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Synthesis, Reaction and Biological Importance of Isatin Derivatives

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ABSTRACT

Isatin is a heterocyclic nitrogen compound that has attracted much interest in recent years due to its diverse biological and pharmacological activities. It can be used in many medical and biological applications, such as antidiabetic, antibiotic, and anticancer agents. The isatin molecule can also be prepared from different substrates by various methods, such as the methods of Sandmeyer, Stolle, Gassman, Meanwell and Hewawasam and others. On the other hand, the isatin molecule can undergo various chemical reactions, such as oxidation, Friedel-Crafts reaction, ring expansion, aldol condensation, and alkylation reactions. As a result of these reactions, several biologically useful biomolecules are formed, including 2-oxindoles, tryptanthrin, indirubins and others. Therefore, the aim of this review was to provide an overview of the synthetic methods of the isatin molecule and its derivatives and to examine the various chemical reactions it undergoes. In addition, a list of some of the recently documented biological activities of isatin derivatives was compiled, such as antidiabetic, antibacterial, anticancer, and other properties.

1. Introduction

Heterocyclic compounds are a type of organic compounds that exhibit a wide range of biological and pharmacological activities. One such biologically active heterocyclic compound is isatin, or 1*H*-indole-2,3-dione, also known as indole quinone or indenedione. It has a nitrogen atom in position 1 and two carbonyl groups in positions 2 and 3. It is consisting of two cyclic rings, one with six members and the other with five. The two rings are flat. The ring with six members is aromatic and the ring with five members has anti-aromatic character (Varun, et al., 2019). Figure 1 shows the chemical structure of isatin molecule.

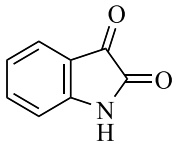

Fig. 1. Isatin structure

Erdmann and Laurent discovered isatin for the first time as an indigo oxidation product made using nitric and chromic acids (Erdmann, 1840; Laurent, 1840). It precipitates as orange-red monoclinic prism crystals from water, alcohol, or acetic acid. Isatin and its derivatives are found naturally in plants and animals. It is a component of secretion from the parotid gland of Bufo frogs and is found as a metabolic derivative of the adrenaline hormone in humans. *Melochia tomentosa*, a *Caribbean tumorigenic* plant, yielded methoxy phenylpentyl isatins (melosatin alkaloids), while *Chaetomium globosum* yielded 5-(3'-methylbut-2'-yl)isatin (Silva et al., 2001).

For the preparation of various isatin derivatives, the Sandmeyer, Stolle, Gassman, and Martinet methods are the most popular. In addition, a number of unique and environmentally friendly synthetic methods for the

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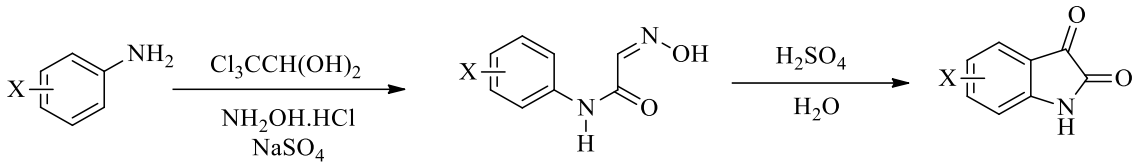
preparation of isatin derivatives have recently been described and are discussed here.

Moreover, isatins undergo to different chemical reactions such as Friedel-Crafts, ring expansion, oxidation reaction, and aldol condensation. These chemical reactions can be used in synthesis of other biologically essential derivatives such as tryptanthrin, indirubin, and 2-oxindoles. A review of the literature showed that isatin and its compounds have anti-cancer, antibacterial, antifungal, anticonvulsant, antitubercular, antiHIV, (Li et al., 2018) antioxidant, (Yakan et al., 2021) anti-inflammatory and analgesic (Obafemi et al., 2021). In addition, Isatin derivatives are used in a variety of industrial uses, including corrosion inhibitors (El-Ghamry et al., 2022) and the dyes industry (Younis et al., 2022).

Since the isatin molecule plays an important role in the building of biologically active compounds used in many medical and pharmaceutical applications, this study focused on summarizing the recent literature on the synthesis, chemical and biological uses of isatin and its derivatives.

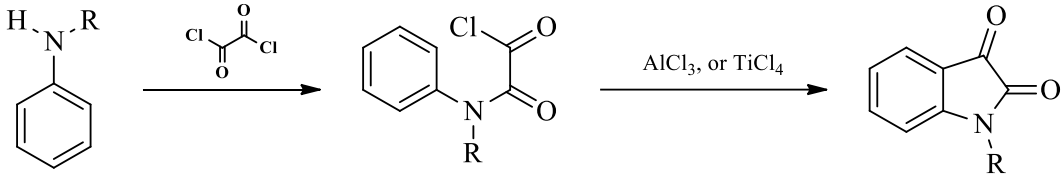
2. Synthesis of Isatin

Sandmeyer introduced the first method for the synthesis of isatin via the reaction of aniline with chloral hydrate ($Cl_3CCH(OH)_2$) and hydroxylamine hydrochloride ($NH_2OH.HCl$) to form isonitrosoacetanilide in an aqueous solution of sodium sulfate. Cyclization of isonitrosoacetanilide to isatin is achieved after treatment with concentrated sulfuric acid. The Sandmeyer method is very effective with aniline derivatives containing electron-removing groups, such as 2-nitroaniline (Sandmeyer, 1919). Scheme 1 represents Sandmeyer method for synthesis of isatin.



