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Synthesis of Isatin and its Derivatives Containing Heterocyclic Compounds

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Abstract: Isatin or 1H-indole-2,3-dione or 2,3-dioxindole is an indole derivative. Isatin and its analogs are synthetically useful substances where they may be utilized for the production of a broad range of heterocyclic molecules, which are depicting a wide reach of biological and pharmacological activities, as well as anticancer, anti-inflammatory, antiviral, anticonvulsant, anti-TB, antidiabetic, anti-microbial, antitumor, antimalarial, anti-HIV, antibacterial, anti-analgesic, and antiplasmodial activities. Isatin is a precursor for many synthesized therapeutic molecules that are amenable to pharmacological action and have excellent biological potential. Isatin has a magnificent scaffold for both the natural and synthetic construction of molecules. These molecules are being used in drug therapy such as anticancer, antibiotic, and antidepressant drugs and have many more clinical applications. Due to its privileged scaffolding, the synthetic versatility of isatin has produced many structurally diverse derivatives, including the substitution of mono-, di- and tri-substitution of the aryl rings A and those derived by derivation of isatin nitrogen and C2 and C3 carbon moieties. As a result, improving and expediting access to isatin-related molecules is a challenging study in synthetic organic chemistry.

Keywords: Isatin, 1H-indole-2,3-dione, heterocyclic compounds, anticancer, anti-inflammatory, antimalaria, anti-HIV, drug therapy.

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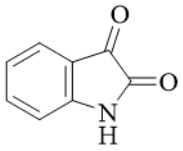
INTRODUCTION

Isatin derivatives (1H-indole-2,3-dione) are among the most important heterocyclic compounds currently occupying an essential place in pharmaceuticals and chemicals (1,2). Isatin, also known as indole quinine and indenedione, is a biologically active compound with a wide range of properties. Isatin has two cyclic rings in its structure, one of which is six-membered (aromatic property) and the other is five-membered (anti-aromatic character). Both rings lie in the same plane, a five-membered ring contains a nitrogen atom and two carbonyl groups. Isatin was first synthesized in 1840 by Erdmann and Laurent as an oxidation product of the indigo dye by nitric acid and chromic acid, which resulted in isatin's bright orange-colored monoclinic crystals product (3). Kekulé established isatin's present form, and the chemistry of isatins was initially studied by Sumpter and then revised by Popp and Silva et al.



Isatin

Figure 1: Chemical structure of Isatin.

Typically, isatin is found in the plant of the Isatis genus (4) in Calanthe stain LINDL.(5) and Couroupita guianensis Aubl. (6) and discharges

from the parotid organ of the bufo frog (7,8) and in people as it is a metabolic subsidiary of adrenaline (9). Different subbed isatin have likewise been distinguished in plants, for example, methoxy phenylmethyl isatin acquired from Melochia tomentosa (10,11), hydroxylated isatins disengaged from Streptomyces (fungi)(12), and marine mollusks (13), where they are proposed to assume a guarded part against pathogenic creatures. Isatin is additionally discovered to be a part of coal tar (14).

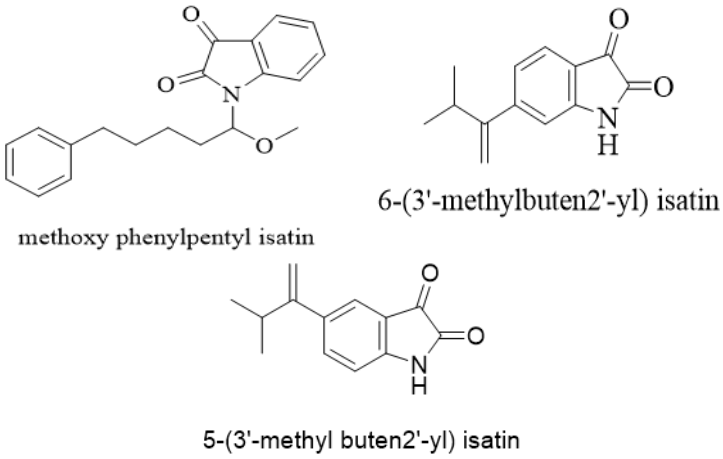


Figure 2: Structures of methoxyphenylpentyl isatin, 6-(3′-methylbuten 2′-yl) isatin and 5-(3′-methylbuten 2′-yl) isatin.

