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

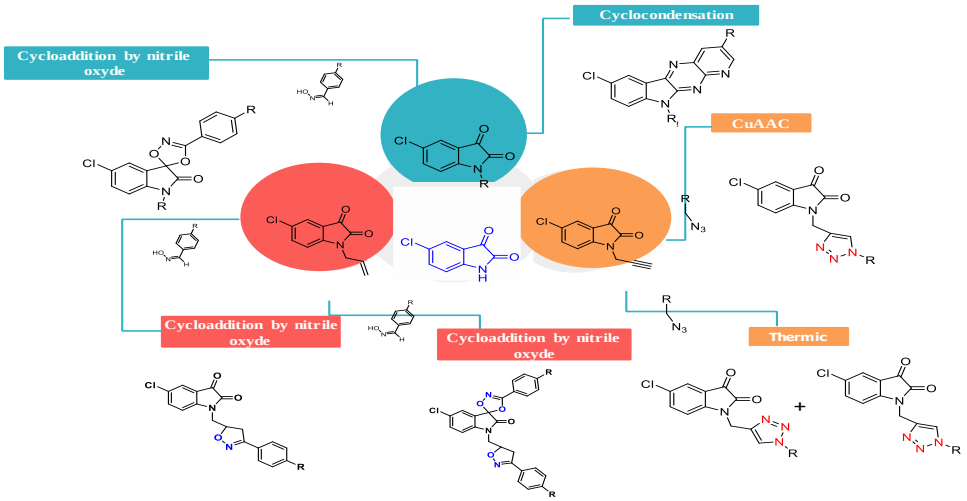
Z. Tribak[1], M.K. Skalli[1*], O. Senhaji[2], Y. Kandri Rodi[1], A. Haoudi[1], E.M. Essassi[3]

[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 Ismaïl 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 chemicals reactions such as N-alkylation, 1.3-dipolar cycloadditions and cyclocondensations.*

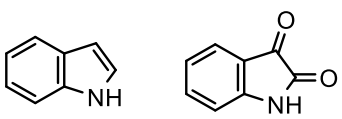
Keywords: *5-Chloroisatin, N-alkylation, 1,3-Dipolar cycloaddition, cyclocondensations, derivatives, synthesis.*

Graphical Abstract:



I. Introduction

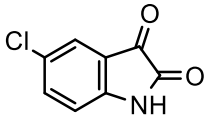
Isatin, indoline-2,3-dione or indole-1*H*-2,3-dione (Figure 1) is an indole derivative and an important group of heterocyclic compounds which are biologically active and of significant importance in medicinal chemistry [1].



indole Isatin

Figure: 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 moeity shows biological activites like antimicrobial, CNS depressant, anti-HIV, cytotoxicity, anti-inflammatory, anlagesic, antianixety 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

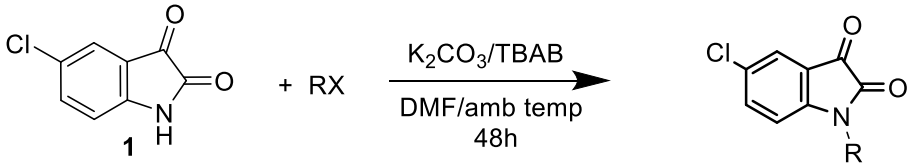
Figure: 2

5-Chloroisatin is a chemical compound with a heterocyclic indole ring with a molecular formula $C_8H_4ClNO_2$. It is an eight membered ring consisting of 1 nitrogen atom,8 carbon atoms,2 oxygen atoms, 1chlor 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°C. It is readily soluble in polar organic solvents such as methanol, acetone, acetonitrile, DMSO, DMF and ethyl acetate [18], partially soluble in CH_2Cl_2, $CHCl_3$, 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-1*H*-indole-2,3-dione:

