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Synthesis of a Novel Series of Dioxazolines by 1.3-Dipolar Cycloaddition between N-alkyl 5-Chloroisatin Derivatives and Nitrile Oxides

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Abstract: ***A new series of dioxazoline of 5-Chloroisatin derivatives has been designed and synthesized involving 1,3-dipolar cycloaddition reaction, preceded by a simple N-alkylation reaction in phase-transfer catalytic conditions The regioselectivity of the reactions was ascertained by ^{1}H, ^{13}C NMR spectroscopy of the synthesized compounds.***

Keywords: *5-Chloroisatin, Dioxazoline, N-alkylation, 1,3-Dipolar cycloaddition, ^{1}H, ^{13}C NMR spectroscopy*

1. Introduction

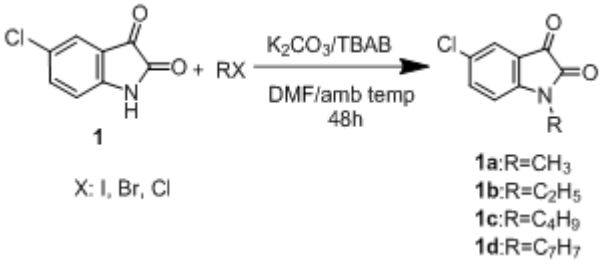
Compounds containing the indole group present an important class of biologically active molecules that are widespread in nature [1–3], notably alkaloids, fungal metabolites and marine natural products. Indole derivatives have been found to possess several biological properties, including antimicrobial, antibiotic, anti-inflammatory, analgesic, anticonvulsant, antimalarial, anticancer, antiulcer, antileishmanial, contraceptive and antioxidant activities [4].
5-Chloroisatine derivatives have been reported to exhibit a wide range of pharmacological activities such as inhibitors of enzymes [5] or as anti-inflammatory, analgesic, anti-rheumatic, and anti-hypertensive drugs [6]. It has also been reported that 5-Chloroisatin derivatives have remarkable anticorrosive activity [7, 8].

Dioxazoline derivatives are an important class of heterocyclic pharmaceuticals and bioactive natural products because of their significant and wide spectrum of biological activities, recent studies tried to improve the treatment of this infection by developing antiamoebic therapy [9, 10], a set of dioxazolines derivatives showed better activity than the reference drug metronidazole; furthermore, they are non toxic to the human kidney epithelial cells [11, 12].

In order to optimize the use of heterocyclic compounds and to better understand the principle of the reaction of the 1,3-dipolar cycloaddition [13], we studied the action of nitrile oxides as dipoles on the derivatives of 5-Chloroisatin [14] as dipolarophiles.

2. Results and Discussion

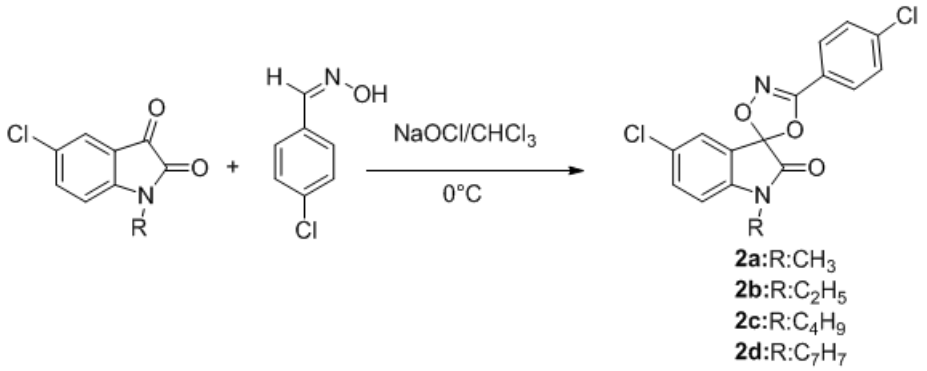
Our proposed strategy was based on a simple and lucid 1,3-dipolar cycloaddition reaction [15-17] of N-alkylchloroisatine with nitrile oxides to prepare new dioxazolines (Scheme **2, 3, 4, 5**). The N-alkylchloroisatines were prepared using the protocol developed by Tribak et al. starting from 5-Chloroisatin [18] using appropriate mono-halides, Benzyl chloride or methyl iodide, in the presence of anhydrous K_2CO_3 in dry DMF and phase-transfer catalytic conditions [19, 20] (Scheme **1**), gave only the *N*-alkylchloroisatine **1a–1d** in moderate to good yields.



