A Review on Recent Advances and Applications of 5-Chloroisatin and its Derivatives in Design and Synthesis of New Organic Compounds

Z. Tribak1, M.K. Skalli1*, O. Senhaji2, Y. Kandri Rodi3, A. Haoudi1, E.M. Essassi3

1 Laboratory of Applied Chemistry, Sidi Mohamed Ben Abdellah University, Faculty of Sciences and Technology of Fez, Morocco.
2 Laboratory of Applied Physical Chemistry, Moulay Ismail University, Faculty of Sciences and Technology of Errachidia, Morocco.
3 Laboratory of Organic Heterocyclic Chemistry, Faculty of Sciences, Mohammed V University in Rabat B.P. 1014, Rabat, Morocco
*Corresponding author

Abstract: This review gives a short summary of the advances in the use of 5-chloroisatin as starting material in the synthesis of various heterocyclic and carbocyclic compounds and considered as a valuable building block in organic synthesis and shows various chemical reactions such as N-alkylation, 1,3-dipolar cycloadditions and cyclocondensations.

Keywords: 5-Chloroisatin, N-alkylation, 1,3-Dipolar cycloaddition, cyclocondensations, derivatives, synthesis.

Graphical Abstract:

I. Introduction

Isatin, indoline-2,3-dione or indole-1H-2,3-dione (Figure 1) is an indole derivative and an important group of heterocyclic compounds which are biologically active and of significant importance in medicinal chemistry [1].
In nature, isatin is found in plants of the genus Isatis, in Calanthe discolor LINDL. It has also been isolated as a metabolic derivative of adrenaline in humans [2]. Isatin moiety shows biological activities like antimicrobial, CNS depressant, anti-HIV, cytotoxicity, anti-inflammatory, analgesic, anti-anxiety and many other activities and are capable of crossing the blood-brain barrier [3].

5-Chloroisatin as an isatin derivative represents an important class of heterocyclic compounds endowed of interesting pharmacological [4, 5] and biological activities such as antimicrobial [6], antitumor [7, 8], antitubercular [9, 10], antimalaria [11], anti-HIV [12], anticorrosive [13, 14] and antibacterial [15, 16] activities.

5-Chloroisatin is a chemical compound with a heterocyclic indole ring with a molecular formula C₈H₄ClNO₂. It is an eight membered ring consisting of 1 nitrogen atom, 8 carbon atoms, 2 oxygen atoms, 1 chlor atom and 5 double bonds. It occurs in nature as an orange to very dark orange solid and has a molecular weight of 181.576 g/mol [17]. It has a melting point of 254-258℃. It is readily soluble in polar organic solvents such as methanol, acetone, acetonitrile, DMSO, DMF and ethyl acetate [18], partially soluble in CH₂Cl₂, CHCl₃, slightly soluble in water and not soluble in non-polar organic solvents such as hexane, toluene, benzene.

In addition, 5-Chloroisatin has not only multifunctionality but also diversity of transformations, which make it a synthetically versatile substrate. During recent years several articles and reviews were published on isatins. Tribak et al. reviewed 5-Chloroisatin as a privileged molecule in synthesis and characterizations of New N-alkyl, isoxazoles, isoxazolines, dioxazoles and 1.2.3-triazoles derivatives of 5-Chloroisatin [19]. The most fascinating application of 5-Chloroisatin in organic synthesis is undoubtedly due to the highly reactive C-3 carbonyl group that is a prochiral center as well.

Herein, in continuation of our studies towards 5-Chloroisatin, and since there is a wide range of reactions that include 5-chloroisatin in the synthesis and design of organic compounds, this article aims to review for the first time the chemistry of 5-chloroisatin employed in the synthesis of different types of organic compounds.

II. N-alkylation of 5-chloro-1H-indole-2,3-dione:

2.1. Action of monohaloegenated carbon chains:

As part of our work, we focused on the formation of new long-chain heterocyclic compounds via N-alkylation between 5-Chloroisatin and the various alkyl halides at room temperature by applying the method of catalyzed by liquid-solid phase transfer, in the presence of potassium carbonate and tetra-n-butylammoium bromide (TBAB), dissolved into N, N-dimethylformamide (DMF). In all cases, the reaction gives new N-alkylchloroisatins 2-11 in good yield [20].

2.2. Action of methyl iodide:

In order to enhance the value of other compounds derived from 5-Chloroisatin, which may have potential activities, we have studied the action of methyl iodide under the conditions of liquid/solid phase-transfer catalysis or PTC in the presence of K₂CO₃ and a catalyst (Scheme 2) [21].
2.3. Action of benzyl chloride:
The action of 1.2 equivalents of benzyl chloride on 5-Chloroisatin permits the alkylation of nitrogens under the conditions of phase transfer catalysis using TBAB as a catalyst and potassium carbonate as the base in DMF for 48 hours later leads to the formation of the N-alkylated product 13 in good yield [22].