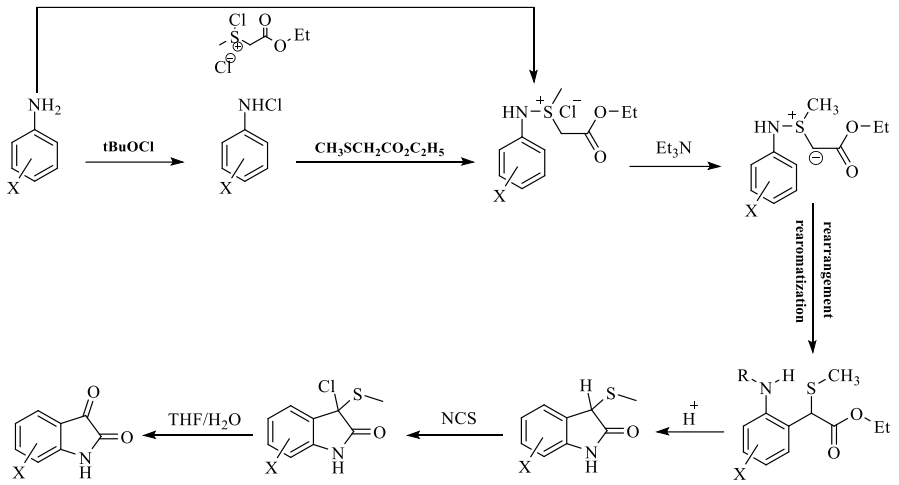
Scheme 1 Sandmeyer method for the synthesis of isatin

Despite its efficacy, The Sandmeyer method has some limitations, such as requiring harsh conditions, failing if the aniline contains electron-donating groups, forming regioisomers mixtures, and generally yielding moderate yields. Some scientists have developed more successful methods than the Sandmayer method to overcome these limitations. The Stolle method, which is an important alternative to the Sandmeyer method, involves reacting N-substituted anilines with oxalyl chloride to form chlorooxalylanilide, which can then be cyclized by Lewis acids such as ($AlCl_3$, or $TiCl_4$) to form N-aryl isatin derivatives (Stollé et al., 1922). Scheme 2 represents Stolle method for the synthesis of isatin.



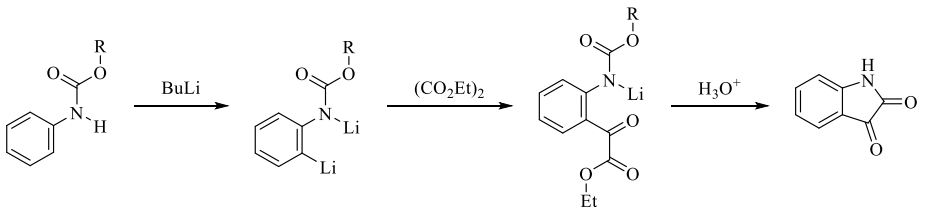
Scheme 2 Stolle method for the synthesis of isatin

As another solution, Gassman described two general strategies of isatin synthesis (Scheme 3) including the conversion of substituted anilines into oxindoles, which give the corresponding substituted isatins upon subsequent oxidation depending on the nature of the electronic effects of the substituents attached to aniline ring. The first strategy used when electron-withdrawing groups are attached to aniline ring, includes treating anilines with tert-butylhypochlorite at low temperatures to produce N-chloroaniline intermediate, which then reacts with methylthioacetate ester to produce azasulfonium salts. The second strategy used when of electron-donating groups attached to the aniline ring. This strategy uses the reaction of a chlorosulfonium salt (obtained by reacting the methylthioacetate ester with chlorine) with an appropriate aniline because the Electron-donating groups tend to decrease the stability of the N-chloro intermediates, resulting in lower yields of azasulfonium salt (Gassman & Van Bergen, 1974).



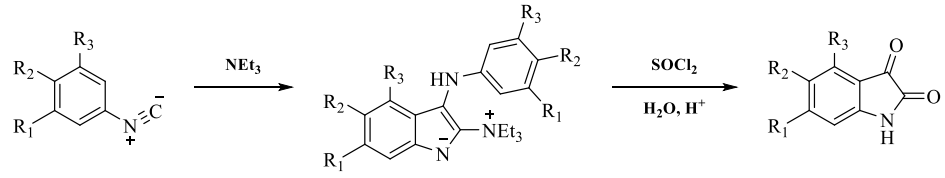
Scheme 3 Gassman method for the synthesis of isatin

Although Stolle and Gassman's techniques solved many of the difficulties of the Sandmeyer approach, they all lack regioselectivity, particularly in the case of meta-substituted anilines, where a mixture of 4- and 6-substituted isatins is obtained. Meanwell and Hewawasam later introduced a new technique for the synthesis of isatins that is insensitive to the electronic nature of the substituents attached to the aromatic ring and is characterized by predictable regiochemical control. This approach relies on the creation of dianion when protected anilines are treated in THF at -78 ° C with an excess of a variety of butyllithium reagents (e.g., n-BuLi, s-BuLi, t-BuLi). The obtained dianions were then react with ethyl oxalate to produce isatins after deprotection and cyclisation processes of the intermediate α-ketoesters by using HCl. The benefit of this method is regioselectivity of the 4- substituted isatins synthesis from meta-substituted anilines where the substituent is a metalation directing group such as an amino protected group (Gassman et al., 1977). Scheme 4 represents Meanwell and Hewawasam method for synthesis of isatin.