2.1. Action of monohalogenated 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].

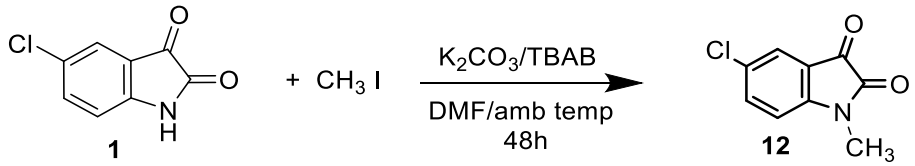


X:Br **2**:R=C_2H_5 **3**:R=C_4H_9 **4**:R=C_8H_{17} **5**:R=C_9H_{19} **6**:R=$C_{10}H_{21}$ **7**:R=$C_{12}H_{25}$ **8**:R=$C_{14}H_{29}$ **9**:R=$C_{16}H_{33}$ **10**:R=$C_{17}H_{35}$ **11**:R=$C_{18}H_{37}$

Scheme 1

2.2. Action of methyl iodide:

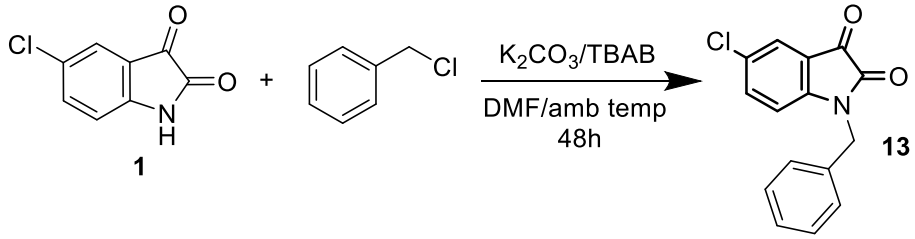
In order to enhance the value of other compounds derived from 5-Chloroisatin, which may have potential activities, we have studied the action of methyl iodide under the conditions of liquid/solid phase-transfer catalysis or PTC in the presence of K_2CO_3 and a catalyst (Scheme 2) [21].



Scheme 2

2.3. Action of benzyl chloride:

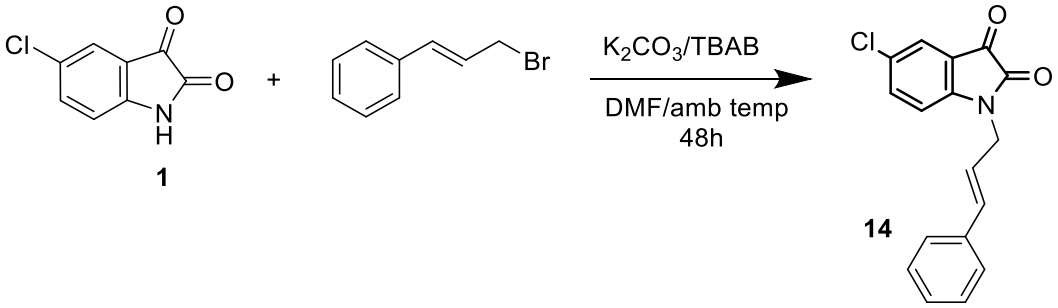
The action of 1.2 equivalents of benzyl chloride on 5-Chloroisatin permits the alkylation of nitrogens under the conditions of phase transfer catalysis using TBAB as a catalyst and potassium carbonate as the base in DMF for 48 hours later leads to the formation of the N-alkylated product **13** in good yield [22].



Scheme 3

2.4. Action of cinnamyl bromide:

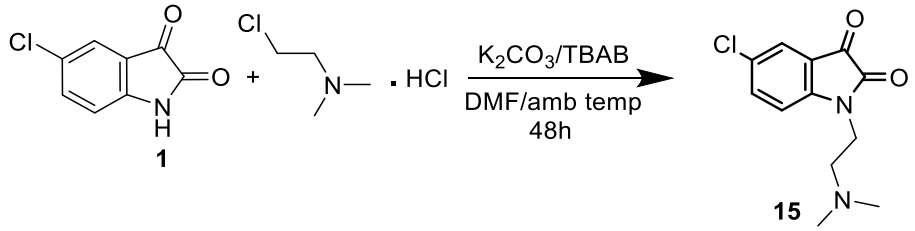
In the framework of synthesizing derivatives associating the 5-Chloroisatin motif, we studied the action of cinnamyl bromide on compound **1** under phase-transfer catalysis (PTC) conditions in the presence of K_2CO_3 as base.