2.4. Action of cinnamyl bromide:
In the framework of synthesizing derivatives associating the 5-Chloroisatin motif, we studied the action of cinnamyl bromide on compound 1 under phase-transfer catalysis (PTC) conditions in the presence of K$_2$CO$_3$ as base.

2.5. Action of 2-chloro-N,N-diethylethylamine hydrochloride and 2-chloro-N,N-dimethylethylamine:
We studied the reaction of N-alkylation of 5-Chloroisatin by the two alkylating agents 2-chloro-N,N-diethylethylamine and 2-chloro-N,N-dimethylethylamine under the conditions of the catalysis by liquid/solid phase-transfer catalysis. Potassium carbonate was used as the K$_2$CO$_3$ base in dimethylformamide (Scheme 5 and Scheme 6).
2.6. Action of allyl bromide:
In order to synthesize new dipolarophiles derived from 5-chloroisatin, which can be used as precursors in 1,3-dipolar cycloaddition reactions, we have developed the reaction between 5-Chloroisatin and allyl bromide at room temperature under the conditions of liquid-solid phase transfer catalysis in DMF as solvent, using K2CO3 as the base and TBAB as catalyst to prepare compound 17 [23]. (Scheme 7)

\[
\text{Cl} \begin{array}{c} \text{N} \\ \text{O} \end{array} + \text{Br} \rightarrow \text{Cl} \begin{array}{c} \text{N} \\ \text{O} \end{array} \quad \text{K}_2\text{CO}_3/\text{TBAB} \\
\text{DMF/amb temp} \\
48h
\]

Scheme 7

2.7. Action of propargyl bromide:
The action of propargyl bromide, with respect to 5-chloroisatin, gives the product: 5-chloro-1-(prop-2-ynyl) indoline-2,3-dione 18, at a solubilized ambient temperature in DMF under the conditions of phase transfer catalysis.

\[
\text{Cl} \begin{array}{c} \text{N} \\ \text{O} \end{array} + \text{Br} \rightarrow \text{Cl} \begin{array}{c} \text{N} \\ \text{O} \end{array} \quad \text{K}_2\text{CO}_3/\text{TBAB} \\
\text{DMF/amb temp} \\
48h
\]

Scheme 8

2.8. Action of dihalogenated carbon chains:
In order to obtain new heterocyclic compounds possessing the 5-chloro-isatin nucleus, we were interested in the condensation of 5-Chloroisatin with dihalogenated chains. This reaction allowed us to isolate the corresponding N-alkylated compounds, with good yields under liquid/solid phase-transfer catalysis conditions [24] (Scheme 9).

\[
\text{Cl} \begin{array}{c} \text{N} \\ \text{O} \end{array} + \text{RBr}_2 \rightarrow \text{Cl} \begin{array}{c} \text{N} \\ \text{O} \end{array} \quad \text{K}_2\text{CO}_3/\text{TBAB} \\
\text{DMF/amb temp} \\
48h
\]

19 : R = C3H6  
20 : R = C6H12  
21 : R = C12H24

Scheme 9

III. Other Specific Reactions

3.1. Action of 1,2-bis (2-chloroethoxy) ethane:
The condensation of 5-chloroisatin with 1,2-bis (2-chloroethoxy) ethane under the conditions of liquid/solid phase transfer catalysis in DMF as solvent and potassium bicarbonate as a weak base at 80°C, allowed us to isolate compound 22 (Scheme 10).

\[
\text{Cl} \begin{array}{c} \text{N} \\ \text{O} \end{array} + \text{Cl} \begin{array}{c} \text{O} \\ \text{O} \end{array} \rightarrow \text{Cl} \begin{array}{c} \text{N} \\ \text{O} \end{array} \quad \text{K}_2\text{CO}_3/\text{TBAB} \\
\text{DMF/80°C} \\
48h
\]

Scheme 10
3.2. Action of Trimethylamine:
Continuing our research in this field, it has appeared interesting to develop the synthesis of new molecules derived from 5-Chloroisatin, capable of presenting potential biological activities. Thus, we have easily isolated a single compound by condensation of 1-(6-bromohexyl)-5-chloroindoline-2,3-dione with trimethylamine solubilized in acetone at ambient temperature [25].