A thorough investigation of the manufacture and response of isatin, a compound with an indole motif, a ketone, and a - lactam moiety, revealed many intriguing chemical reactions and processes. Isatins' unique capacity to act as both an electrophile and a nucleophile and their wide distribution has made them important building blocks in organic synthesis. Syntheses of several heterocyclic structures of biological importance, such as indoles, β-lactams, pyrrolidine, quinolones and 2-oxindoles, etc. Literature survey revealed that isatin derivatives such as hydrazine, mannich bases, Schiff bases, and spiroindolinones possesses an extensive range of biological activities such as antimicrobial (15), antitumor (16), antimalarial (17), anti-HIV (18), analgesic, antibacterial (19), anti-inflammatory (20), antiglycation (21), neuroprotective (22), antioxidant (23), anti-tubercular (24), antifungal (25), anticonvulsant (26), antidepressant (27), anticancer (28,29), antiplasmodial activity (30), anti-corrosive (31), antiepileptic (32), antidiabetic (7) and antiviral (33) antianxiety (34), and antiasthma (35). In 1965, an isatin-2,3-dione-based compound Metisazone was developed, it is an antiviral agent used against viral infections as a prophylactic agent (36). Food and Drug Administration, USA (FDA) approved an isatin derivative Sunitinib maleate to treat different malignancies such as advanced renal-cell carcinoma, pancreatic neuroendocrine tumors and gastrointestinal stromal tumors (37,38).

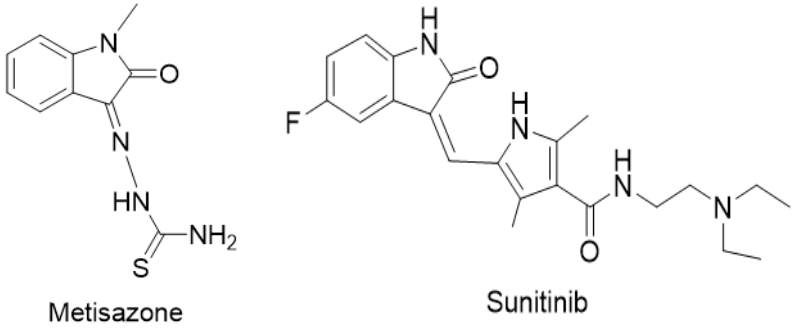


Figure 3: Structure of Metisazone and Sunitinib.

GENERAL METHODS FOR SYNTHESIS OF ISATINS

Metalation of Anilide Isatin Compound

A new strategy for creating isatin includes ortho-metalation (DoM) of N-pivaloyl-and N-(t-butoxycarbonyl)- anilines is presented. The dianions are treated with diethyl oxalate after deprotection and cyclization of the middle of the

road a-ketoesters, and isatins are created (Scheme 1). This technique for orchestrating 4-subbed isatins from meta-subbed anilines has the advantage of being regioselective (39).

Martinet's Isatin Synthesis

Isatin was made by responding a fragrant amino atom with an oxomalonate ester or its hydrate within sight of a corrosive to frame a 3-(3-hydroxy-2-oxindole) carboxylic corrosive subsidiary, which was then oxidatively decarboxylated to yield isatin (Scheme 2)(40).

Stolle's Isatin Synthesis

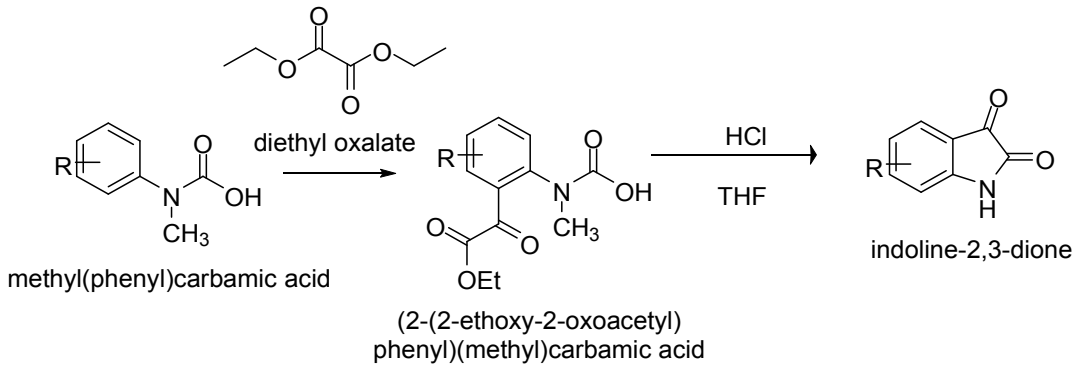
The Stolle isatin synthesis involves reacting anilines by oxalyl chloride to generate a chlorooxalylanilide intermediate, which is subsequently cyclized in a Lewis acid, commonly BF_3, Et_2O, or aluminum chloride. However, $TiCl_4$ has been used as well (41).