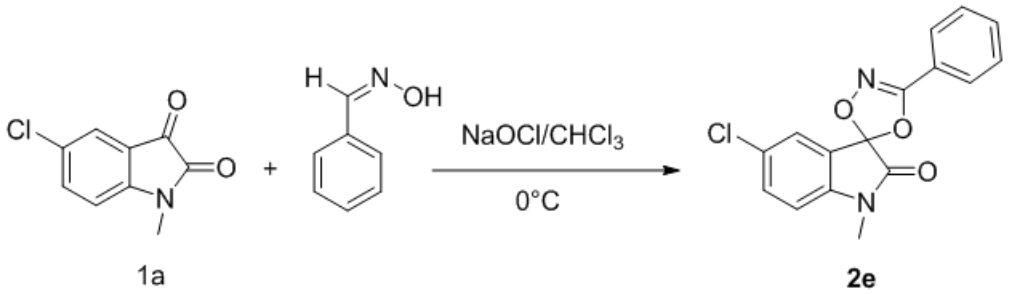
Scheme 1

The *N*-alkylation reaction in the 5-Chloroisatine series is generally produced by regioselective synthesis belong to an extremely attractive domain in heterocyclic chemistry as a result of their unusual bioactivities [21, 22]. Les structures of *N*-substituted 5-Chloroisatin **1a–1d** were characterized using ^{1}H NMR and ^{13}C NMR spectra.

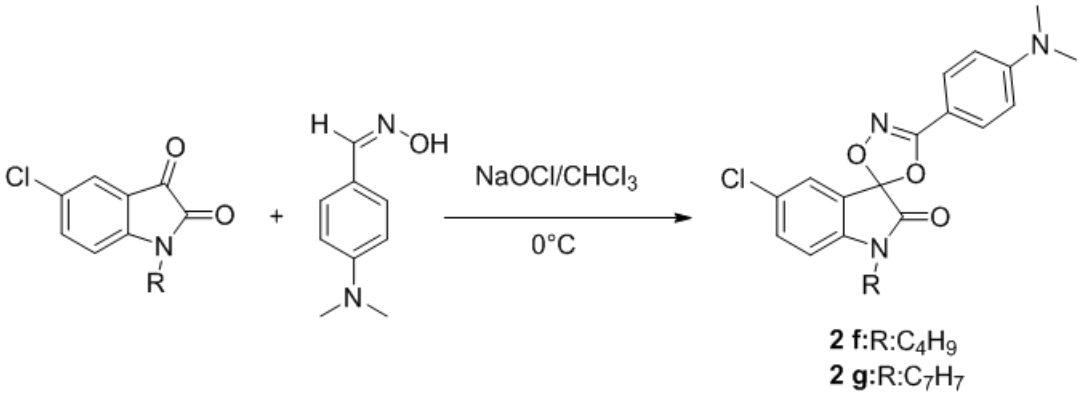
1,3-Dipolar cycloaddition occurs between a dipole and a dipolarophile. During the course of the reaction, they get fused in headehead/tailetail or headetail/tailehead fashion to generate the corresponding cycloadducts. There were originally two proposals that describe the mechanism of the 1,3-dipolar cycloaddition. Depending on several features of 1,3-dipolar cycloaddition such as solvent effects, stereochemistry and thermodynamic parameters, Huisgen proposed a one-step concerted process with a single transition state most likely as a pericyclic reaction [23, 24].
In the present work, we report a full account on the examination on 1,3-dipolar cycloaddition reaction of N-alkylchloroisatines **1a–1d** [25-27] with nitrile oxides solubilized in chloroform by the action of sodium hypochlorite at 0°C to give new cycloadduits dioxazolines. The former compound has one potential dipolarophilic site C=O double bond, no adducts resulting from condensation on the double bonds C=C and/or C=O were detected. The structural assignments of the new dioxazolines are based on a full characterization by ^{1}H NMR and ^{13}C NMR spectra.



