The peak at δ 21.50 ppm is due to the CH_3 carbon atom, the peak at δ 42.84 ppm is due to the C_3 carbon atom, the solvent $CDCl_3$ show three peaks at δ 76.64 – 77.49 ppm, the six peaks appeared between δ 124.07 - 135.10 ppm is due to C_4, C_5, C_6, C_7, C_8, C_9, aromatic carbon atoms, C=O carbon appeared at δ 167.83ppm.

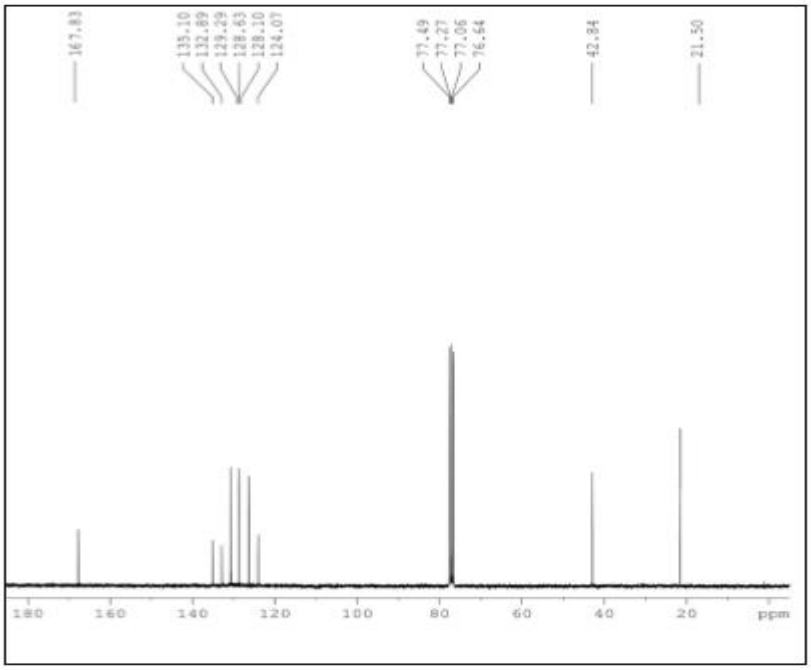


Fig.8. ^{13}C NMR spectrum of 5-methyl-1, 3-Dihydro-indol-2-one

Summary

We have reported the synthesis of 5-methyl-1,3-Dihydro-indol-2-one (**4**). Via; nucleophilic substitution reaction of chloroacetyl chloride and aniline to furnish the respective 2-chloro-N-p-tolyl-acetamide, which on heating with aluminium chloride catalyst, cyclization gave 5-methyl- 1,3-Dihydro-indol-2-one in good yield. The different functional groups in the product were confirmed by satisfactory vibrational band assignment in the FT-IR spectrum. The assignments of various peaks in ^{1}H-NMR spectra for the different kinds of protons and ^{13}C-NMR spectra for different kinds of carbon atoms have been successfully carried out. The 5-methyl-1,3-Dihydro-indol-2-one can act as a precursor for various biologically active compounds.

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