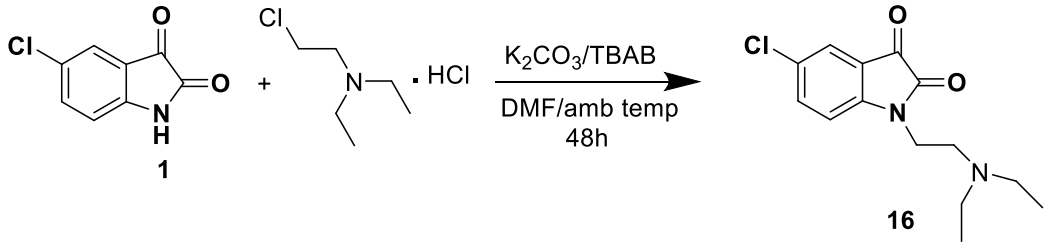
Scheme 4

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_2CO_3 base in dimethylformamide (Scheme 5 and Scheme 6).



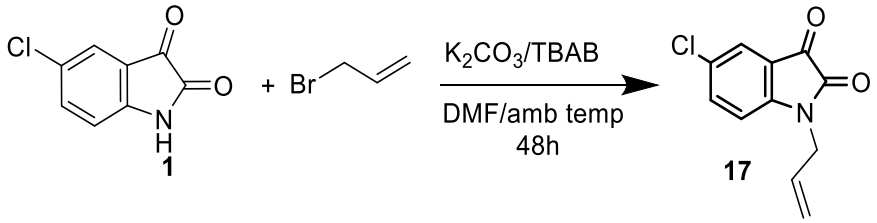
Scheme 5



Scheme 6

2.6. Action of allyl bromide:

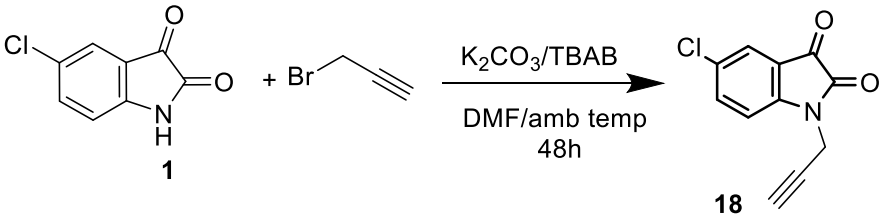
In order to synthesize new dipolarophiles derived from 5-chloroisatin, which can be used as precursors in 1,3-dipolar cycloaddition reactions, we have developed the reaction between 5-Chloroisatin and allyl bromide at room temperature under the conditions of liquid-solid phase transfer catalysis in DMF as solvent, using K_2CO_3 as the base and TBAB as catalyst to prepare compound **17** [23]. (Scheme 7)



Scheme 7

2.7. Action of propargyl bromide:

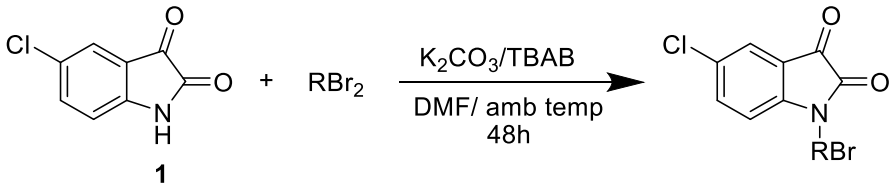
The action of propargyl bromide, with respect to 5-chloroisatin, gives the product: 5-chloro-1- (prop-2-ynyl) indoline-2,3-dione **18,** at a solubilized ambient temperature in DMF under the conditions of phase transfer catalysis.



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).



