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Synthesis and Reactivity of New versatile Hetero cyclic compound Izatin and its derivativesr

KEYWORDS: isatin, heterocyclic synthesis, drug synthesis, metal complexes

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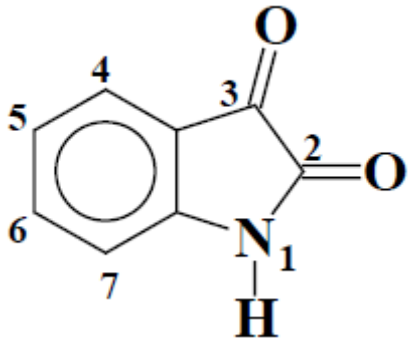
ABSTRACT *Isatin (1H-indole-2,3-dione) is a synthetically versatile substrate, where itcan be used for the synthesis of a large variety of heterocyclic compounds,such as indoles and quinolines, and as a raw material for drug synthesis.Isatin has also been found in mammalian tissues, and its function as amodulator of biochemical processes has been the subject of severaldiscussions. The advances in the use of isatin for organic synthesis during the last twenty-five years, as well as a survey of its biological andpharmacological properties are reported in this review and in theaccompanying supplementary information.*

INTRODUCTION

Isatin (1H-indole-2,3-dione) was first obtained by Erdman and Laurent in1841 as a product from the oxidation of indigo by nitric and chromic acids.

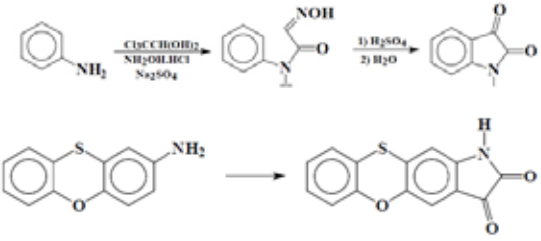


The synthetic versatility of isatin has led to the extensive use of this compound in inorganic synthesis. The synthetic versatility of isatin has stemmed from the interest in the biological and pharmacological properties of its derivatives. These properties are more fully detailed in the supplementary material.In nature, isatin is found in plants of the genus Isatis4, in Calanthe discolor LINDL.5and in Couroupita guianensis Aubl.6, and has also been foundas a component of the secretion from the parotid gland of Bufo frogs7, and in humans as it is a metabolic derivative of adrenaline8-10. Substituted isatins are also found in plants, for example the melosatin alkaloids (methoxy phenylpentyl isatins) obtained from the Caribbean tumorigenic plant Melochia tomentosa11-13 as well as from fungi: 6-(3′-methylbuten-2′-yl)isatin was isolated from Streptomyces albus14 and 5-(3′-methylbuten-2′-yl)isatin from Chaetomium globosum15. Isatin has also been found to be a component of coal tar16.This review aims to document the publications concerning isatin, its synthesis, chemical reactivity and pharmacological properties during the period from 1975 to 1999.

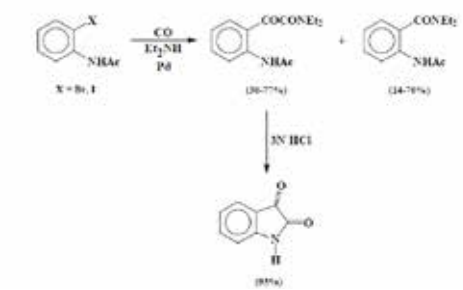
2. Synthesis of isatins

2.1 The Sandmeyer methodology

The method developed by Sandmeyer is the oldest and the most frequently used for the synthesis of isatin. It consists in the reaction of aniline with chloral hydrate and hydroxylamine hydrochloride in aqueous sodium sulfate to form an isonitrosoacetanilide, which after isolation, when treated with concentrated sulfuric acid, furnishes isatin in >75% overall yield17. The method applies well to anilines with electron-withdrawing substituents, such as 2-fluroaniline18, and to some heterocyclic amines, such as 2-aminophenoxathine19 (Scheme 1).