Sandmeyer's Isatin Synthesis

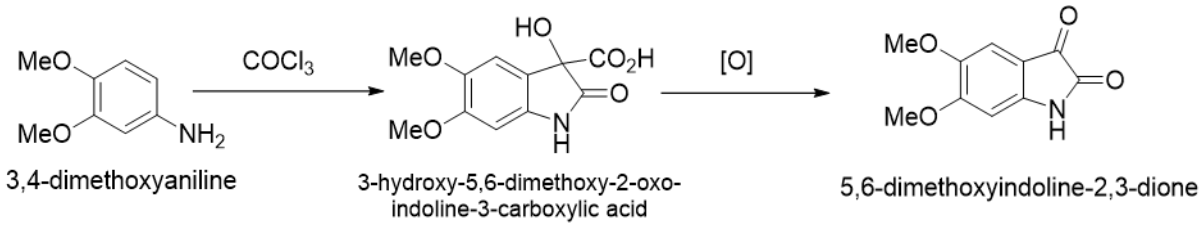
Isatin was made by combining aniline with chloral hydrate and hydroxylamine hydrochloride in aqueous sodium sulfate to generate an isonitrosoacetanilide, which was then separated following treatment with concentrated sulfuric acid to obtain >75 percent isatin (42).

Gassman's Isatin Synthesis

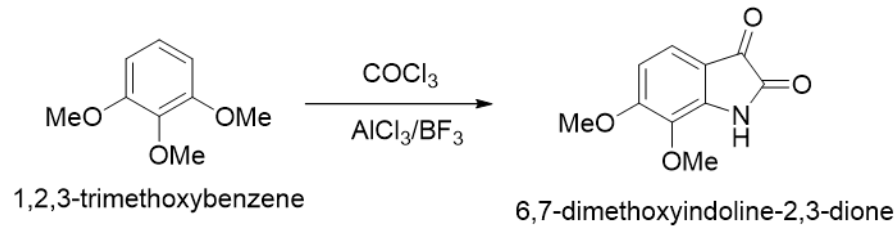
This procedure starts with creating an intermediate 3-methylthio-2-oxindole, which is then oxidized to produce substituted isatin (40-81 percent yield) (41).



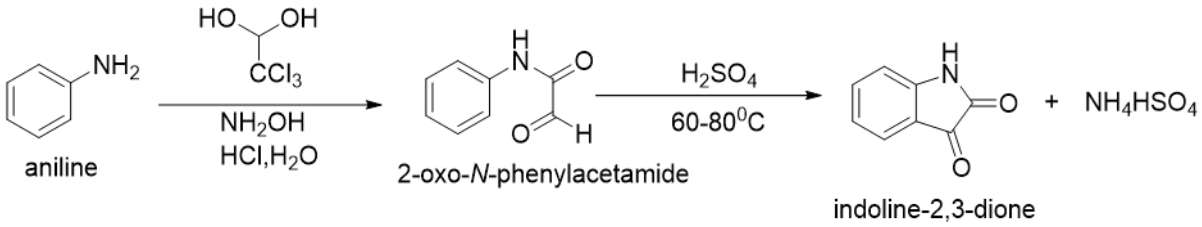
Scheme 1: Metalation of anilide isatin synthesis. Adapted from (39).