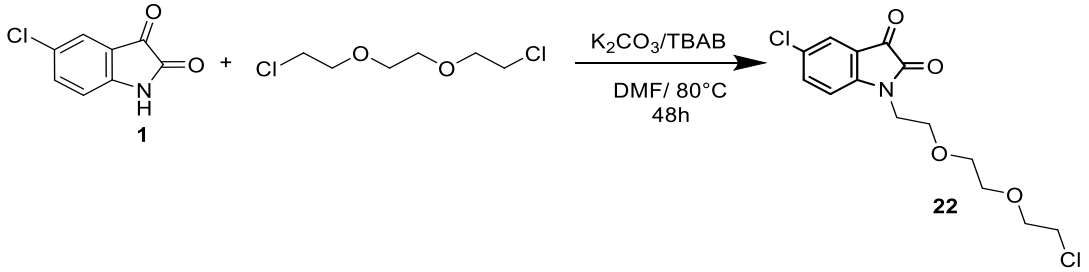
19 : R = C_3H_6
20 : R = C_6H_{12}
21 : R = $C_{12}H_{24}$

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).

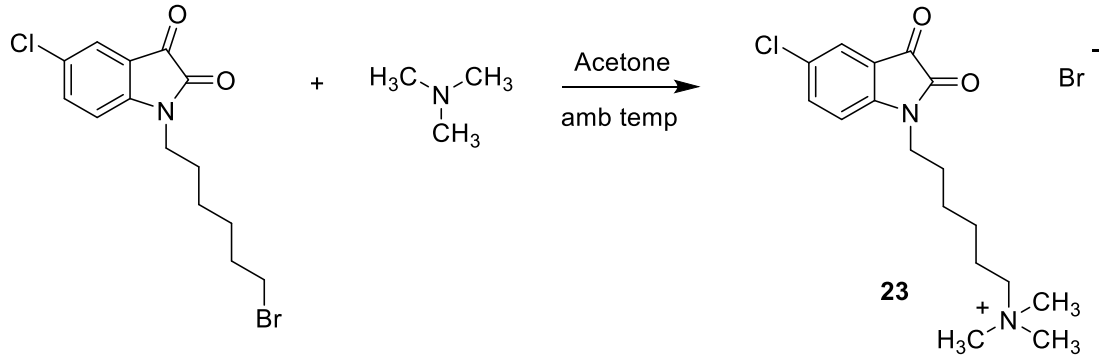


Scheme 10

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].



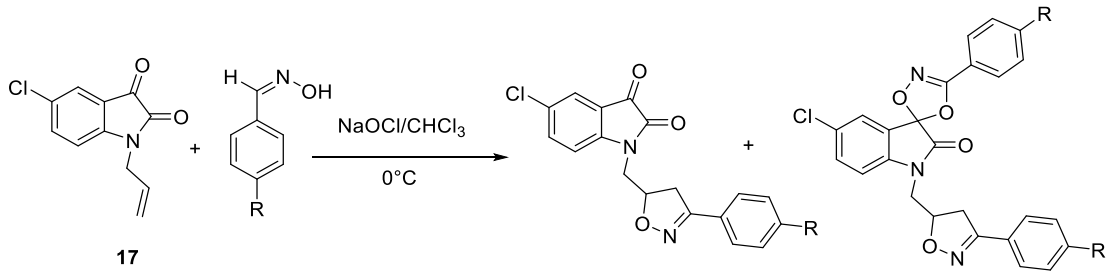
Scheme11

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 nitriles oxides with N-allylchloroisatin by the action of sodium hypochlorite (NaClO) in a biphasic medium (water/chloroform) at 0°C for 4 hours, leads to the separation of the two cycloadducts, with good yields [26].



