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Synthesis and reactivity of new heterocyclic systems derived from 5-chloro-1*H*-indole-2,3-dione

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Abstract

In this article, we described the synthesis of various derivatives of 5-Chloroisatin by the action of halogenated mono channels, benzyl chloride and methyl iodide under the conditions of phase transfer catalysis (PTC), which are widely used as a starting material for the synthesis of heterocyclic compounds and as substrates for the synthesis of drugs.

In order to multiply the family heterocyclic compound from 5-Chloro-1*H*-indole-2,3-dione using the N-alkylation reaction which is answered in the field of organic chemistry and on which several studies were performed. The various products were determined by ^{1}H NMR, and ^{13}C NMR spectroscopy with good yield.

Keywords: 5-Chloro-1*H* indole-2,3-dione; PTC; synthesis; N-alkylation; derivatives.

1. INTRODUCTION

The isatin and its derivatives such as 5-Chloroisatin have become an interesting and popular topic due to their potential application in medicinal chemistry. They contain a wide range of pharmaceutical and biological properties, and as therapeutics for degenerative diseases [1, 2]. 5-Chloroisatin, chemically known as "5-Chloro-1*H*-indole-2,3-dione", is a polyvalent device [3,4] capable of constructing a large number of heterocyclic molecules which play an important role In the process of drug discovery, they biologically exhibit anti-epileptic, anti-HIV, antifungal [5], antimicrobial [6] properties. The results of its derivatives make it possible to increase the percentage of heterocyclic products which will be used in the 1,3-dipolar cycloaddition reactions, considered as efficient methods for forming highly functionalized compounds [7]. 5-Chloroisatin derivatives represent the basic skeleton for many heterocyclic compounds, they are also given activity: anti-convulsant [8], antioxidant [9], anti-cancer [10] and anti-inflammatory [11]. In order to synthesize new 5-Chloroisatin derivatives and make it possible to participate in a large number of chemical reactions, we have studied the action of 5-chloro-1*H*-indole-2,3-dione, Alkyl, benzyl chloride, methyl iodide and other alkylating agents under phase transfer catalysis conditions [12].

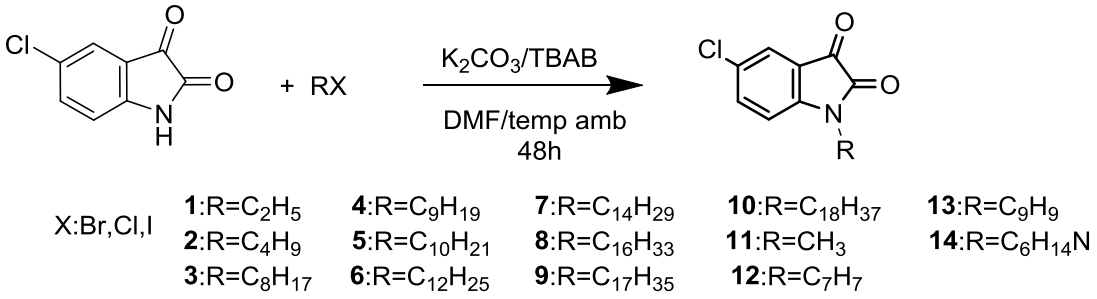
2. Results and discussions

The N-alkylation method is considered to be one of the very important reactions in synthetic organic chemistry [13-15], here we report by way of example a general N-alkylation reaction of lactams with hetero bromides -secondary, under mild, moderate conditions with high isolation efficiency of the product, and also a good chemical and structural tolerance has also been demonstrated both by the benzylic hetero-secondary bromides and lactam substrates [16].

However, Lactams are chemical structures frequently encountered in organic chemistry, are widely used in products of natural origin [17-18] and widely applied in the design and synthesis of bioactive compounds [19].

Although the N-alkylation of lactams has been well documented with primary and secondary benzyl halides [20, 21].

The objective of our work is to react 5-chloro-1*H*-indole-2,3-dione with long chain bromoalkanes, benzyl chloride, methyl iodide, (E) - (3-chloroprop -1-en-1-yl) benzene and 2-bromo-N,N-diethylethan-1-amine in order to prepare a wide variety of its derivatives, using DMF as solvent in phase transfer catalysis conditions, in the presence of a K_2CO_3 base and a BTBA catalyst at room temperature, gives good yield, these reactions are shown schematically below (Scheme 1). After filtration of the salts, the DMF was evaporated under reduced pressure, the reaction was checked by thin-layer chromatography, and the product was purified on the silica gel column (eluent: ethyl acetate / hexane (3 / 1)).