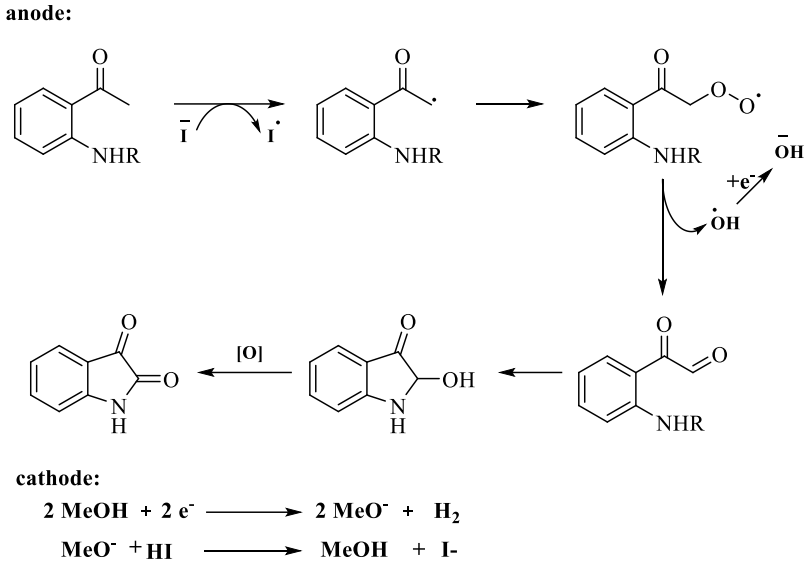
Scheme 4 Meanwell and Hewawasam method for the synthesis of isatin

Mironov revealed a versatile and unique two-step synthesis strategy for isatins with electron withdrawing groups like CF_3, NO_2, and Cl as shown in Scheme 5. The method is based on the reaction of aromatic isocyanides with tertiary amines to produce 2-triethylammonio-3-arylaminoindolates in the first step, which are then heated without isolation in excess thionyl chloride and hydrolyzed to yield the target isatins (Mironov & Mokrushin, 1998).



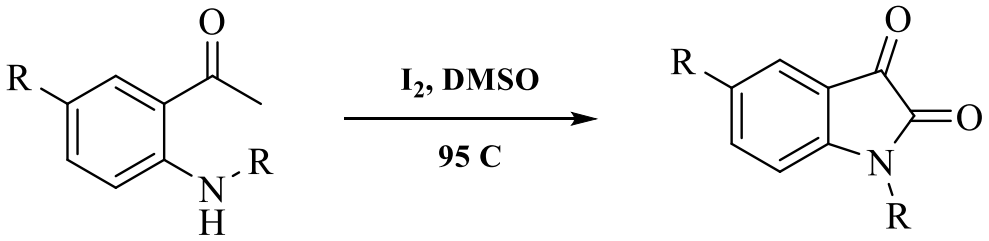
Scheme 5 Mironov synthesis strategy of isatins containing electron withdrawing groups

One of the modern strategies for the synthesis of N-alkylated isatins is the oxidation of indole derivatives. Peng Qian et al. described a versatile and ecofriendly isatin synthesis via electrocatalytic oxidation of 2′-aminoacetophenones. 2′-aminoacetophenones undergo a C-H oxidation followed by an intramolecular C-N bond formation via a simple electrochemical oxidation in the presence of n-Bu_4NI as the electrolyte and methanol as the solvent. This method produce various isatins of different substituted groups with good yields (Qian et al., 2017). Scheme 6 represents the synthesis of isatin by electrochemical oxidation reactions.



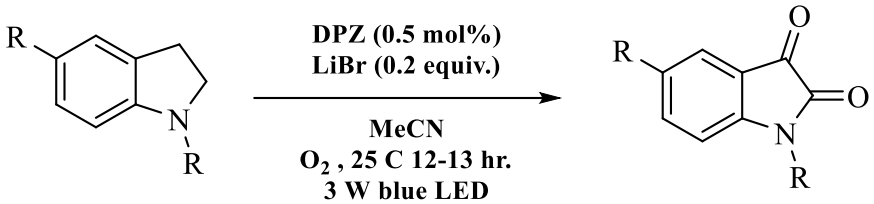
Scheme 6 Synthesis of isatin by electrochemical oxidation reactions

A new metal-free synthesis using I_2-DMSO as a catalyst has been developed for the synthesis of N-substituted isatins. Through C-H bond activation and subsequent inter-cyclization, N-alkylated and N-arylated isatins can be made from 2-amino acetophenones (Reddy et al., 2014). Scheme 7 shows the synthesis of isatin by chemical oxidation.



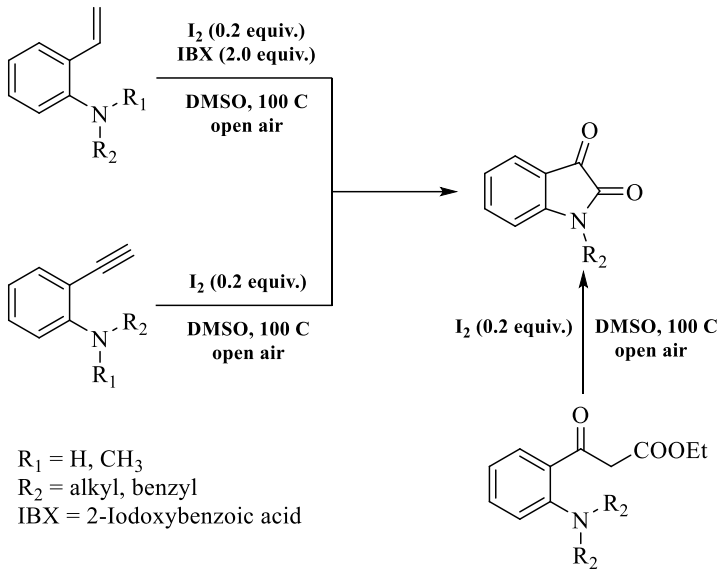
Scheme 7 Synthesis of isatin by chemical oxidation reactions

Zhang *et al.* reported an eco-friendly approach (Scheme 8) that involves the oxidation of indole in the presence of a photosensitizer (dicyanopyrazine derivative), with O_2 as the oxidizing agent (Zhang et al., 2016).