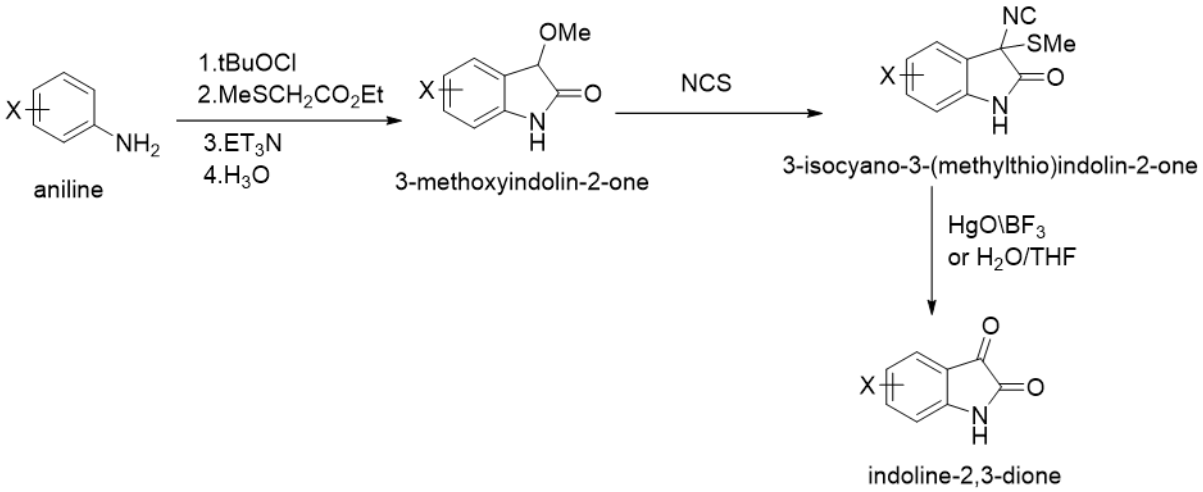
Scheme 2: Martinet's isatin synthesis. Adapted from (40).



Scheme 3: Stolle's isatin synthesis. Adapted from (41).

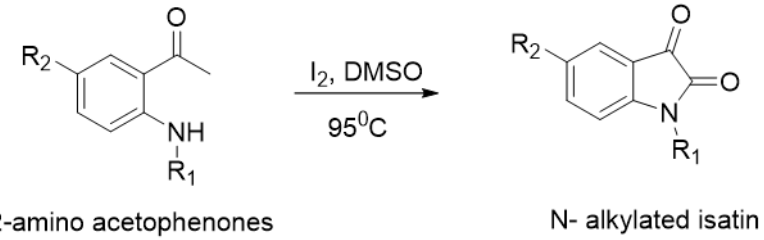


Scheme 4: Sandmeyer's isatin synthesis. Adapted from (42).



Scheme 5: Gassman's isatin synthesis. Adapted from (41).

To complete the synthesis of N-substituted isatins, several new synthetic methods have been devised. One such endeavor uses I_2-DMSO as a catalyst in a metal-free synthesis Scheme 6. The technique involves activating the C-H bond and then internal cyclizing 2- amino acetophenones to make N-alkylated and N-arylated isatins (43).

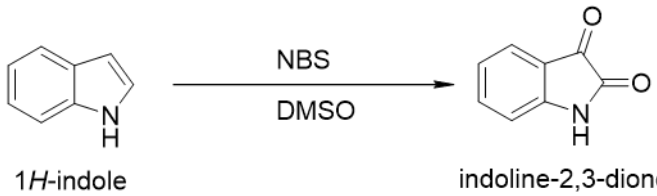


R_1 = H, Me, allyi, Et, Bn, 4-MeOBn, 4-ClBn, 4-FBn

R_2 = H, Cl, Me

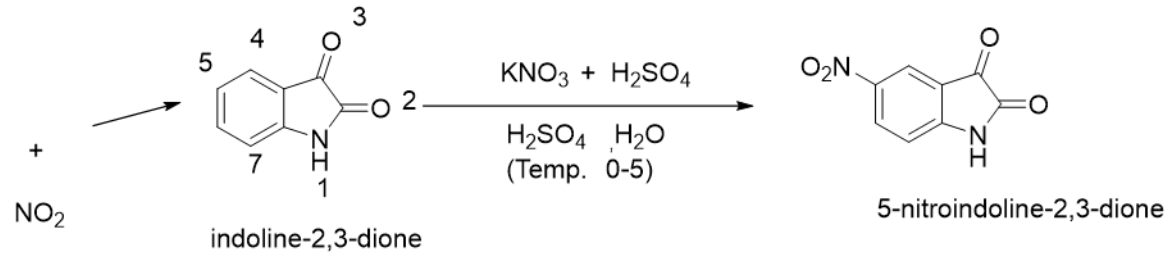
Scheme 6: Combination of N-alkylated isatin subsidiaries from 2-amino acetophenones. Adapted from (43).