Scheme 1: Synthesis of new products from 5-chloro-1*H*-indole-2,3-dion.

The structures of the alkylated products (**1-14**) were indicated by the usual spectroscopic methods: ^{1}H NMR, ^{13}C NMR and X-ray crystallographic study. The ^{1}H NMR and ^{13}C NMR spectra show the signals relating to the protons and carbons of the alkyl groups carried by the nitrogen atom. A crystallographic study by X-ray diffraction of compound **11** made it possible to determine the complete structure. This compound crystallizes in the monoclinic system. (**Figure 1**).

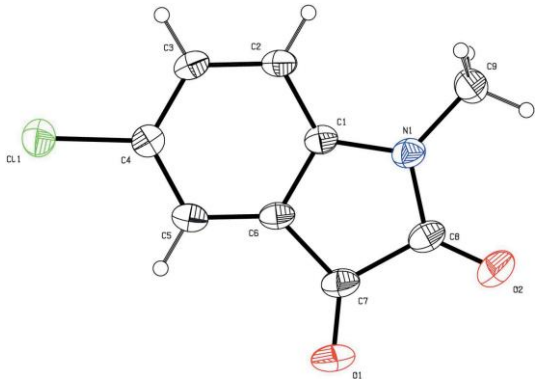


Figure 1: STEP of compound **11** with atomic numbering

Table 1: Crystallographic data of Compound **11**

$C_9H_6ClNO_2$	$F(000)$ = 400
Mr = 195.60	Dx = 1.532 Mg m−3
Monoclinic, $P21/c$	Mo $K\alpha$ radiation, λ = 0.71073 A
a = 3.9766 (4) A	Cell parameters from 4975 reflections
b = 11.9503 (13) A	θ = 2.9–25.6°
c = 17.947 (2) A	μ = 0.41 mm−1
β = 96.163 (3)°	T = 300 K
V = 847.94 (16) A3	Prism, red
Z = 4	0.29 × 0.11 × 0.11 mm
Bruker APEXII CCD diffractometer	2080 independent reflections
φ and ω scans	1705 reflections with $I > 2\sigma(I)$
Absorption correction: multi-scan (*SADABS*; Bruker, 2009)	Rint = 0.027
Tmin = 0.697, Tmax = 0.746	θmax = 28.3°, θmin = 1.7°
12975 measured reflections	h = −5→5
Refinement on $F2$	k = −15→15
Least-squares matrix: full	l = −22→23
$R[F2 > 2\sigma(F2)]$ = 0.041	Primary atom site location: structure-invariant direct methods
$wR(F2)$ = 0.103	Hydrogen site location: inferred from neighbouring sites
S = 1.05	H-atom parameters constrained

2080 reflections	$w = 1/[\sigma 2(Fo2) + (0.0449P)2 + 0.264P]$ where $P = (Fo2 + 2Fc2)/3$
120 parameters	$\Delta/\sigma)max < 0.001$
0 restraints	$\Delta\rho max = 0.25$ e A−3
	$\Delta\rho min = -0.23$ e A−3

3. Experimental part

The uncorrected melting points were determined by the kofler bench apparatus as well as the ^{1}H NMR and ^{13}C NMR spectra were recorded on the Brucker Avance 300 MHz in a $CDCl_3$ solution, the chemical shifts are in scale and expressed in part Per million (ppm) with (TMS) tetramethylisal as internal reference ($\delta = 0$). The coupling constants (J) are in hertz, the abbreviations used as follows: s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet).

3.1. Procedure

The organic compounds obtained are synthesized by the following experimental procedure:

0.2 g (1.1 mmol) of 5-chloro-1*H*-indole-2,3-dione, (0.23 g, 1.16 mmol) of potassium carbonate in 15 ml of N-N-dimethylformamide (DMF) and (0.035 g, 0.10 mmol) of BTBA are introduced into a 100 ml two-necked flask, the brominated reagent is slowly added, the mixture is left at room temperature for 48 hours. During this period the progress of the reaction is monitored by TLC (thin layer chromatography). After the reaction is complete, the salts are removed by filtration, the solvent (DMF) is evaporated under reduced pressure. The product obtained is purified on a column of silica gel eluent (ethyl acetate / hexane).