Scheme 8 Synthesis of isatin by photochemical oxidation reactions

Satish et al. (2015) developed an integrated multisubstrate domino method for the direct amidation of 2'-aminostyrenes, 2'-aminophenylacetylene, and 2'-amino-ketoesters to produce N-alkylated isatin derivatives as shown in Scheme 9. The significant benefit of this procedure is peroxide-free and metal-free synthesis of N-alkylated isatin derivatives.

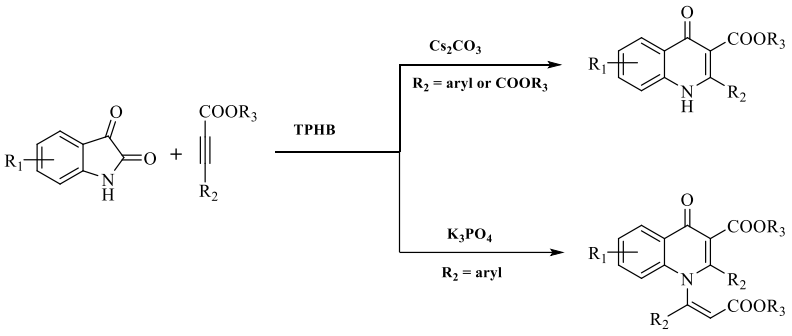


Scheme 9 Unified multisubstrate domino method for the synthesis of N-alkylated isatins

In summary, as we have noted, there are multiple routes for the synthesis of the isatin molecule from different starting materials, making it easier for researchers to synthesize this important molecule with a variety of options. For example, it is possible to rely on the methods of Sandmeyer, Stolle or Gassman for the synthesis of isatins with a high product. Or rely on the method of Meanwell and Hewawasam method in case of synthesis of isatins with high regiochemical control. It is also possible to rely on other green methods such as (Zhang, Raghavender, Qian) to save cost, time and environment, which are the best choice at present.

3. Reactions of Isatin

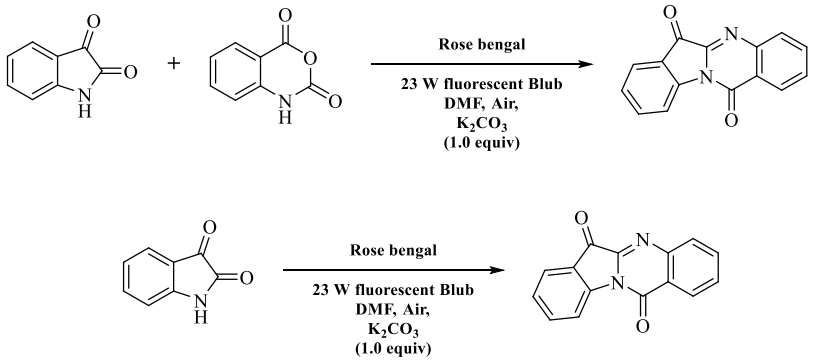
Isatin molecule can undergo to oxidation reaction in presence of chromic acid in acetic acid solution to yield isatoic anhydride. Isatoic anhydride, is an abundant employed compound in herbicide production and in medicinal chemistry (Sumpter, 1944). A simple and transition metal-free method for the oxidation of isatins was described, including an oxidative cyclization process using isatins and alkynes to prepare structurally diverse 4-quinolones. Intriguingly, Switchable access to substituted 1-vinyl-3-carboxylate-4-quinolones and 3-carboxylate-4-quinolones could be obtained by switching the reaction's base. The obtained products could undergo further transformations, increasing the application potential of the method in organic synthesis (Jiang et al., 2018). Scheme 10 represents Organocesium-catalyzed oxidation of isatin to isatoic anhydride.



Scheme 10 Organocesium-catalyzed oxidation of isatin to isatoic anhydride

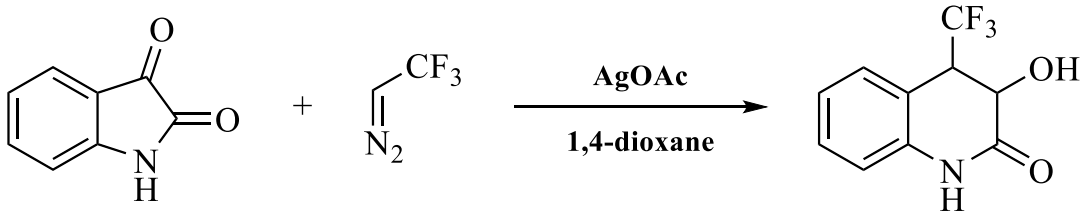
Tryptanthrin, another pharmacologically active molecule, can be prepared by oxidation of isatin or its 5-substituted derivatives with potassium permanganate (K_2MnO_4) in anhydrous acetonitrile (Moskovkina et al., 2013). In addition, a variety of tryptanthrins can be prepared by visible light catalyzed synthesis using a fluorescent organic dye. An energy transfer reaction process leads to the self-condensation of isatin as well as the cross-condensation of

isatin and isatoic anhydride. Irradiation of the reaction mixture with 23 W fluorescent light in the presence of Rose Bengal provides a transition metal-free, environmentally friendly, and cost-effective route to the synthesis of an important heterocycle (Hou et al., 2018). Scheme 11 represents organic dye-catalysed aerobic oxidation of isatins to tryptanthrins.



