Kurdistan Region

Ministry of Higher Education and Scientific Research

Salahaddin University- Erbil

College of Science

A mini-Review on the Synthesis and biological evaluation of Isatin Derivatives

Research project

submitted to the department of chemistry in partial fulfillment of the requirement for the degree of Bsc. in chemistry science

Prepared By

Mardin Abdulla Ali

Supervised by

Prof. Dr. Media Noori Abdullah

2023-2024

Dedication

I dedicate this report to my family who give me their utmost support, and never-ending inspiration throughout the study. I also dedicate to my supervisor Prof. Dr. Media N. Abdullah and to the scientific committee of the chemistry department, college of science, university of Salahaddin. Above all, to Almighty God who always gives me strength, knowledge, and wisdom in everything I do.

Acknowledgment

Thanks to Allah for providing me the strength to accomplish this report. I also want to express my gratitude to my supervisor, Prof. Dr. Media N. Abdullah, I appreciate her effort. Thanks to my family for their support, help, and motivation. Thanks to the Chemistry department and all the academic staff.

Table of Contents

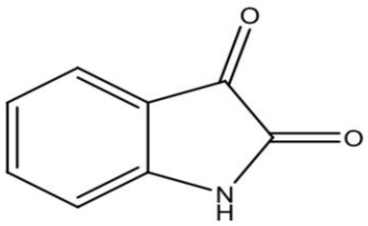
Abstract

Isatin, 1H-indole-2,3-dione, is a heterocyclic compound of significant importance in medicinal chemistry. It is a synthetically versatile molecule, a precursor for a large number of pharmacologically active compounds. Isatin and its derivatives have aroused great attention in recent years due to their wide variety of biological activities, relevant to applications as insecticides and fungicides and in a broad range of drug therapies, including anticancer drugs, antibiotics, and antidepressants. The purpose of this review is to provide an overview of the bioactivities of isatin derivatives and their synthesis.

Keywords: Isatine, Synthesis of Derivatives, Biological Activities.

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 1H-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 consists 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 an anti-aromatic character (Varun, et al., 2019). Figure 1 shows the structure of the isatin molecule:



indoline-2,3-dione

The most widely used techniques for creating different isatin derivatives are those developed by Sandmeyer, Stolle, Gassman, and Martinet. In addition, several distinct and preparation of isatin derivatives using recently published and discussed ecologically friendly synthetic techniques. (Ferraz de Paiva et al., 2021) The chemical reactions that isatins go through also include Friedel-Crafts, ring expansion, oxidation reaction, and aldol condensation. Several medically necessary derivatives, such as tryptanthrin, indirubin, and 2-oxindoles, can be made using these chemical processes. A survey of the literature revealed that isatin and its components have anti-cancer, antibacterial, antifungal, anticonvulsant, antitubercular, and anti-HIV properties, as well as antioxidant, anti-inflammatory, and analgesic properties.(Al-

Khuzaie et al., 2022) This study concentrated on the isatin molecule since it is crucial for the synthesis of physiologically active chemicals that are employed in numerous pharmacological and medical applications. On compiling the most recent research on the creation, applications in chemistry and biology of isatin and its derivatives. (Ferraz de Paiva et al., 2021)

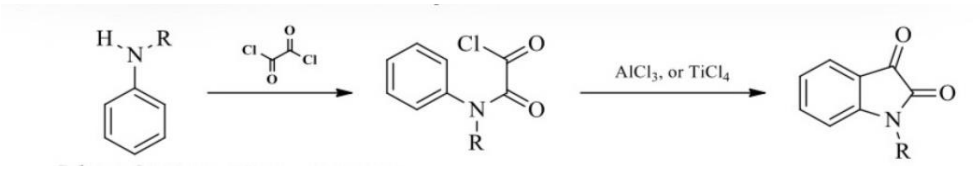
History

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 tomentose, a Caribbean tumorigenic plant, yielded methoxy phenyl pentyl isatins (melastatin alkaloids), while Chaetomium globosum yielded 5-(3'-methylbut-2'-yl)isatin (Silva et al., 2001).

Different methods for synthesis of Isatin derivatives

1. Stole method Synthesis

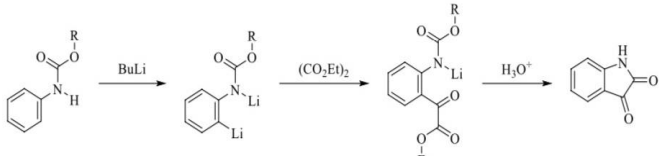
The Stole method which is an important alternative to the Sandmeyer method, involves reacting N-substituted anilines with oxalyl chloride to form chorooxa vande. which can then be cyclized by Lewis acids such as (AICI3, or TiCh) to form N-aryl isatin derivatives (Stollé et al., 1922).