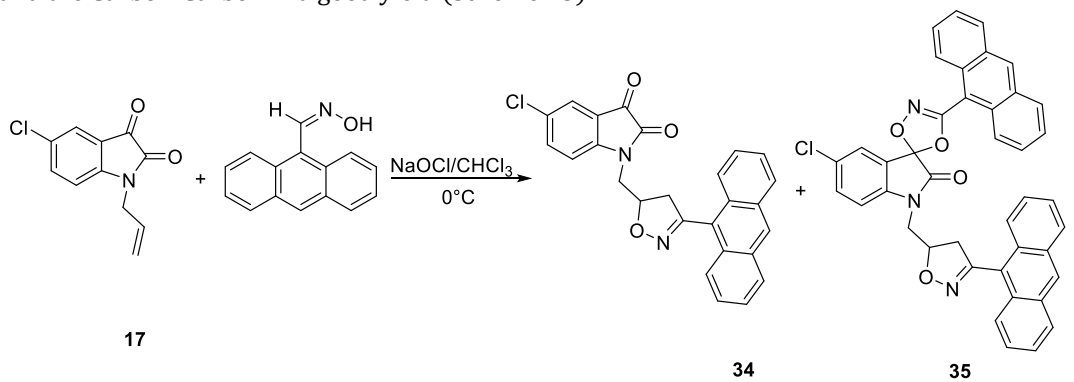
24:R=Cl
26:R=H
28:R=NO_2
30:R=OCH_3
32:R=$N(CH_3)_2$

25:R=Cl
27:R=H
29:R=NO_2
31:R=OCH_3
33:R=$N(CH_3)_2$

Scheme 12

4.1.2. Action of 9-anthraldehyde oxime on N-allylchloroisatin:

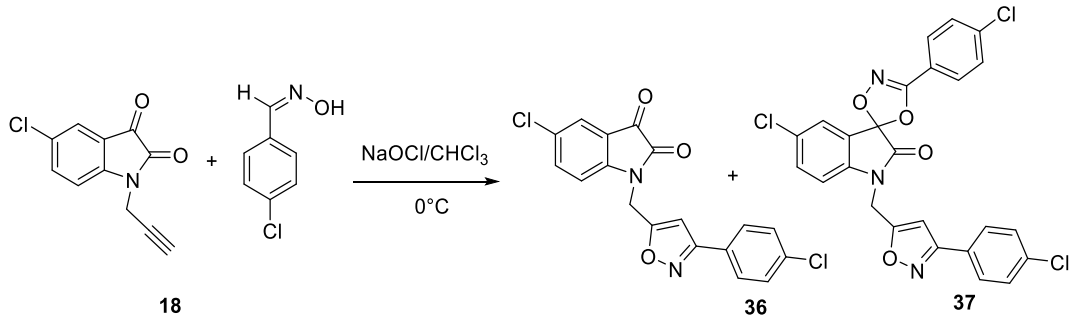
The reaction of N-allylchloroisatin **17** with a slight excess of *9-anthraldehyde oxime* results in the formation of two cycloadducts 34,3 5 resulting from the condensation of the dipole with the carbon-oxygen double bond and the Carbon-Carbon in a good yield (Scheme 13).



Scheme 13

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, allowed us to isolate two cycloadducts of the two cycloadducts 36 and 37 (Scheme 14).