![Scheme 11](image)

IV. Study of 1,3-dipolar cycloaddition reactions on 5-Chloroisatin derivatives:

4.1. 1,3-Dipolar Cycloaddition Reactions of Nitrile Oxides with 5-Chloroisatin derivatives:

4.1.1. Condensation of N-allylchloroisatin with Nitrile Oxides:
In our work, we have mainly focused on the reactivity of nitrile oxides with N-allylchloroisatin by the action of sodium hypochlorite (NaClO) in a biphasic medium (water/chloroform) at 0°C for 4 hours, leading to the separation of the two cycloadducts, with good yields [26].

![Scheme 12](image)

4.1.2. Action of 9-anthraldehyde oxime on N-allylchloroisatin:
The reaction of N-allylchloroisatin 17 with a slight excess of 9-anthraldehyde oxime results in the formation of two cycloadducts 34,35 resulting from the condensation of the dipole with the carbon-oxygen double bond and the Carbon-Carbon in a good yield (Scheme 13).

![Scheme 13](image)

4.1.3. Action of 4-Chlorobenzaldehyde oxime on N-propargylchloroisatin:
The reaction of N-propargylchloroisatin 18 with 4-chlorobenzaldehyde oxime obtained in situ by the action of sodium hypochlorite on nitrile oxide was carried out in chloroform at 0°C for 4 hours, allowing us to isolate two cycloadducts of the two cycloadducts 36 and 37 (Scheme 14).
4.1.4. *Action of 4-chlorobenzaldehyde oxime on N-alkylchloroisatin:*

The condensation reaction of 4-chlorobenzaldehyde oxime, prepared in situ by the action of sodium hypochlorite on nitrile oxide, with N-alkylchloroisatines in a two-phase medium (water/chloroform) at 0°C for 4 hours, leads in each case to the formation of a single cycloadduct, resulting from the cycloaddition of dipole on the dipolarophile group C=O in position 3 [27].

4.1.5. *Action of benzaldoxime on 5-chloro-1-methylindoline-2,3-dione:*

4.1.6. *Action of N,N-dimethylbenzenamine oxime on N-alkylchloroisatin:*

![Scheme 14](image1)

![Scheme 15](image2)

![Scheme 16](image3)

![Scheme 17](image4)
4.1.7. Action of 9-anthraldehyde oxime on N-alkylchloroisatines:

![Chemical structure](image)

Scheme 18

4.2. Cycloaddition with azides:

4.2.1. Cycloaddition of Azide-Alkyne without catalyst:

4.2.1.1 Condensation of N-propargylchloroisatin with benzyl azide and other azides:

The action of azide on the dipolarophile 18 under reflux of ethanol for 3 days led to the formation of the two regioisomers 47-48 resulting from the attack of the nucleophilic nitrogen of the dipole on the Carbon sp3, the most electrophilic of the dipolarophile 18. We have not observed, in any case, the cycloaddition on the carbon-oxygen double bond [28, 29].

![Chemical structure](image)

Scheme 19

![Chemical structure](image)

Scheme 20

4.2.2 Cycloaddition of copper-catalyzed alkyne-azole (CuAAC):

It is another method of obtaining 1,2,3-triazoles, one of the most widely used, since it does not require the addition of a base, it consists of the in situ reduction of the copper (II) salts brought under CuSO\(_4\)·H\(_2\)O form of copper sulfate pentahydrate is the most commonly encountered method. It requires the introduction of an excess reducing agent, generally sodium ascorbate in a water-ethanol mixture. This procedure made it possible to selectively obtain the disubstituted 1,4-triazole regioisomer and greatly reduces the reaction time and temperature (Scheme 21 and Scheme 22) [30].
V. Cyclocondensations of 5-Chloroisatin derivatives:
The action of Diamino-5-bromopyridine on a stoichiometric amount of the 5-chloro-isatin derivatives (5, 12 and 53) in xylene under reflux for 24 hours resulted in a single product. The reaction consists in the condensation of the two diamino-5-bromopyridine amine groups on the C-2 and C-3 carbonyl functions of 5-chloro-isatin derivatives with the elimination of two molecules of water.

Thus, we have been able to synthesize new compounds containing the pyridine ring: Compounds 56, 57 and 58 (Scheme 23, 24).

VI. Conclusion
5-Chloroisatin and its C-3 functionalized derivatives have gained an emergent interest in the last years in organic and medicinal chemistry since they constitute the backbone of a great number of interesting compounds. More
The authors would like to thank all the people who helped to carry out this work.
IX. Abbreviations

Amb temp: ambient temperature
CHCl₃: Chloroform
DMF: Dimethylformamide
DMSO: Dimethyl Sulfoxide
K₂CO₃: potassium carbonate
NaClO: sodium hypochlorite
PTC: phase-transfer catalysis
TBAB: tetra-n-butylammonium bromide