IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

A Review on Different Approaches to Isatin Synthesis

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Abstract

Isatin is an indole analogue that belongs to a broad group of heterocyclic chemicals. Isatin analogues are essential chemical precursors that can be utilized to make a wide range of heterocycles and as a precursor for pharmaceutical synthesis. Because of their robust biological and pharmacological activity, isatin analogues have now piqued the interest of organic and medicinal chemists. Antitumor, antimicrobial, anti-inflammatory, analgesic, anti-mycobacterial, anticonvulsant, antiviral, anthelmintic, anti-HIV, antioxidant, and CNS depressive activity are among the biological features of isatin and its analogues. The current review discusses some of its most prevalent techniques for synthesizing the isatin moieties and its analogues, as well as recent breakthroughs in the utilization of isatin derivatives for diverse pharmacological purposes.

Index Terms: Isatin, synthesis, aniline, heterocyclic, moiety.

1. Introduction

Isatin, also known as 1H-indole-2,3-dione, is an indole derivative that belongs to a class of heterocycles that are both pharmacologically active and useful in medicinal chemistry (1). It is orange-red in colour with melting point 200^0C.The pyrrole chain is bonded with the benzene ring in the isatin ring system. Erdman and Laurent initially produced isatin in 1841 by oxidizing indigo using nitric acid and chromic acids (2). The coloration of the dyes "Maya blue" and "Maya yellow" comes from the isatin nucleus. Certain species, such as Corupita guianensis, Isatis tinctoria, and Calanthe discolor, contain this chemical. Melosatin alkaloids (methoxy phenylpentyl isatins) have been identified from the Caribbean tumorigenic plant Melochia tomentosa, as well as 6-(3'-methylbuten-2'-yl) isatin from Streptomyces albus and 5- (3'-methylbuten-2'-yl) isatin from Chaetomium globosum. Isatin has also been discovered to be present in coal tar (3). It seems to be a constituent of the secretion of the parotid gland in Bufo frogs, and it's a metabolism product of epinephrine in mammals. Its amount varies substantially in mammalian tissues, ranging from 0.1 to > 10 mM, and it is raised in particular conditions. It was the first tautomeric substance described, and its several tautomeric forms were described in 1882. It had 2 different chemical structures, a lactam-carbonyl (α), and a keto-carbonyl (β) (4). Isatin falls to the Indoline category of chemical substances (5).

The isatin ring is a prevalent structural motif that can be widely found in range of pharmacologically bioactive components. It is because to the ease with which they can be made and the significance of pharmacological effects (6). Semaxanib, orantinib, sunitinib, and nintedanib, for example, are isatin-based drugs which have been recognized for therapeutic application or are in advance clinical studies (7). In addition to reduce cell viability, isatin has been shown to cause DNA breakage and chromosome segregation, both of which indicate the onset of apoptosis (8). Isatin analogues are efficient against a variety of bacteria, including S aureus, S epidermis, Micrococcus luteus, and B cereus (9). Isatins can cross the blood–brain-barrier (10). Isatin was

discovered to be a key component of tribulin, a low-molecular-weight antagonist of MAO type B, in 1988. Isatin reduces acetylcholine esterase (AChE) activity in rat brain and erythrocytes, according to Kumar et al.

With various di and tri halogenated isatin, C5, C6, and C7 substitutions significantly increased CNS activity (11). The keto group at C-2 position and especially at C-3 position can participate in both addition and condensation processes at the C-O bond. Compounds of the isatin series can undergo N-alkylation and N-acylation, as well as Mannich and Michael processes, due to their primary amine group (12). The NH group in isatin can be N-alkylated, N-arylated, and N-acylated, while the reactivity of the carbonyl group at C2 would be used to make spirocyclic molecules, indigo, and indirubins. At the fifth position, electrophilic substitution reactions such as halogenation, nitration, and sulphonation take place (13).