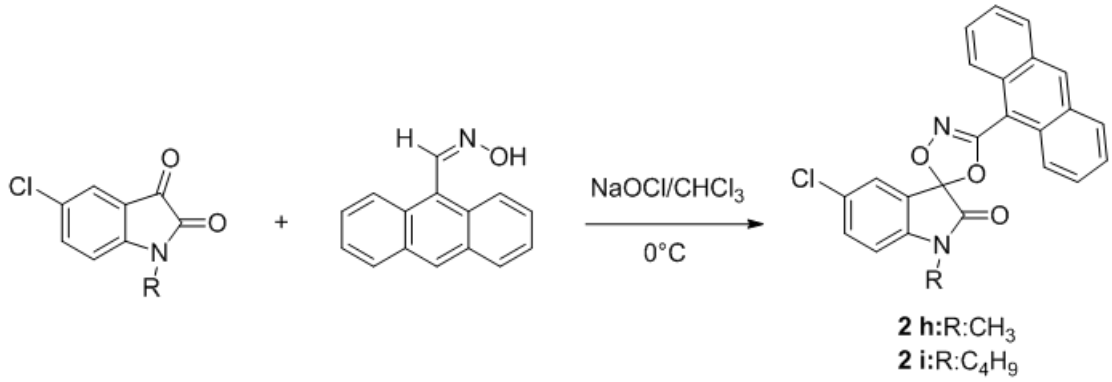
Scheme 2



Scheme 3



Scheme 4



Scheme 5

3. Conclusion

In conclusion, we have developed an efficient and simple method to synthesize a series of new dioxazoline 5-Chloroisatine using N-alkylation in phase-transfer catalytic conditions and 1,3-dipolar cycloaddition reactions as key steps between 5-Chloroisatin derivates and nitrile oxide as dipole with moderate to good yields.

4. Experimental Part

4.1. Generality

Commercially available chemicals were purchased from Sigma-Aldrich. All melting points were taken in open capillaries and the kofler bench is uncorrected. Analytical thin-layer chromatography (TLC) was performed on commercially available Merck TLC Silica gel 60 F254. Silica gel column chromatography was performed on silica gel 60 (spherical100–200 μm). ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d6 with tetramethylsilane (TMS) as an internal reference using a Bruker AC 300 (^{1}H) or 75 MHz (^{13}C) instruments. Chemical shifts are given in δ parts per million (ppm).

4.2. Synthesis of dipolarophiles

To a solution of 5-chloro-1*H*-indole-2,3-dione (0.4 g, 2.20 mmol) in DMF (15 mL) was added 0.5 g (3.3 mmol) of K_2CO_3, 0.1 g (0.3 mmol) of BTBA followed by 1.2 equivalents of alkylating agent (monohalogenated chains, methyl iodide and benzyl chloride). The reaction mixture is stirred at room temperature for 48 hours after drying over Na_2SO_4, filtration and evaporation of the organic phase; the solid is obtained after recrystallization in the form of a powder with good yield.

5-chloro-1-methylindoline-2,3-dione (1a) : yield=89%; mp: 88-91°C; R_f= 0.72; (EtOAc/hexane: 1/1). ^{1}H NMR ($CDCl_3$; 300MHz): δ (ppm) 7.56 (d, H, H_{Ar}, $^{4}J_{H-H}$ =3Hz); 7.54 (d, H, H_{Ar}, $^{4}J_{H-H}$ =3Hz); 6.82 (d, H, $H_{Ar,}$ $^{3}J_{H-H}$ =6Hz); 3.23 (s, CH_3). ^{13}C NMR ($CDCl_3$; 75MHz): δ (ppm) 186.08(C=O); 164.45 (N-C=O); 143.69, 130.95, 121.63 (Cq); 138.60, 126.14, 112.30 (CH_{Ar}); 35.16 (CH_3).