Indole, NBS, and anhyd. DMSO mixture were taken in a 3-necked R.B. flask that was clean and dry. The flask was heated to 60 °C for 6 hours under decreased pressure and 80 °C for 16 hours. After the reaction was finished, the mixture was placed in water, and the extracts were extracted with dichloromethane. The sections were then dried over $MgSO_4$ and purified using silica gel chromatography with DCM as the eluent M.P.202 °C (Scheme 7)(44).



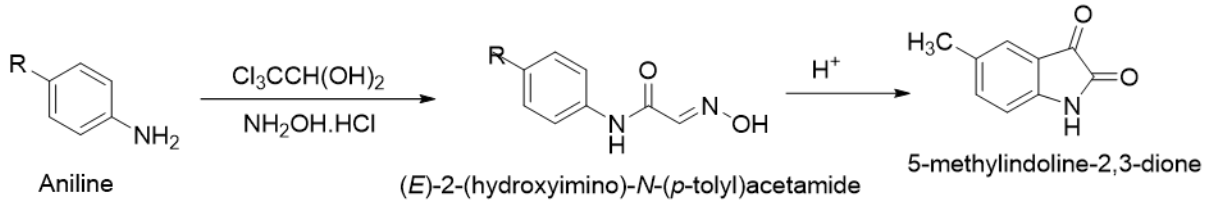
Scheme 7: Blend of isatin. Adapted from (44).

The reaction was carried out by dropping a solution of isatin, con. H_2SO_4, into a solution of at 0 to 5 °C for 1 hour, yielding 5- nitroisatin. 249-250 °C M.P. Isatin is nitrated at C-5 with KNO_3, in the presence of H_2SO_4. (Scheme 8)(44).



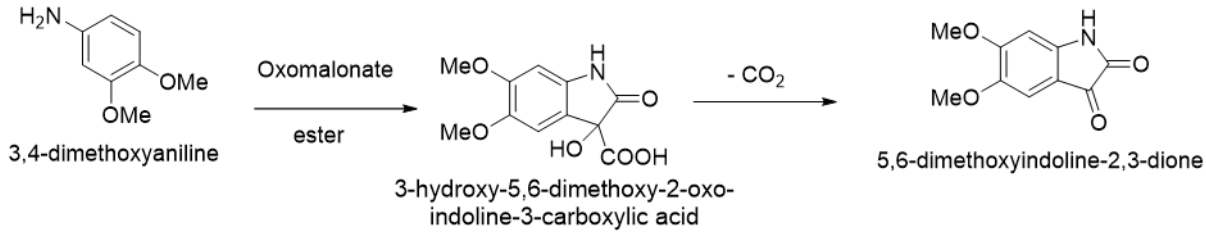
Scheme 8: Synthesis of 5-nitro-1H-indole-2,3-dione. Adapted from (44).

On reaction with chloral hydrate and hydroxylamine hydrochloride, isonitrosoacetanilides were produced from substituted anilines. Substituted isonitrosoacetanilides gave equivalent indolin-2, 3-diones after reaction with sulfuric acid (Scheme 9) (45).



Scheme 9: Isonitrosoacetanilides have been synthesized from substituted anilines on reaction with chloral hydrate and hydroxylamine hydrochloride (45).

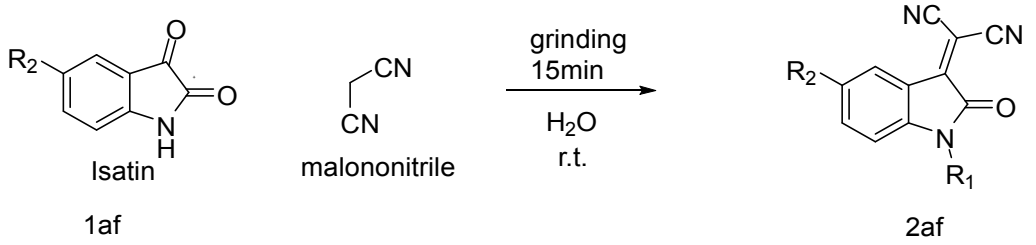
Isatins are made by responding a sweet-smelling amino atom with an oxomalonate ester or its hydrate within sight of a corrosive to create a 3-(3-hydroxy-2-oxindole) carboxylic corrosive subsidiary, which is along these lines oxidatively decarboxylated to give the ideal isatin (Scheme 10)(46).