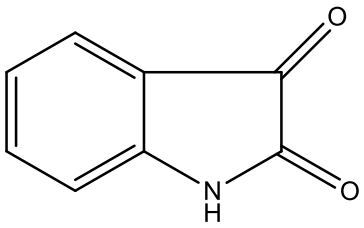
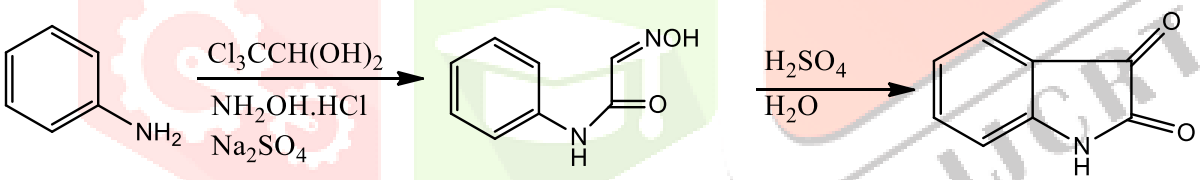


Fig. 1: Structure of Isatin

2. Synthesis of Isatin and its derivatives

2.1. Sandmayer synthesis

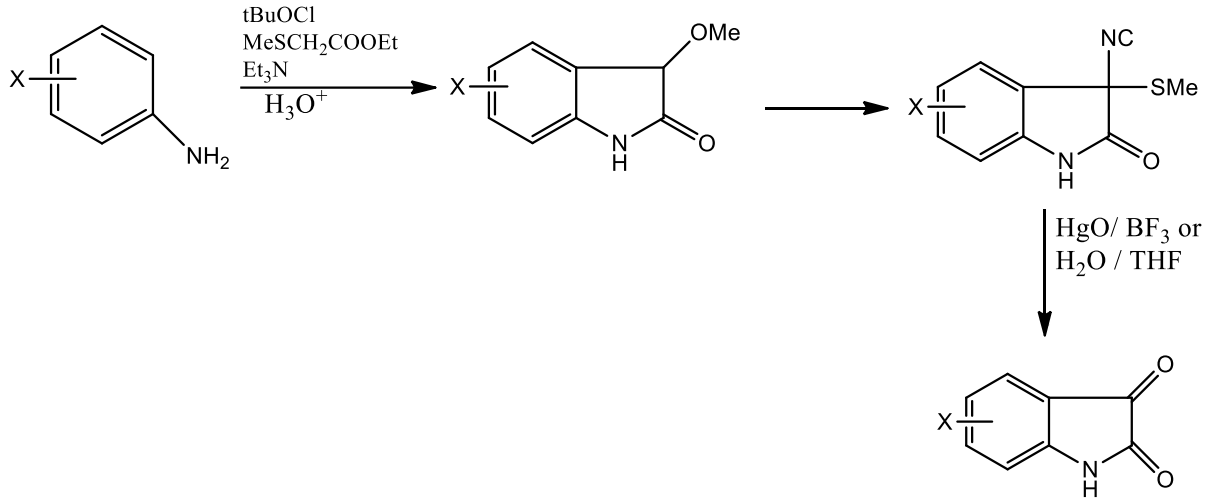
The interaction of aniline using chloral hydrate and hydroxylamine hydrochloride in aqueous sodium sulphate generates an isonitrosoacetanilide, which is separated after treating with concentrated sulfuric acid to produce isatin with a yield of more than 75 percent (14). This reaction has a general application in the synthesis of isatin derivatives, which could be used as the starting materials for quinolines, acridines and indophenazines etc. (15). It has been demonstrated that the Sandmeyer approach (>99 percent ee, yield 50 percent) produces superior results for synthesizing isatins with a chiral ligand on the nitrogen atom than Stolle method to produce isatins with a chiral ligand on the nitrogen atom (95 percent ee, yield 16 percent) (16) (Scheme 1).



