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# Syntheses and Characterizations of Some New N-alkyl, Isoxazole and Dioxazole Derivatives of 5-Chloroisatin

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***Abstract—*** *N-alkyl and cycloadducts derivatives of 5-Chloroisatin were synthesized in good to excellent yields. The method evidences a selective N-alkylation when using 1,2-bis (2-chloroethoxy) ethane as efficient spacer at room temperature on the 5-Chloroisatin moiety. A general method for the 1,3-dipolar cycloaddition of 4-Chlorobenzaldoxime to alkynes provides a useful alternative route to get newisoxazole et dioxazole derivatives.*

***Keywords— 1, 3-dipolar cycloaddition, 4-Chlorobenzaldoxime, N-alkylation, $^{1}H$ NMR, $^{13}C$ NMR.***

## I. INTRODUCTION

The interest for the synthesis of the isatin derivatives has increased in organic and pharmaceutical chemistry. In 1988 the isatin is isolated and reported to possess a wide range of activities involving the central nervous system as an endogenous compound [1-3]. This heterocyclic system is found in a number of molecules possessing biological and pharmacological properties. The usage of some isatin derivatives for antibacterial, antimalarial, anti-proliferative and anti-coagulant [4-9], antimicrobial, anticonvulsative, anticancer, antiHIV, etc. activities and also antifungal, herbicidal agents [10-17].Many other remarkable applications are reported in the literature, such as the selective inhibition of corrosion in mild steel by *5-chloro-1-(2-(dimethylamino)ethyl)indoline-2,3-dione* and *5-chloro-1-octylindoline-2,3-dione*[18, 19]. These 5-Chloroisatin derivatives were synthesized using N-alkylation reaction under catalysis by phase transfer [20-23].

Tribak et al. have been prepared new 5-Chloroisatin derivatives such as *5-chloro-1- ((3-(4-chlorophenyl) -4,5-dihydroisoxazol-5-yl) methyl) indoline-2,3-dione* and 5-chloro-3'- (4-chlorophenyl) -1- ((3- (4-chlorophenyl) -4,5-dihydroisoxazol-5-yl) methyl) spiro [indoline-3,5'- [1,4,2] dioxazol]- 2-one that would carry medicinal properties of mainly as antibacterial against two bacteria Gram+ and two other bacteria Gram- [24, 25]. These derivatives have also been synthesized by 1.3-dipolar cycloaddition between nitrile oxydes and N-alkylchloroisatin using Sodium hypochlorite [26].Therefore, as part of our ongoing study, we report herein the synthesis, and characterization of new N-alkylchloroisatin by N-alkylation method and also new isoxazole and dioxazole compounds formed from the condensation of 4-Chlorobenzaldoxime with 5-chloro-1-(prop-2-yn-1-yl) indoline-2,3-dione.

## II. EXPERIMENTAL DETAILS

All chemicals were purchased from sigma - Aldrich and used as such. Solvents hexane, methanol and $CHCl_3$ (AR grade) were used without further purification.

The reactions were monitored by thin-layer chromatography (TLC) analysis by using silica gel (60 F254) plates. Compounds were visualized by UV irradiation at 256 or 365 nm. Flash column chromatography was performed on silica gel 60 (230–400 mesh, 0.040–0.063 mm). Melting points (m.p.[°C]) were taken on samples in open capillary tubes and are not corrected

$^{1}H$ and $^{13}C$ NMR spectra were recorded with a Bruker spectrometer at 300 and 75 MHz respectively. Chemical shifts are given in parts per million (ppm) from tetramethylsilane (TMS) as internal standard in $CDCl_3$, and the residual peak of DMSO in [D6] DMSO. The following abbreviations are used for the $^{1}H$ NMR spectra multiplicities: br. s: broad singlet, s: singlet, d: doublet, t: triplet, q: quartet, qt: quintuplet, m: multiplet. Coupling constants (J) are reported in Hertz [Hz].

### 2.1. *Preparation of the compound (1a):*

To a solution of (0.4 g, 2.20 mmol) 5-chloro-1*H*-indole-2,3-dione in 20 ml of DMF, 0.5 g, 3.3 mmol of $K_2CO_3$ and 0.1 g , 0.3 mmol of tetran-butyl ammonium bromide (BTBA), 0.20 mL (1.32 mmol) of 1,2-bis (2-chloroethoxy) ethane is added dropwise.