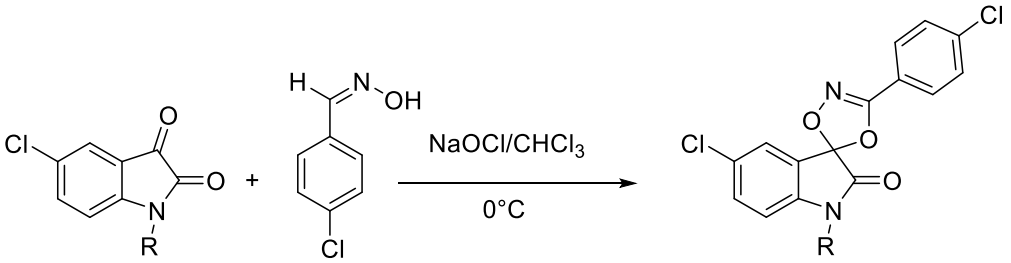


18 36 37

Scheme 14

4.1.4. Action of 4-chlorobenzaldehyde oxime on N-alkylchloroisatin:

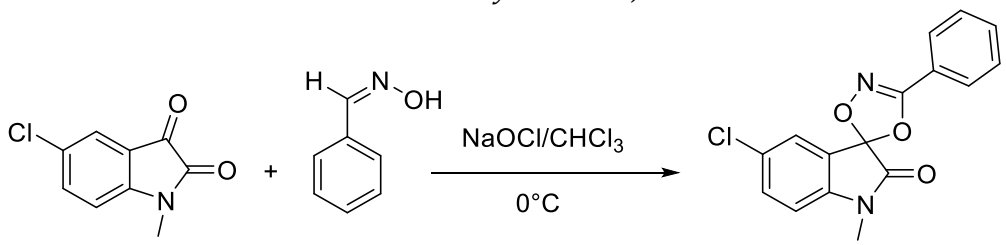
The condensation reaction of 4-chlorobenzaldehyde oxime, prepared in situ by the action of sodium hypochlorite on nitrile oxide, with N-alkylchloroisatines in a two-phase medium (water/chloroform) at 0°C for 4 hours, leads in each case to the formation of a single cycloadduct, resulting from the cycloaddition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



38:R:CH_3
39:R:C_2H_5
40:R:C_4H_9
41:R:C_7H_7

Scheme 15

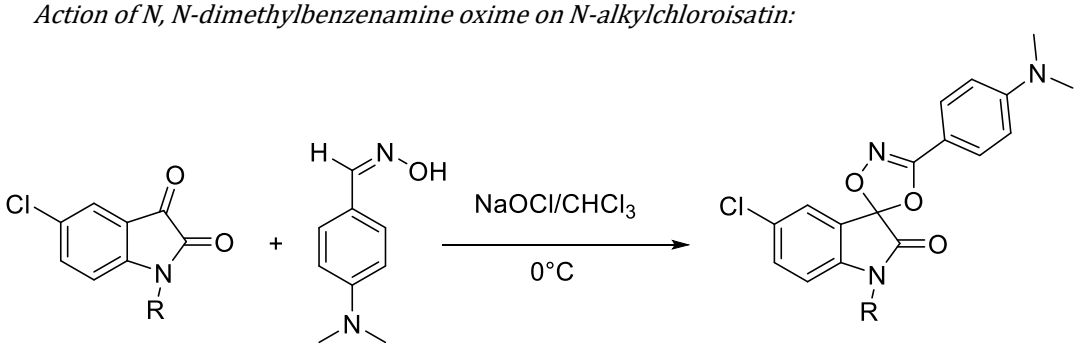
4.1.5. Action of benzaldoxime on 5-chloro-1-methylindoline-2,3-dione:



42

Scheme 16

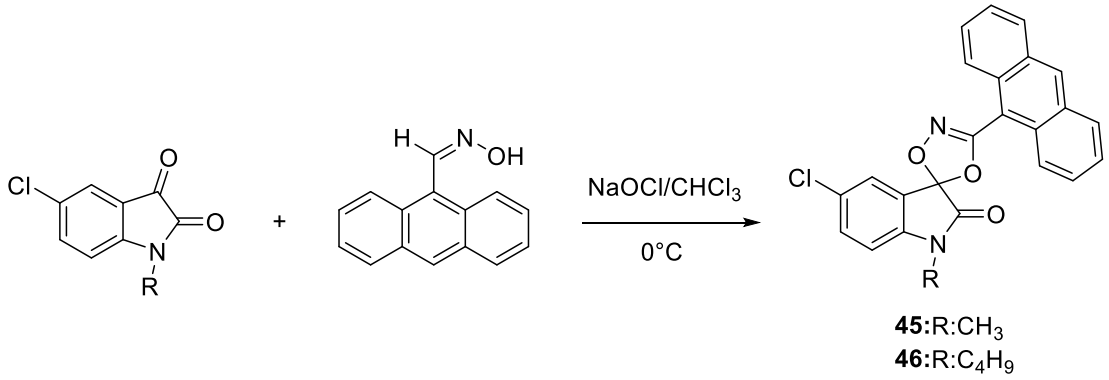
4.1.6. Action of N, N-dimethylbenzenamine oxime on N-alkylchloroisatin:



43:R:C_4H_9
44:R:C_7H_7

Scheme 17

4.1.7. Action of 9-anthraldehyde oxime on N-alkylchloroisatines:



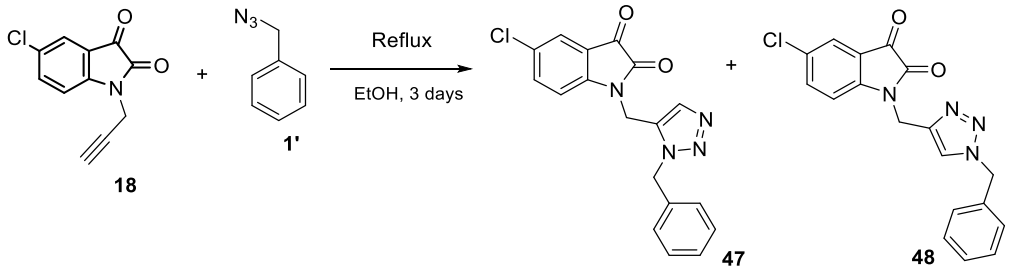
Scheme 18

4.2. Cycloaddition with azides:

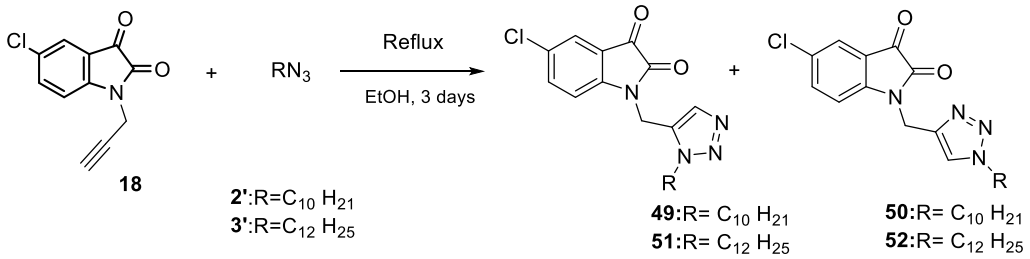
4.2.1. Cycloaddition of Azide-Alcyne without catalyst:

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].