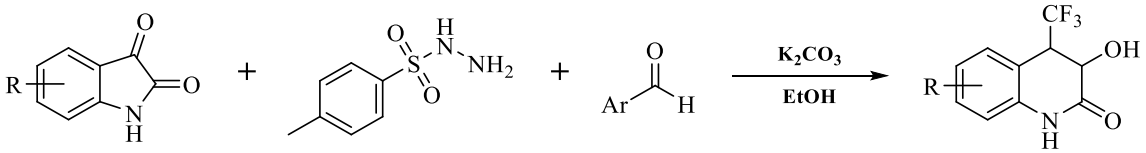
Scheme 11 Organic dye-catalysed aerobic oxidation of isatins to tryptanthrins

Reactions of ring expansion are useful in organic synthesis because they provide access to larger rings that would otherwise be difficult to construct using conventional techniques. The strong electrophilic nature of the C3 carbon of isatin allows ring expansion reactions to be carried out. The trifluoromethylative ring expansion reaction of isatin with trifluorodiazoethane has been established as a general method for the preparation of trifluoromethylated 2-quinolinones. This method provides a platform for the rapid synthesis of a wide range of substituted 3-hydroxy-4-trifluoromethyl-2-quinolinones. It is a simple and reliable Ag-catalysed technique that effectively converts isatin ketimines to 3-amino-4-trifluoromethylquinolinones in high yield (Jamali et al., 2020). Scheme 12 represents Ag-catalysed formation of isoxazoloquinolines.



Scheme 12 Ag-catalysed formation of isoxazoloquinolines

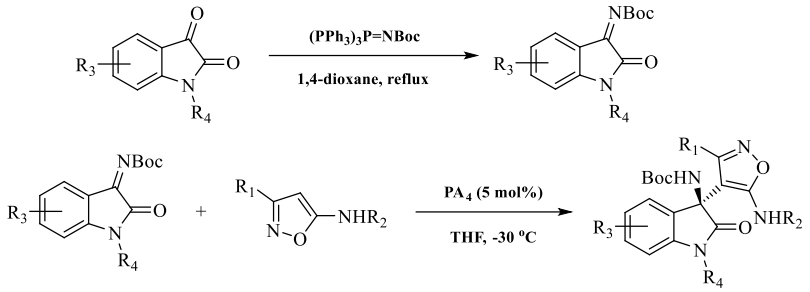
Under metal-free circumstances, (Tangella et al., 2018) described a unique efficient one-pot regioselective ring-expansion reaction of isatins with in situ produced -aryl/ heteroaryldiazomethanes for the production of viridicatin alkaloids as shown in Scheme 13. The protocol's utility is further demonstrated in the synthesis and scaling up of naturally occurring viridicatol, viridicatin, and substituted 3-O-methyl viridicatin.



Scheme 13 Synthesis of dibenzo[b,d]azepin-6-ones scaffold via two carbon ring expansion of isatin

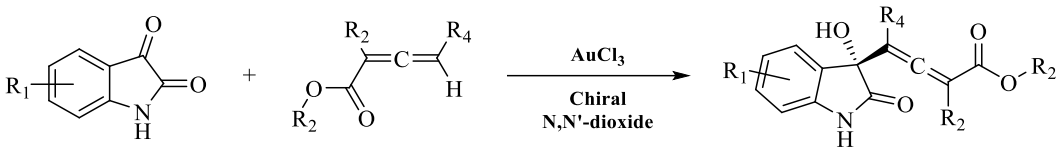
Friedel-Crafts reactions are a type of organic synthesis reaction that produces highly functionalized aromatic compounds, which can then be used to make pharmaceutically significant molecules (Bandini et al., 2004). The physiologically important and optically active 3-aryl-3-hydroxy-2-oxindoles derive from the asymmetric Friedel-Crafts alkylation of isatin with electron-rich aromatic molecules. The first and only effective asymmetric Friedel Crafts alkylation of isatins with pyrroles to yield oxindoles was reported by Franz and coworkers (Franz et al., 2011).

Furthermore, in order to improve the oxindoles' enantioselectivity, Liu and coworkers (Liu et al., 2021) used a chiral phosphoric acid as a catalyst with isatin-derived *N*-Boc ketimines was realized. The procedure yielded a wide range of new 3-isoxazole 3-amino-oxindoles with high yields and good to moderate enantioselectivity. Friedel-Crafts alkylation of isatins with pyrroles is shown in Scheme 14.



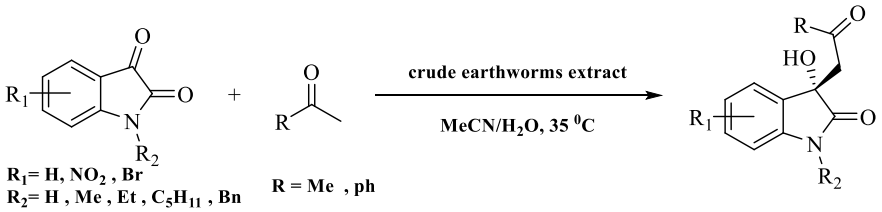
Scheme 14 Friedel-Crafts alkylation of isatins with pyrroles to give oxindoles

Aldol reactions yield β-hydroxyl carbonyl compounds, which are useful intermediates in the production of physiologically active derivatives. Isatin is an excellent substrate for condensation reactions because of its strong H-bond acceptor activity. Using a metal complex as the catalyst, the first diastereospecific and enantioselective alleno-aldol reaction of isatins with allenic esters yields tri- and tetra–substituted carbinol-allenoates (Wang et al., 2016). Scheme 15 shows Alleno-aldol condensation of isatins with allenic esters.