This method has some economic advantages, as the reagents are cheap and readily available, and the yields are usually high. Recently, the Sandmeyer methodology has been modified by the incorporation of ethanol as a co-solvent20. This modification proved to be particularly useful in cases where the aniline derivative was insoluble in the conventional reaction matrix. Application of the modified Sandmeyer methodology allowed the synthesis of 4,6-dibromoisatin, a key intermediate for the synthesis of the marine natural product convolutamydine A, in 85% yield, thus representing a greater than 700% improvement in yield over the existing published rocedure. The use of microwave irradiation during both stages of the Sandmeyer procedure has been investigated, and this modified procedure was also employed for the synthesis of lutamydine A21. In addition to the use of H2SO4 for the cyclization step, nitrosoacetanilides can be heated in BF3.Et2O at 90 oC. After cooling the reaction mixture, addition of water allows isolation of the respective isatins. This methodology has proved to be particularly effective for the preparation of benzo-oxygenated isatin derivatives22,23 The Sandmeyer synthesis has been described as being unapplicable to ortho-hydroxy or ortho-alkoxyanilines. Therefore an alternative procedure for the synthesis of the isonitrosoacetanilides was reported24,25 (Scheme 2).



A de novo isatin synthesis based upon a palladium catalysed double carbonylation of ortho-haloacetanilides in the presence of Et2NH to yield the corresponding glyoxylic acid amide was reported by Yamamoto and co-workers28. Hydrolysis of this amide yielded the respective isatin .

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3. Reactivity of isatin and derivatives towards electrophiles

3.1 N-alkylation

Many methods have been devised for the N-alkylation of isatins. These derivatives are commonly synthesized from the reaction of the sodium salt of isatin with alkyl halides or sulphates29,30. Various methods for the preparation of this salt have been reported, and include the reaction of isatin with sodium hydride, either in toluene under reflux31 or in DMF32. Other methods include the use of potassium carbonate in DMF33,34 or in acetone35. In the latter case an aldol reaction of the solvent also occurs with the C-3 carbonyl of the isatin derivative.

Heating in ortho-dichlorobenzene results in a retro-aldol reaction and the obtention of the Nalkylated isatin. More recently the use of CaH2 in DMF has been reported36 and this method was used for the synthesis of both mono and bis-N-alkylisatins. These latter compounds have been previously prepared using dihaloalkanes and NaH in dioxane37 or DMF38 or by the use of LiH39. Some of these alkylation methodologies were evaluated for the synthesis of isatins bearing a glycosidic residue linked to the N-1 position 40.An alternative method for preparing 1-alkylisatins consists in the reaction of isatin and alkyl halides in a benzene-chloroform/50% aq. KOH biphasic system, employing tetrabutylammonium hydrogensulfate as the phase transfer catalyst41. N-Propargylisatins, obtained from isatin and propargyl halides42, can be converted to N-acetonylisatins through hydration with Hg(II) salts in acidic media43. The synthesis of 1-methylisatin by the method of Stolle, using tris(methylphenylamino) methane instead of N-methylaniline, leads to the desired product in low yields44. The reaction of isatin with vinyl acetate in the presence of Na2PdCl4 yields 1- vinylisatin45. On the other hand, O-alkylation at position 2 has been reported, along with the N-alkyl product, using -butyrolactone46 or allyl bromide47 as alkylating agents and the sodium salt of isatin. O-Methylisatin is described as the product of the reaction of methyl iodide with the silver salt of isatin, which can be prepared from isatin and silver acetate48. The alkoxy group has been reported to be displaced by nucleophiles such as hydrazines49.

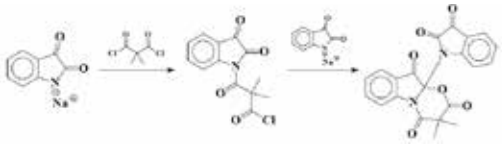
3.2 N-arylation

N-Arylisatin can be obtained from isatin in quantitative yields by reaction with Ph3Bi(OAc)2 and Cu0 under an inert atmosphere50 or from aryl bromides and cupric oxide51.

3.3 N-methyleneamino derivatives The Mannich reaction is readily applied to isatins. The products of this reaction, the Naminomethylisatins (Mannich bases), can also be obtained from the N-hydroxymethyl derivatives by reaction with an amine52 or by reaction with acetyl chloride to yield Nchloromethylisatin which can be further treated with potassium phthalimide or alcohols to give the corresponding N-phthalimidomethyl or N-alkoxymethyl isatins53. The Mannich reaction can also be performed with isatin derivatives, such as isatin-3-hydrazones54 and isatin-3-thiosemicarbazones55.