1 : 5-chloro-1-ethylindoline-2,3-dione

Yield (%)=86% ; mp: 88-90°C ; Rf= 0.88 RMN ^{1}H ($CDCl_3$; 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).RMN ^{13}C($CDCl_3$;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).

2 : 1-butyl-5-chloroindoline-2,3-dione

Yield (%)=85%; mp: 80-82°C; R_f= 0.85; ^{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).

3 : 5-chloro-1-octylindoline-2,3-dione

Yield (%)=88%; mp: 68-70°C; R_f= 0.85; ^{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}, $^{3}J_{H-H}$ =9Hz); 3.68 (t, 2H, CH_2, $^{3}J_{H-H}$ = 6Hz); 1.71-1.53(m, 2H, CH_2); 1.24-1.31 (m, 10H,CH_2), 0.85 (t, 3H, CH_3, $^{3}J_{H-H}$ =6Hz).^{13}C NMR ($CDCl_3$;75MHz): δ(ppm) 183.20 (C=O); 160.73 (N-C=O); 144.60, 137.60, 125.37 (Cq); 129.45, 115.79, 111.42 (CH_{Ar}); 40.47, 31.73, 29.19, 27.20, 26.88, 22.60 (CH_2); 14.04 (CH_3).

4 : 5-chloro-1-nonylindoline-2,3-dione

Yield(%)=87%; mp: 67-68°C; R_f= 0.82; ^{1}H NMR ($CDCl_3$; 300MHz): δ (ppm) 7.58-7.59 (d, H, H_{Ar}, $^4J_{H-H}$ =3Hz); 7.54-7.55 (d, H, H_{Ar}, $^4J_{H-H}$ =3Hz); 6.85(d, H, H_{Ar}, $^3J_{H-H}$ =9Hz) ; 3.70 (t, 2H, CH_2, $^3J_{H-H}$ =9Hz); 1.65-1.75 (m, 2H, CH_2) ; 1.28 (m, 12H,CH_2), 0.89 (t, 3H, CH_3, $^3J_{H-H}$ =6Hz). ^{13}C NMR ($CDCl_3$;75MHz): δ (ppm) 181.84 (C=O); 167.00 (N-C=O); 147.07, 137.63, 129.39 (Cq); 141.28, 116.10, 110.29 (CH_{Ar}); 42.53, 32.42, 29.49, 29.27, 29.21, 27.21, 26.89, 23.18 (CH_2); 15.83 (CH_3).

5 : 5-chloro-1-decylindoline-2,3-dione

Yield (%)=86% ; mp: 62-64°C; R_f= 0.77 ; ^{1}H NMR ($CDCl_3$; 300MHz): δ (ppm) 7.53 (d, H, H_{Ar}, $^4J_{H-H}$ =3Hz); 7.50 (d, H, H_{Ar}, $^4J_{H-H}$ =3Hz) ; 6.80 (d, H, H_{Ar} , $^3J_{H-H}$ =9Hz) ; 3.67 (t, 2H, CH_2, $^3J_{H-H}$ =6Hz); 1.60-1.67 (m, 2H, CH_2); 1.22 (m, 14H, CH_2), 0.84 (t, 3H, CH_3, $^3J_{H-H}$ =6Hz). ^{13}C NMR ($CDCl_3$;75MHz): δ(ppm) 183.15 (C=O); 166.03 (N-C=O); 145.52, 129.39, 125.39 (Cq) ; 141.28, 115.58, 111.40 (CH_{Ar}); 40.49, 31.87, 29.49, 29.27, 29.21, 27.21, 26.89, 22.70 (CH_2) ;14.12 (CH_3).

6 : 5-chloro-1-dodecylindoline-2,3-dione

Yield (%)=85% ; mp: 64-66°C; R_f= 0.75; ^{1}H NMR ($CDCl_3$; 300MHz) : δ (ppm) 7.55(d, H, H_{Ar}, $^4J_{H-H}$ =3Hz); 7.51 (d, H, H_{Ar}, $^4J_{H-H}$ =3Hz) ; 6.82 (d, H, H_{Ar}, $^3J_{H-H}$ =9Hz) ; 3.69 (t, 2H, CH_2, $^3J_{H-H}$ =9Hz); 1.61-1.70 (m, 2H, CH_2); 1.23(s, 18H, CH_2), 0.86(t, 3H, CH_3, $^3J_{H-H}$ =6Hz). ^{13}C NMR ($CDCl_3$;75MHz) : δ(ppm) 184.39 (C=O) ; 162.95 (N-C=O) ; 149.63, 129.47, 118.17 (Cq); 137.64, 125.38, 111.44 (CH_{Ar}); 40.49, 31.93, 29.61, 29.45, 29.46, 29.34, 29.21, 27.21, 26.89, 22.70 (CH_2) ; 14.13 (CH_3).