Scheme 1.

2.2. Gassman synthesis

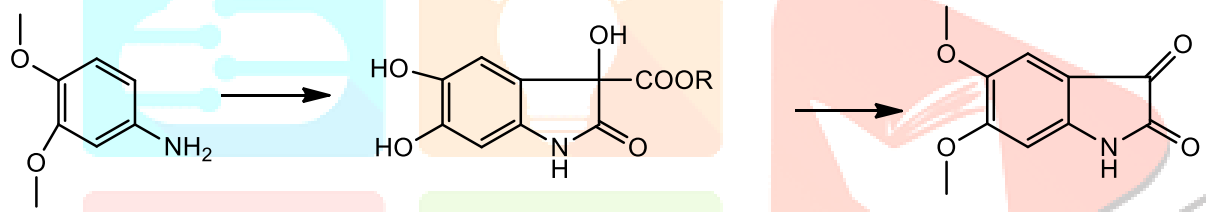
Gassman pioneered a new method for synthesizing isatin. To turn aniline to intermediate 3-methylthyiooxidinol, this process uses the fundamental interaction among electrons donating and electron withdrawing groups. The moiety is oxidized by N-chlorosucinamide in this intermediates, which is followed by the breakdown of the chlorinated intermediate (17) (Scheme 2).



Scheme 2.

2.3. Martinet synthesis

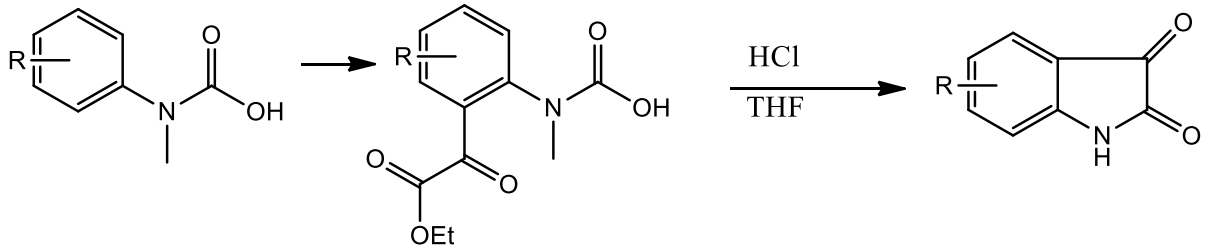
The Martinet method for synthesizing of indole-2,3- diones is a significant interaction of an amine containing aromatic compound with either an oxomalonate ester or rather its hydrate in the presence of acid to produce a 3-(3-hydroxy-2-oxindole)carboxylic acid variant, which is then oxidatively decarboxylated to obtain the desired isatin. The preparation of 5,6-dimethoxyisatin using 4-aminoveratrole proved effective using this approach, however the usage of 2,4-dimethoxyaniline was less effective (18) (Scheme 3).



Scheme 3.

2.4. Metalation of anilide

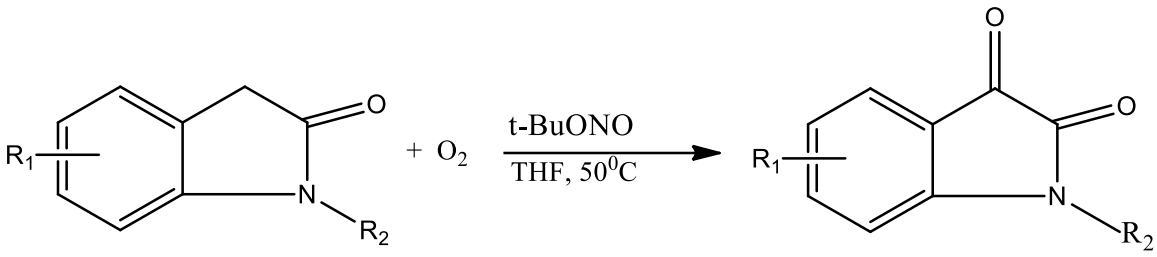
The direct O-metalation of N-pivaloyl and N-(t-butoxycarbonyl)-anilines has been used to synthesize isatins in a more contemporary technique. Following deprotection and cyclization of the subsequent a-ketoesters, the respective dianions are processed with diethyl oxalate, yielding isatins. For the synthesis of 4-substituted isatins using m-substituted anilines with a metalation directing element, this technique consists of being regioselective (19) (Scheme 4).