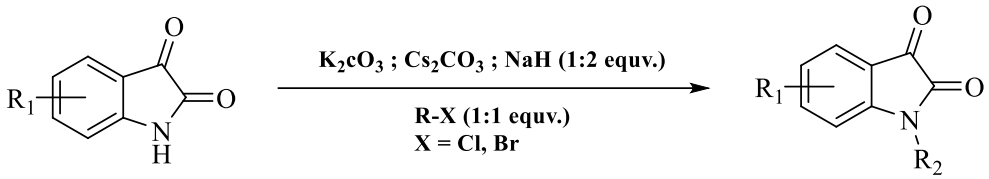
Scheme 15 Alleno-aldol condensation of isatins with allenic esters to give carbinol-allenoates

3-hydroxy-2-oxindoles derivatives can be gains easily an asymmetric cross-aldol reaction of simple ketones with isatins by crude extract from earthworms as effective and green biocatalyst in MeCN/H_2O (1:1) (Shams et al., 2020). Scheme 16 shows Cross aldol reaction of isatins with acetaldehyde.



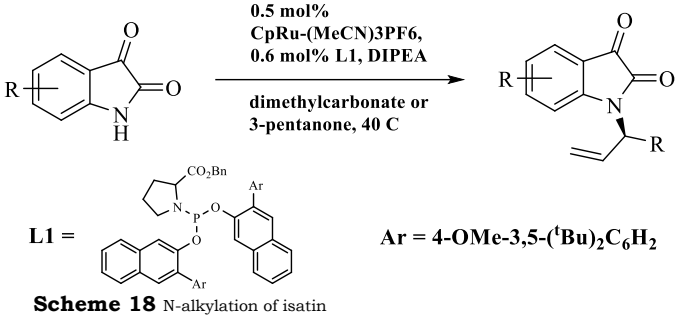
Scheme 16 Cross aldol reaction of isatins with acetaldehyde

Isatin alkylation is a synthetically feasible reaction that involves the utilization of an alkylating agent, usually an alkyl or aryl halide, in the presence of a base such as K_2CO_3, Cs_2CO_3 or NaH. It was recently synthesized using microwave radiation or heterogeneous or nano catalysts. The alkylation reaction rate depends on the alky halide reactivity used, so the reactions with high reactive alkyl halides need less time for completion (Alvin Tan et al., 2021; Kaur et al., 2021; Vine et al., 2007). N-alkylation of isatin is shown in Scheme 17.



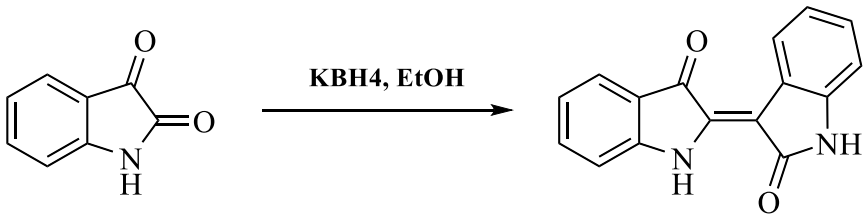
Scheme 17 N-alkylation of isatin

The synthesis of chiral isatin derivatives was made possible using a novel ruthenium-based catalytic system for branched-selective asymmetric allylic alkylation. The catalyst is synthesized in situ from CpRu-$(MeCN)_3PF_6$ and a BINOL-derived phosphoramidite, is both highly active and insensitive to moisture and air. In addition, The N-alkylated isatins obtained by this approach are flexible building blocks that can be easily converted into chiral analogs of achiral medicinal compounds (Trost et al., 2020). Scheme 18 shows N-alkylation of isatin.



Scheme 18 N-alkylation of isatin

The dimerization of isatins with 3- acetoxyindole in the presence by Na_2CO_3 in methanol produces Indirubin. It is a well-known cytotoxic compound and reported as inhibitors of cyclindependent kinase 1 (CDK1). The limited availability of 3- acetoxyindole and the low overall yield have impeded this dimerization technique. Indirubins were produced by dimerizing isatins (1 equiv.) with KBH_4 (0.5 equiv.) in ethanol or methanol to circumvent these constraints, according to a recent study (Wang et al., 2017). Scheme 19 shows dimerization reaction of isatin.



Scheme 19 Dimerization reaction of isatin

4. Biological Applications of Isatin

4.1. Anti-Cancer Activity

Cancer has been a rapidly rising problem worldwide under the current scenario. Worldwide, 8.8 million people have died of cancer, according to the WHO 2015 World Health Observatory Survey. By 2030, almost two hundred million new cases of cancer worldwide and 17 million deaths from cancer are expected annually. Therefore, developing new powerful anticancer agents with both selectivity and lower toxicity is a great challenge for researchers. Researchers also extensively investigated the anti-cancer efficacy of isatin and its derivatives. Sunitinib V and toceranib phosphate shown in Figure 2, both commercially approved anticancer medications, include isatin as a key pharmacophore unit (Yousef et al., 2020).