Scheme 1: Stolle method for the synthesis of isatin derivatives.

2. Meanwell and Hawawasam method

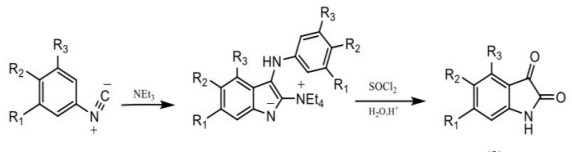
Meanwell and Hewawasam later introduced a new technique for the synthesis of isatins that is insensitive to the electronic nature of the substituents attached to the aromatic ring and is characterized by predictable regiochemical control. This approach relies on the creation of dianion when protected 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 reacting with ethyl oxalate to produce isatins after the deprotection and cyclization processes of the intermediate α-ketoesters by using HCl. The benefit of this method is regioselectivity of the 4- 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 2: Meanwell and Hewawasam method for synthesis of Isatin derivatives

3. Mironov method synthesis

Mironov revealed a versatile and unique two-step synthesis strategy for isatins with electron-withdrawing groups like CF3, NO2, and Cl as shown in Scheme 4. 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).

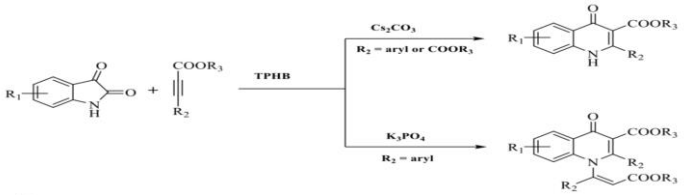


Scheme 3: Mironov synthesis strategy of isatins containing electron withdrawing groups

4. oxidation reaction method

Isatin molecules can undergo to oxidation reaction in the presence of chromic acid in an acetic acid solution to yield stoic 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).

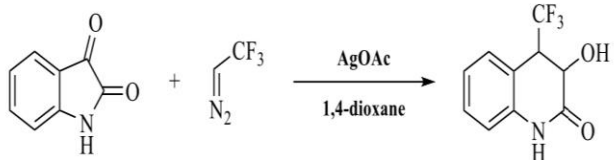


Scheme 4 : Organocesium-catalyzed oxidation of isatin to isatoic anhydride.

5. Ag-catalysed formation method synthesis

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).

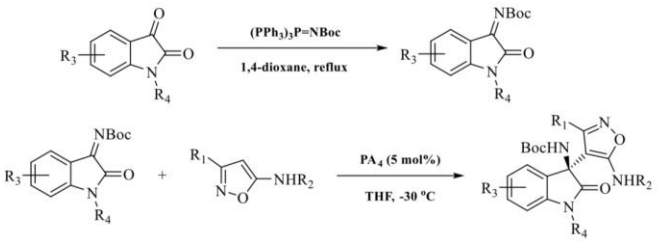


Scheme 5 : Ag-catalysed formation of isoxazoloquinolines.

6. Frieddle-craft alkylation method synthesis

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

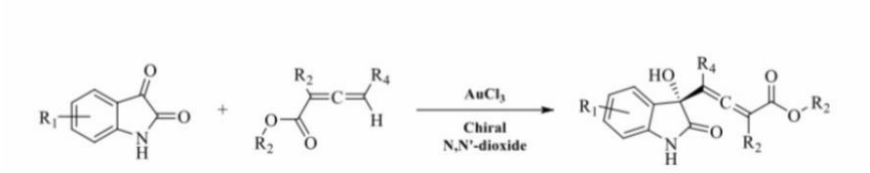
coworkers (Liu et al., 2021) used a chiral phosphoric acid as a catalyst with isatin-derived N-Boc ketimines was realized. The procedure yielded a wide range of new 3-isoxazole 3-amino-oxindoles with high yields and good to moderate enantioselectivity.



Scheme 6: Friedel-Crafts alkylation of isatins with pyrroles.

7. Alleno-aldol condensation method

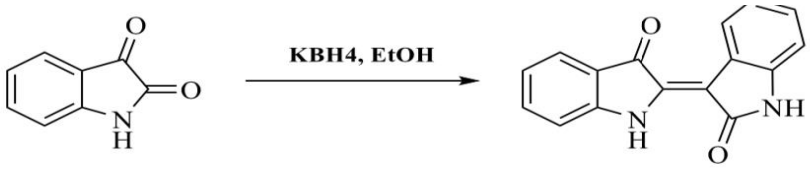
Aldol reactions yield □-hydroxyl carbonyl compounds, which are useful intermediates in the production of physiologically active derivatives. Isatin is an excellent substrate for condensation reactions because of its strong H-bond acceptor activity. Using a metal complex as the catalyst, the first diastereospecific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



Scheme 7: Alleno-aldol condensation of isatins with allenic esters.