Scheme 4.

2.5. Metal-free Oxidation

The oxidation of oxindoles with molecular oxygen in the presence of tert-butyl nitrite as an auxiliary resulted in a metal-free formation of isatins. Even without a catalyst or a base, this technique gives a fast and easy synthesis method for formation of C=O linkages. This reaction is appealing because of its simple method and mild reaction conditions (20) (Scheme 5).

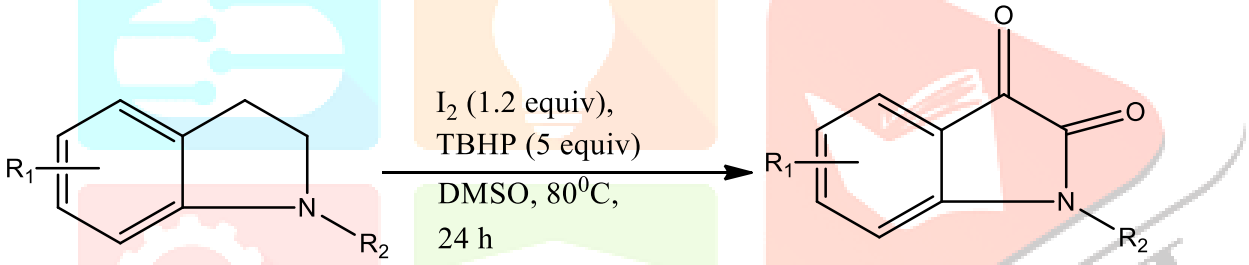


Where, R1 = H,OMe, Cl, etc.
R2 = H, Me, Ph, etc.

Scheme 5.

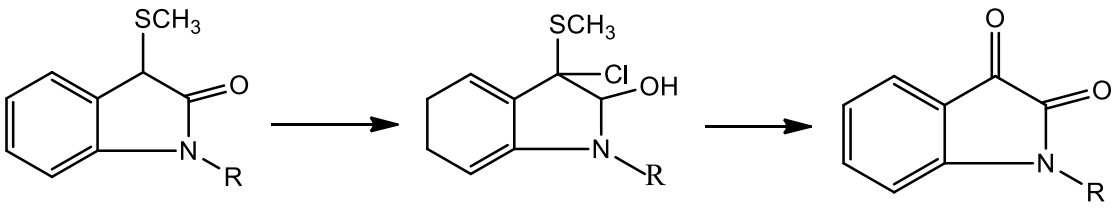
2.6. Oxidation of Indoles

The oxidation of commercially available indoles using I_2/TBHP has been reported, which yields isatins in medium to better results. This method involves the possible two mechanisms. First, indole combines with I2 to produce an iminium molecule, which then reacts with a tert-butylperoxy free radical to produce an intermediate that may be oxidized with TBHP and isomerized to produce 3-iodo-indolin-2-one. Water, on the other hand, attacks the iminium complex and produces an intermediate. Isatin is generated via simple oxidation with TBHP or DMSO (21) (Scheme 6).



Scheme 6.

A straightforward method to isatins is to oxidize the methine carbon at the third carbon of the 3-methylthiooxindoles with N-chlorosuccinimide, proceeded by breakdown of the chlorinated intermediary. The incorporation of either strong electron-withdrawing or strong electron-donating moieties on the initial aniline is favorable with this approach. The results are good to excellent (22) (Scheme 7).