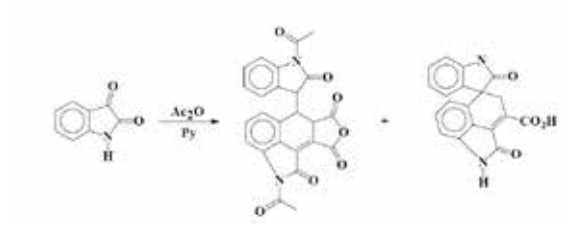
3.4 N-acylation and N-sulfonylation

The synthesis of N-acylisatins under a variety of conditions has been described using acyl chlorides or anhydrides under reflux, either alone56 or using perchloric acid in benzene, triethylamine in benzene57, pyridine in benzene58, or triethylamine in chloroform59,60 as catalysts; or by conversion of isatin to sodium isatide using NaH in toluene under reflux and subsequent reaction with acyl chlorides77. The use of diacyl chlorides, e.g. oxalyl chloride61, octanedioyl or nonanedioyl chlorides62, yields bis-acylisatins. Attempts to use 2,2- dimethylmalonyl chloride to furnish 2,2-dimethylmalonyl-bis-isatin failed, and led instead to an unusual tricyclic compound which was characterized by spectroscopic methods and by X-ray diffraction63 .



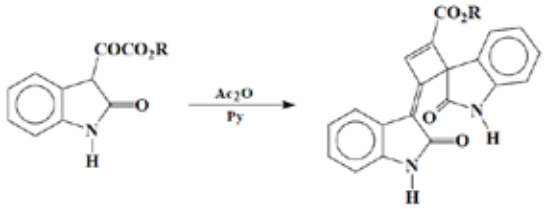
Other complex products have been obtained from the reaction of isatin and acetic

anhydride in the presence of pyridine64 (Scheme 27).



Similarly, dimers may be formed in the acetylation of indolylglyoxalates with acetic

anhydride in pyridine65 (Scheme 28).



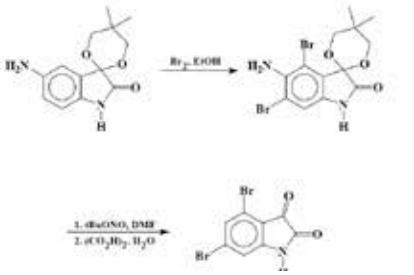
3.5 N-Haloderivatives

The treatment of isatin with sodium hypochlorite in acetic acid leads to 1-chloroisatin, an effective mild oxidizing agent for the conversion of alcohols to aldehydes and ketones66 and of indoles to 3-chloroindoles without formation of byproducts67. N-[phenyliodine(III)] bisisatin can be obtained from the sodium salt of isatin and phenyliodine (III) bistrifluoroacetate in 85% yield. This compound is a member of a group of iodine(III)imides, which possess mild oxidizing properties68.

3.6 Reactivity of the aromatic nucleus

Although isatins with substituents attached to the aromatic ring are usually obtained from the corresponding functionalized anilines, they can be synthesized by electrophilic aromatic substitution. Nitration of isatin using the sulfonitric mixture yields 5-nitroisatin69. Precise temperature control is needed70, otherwise a mixture of nitrated products are formed71.

The bromination of isatin in alcohols gives 5,7-dibromo-3,3-dialkoxyoxindoles in an acid catalyzed ketalization of the halogenated isatin72. Monobromination at position 5 can be achieved, at least on a microscale, with the use of N-bromoacetamide in acetic acid medium73. 5-Bromoisatins can suffer arylation by the use of aryl or heteroarylboronic acids via a palladium-catalyzed Suzuki cross-coupling reaction74. Recently, 4,6-dibromoisatin, a key intermediate in the synthesis of convolutamidine A, was prepared by bromination in ethanol of a 5-aminoisatin derivative75 (Scheme 29).



Miscellaneous applications

Isatins and derivatives have been used in the development of colour photographic recording materials, of blood coagulation promoters, of liquid crystal components for display de-

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vices and in the inhibition of corrosion of aluminum and Fe-Ni alloys and of ironf.

Isatin can be used as a photosensitizer, together with a photoinitiator, for methacrylate and epoxysilicone polymerization. It is also used for the synthesis of branched polycarbonate resins, improving the moldability of this polymer. The reaction of isatin with thiophene in an acidic medium, containing ferrous ion, gives rise to an intense violet color, due to the formation of indophenine dyes. Due to this phenomenon, it was proposed that isatin could be used as a revealing agent for the presence of thiophene in water-soluble organic solvents where it is used as a denaturating agent. The lithium and thallium (I) salts of isatin-3-oxime (isatin oximates) were employed in the development of ion-selective electrodes for these cations. Transition metal complexes of isatin derivatives can also be employed as catalysts for the oxidative self-coupling of alkylphenols.

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