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The reaction was refluxed with DMF for 48 hours. After removal of the salts by filtration, the DMF is evaporated under reduced pressure and the residue obtained is dissolved in dichloromethane, the mixture obtained is chromatographed on a silica gel column (eluent: ethyl acetate / Hexane (4/1)). The reaction allowed the solid 22 to be isolated

**1-(2-(2-(2-chloroethoxy)ethoxy)ethyl)-5chloroindoline-2,3-dione (1a):** Yield: 88% ; mp: 90-120; $R_f$= 0.85; (eluent Ethyl acetate / hexane (4: 1)). $^1$H NMR ($CDCl_3$; 300MHz) : δ (ppm) 7.49-7.52 (m, 2H, $H_{Ar}$,) ; 7.05 (d, H, $H_{Ar}$,$^3J_{H-H}$ =6Hz, ); 3.91 (t, 2H, $CH_2$, $^3J_{H-H}$ = 6Hz, $^4J_{H-H}$ =3Hz,) ; 3.75(t, 2H, $CH_2$, $^3J_{H-H}$ = 6Hz, $^4J_{H-H}$ =3Hz) ; 3.67 (t, 2H, $CH_2$, $^3J_{H-H}$ = 6Hz, $^4J_{H-H}$ =3Hz) ; 3.59(m, 4H, $CH_2$,); 3.21(t, 3H, $CH_3$, $^3J_{H-H}$ = 6Hz, $^4J_{H-H}$ =3Hz). $^{13}$C NMR ($CDCl_3$; 75MHz): δ (ppm) 183.11 (C=O); 167.00 (N-C=O); 143.67, 130.74, 119.51 (Cq); 134.98, 130.32, 123.75 ($CH_{Ar}$); 71.38, 63.11, 40.85, 20.92 ($CH_2$).

**2.2.General procedures for cycloaddition of N-propargylchloroisatin with nitrile oxide:**

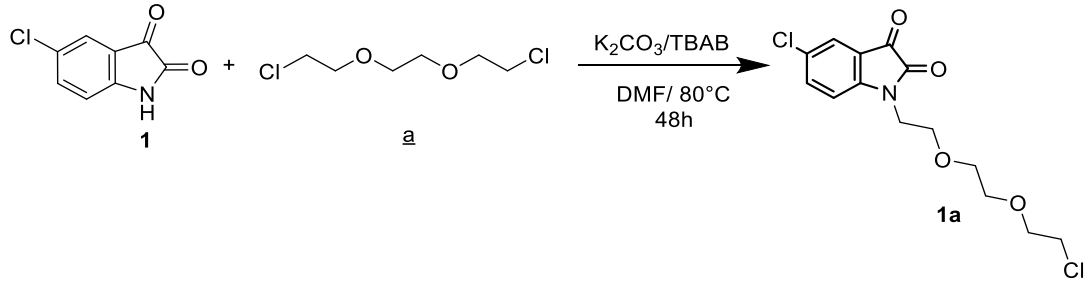
0.2 g of 5-chloro-1-(prop-2-yn-1-yl)indoline-2,3-dione and (0.17 g, 1.079 mmol) of 4-Chlorobenzaldoxime were dissolved in 12 mL of chloroform ($CHCl_3$) when the mixture reaches 0°C, 4 mL of bleach (NaOCl ) was introducted and then allowed to stir for 4 hours. The resulting compound purified and recrystallized from ethanol.

***5-chloro-1-((3-(4-chlorophenyl)isoxazol-5-yl)methyl)indoline-2,3-dione (1b):*** Yield : 77%; mp : 194-197 ; $R_f$= 0.77; (eluent Ethyl acetate / hexane (6: 1)). $^1$H NMR ($CDCl_3$) δppm 7.71-7.81(m, 2H, $H_{Ar}$); 7.57 (d, H, $H_{Ar}$,J=8.4Hz); 6.97-7.04 (m, 4H, $H_{Ar}$); 6.55 (s, H, CH) ;3.87 (m, H, $CH_2$). $^{13}$C NMR ($CDCl_3$) δppm: 185.86 (C=O) 160.64 (N-C=O); 163.18, 157.88, 147.07, 134.14, 131.17, 130.95, 118.02(Cq)134.56, 130.11, 129.26, 128.62, 123.96 ($CH_{Ar}$) ; 105.51 (CH); 50.60 ($CH_2$)