8. Dimerization reaction synthesis

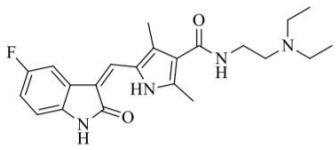
The dimerization of isatins with 3- acetoxyindole in the presence of Na2CO3 in methanol produces Indirubin. It is a well-known cytotoxic compound and reported as inhibitor of cyclin-dependent kinase 1 (CDK1). The limited availability of 3- 3-acetoxyindole and the low overall yield have impeded this dimerization technique. Indirubins were produced by dimerizing isatins (1 equiv.) with KBH4 (0.5 equiv.) in ethanol or methanol to circumvent these constraints, according to a recent study (Wang et al., 2017).



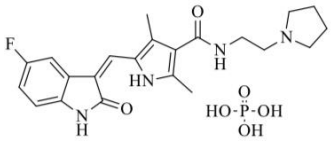
Scheme 8: dimerization reaction of Isatin derivatives.

Biological activity of isatin

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

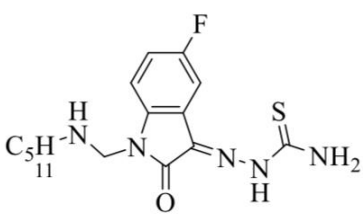


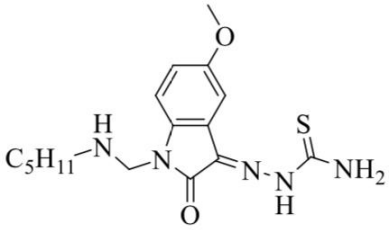
Sunitinib V



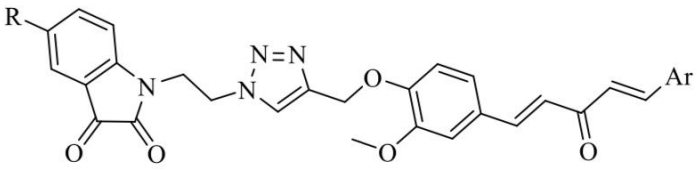
Toceranib phosphate

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



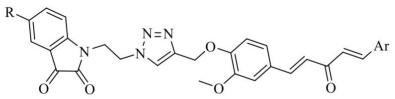


3. Isatin derivatives as tubulin inhibitors (Sharma et al., 2015)

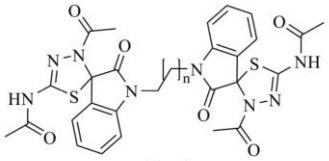


R= H , Cl, Br
Ar= furan , thiofuran , phenyl, p-nitrophenyl, p-chlorophenyl, p-methoxyphenyl

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

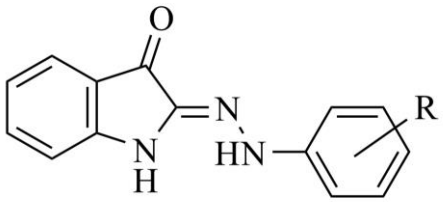


R= H , Cl, Br
Ar= furan , thiofuran , phenyl, p-nitrophenyl,
p-chlorophenyl, p-methoxyphenyl

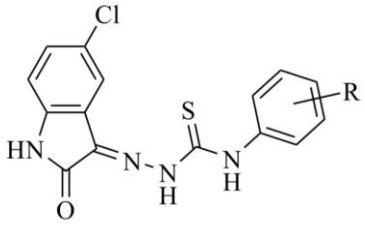


n= 2 or 3

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



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



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

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.