5-chloro-1-ethylindoline-2,3-dione (1b) : yield =86% ; mp: 88-90°C ; Rf= 0.88 (Hexane/EtOAc: 2/1); ^{1}H NMR ($CDCl_3$; 300MHz) : δ (ppm) 7.53-7.54 (d, H, H_{Ar}, $^{4}J_{H-H}$ =3Hz) ;7.51-7.52 (d, H, $H_{Ar;}$ $^{4}J_{H-H}$ = 3Hz); 6.83-6.86(d, H, $H_{Ar,}$ $^{3}J_{H-H}$ =9Hz); 3.72-7.79(q, CH_2, $^{3}J_{H-H}$ =9Hz, $^{4}J_{H-H}$ =6Hz); 1.28 (t, CH_3, $^{3}J_{H-H}$= 6Hz). ^{13}C NMR ($CDCl_3$; 75MHz): δ (ppm) 186.65 (C=O); 163.38 (N-C=O); 142.86, 129.49, 122.96 (Cq); 137.68, 125.45, 111.29 (CH_{Ar}); 35.16 (CH_2); 12.46 (CH_3).

1-butyl-5-chloroindoline-2,3-dione (1c): yield=85%; mp: 80-82°C ; R_f= 0.85; (EtOAc /hexane: 1/2), ^{1}H NMR ($CDCl_3$; 300MHz): δ (ppm) 7.54-7.55 (d, H, H_{Ar} , $^{4}J_{H-H}$ =3Hz) 7.50 7.51 (d, H, H_{Ar}, $^{4}J_{H-H}$ =3Hz); 6.84 (d, H, $H_{Ar;}$ $^{3}J_{H-H}$ =6Hz); 3.72 (t, 2H, CH_2, $^{3}J_{H-H}$ =6Hz); 1.60-1.70 (m, 2H, CH_2) ;1.35-1.42(m, 2H,CH_2), 0.95 (t, 3H, CH_3, $^{3}J_{H-H}$ = 9Hz). ^{13}C NMR ($CDCl_3$; 75MHz): δ (ppm) 183.83 (C=O); 163.28 (N-C=O); 142.43, 136.12, 121.06 (Cq); 137.61, 125.38, 111.40 (CH_{Ar}); 40.16, 29.24, 20.14 (CH_2); 13.67 (CH_3).

1-benzyl-5-chloroindoline-2,3-dione (1d) : yield=72%; mp: 140-143°C ; R_f=0.76 ; (EtOAc/hexane: 1/2). ^{1}H NMR ($CDCl_3$; 300MHz): δ (ppm) 7.56 (d, H, H_{Ar}, $^{4}J_{H-H}$ =3Hz); 7.43 (d, H, H_{Ar}, $^{4}J_{H-H}$ =3Hz); 7.40 (d, H, H_{Ar}, $^{4}J_{H-H}$ =3Hz); 7.26-7.37 (m, 5H, H_{Ar}); 4.90 (s, 2H, CH_2). ^{13}C NMR ($CDCl_3$; 75MHz): δ (ppm) 183.24 (C=O); 164.45 (N-C=O); 144.43, 141.82, 118.04 (Cq); 138.69, 137.64, 129.18, 128.38, 127.41, 125.34, 112.30 (CH_{Ar}); 44.24 (CH_2).

4.3. Experimental procedure for the preparation of dioxazolines

A mixture of 0.2 g of a dipolarophile and 1.2 equivalent of nitrite oxide dissolved in 12 mL of chloroform ($CHCl_3$) with stirring, when the reaction reaches 0°C., 4 mL of sodium hypochlorite (NaOCl) was added then, left it for 4 hours. Subsequently, the chloroform was evaporated under reduced pressure, and treated. The product obtained is purified by column chromatography (eluent Ethyl acetate/hexane (5: 1)).