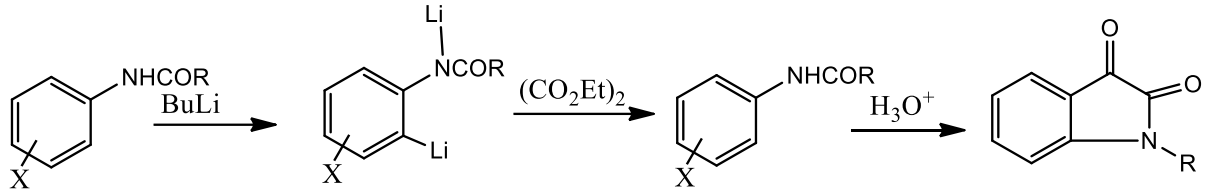


Scheme 7.

2.7. Regiospecific synthesis

Regiospecific transformation of substituted anilines to isatins has been generated using a novel approach. To make a α-ketoester, an ortho-lithiated, protective aniline analogue is combined using diethyl oxalate. To make isatin, the amino group is hydrolysed and then cyclized. This approach is characterized by reliable regiochemical controls and is unaffected by the electronic state of ligands attached to the aromatic ring. The

required a-keto esters are produced in high yield by reacting dianion radicals with 1.2 units of diethyl oxalate at -78 °C (23) (Scheme 8).

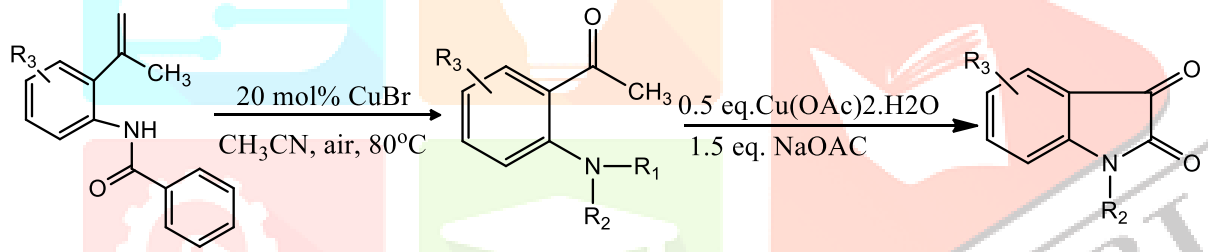


R = O^{t}Bu, ^{t}Bu

Scheme 8.

2.8. C-N annulation

Cross-dehydrogenative C-N annulation and dealkylative C-N annulation of 20-N-aryl/alkylaminoacetophenones yielded isatins. To produce comparable benzamides, 20-N-benzylaminoacetophenones were selectively oxidized of a Substituent of amine instead of the 2-acetyl group. By decreasing the temperature and length of time for selective oxidation, base performed a major role (24) (Scheme 9).

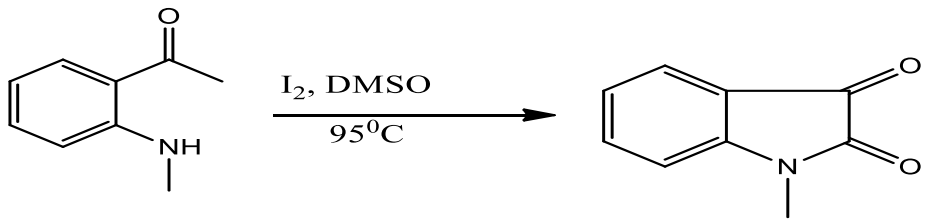


Scheme 9.

2.9. C-H bond activation

C-H bond activation is used to make isatin derivatives using 2-amino acetophenones. The I2-DMSO-catalyzed stereo selective preparation of isatins by dual C-H activation of 2-amino acetophenones and followed by internal cyclisation leading to isatins is used in this method.