7 : 5-chloro-1-tetradecylindoline-2,3-dione

Yield (%)=84% ; mp: 65-67°C; R_f= 0.73 ; ^{1}H NMR ($CDCl_3$; 300MHz) : δ (ppm) 7.54(d, H, H_{Ar}, $^4J_{H-H}$ =3Hz) ; 7.50 (d, H, H_{Ar}, $^4J_{H-H}$ =2.1Hz); 6.84 (d, H, H_{Ar}, $^3J_{H-H}$ =9Hz) ; 3.68 (t, 2H, CH_2, $^3J_{H-H}$ =9Hz); 1.60-1.70(m, 2H, CH_2); 1.22 (s, 22H,CH_2), 0.85(t, 3H, CH_3, $^3J_{H-H}$ =6Hz). ^{13}C NMR ($CDCl_3$;75MHz): δ(ppm) 182.24 (C=O); 161.85 (N-C=O); 137.62, 125.35, 111.41 (Cq) ; 130.45, 129.43, 118.46 (CH_{Ar}); 40.48, 31.94, 29.65, 29.62, 29.61, 29.54, 29.46, 29.36, 29.21, 27.20, 26.88, 22.70(CH_2); 14.12(CH_3).

8 : 5-chloro-1-hexadecylindoline-2,3-dione

Yield (%)=85% ; mp: 66-68°C; R_f=0.70; ^{1}H NMR ($CDCl_3$; 300MHz) : δ (ppm) 7.60 (d, H, H_{Ar}, $^4J_{H-H}$ =3Hz); 7.56 (d, H, H_{Ar}, $^4J_{H-H}$ =2.1Hz) ;6.90 (d, H, H_{Ar}, $^3J_{H-H}$ =9Hz); 3.74 (t, 2H, CH_2, $^3J_{H-H}$ =9Hz) ; 1.68-1.76(m, 2H, CH_2) ; 1.28(s, 26H,CH_2), 0.91 (t, 3H, CH_3, $^3J_{H-H}$ =6Hz). ^{13}C NMR ($CDCl_3$;75MHz) : δ (ppm) 183.66 (C=O) ; 162.36 (N-C=O) ; 138.03, 124.93, 111.01 (Cq); 131.31, 128.79, 118.70 (CH_{Ar}) ; 40.91, 32.86, 29.66, 29.54, 29.46, 29.36, 29.21, 28.20, 27.90,22.93 (CH_2) ; 14.71 (CH_3).

9 : 5-chloro-1-heptadecylindoline-2,3-dione

Yield (%)=87% ; mp: 69-71°C; R_f= 0.68 ; ^{1}H NMR ($CDCl_3$; 300MHz) : δ (ppm) 7.58 d, H, H_{Ar}, $^4J_{H-H}$ =3Hz) ; 7.54 (d, H, H_{Ar}, $^4J_{H-H}$ =2.1Hz) ;6.88 (d, H, H_{Ar} , $^3J_{H-H}$ =9Hz) ; 3.72 (t, 2H, CH_2, $^3J_{H-H}$ =9Hz) ; 1.64-1.74 (m, 2H, CH_2); 1.26 (m, 28H,CH_2), 0.89(t, 3H, CH_3, $^3J_{H-H}$= 6Hz). ^{13}C NMR ($CDCl_3$; 75MHz) : δ(ppm) 184.59 (C=O); 166.15 (N-C=O); 140.28, 126.50, 112.51(Cq); 130.47, 128.80, 119.33 (CH_{Ar}); 40.92, 34.03, 29.66, 29.54, 29.46, 29.36, 29.21, 27.20, 26.88,21.83 (CH_2) ; 14.45 (CH_3).