5-chloro-3'-(4-chlorophenyl)-1-methylspiro[indoline-3,5'-[1,4,2]dioxazol]-2-one (2a) : yield =77% ; mp: 108-112°C ; ^{1}H NMR ($CDCl_3$) δppm 8.08-8.19 (m, 2H, H_{Ar}); 7.77-7.79 (d, H, H_{Ar} ,J_1=1.8Hz) ;7.46-7.59 (m, 2H, H_{Ar}); 1.59 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δppm: 167.84 (N-C=O); 163.18 (C=N); 145.79, 137.31, 128.41, 115.69 (Cq); 130.53, 129.47, 123.75 (CH_{Ar}); 32.16 (CH_3).

5-chloro-3'-(4-chlorophenyl)-1-ethylspiro[indoline-3,5'-[1,4,2]dioxazol]-2-one (2b): yield =73%; mp: 114-116°C; ^{1}H NMR ($CDCl_3$) δ (ppm): 7.79 (d, 2H, H_{Ar}, J=7.5Hz) ; 7.52 (d, 2H, H_{Ar}, J_1=1.8Hz); 7.47 (d, 2H, H_{Ar}, J=8.4Hz) ; 6.89 (d, H, H_{Ar}, J=8.4Hz); 3.77(q, 2H, CH_2, J=6.9Hz) 1.32(t, 3H, CH_3, J=7.2Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 168.04 (N-C=O); 158.85 (C=N); 142.44, 138.41, 123.11, 120.29 (Cq); 133.06, 129.23, 129.16, 128.50, 126.45, 110.49 (CH_{Ar}); 35.24 (CH_2); 13.37 (CH_3).

1-butyl-5-chloro-3'-(4-chlorophenyl)spiro[indoline-3,5'-[1,4,2]dioxazol]-2-one (2c): yield =75%; mp: 100-115°C; ^{1}H NMR ($CDCl_3$) δ (ppm): 7.80(d, 2H, H_{Ar}, J=8.4Hz); 7.52(d, 2H, H_{Ar},J=2.1Hz); 7.44(d, 2H, H_{Ar}, J=8.7Hz); 6.87(d, H, H_{Ar}, J=8.4Hz); 3.70(t, 2H, CH_2, J=7.2Hz); 1.73-1.66 (m, 2H, CH_2); 1.48-1.38 (m, 2H, CH_2); 0.98 (t, 3H, CH_3, J=7.5Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 168.35 (N-C=O); 158.84 (C=N); 142.81, 138.39, 129.16, 123.07, 120.32, 105.81 (Cq); 133.02, 129.22, 128.50, 126.38, 110.63 (CH_{Ar}); 40.23, 29.13, 20.05 (CH_2); 13.67 (CH_3).

1-benzyl-5-chloro-3'-(4-chlorophenyl)spiro[indoline-3,5'-[1,4,2]dioxazol]-2-one (2d): yield =73% ; mp: 180-183°C; ^{1}H NMR ($CDCl_3$) δ (ppm) 7.80 (d, 2H, H_{Ar}, J=8.6Hz); 7.53(d, 2H, H_{Ar}, J=2.1Hz) ; 7.48 (d, 2H, H_{Ar}, J=8.7Hz); 7.38-7.30 (m, 5H, H_{Ar}); 6.72(d, H, H_{Ar}, J=8.4Hz) ;1.71 (s, 2H, CH_2), ^{13}C NMR ($CDCl_3$) δ (ppm): 168.58 (N-C=O); 158.92 (C=N); 142.42, 138.47, 134.13, 129.49, 122.87, 120.26 (Cq); 133.02, 129.25, 129.10, 128.54, 128.23, 127.32, 126.33, 111.40 (CH_{Ar}) ; 44.21 (CH_2).

5-chloro-1-methyl-3'-phenylspiro [indoline-3,5'-[1, 4, 2] dioxazol]-2-one (2e): yield =76%; mp: 110-113°C; ^{1}H NMR ($CDCl_3$) δ (ppm): 8.02-8.14(m, 4H, H_{Ar}); 7.40-7.53(m, 4H, H_{Ar}); 1.53(s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ (ppm): 165.93 (N-C=O); 161.48 (C=N); 148.34, 131.38, 129.26, 111.88, 102.97 (Cq); 131.08, 129.42, 128.95, 128.22, 127.97, 122.69 (CH_{Ar}); 43.61 (CH_3).