Catalysts such as PhI $(OAc)_2$, TBAI, NIS, NaI, and KI results into minimal yields or nothing at all. In comparison to many other solvents examined, such as DMF and dioxane, DMSO found as being the most effective. The combined quantities of 1.3 equiv. I2 and 2 equiv. DMSO proven to be very effective among the catalyst (I2) and oxidant (DMSO) examined. It was discovered that 95°C is the optimum process temperature for obtaining a high-yielding output (25) (Scheme 10).



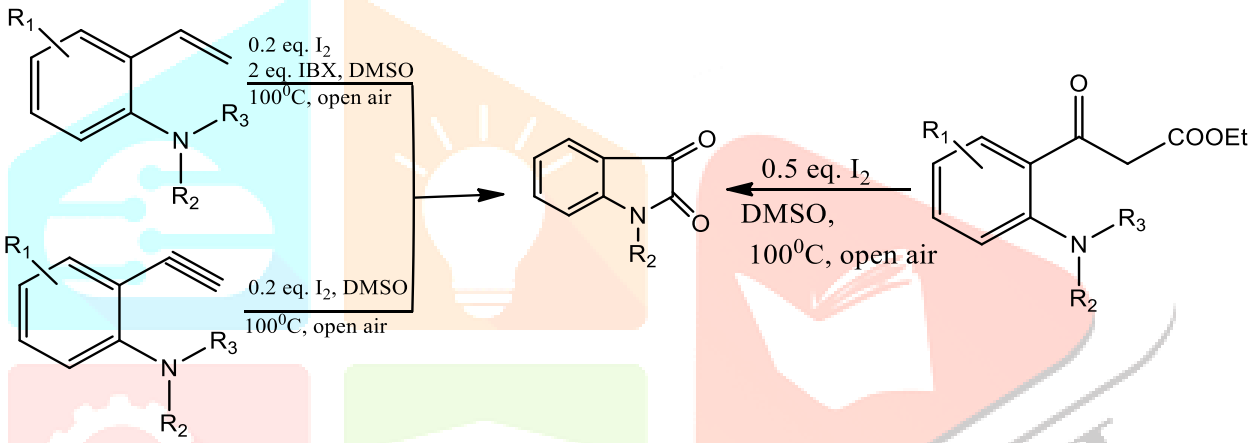
Scheme 10.

2.10. Oxidative amidation

By oxidative amidation of sp, sp2 and sp3 C-H bonds, molecular iodine endorsed effective synthesis of isatins from 2'- aminophenylacetylenes, 2'-aminostyrenes, and 2'-amino-ketoesters. In a fixed bed reactor, the process involves sequential iodination, Kornblum oxidation, then intra - molecular amidation. All of the atomic or redox economic criteria are fulfilled by this method (Scheme 11).

The advantages of this method includes:

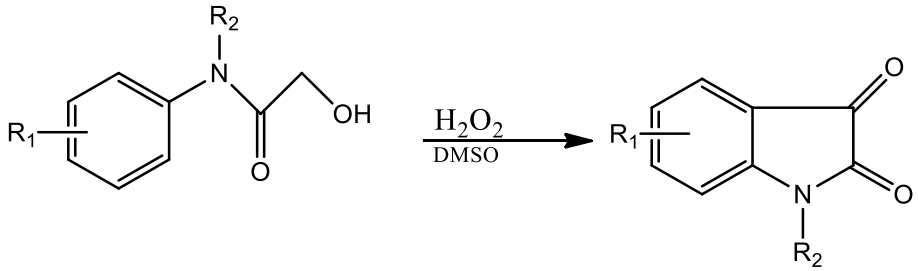
- Metal-free
- Peroxide-free
- Mild operation
- Open air
- Good to excellent yields
- Broad substrate scope (26).



Scheme 11.