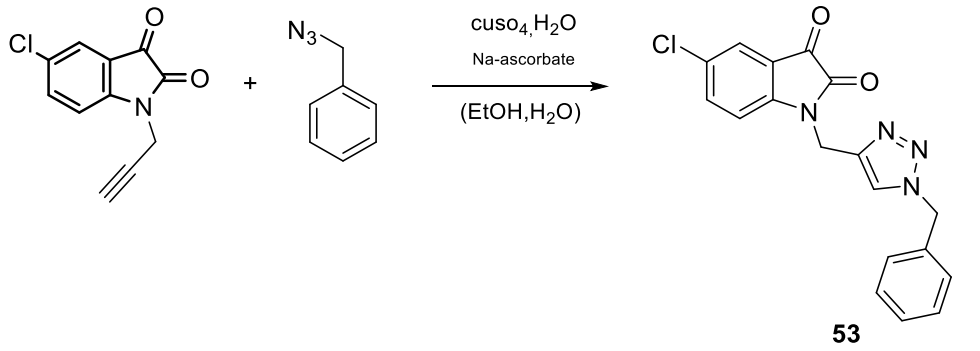
Scheme 19



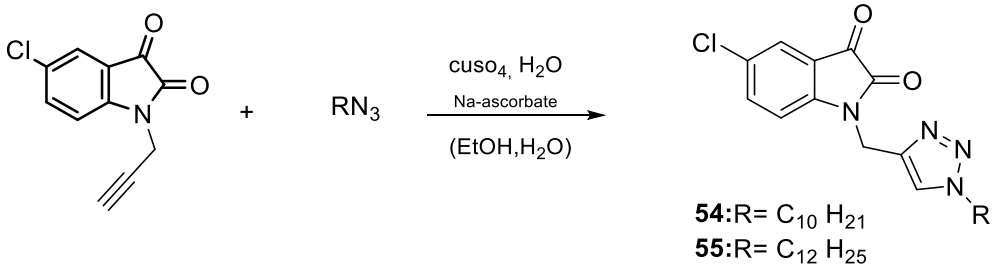
Scheme 20

4.2.2 Cycloaddition of copper-catalyzed alkyne-azide (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 $CuSO_4H_2O$ 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].



Scheme 21

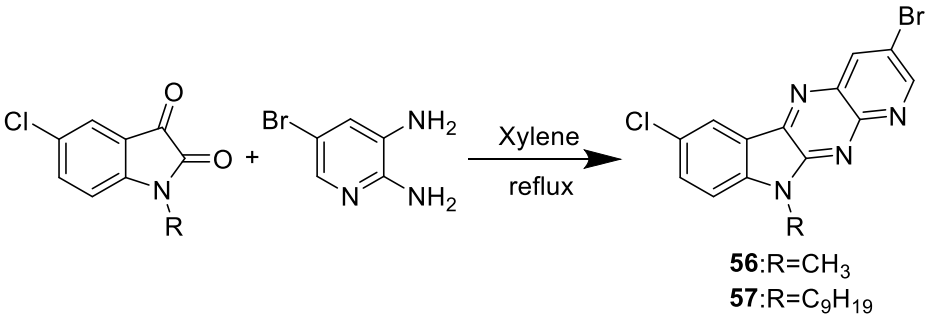


Scheme 22

V. Cyclocondensations of 5-Chloroisatin derivatives:

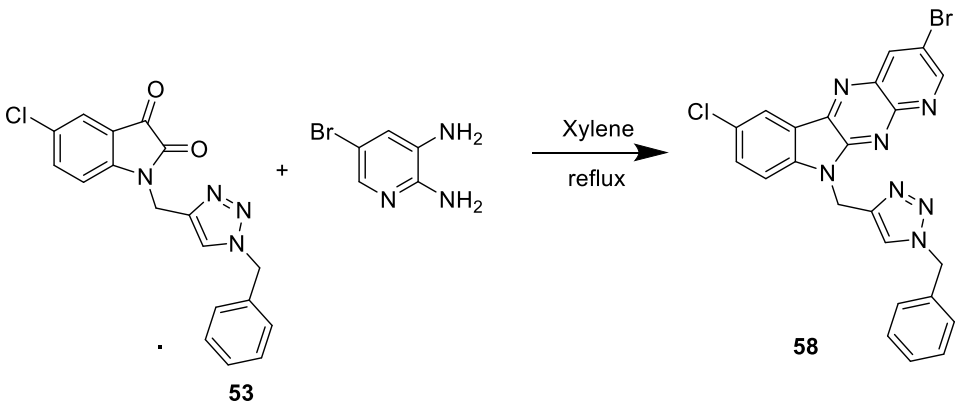
The action of Diamino-5-bromopyridine on a stoichiometric amount of the 5-chloro-isatin derivatives (5, 12 and 53) in xylene under reflux for 24 hours resulted in a single product.

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.



Scheme 23

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



Scheme 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

importantly, most of these compounds exhibit biological and pharmaceutical activities. We have collected in this review the most representative examples in the field of N-alkylation, 1.3-dipolar cycloaddition and cyclocondensations giving to the reader a broad vision of 5-Chloroisatin's role in organic reactions and pursuant to our previous studies.

VII. References

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IX. Abbreviations

Amb temp: ambient temperature
$CHCl_3$: Chloroform
DMF: Dimethylformamide
DMSO: Dimethyl Sulfoxide
K_2CO_3: potassium carbonate
NaClO: sodium hypochlorite
PTC: phase-transfer catalysis
TBAB: tetra-n-butylammoium bromide