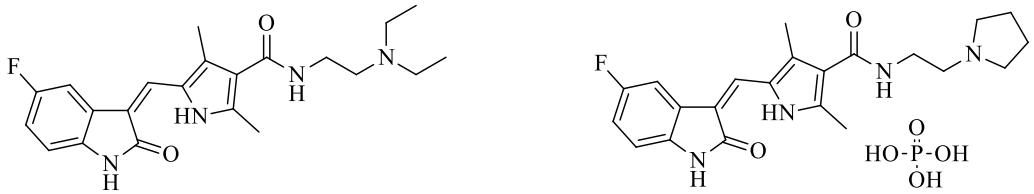


Fig. 2. Isatin derivatives as anti-cancer activity (Yousef et al., 2020)

Microtubules, the primary cytoskeletal filaments, are involved in a variety of cellular functions, including cell formation and form maintenance, as well as mitosis and cell division. Antimitotic drugs work by interfering with microtubule dynamics by attacking tubulin, a major protein portion of microtubules and thus one of the most critical strategic targets for creating new anticancer drugs. So far, six tubulin families have been identified: α-, β-, γ-, δ-, ε-, and ζ-tubulin. Microtubules, on the other hand, are made up entirely of α- and β-tubulin, so developing inhibitors for them could improve cancer treatment (Jordan & Wilson, 2004; Vindya et al., 2015). Sharma *et.al* were reported synthesis of series of molecular hybrids of isatin and mono carbonyl curcumin tethered by triazole ring as shown in Figure 3 and evaluated their tubulin inhibition activity. One compound was found to significantly inhibit the tubulin polymerization (IC50 = 1.2 μM against HCT-116). Moreover, another compound was led to the disruption of microtubules as confirmed by immunofluorescence technique (Sharma et al., 2015).

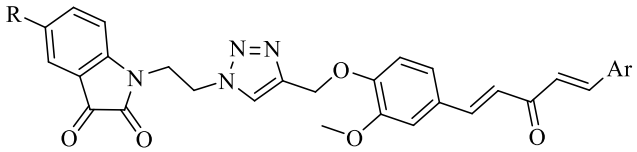


Fig. 3. Isatin derivatives as tubulin inhibitors (Sharma et al., 2015)

Fayed et. al., (2021) were reported the synthesis of a sequence of isatin-bases Schiff's and chalcones as shown Figure 4 in and tested for anticancer activity against MCF-7, HepG-2, and HCT-116 human cell lines. When compared to Imatinib as a reference standard, all of the compounds tested showed moderate to high antitumor activity, with IC_{50} values ranging from 0.68–35.60 M.

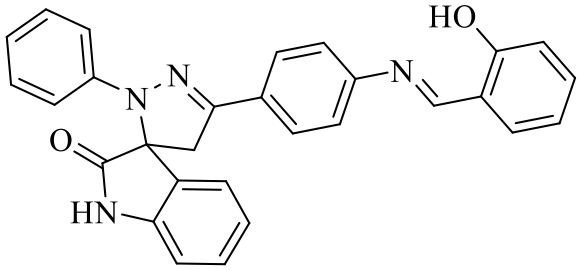


Fig. 4. Isatin derivatives as anti-cancer activity (Fayed et al., 2021)

4.2. Anti-Bacterial Activity

Isatin derivatives have therapeutic efficacy against a diverse range of pathogenic microbes and are being studied extensively for anti-bacterial action by researchers (Meenakshi et al., 2014). da Costa et al., (2021) were reported the synthesis of spiro derivatives of 1,3,4-thiadiazolines from isatin-β-thiosemicarbazone acetylation, using microwave irradiation as a source of heating the reaction medium. All prepared compounds were evaluated (*in silico* and *in vitro*) for their anti-microbial activity. *In silico* studies shown that the spiro compounds respected Lipinski's parameters, indicating a high level of oral accessibility. In addition, the results obtained for toxicity, drug-score and drug-likeness enhance the thiadiazolines' potential as drug candidates. *in vitro* studies shown that all compounds possess intense antimicrobial activity (da Costa et al., 2021). Figure 5 shows Isatin derivatives as anti-bacterial activity.

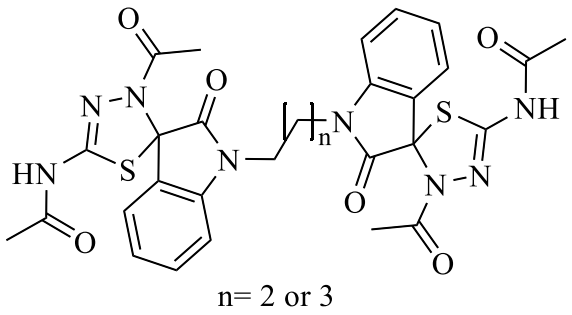


Fig. 5. Isatin derivatives as anti-bacterial activity (da Costa et al., 2021)

4.3. Anticonvulsant Activity

Epilepsy, also known as convulsions, is a nervous disorder characterized by unprovoked seizures. It normally starts in childhood and is caused by a malfunction in the brain's electrical activity. Vigabatrin, zonisamide, topiramate, and other medications are widely used to treat epilepsy. Antiepileptic medications (AEDs) currently available have a variety of side effects, including ataxia, drowsiness, gingival hyperplasia, stomach disorders, and megaloblastic anaemia, necessitating the development of new anti-convulsant with less toxic side effects (Jose, 2000; Perucca, 2001). Emami et al (2021) have been synthesized new isatin aroylhydrazone derivatives and evaluated their activity *In vivo and In vitro* as anticonvulsant agents. *In vivo* studies were performed in mice using the maximum electric shock and pentylenetetrazol models of epilepsy. This showed that most drugs provided substantial protection against electrically triggered seizures at a dose of 5 mg/kg.in addition, in silico studies were used to confirm the results obtained from In vivo and In vitro studies (Emami et al., 2021). Figure 6 shows the structure of isatin derivatives that have anticonvulsant activity.