10 : 5-chloro-1-octadecylindoline-2,3-dione

Yield (%)=84%; mp: 70-73°C; R_f= 0.69 ; ^{1}H NMR ($CDCl_3$; 300MHz) : δ (ppm) 7.61(d, H, H_{Ar}, $^4J_{H-H}$ =3Hz); 7.57 (d, H, H_{Ar}, $^4J_{H-H}$ =2.1Hz); 6.91(d, H, H_{Ar}, $^3J_{H-H}$ =9Hz); 3.75 (t, 2H, CH_2, $^3J_{H-H}$ =9Hz); 1.67-1.77(m, 2H, CH_2) ; 1.29(s, 30H,CH_2), 0.92 (t, 3H, CH_3, $^3J_{H-H}$ = 6Hz). ^{13}C NMR ($CDCl_3$;75MHz) : δ(ppm) 185.30 (C=O); 164.48 (N-C=O); 136.57, 124.15, 110.60 (Cq) ; 129.45, 128.20, 117.69 (CH_{Ar}); 40.95, 32.79, 29.65, 29.54, 29.46, 29.36, 29.21, 26.68, 26.55,21.39 (CH_2) ; 14.99 (CH_3).

11 : 5-chloro-1-methylindoline-2,3-dione

Yield (%)=89% ; mp:88-91°C; R_f= 0.72 ; ^{1}H NMR ($CDCl_3$; 300MHz) : δ (ppm) 7.56 (d, H, H_{Ar}, $^4J_{H-H}$ =3Hz); 7.54 (d, H, H_{Ar}, $^4J_{H-H}$ =3Hz) ; 6.82 (d, H, $H_{Ar,}$ $^3J_{H-H}$ =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).

12 : 1-benzyl-5-chloroindoline-2,3-dione

Yield (%)=72% ; mp:140-143°C; R_f= 0.76 ; ^{1}H NMR ($CDCl_3$; 300MHz): δ (ppm) 7.56 (d, H, H_{Ar}, $^4J_{H-H}$ =3Hz); 7.43 (d, H, H_{Ar}, $^4J_{H-H}$ =3Hz); 7.40 (d, H, H_{Ar}, $^4J_{H-H}$ =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).

13: 5-chloro-1-cinnamylindoline-2,3-dione

Yield (%)=77% ; mp:140-145°C; R_f= 0.76 ; ^{1}H NMR ($CDCl_3$; 300MHz) : δ (ppm) 7.73-7.81(m, 2H, H_{Ar}); 7.65-7.69(m, H, H_{Ar}); 7.50(d, 2H, H_{Ar}, $^4J_{H-H}$ =3Hz); 7.42-7.46 (m, 2H, H_{Ar}) ; 6.95 (d, H, H_{Ar}, $^3J_{H-H}$ =12Hz); 3.80-3.83 (m, H, CH) ; 3.61-3.69 (m, H, CH); 1.15-1.20 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$; 75MHz) : δ(ppm) 188.20 (C=O); 165.09 (N-C=O); 149.67, 138.59, 130.95, 116.75 (Cq); 135.19, 130.32, 127.56, 126.71, 125.02, 123.11 (CH_{Ar}); 132.43, 129.22 (CH) ; 46.36(CH_2).

14: 5-chloro-1-(2-(diethylamino)ethyl)indoline-2,3-dione

Yield (%)=88%; mp: 112-116°C; R_f= 0.75 ; ^{1}H NMR ($CDCl_3$; 300MHz) 7.45-7.48 (m, 2H, H_{Ar}) ; 6.14 (d, H, H_{Ar}, J=9Hz); 3.76 (t, 2H, CH_2, J=9Hz); 2.66 (t, 2H, CH_2, J=9Hz); 1.39 (q, 2H, CH_2, J=9Hz); 0.90 (m, 6H, $2CH_3$).^{13}C NMR ($CDCl_3$; 75MHz): 180.56 (C=O); 161.69 (N-C=O); 145.16, 130.74, 116.33 (Cq); 135.19, 130.53, 123.13 (CH_{Ar}); 47.42, 43.39, 50.39 (CH_2); 13.08 (CH_3).

4.Conclusion

In the context of our work we concentrate on the formation of the new heterocyclic compounds via the N-alkylation between 5-Chloroisatin and the various alkylating agents (long-chain bromoalkanes, benzyl chloride and methyl iodide ...), By applying the liquid-solid phase transfer catalysis method in the presence of potassium carbonate, tetra-n-butylammonium bromide (BTBA), and N, N-dimethylformamide.

This reaction is one of the main methods which leads to heterocyclic organic products which dominate most of the biological and pharmaceutical properties in the field of chemistry.

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