***5-chloro-3'-(4-chlorophenyl)-1-((3-(4-chlorophenyl) isoxazol-5-yl)methyl)spiro[indoline-3,5'[1,4,2]dioxazol]-2-one (2b):*** Yield: 65%, mp: 197-199; $R_f$= 0.75; (eluent Ethyl acetate /hexane (5: 1)). $^1$H NMR ($CDCl_3$) δppm 7.80 (d, 2H, $H_{Ar}$, J=9Hz); 7.73 (d, 2H, $H_{Ar}$, J=8.4Hz); 7.56 (d, H, $H_{Ar}$, J=1.8Hz); 7.48-7.46 (m, 5H, $H_{Ar}$); 7.05 (d, H, $H_{Ar}$, J=8.4Hz); 6.59 (s, H, CH); 5.05 (s, 2H, $CH_2$). $^{13}$C NMR ($CDCl_3$) δppm: 168.12 (NC=O); 166.03, 162 (C=N); 141.45, 138.63, 136.51, 130.20, 126.77, 122.62, 120.05 (Cq); 133.39, 128.52, 128.10, 126.65, 111.11 ($CH_{Ar}$); 101.60 (CH); 35.71 ($CH_2$).

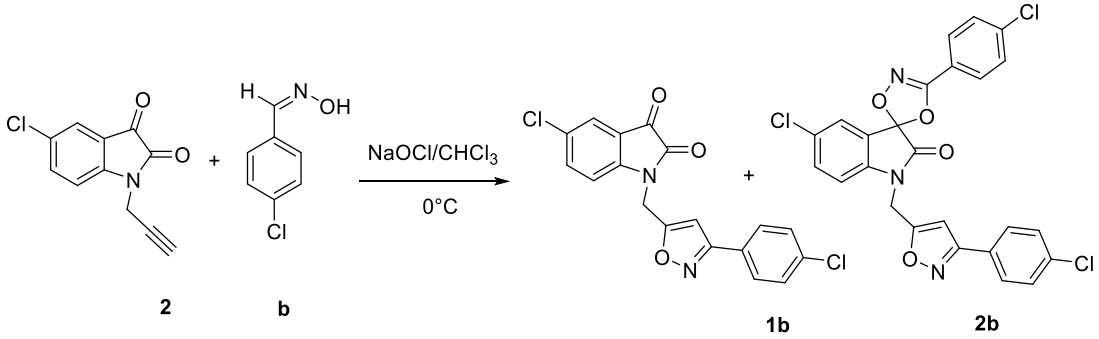
## III. RESULTS AND DISCUSSION

Based on the interest of our research group in the synthesis of new heterocycles [27], we studied 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 compound5-chloro-1-(2-(2-(2 chloroethoxy)ethoxy)ethyl)indoline-2,3-dione (scheme1 )




**Scheme 1**

The 1,3-dipolar cyloaddition reaction of nitrile oxide, prepared in situ by the action of bleach on 4-Chlorobenzaldoxime, with 5-chloro-1-(prop-2-yn-1-yl)indoline-2,3-dione in a biphasic medium (water/ethanol) at 0°C for 4 hours. It leads in each case to the formation of the two cycloadducts resulting from the 1.3-dipolar cycloaddition on the dipolarophile group C-O in position 3 and the propargyl group in position 1.




**Scheme 2**

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## IV. CONCLUSION

In conclusion, we have developed an efficient synthetic method for the selective N-alkylation of 5-Chloroisatin using an easily available mild base $K_2CO_3$ by the action of 1,2-bis (2-chloroethoxy) ethane. Subsequently, an easy and general 1.3-dipolar cycloaddition method has also been demonstrated using nitrieoxyde at 0°C temperature with 5-chloro-1-(prop-2-yn-1-yl)indoline-2,3-dioneas dipolarophile allows getting new cycloadducts containing the two nuclei isoxazole and dioxazole. Their structures has been identified by the usual spectroscopy.

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