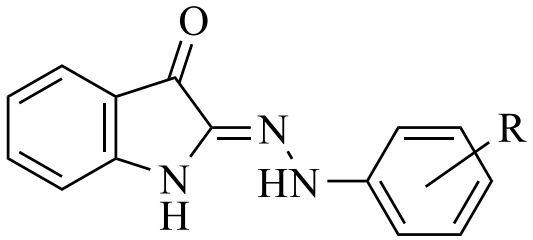


Fig. 6. Isatin derivatives as anticonvulsant activity (Emami et al., 2021)

4.4. Anti- Alzheimer

Amyloid β-peptide Inhibition accumulation in Alzheimer's disease is one of the clinical approaches to the disease that continues to pique clinical interest. Tiny natural organic molecules with low molecular weight and low toxicity are highly desired after in the quest for compounds that interact with Amyloid β-peptide Aβ and interrupt its usual aggregation path towards oligomeric or polymeric toxic assemblies. Isatin, a naturally occurring indole, and many of its compounds have a broad range of neuropharmacological and chemotherapeutic properties. *Sagnou et al.* synthesized two new isatin thiosemicarbazone derivatives as strong inhibitors of amyloid β-peptide aggregation. Thioflavin T-fluorescence, Circular dichroism, assays, and transmission electron microscopy show that isatin thiosemicarbazones have the ability to alter the pathway of Aβ-aggregation. Two of the synthesized derivatives showed excellent aggregation inhibition and completely prevented the development of amyloid fibrils. Moreover, in vitro studies in primary neuronal cell cultures showed that isatin thiosemicarbazones reduced Aβ-induced neurotoxicity and reactive oxygen species formation at concentrations as low as 1 μM (Sagnou et al., 2020). The Isatin derivatives as anti-Alzheimer showed Figure 7.

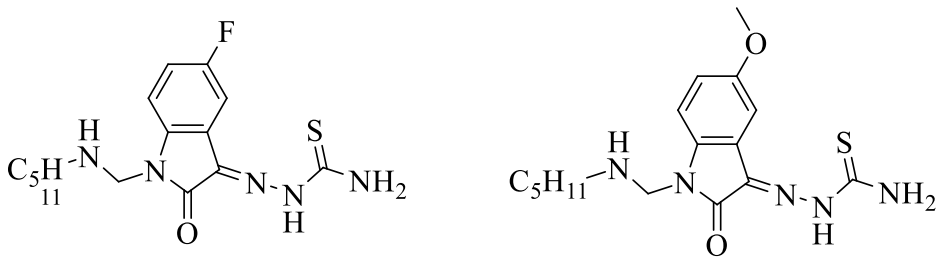
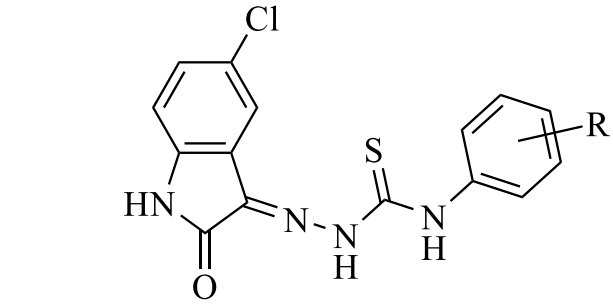


Fig. 7. Isatin derivatives as anti- Alzheimer (Sagnou et al., 2020)

4.5. Inhibitor of α-glucosidase Enzyme

α-Glucosidase is a membrane-bound enzyme that digests carbohydrates and is found on the brush-border surface of the small intestine. It catalyzes the cleavage of a polysaccharide chain's 1-4 bound glycosidic bond to monosaccharide, releasing D-glucose, which aids in normal body function (Ha et al., 2020). In humans, □-glucosidase increasement raises blood glucose levels, and has been attributed to azoospermia, (Mahmoud et al., 1998) diabetes, (Yousefi et al., 2015) virus infection, (Mehta et al., 1998) and pomp disease (Shimada et al., 2015). As a result, □-glucosidase has been identified as a key target in drug development. Rahim et al. (2020) were reported a new sequence of isatin-based thiosemicarbazide derivatives was synthesized and characterized using ^{1}H-NMR, ^{13}C-NMR, and HR-EIMS. The synthetic derivatives were tested for their ability to inhibit -glucosidase. The α glucosidase inhibitors of all compounds are excellent. Figure 8 shown Isatin derivatives as inhibitor of α-glucosidase enzyme.



R= 4-CH_3 , 2-Br , 2,3-diChloro , 2,6-dimethyl

Fig. 8. Isatin derivatives as inhibitor of α-glucosidase enzyme (Rahim et al., 2020)

5. Conclusion

Isatin is an important molecule with unique biological properties that make it suitable for many medical and pharmaceutical applications, such as an antidiabetic, antibiotic, and anticancer agent. Therefore, research in this field has been greatly expanded to discover new and environmentally friendly methods for isatin synthesis and overcome the difficulties associated with it. In addition, isatin reactions have been extensively explored as they provide the route to many new derivatives with strong biological properties, which can be used in many different medical and biological applications. For all these reasons, isatin is an important nucleus and open new paths for future research.

Competing Interests

The authors have declared that no competing interests exist.

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