Scheme 10: Isatins are created when one aromatic amino molecule reacts with another aromatic amino molecule. Adapted from (46).

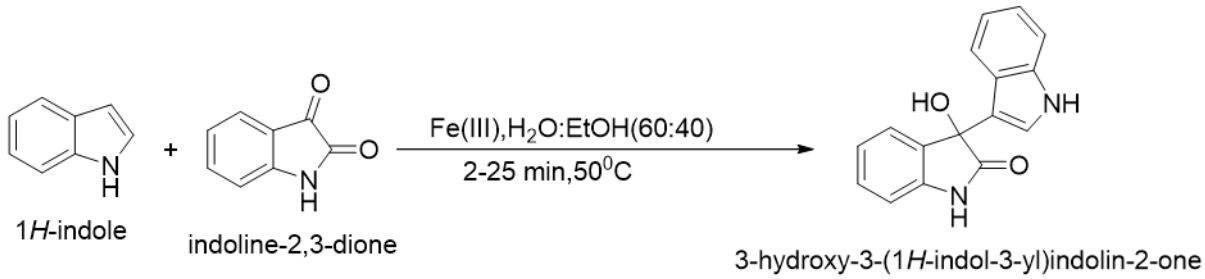
The related (2-oxo-1,2-dihydro-3H-indol-3-ylidene)malononitriles, the Knoevenagel condensation products, are obtained by grinding isatins with malononitrile for 15 minutes at room temperature in the presence of 1–5 equivalent of water (Scheme 11)(47).

Under ultrasonic irradiation, 3-(indol-3-yl)-3-hydroxyindolin-2-ones were synthesized from isatins and indoles using Fe(III) as a recyclable homogeneous catalyst (Scheme 12). It was discovered that the circumstances used resulted in 85–95 percent yields (48).



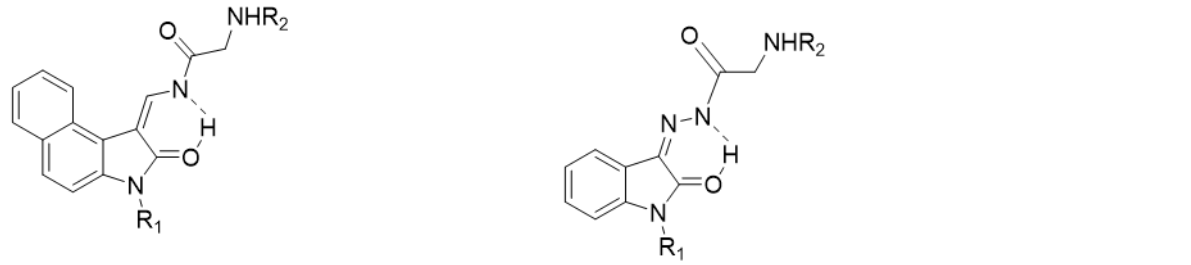
a $R^1 = R^2 = H$
b $R^1 = Me$, $R^2 = H$
c $R^1 = Et$, $R^2 = H$
d $R^1 = CH_2Ph$, $R^2 = H$
e $R^1 = H$, $R^2 = Cl$
f $R^1 = H$, $R^2 = Br$

Scheme 11: Synthesis of isatines with malononitrile via Knoevenagel condensation. Adapted from (47).



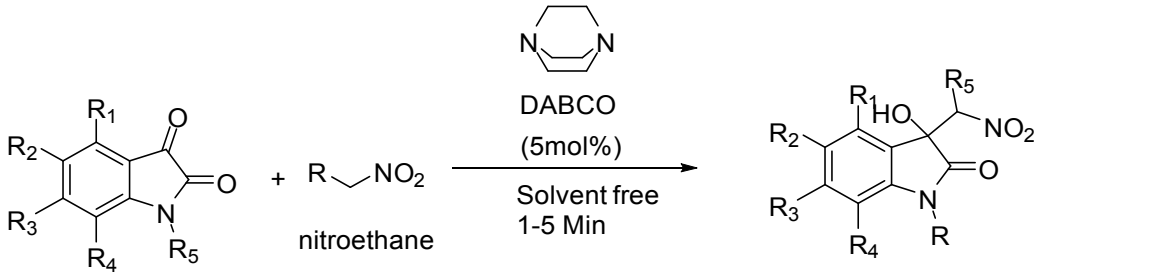
Scheme 12: Ultrasound-advanced, Fe(III)-catalyzed 3-indolylation of isatins. Adapted from (48).