Reference

- Al-khuzaie, M. G., Fahad, M. M. & Al-safi, A. J. 2022. Synthesis, Reaction and Biological Importance of Isatin Derivatives. Biomedicine and Chemical Sciences, 1, 193-206.
- Bandini, M., Melloni, A., & Umani-Ronchi, A. (2004). New Catalytic Approaches in the Stereoselective Friedel–Crafts Alkylation Reaction. Angewandte Chemie International Edition, 43(5), 550-556.
- Da Costa, D. P., de Castro, A. C., da Silva, G. A., Lima-Junior, C. G., de Andrade Júnior, F. P., de Oliveira Lima, E., . . . da Silva, L. C. (2021). Microwave-assisted synthesis and antimicrobial activity of novel spiro 1,3,4-thiadiazolines from isatin derivatives. Journal of Heterocyclic Chemistry, 58(3), 766-776.
- Emami, S., Valipour, M., Kazemi Komishani, F., Sadati-Ashrafi, F., Rasoulian, M., Ghasemian, M., . .. Ahangar, N. (2021). Synthesis, in silico, in vitro and in vivo evaluations of isatin aroylhydrazones as highly potent anticonvulsant agents. Bioorganic Chemistry, 104943
- Erdmann, O. L. (1840). Untersuchungen über den Indigo. Journal für Praktische Chemie, 19(1), 321-362.
- Franz, A. K., Gutierrez, E. G., Wong, C. J., & Sahin, A. H. (2011). Enantioselective and Regioselective Indium(III)-Catalyzed Addition of Pyrroles to Isatins. Organic Letters, 13(21), 5754-5757.
- Gassman, P. G., & Van Bergen, T. J. (1974). Oxindoles. New, general method of synthesis. Journal of the American Chemical Society, 96(17), 5508-5512.
- Jamali, M. F., Gupta, E., Kumar, A., Kant, R., & Mohanan, K. (2020). Ag-Catalyzed Trifluoromethylative Ring Expansion of Isatins and Isatin Ketimines with Trifluorodiazoethane. Chemistry – An Asian Journal, 15(6), 757-761.
- Jiang, S.-F., Xu, C., Zhou, Z.-W., Zhang, Q., Wen, X.-H.,Jia, F.-C., & Wu, A.-X. (2018). Switchable Access to 3-Carboxylate-4-quinolones and 1-Vinyl-3-carboxylate-4-quinolones via Oxidative Cyclization of Isatins and Alkynes. Organic Letters, 20(14), 4231-4234.

- Liu, H., Yan, Y., Li, M., & Zhang, X. (2021). An enantioselective aza-Friedel–Crafts reaction of 5-aminoisoxazoles with isatin-derived N-Boc ketimines. Organic & Biomolecular Chemistry, 19(17), 3820-3824.
- Mironov, M. A., & Mokrushin, V. S. (1998). Reaction of aromatic isocyanides with triethylamine: a new method for the synthesis of indole betaines. Mendeleev Communications, 8(6), 242-243.
- Rahim, F., Taha, M., Iqbal, N., Hayat, S., Qureshi, F., Uddin, I., . . . Khan, K. M. (2020). Isatin based thiosemicarbazide derivatives as potential inhibitor of α-glucosidase, synthesis and their molecular docking study. Journal of Molecular Structure, 1222, 128922.
- Sagnou, M., Mavroidi, B., Kaminari, A., Boukos, N., & pelecanou, M. (2020). Novel Isatin Thiosemicarbazone Derivatives as Potent Inhibitors of β-Amyloid Peptide Aggregation and Toxicity. ACS Chemical Neuroscience, 11(15), 2266-2276.
- Silva, J. F. M. d., Garden, S. J., & Pinto, A. C. (2001). The chemistry of isatins: a review from 1975 to 1999. Journal of the Brazilian Chemical Society, 12, 273-324.
- Stollé, R., Bergdoll, R., Luther, M., Auerhahn, A., & Wacker, W. (1922). Über N-substituierte Oxindole und Isatine. Journal für Praktische Chemie, 105(1), 137-148.
- Sharma, S., Gupta, M. K., Saxena, A. K., & Bedi, P. M. S. (2015). Triazole linked mono carbonyl curcumin-isatin bifunctional hybrids as novel anti tubulin agents: Design, synthesis, biological evaluation and molecular modeling studies. Bioorganic & Medicinal Chemistry, 23(22), 7165-7180.
- Sumpter, W. C. (1944). The Chemistry of Isatin. Chemical Reviews, 34(3), 393-434.
- Varun, Sonam, & Kakkar, R. (2019). Isatin and its derivatives: a survey of recent syntheses, reactions, and applications. MedChemComm, 10(3), 351-368.
- Wang, C., Yan, J., Du, M., Burlison, J. A., Li, C., Sun, Y.,. . . Liu, J. (2017). One step synthesis of indirubins by reductive coupling of isatins with KBH4. Tetrahedron, 73(19), 2780-2785.
- Wang, G., Liu, X., Chen, Y., Yang, J., Li, J., Lin, L., & Feng, X. (2016). Diastereoselective and Enantioselective Alleno-aldol Reaction of Allenoates with Isatins to Synthesis of Carbinol Allenoates Catalyzed by Gold. ACS Catalysis, 6(4), 2482-2486.

- Yousef, M. A., Ali, A. M., El-Sayed, W. M., Qayed, W. S., Farag, H. H. A., & Aboul-Fadl, T. (2020). Design and synthesis of novel isatin-based derivatives targeting cell cycle checkpoint pathways as potential anticancer agents. Bioorganic Chemistry, 105, 104366.