1-butyl-5-chloro-3'-(4-(dimethylamino) phenyl) spiro [indoline-3,5'-[1,4,2]dioxazol]-2-one (2f): yield=65% ; mp: 95-120°C; ^{1}H NMR ($CDCl_3$) δ (ppm): 7.54 (d, H,

H_{Ar} ,J=8.4Hz); 7.26-7.35 (m, 4H, H_{Ar}) ; 6.70-6.77 (d, 2H, H_{Ar}, J=8.7Hz); 3.63 (t, 2H, CH_2, J=7.2Hz) ; 1.26-1.31 (m, 4H, CH_2); 1.48(m, 6H,CH_3) ; 0.81 (t, 3H, CH_3, J=7.5Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 167.42 (N-C=O); 162.12 (C=N); 152.79, 144.31, 117.17, 113.17, 106.36 (Cq); 131.17, 129.47, 128.41, 123.75, 113.14 (CH_{Ar}); 41.70, 30.68 (CH_2); 22.41, 12.65 (CH_3).

1-benzyl-5-chloro-3'-(4 (dimethylamino) phenyl)spiro [indoline-3,5'-[1, 4, 2]dioxazol]-2-one (2g).: yield=74%; mp: 188-190 °C; ^{1}H NMR ($CDCl_3$) δ (ppm): 7.41-7.43 (d, 2H, H_{Ar} ,J=8.6Hz); 7.24-7.33 (m, 4H, H_{Ar}) ; 6.64-6.68 (m, 6H, H_{Ar}); 5.27 (s, 2H, CH_2); 2.98 (m, 6H, CH_3); ^{13}C NMR ($CDCl_3$) δ (ppm): 162.12 (N-C=O); 160.42 (C=N) ; 159.36, 145.37, 131.59, 114.21, 106.57 (Cq); 136.26,129.26, 128.41, 127.94, 127.37,125.23, 122.26, 116.54, 112.72 (CH_{Ar}); 49.54 (CH_2); 42.33 (CH_3).

3'-(anthracen-9-yl)-5-chloro-1-methylspiro[indoline-3,5'-[1,4,2]dioxazol]-2-one(2h): yield=71%; mp: 120-127 °C; ^{1}H NMR ($CDCl_3$) δ (ppm): 8.30-8.35 (m, H, H_{Ar}); 8.08-8.10 (d, H, H_{Ar}, J^4=1.8Hz,) ; 7.81-7.83(m, 4H, H_{Ar}); 7.69-7.76(m, 6H, H_{Ar},); 1.59(s, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ (ppm): 165.72 (N-C=O); 162.55 (C=N); 148.34, 132.44, 130.57, 130.11, 129.41, 112.72, 107.42 (Cq); 143.25, 129.02, 128.88, 128.41, 127.98, 127.56, 126.29 (CH_{Ar}); 33.01(CH_3).

3'-(anthracen-9-yl)-1-butyl-5-chlorospiro[indoline-3,5'-[1,4,2]dioxazol]-2-one (2 i): yield =69% ; mp: 123-130 °C ; ^{1}H NMR ($CDCl_3$) δ (ppm): 8.04-8.21(m, H, H_{Ar}) ; 7.79-7.88(m, 4H, H_{Ar}); 7.37-7.53(m, 6H, H_{Ar}); 6.80-6.82(d, H, H_{Ar} ,J=8.4Hz) ; 3.67(t, 2H, CH_2, J=7.2Hz) ; 1.60-1.68(m, H, CH_2);1.33-1.42(m, H, CH_2); 0.95 (t, 3H, CH_3, J=7.5Hz). ^{13}C NMR ($CDCl_3$) δ (ppm): 167.84 (N-C=O); 165.09 (C=N); 143.89, 132.44, 113.57, 104.24 (Cq); 130.74, 129.47, 128.41, 127.14, 126.71, 122.69 (CH_{Ar}); 45.09, 28.56, 20.29 (CH_2); 14.56 (CH_3).

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