The electrocatalytic change of isatins and barbituric acids in ethanol in a unified cell within sight of sodium produces subbed 5,5'- (2-oxo-2,3-dihydro-1H-indole-3,3-diyl) bis (pyrimidine-2,4,6(- 1H, 3H 5H)- triones (B) with 89–95 percent substance yields and 89–95 percent current yields (Scheme 13). This novel and effective synergist strategy is fundamental because of its variety situated massive scope activities. It is an illustration of an electrocatalytic double response that is simple and biologically amicable (49).



Scheme 13: Isatin and barbituric acids are used to make a functionalized (2-oxo-2,3-dihydro-1H-indole-3,3-diyl) bis (pyrimidine) system. Adapted from (49).

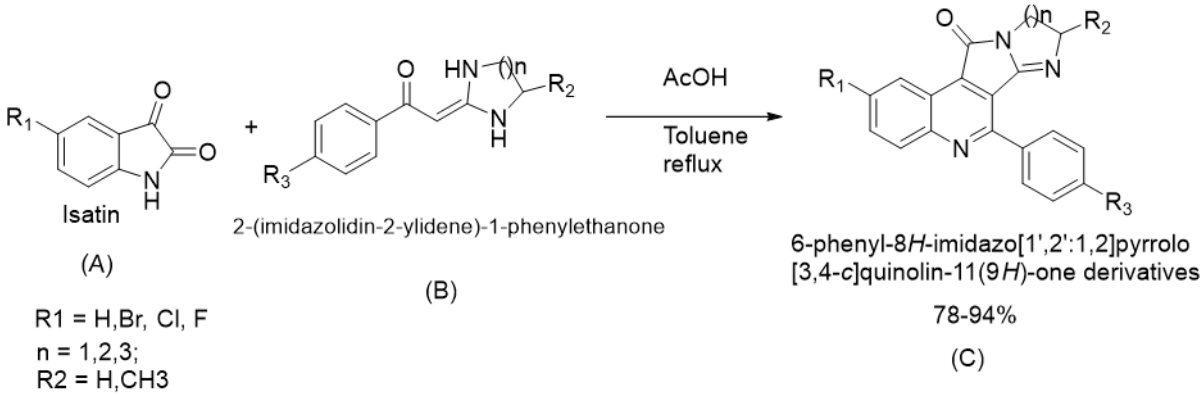
The response of isatins to nitromethane/nitroethane in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO)(50) has been described as an efficient and universal technique for the production of 3-hydroxy-3-(nitromethyl)-indolin-2-one (C). The reaction is catalytic and swift; yields are incredibly high, and no solvents are used.



R = H, CH3, Bn
R1= R2= R3 =R4= H, 5-CH3, 5-Cl, 5-Br, 5-1, 5-NO2, 5-OCF3
R5= H, CH3
1,4 diazabicyclo[2,2,2]octane(DABCO)

Scheme 14: 3-Formation of hydroxy-(nitromethyl) indolin-2-one derivatives utilizing DABCO as a catalyst. Adapted from (50).

By basically refluxing a response mixture of several types of isatins and heterocyclic ketene aminals (HKAs) with acetic acid, a straightforward and practical approach for synthesizing highly substituted imidazopyrroloquinoline derivatives was devised (Scheme 15). In drug discovery, this method is appropriate for both combinatorial and equal blends (51).



R1 = H,Br, Cl, F
n = 1,2,3;
R2 = H,CH3
R3 = CH3O, CH3, H, Cl

Scheme 15: Imidazopyrroloquinoline compounds with extensively modified substituents were synthesized. Adapted from (51).

CONCLUSIONS

Isatin is a heterocyclic compound that is vital for the blend of natural mixtures. Schiff bases of isatin, 3,3-disubstituted oxindoles, and spirooxindoles are a portion of the remarkable frameworks that might be created utilizing isatin as an antecedent material. They can function as electrophilic partners in many of the traditional aldehyde transformations, such as the production of 1,3-dipoles, the Knoevenagel reaction, and so on. On the other side, isatins have a sensitivity that is not seen in aldehydes, including ring-opening processes. The majority of these compounds also have biological and pharmacological characteristics. In recent times, isatin has also been extensively used to produce a variety of chemical compounds.

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