2.11. Employing hydrogen peroxide

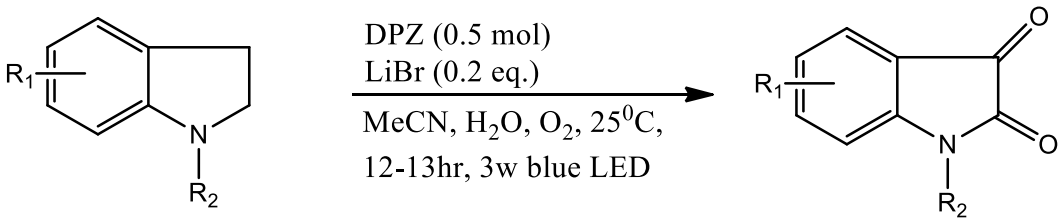
Employing hydrogen peroxide as an oxidant, a new, effective, and ecologically acceptable process for transforming -hydroxy N-arylamides into isatins (1H-in- dole-2, 3-diones) was created. With metal-free circumstances, the processes ran perfectly and produced the desired products in good to high yields. The benefits of this technique include a wide range of substrates and uncomplicated processes. Amides on a phenyl ring with electron-donating or electron-withdrawing substituents generated good to great percentages of the required products, demonstrating that the process is unaffected by electronic effects (27) (Scheme 12).



Scheme 12.

2.12. Indole oxidation

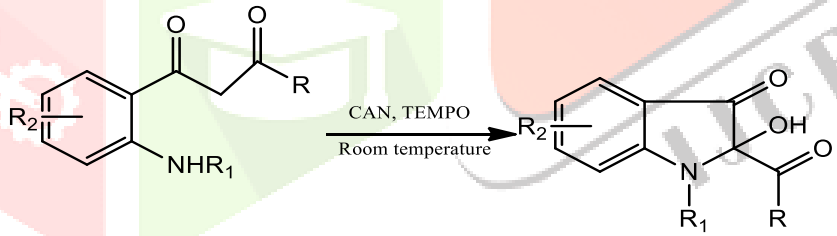
A procedure for the oxidation of indoles with O2 in the presence of a photo-sensitizer (DPZ, a dicyanopyrazine derivative) had been proposed based on green chemistry concepts and the need of introducing new ecologically sound ways for the formation of isatin derivatives. The addition of an additive salt proved essential in this synthesis technique. Replacing LiBr to K3PO4 yielded simply 2-formylformanilides underneath the identical experimental parameters, whereas Cs2CO3 yielded tryptanthrin in 56 %. It was also demonstrated that isatin may be made by oxidizing indole using oxygen dissolved in aqueous TiO2 solution while exposed to a mercury light (28) (Scheme 13).



Scheme 13.

2.13. Miscellaneous

A significant family of C2-substituted isatin derivatives are 2-hydroxy-2-substituted indol-3-ones with a C2-quaternary nucleus. Several natural and bioactive compounds contain such analogues, which also serve as important precursors in their synthesis. Utilizing ceric ammonium nitrate (CAN) and 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) as oxidants, 2-hydroxy-2-substituted indol-3-ones with a C2-quaternary nucleus have recently been produced by oxidative cyclization of 2-aminophenyl-1,3-dione (29) (Scheme 14).



Scheme 14.

3. Conclusion

Isatins are synthetically versatile compounds. It can be synthesized using different approaches like Martinet procedure, stolle procedure, gassman procedure, etc. Isatin analogues possess different biological and pharmacological activities. Isatin is a flexible starting compound for creating prospective active medicines, according to the literature, and its analogues have been shown to have wide anticonvulsant, anxiety, as well as other biological properties. We may also deduce that numerous more isatin analogues can be generated, all of which are likely to have significant pharmacological effects.

4. Acknowledgements:

The authors of this review article are thankful to the Principal, Government College of Pharmacy, Karad for allowing us to present this paper. We are also thankful to the AICTE for providing research fellowship to complete our research work and convert our research work into the publications.

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