SYNTHESIS OF NEW HETEROCYCLIC SYSTEMS CONTAINING QUINOXALINE MOIETY

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Abstract

The synthesis of a new brick heterocyclic system of quinoxaline was developed by a cyclo-condensation reaction starting from *o*-phenylenediamine derivatives. Thus 6-chloroquinoxaline-2,3(1H,4H)–dione was obtainedin excellent yield by condensation of 4-Chloro-*o*-phenylenediamine with oxalic acid at reflux in a hydrochloric acid solution. Thealkylationreactions werethen carried out and optimized by using monohalogenated agents under phase transfer catalysis conditions. The reaction studied lead to the expected products in good yields and the structures of various obtained compounds are easilydetermined by the usual spectroscopic methods. This kind of products can show a potent pharmacological and therapeutic activitiesas given in the studies reported in the literature.

Keywords: 6-chloroquinoxaline-2,3(1H,4H)–dione, Condensation, Alkylation, *o*-phenylenediamine.

Résumé

La synthèse de nouveaux systèmes hétérocycliquesdérivés de laquinoxaline a été développée en adoptantdes réactions de cyclocondensation utilisant comme précurseurs les dérivés de partir de dérivés de l'*o*-phenylenediamine.Ainsi, La 6-chloroquinoxaline-2,3(1H,4H)-dione a été obtenue par condensation de la 4-Chloro-*o*-phénylènediamine avec l'acide oxalique au reflux dans une solution aqueusehydrochlorée. Les réactions d'alkylation ont été réalisées et optimisées en utilisant des agents monohalogénés dans les conditions de la catalyse par transfert de phase.Les réactions étudiées conduisent aux produits attendus avec de bons rendements et les structures des divers composés obtenus sont déterminées par les méthodes spectroscopiques usuelles.Ce type de produits sont susceptibles de présenter des activités pharmacologiques et thérapeutiques potentielles.

Mots clés : 6-chloroquinoxaline-2,3(1H,4H)-dione, Condensation, Alkylation, *o*-phenylenediamine.

Introduction

Quinoxaline and its derivatives are nitrogen heterocycles compounds, which plays an interesting role as a basic skeleton for the synthesis of many other pharmacologically and biologically active products. Theseproducts were found as : Antiamoebic[1], anticancer[2], antifungal[3], antibacterial[4], anti-inflammatory[4], antimicrobial[5], antimalarial[6], anticonvulsant[7], antidiabetic[8], antinomic[9], antioxidant[10] and antiviral[11] agents.

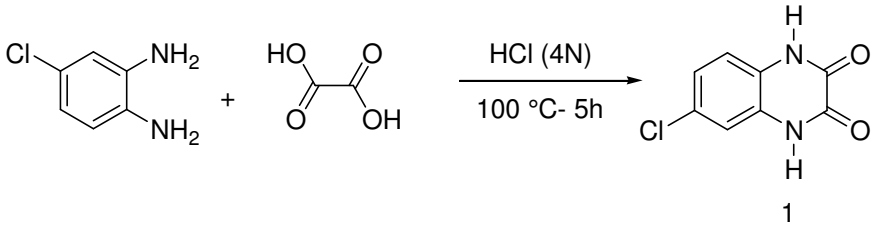
Thus it is interesting to prepare new heterocyclic systems containing the quinoxaline moiety for potential biological applications.

In this work, we describe the synthesis of 6-chloroquinoxaline-2,3(1H,4H)-dione**1** and its alkylated derivatives using conventional reagents. The alkylation reactions were carried out, under the phase transfer catalysis conditions, leading to compounds alkylated simultaneously at positions 1 and 4 of the bicyclic compound.

Results and discussion

The condensation of the 4-Chloro-*o*-phenylenediamine with oxalic acid under reflux for 5 hours in hydrochloric acid solution (4N) leads to 6-chloroquinoxaline-2,3(1H,4H)-dione **1** with 94% yield (Scheme 1)[12].

The final product **1** was obtained by simple filtration followed by washing with water.



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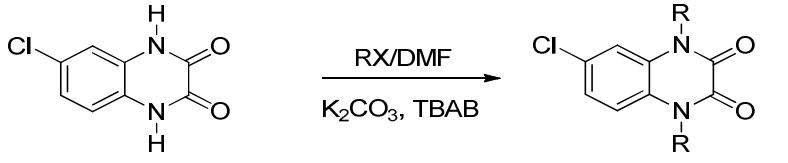
Scheme 1

In order to prepare new 6-chloroquinoxaline-2,3(1H,4H)-dione derivatives by alkylation reactions, compound **1** was put on reaction with monohalogenated reagents. This process was carried out under phase transfer catalysis conditionsusing tetrabutylammonium bromide (TBAB) as catalyst, K_2CO_3 as base and N,N-dimethylformamide as solvent, to lead compounds **2a-2e** in good yields (scheme 2).



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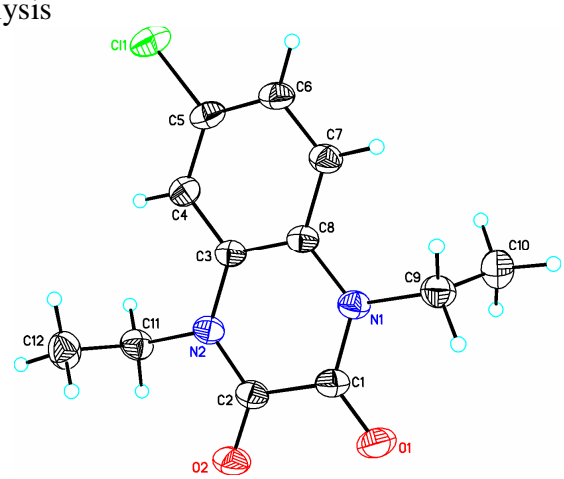
2a: R = CH_3
2b: R = C_2H_5
2c: R = C_4H_9
2d: R = C_8H_{17}
2e: R = C_9H_{19}

Scheme 2

The structures of compounds **2a-2e** have been elucidated on the basis of spectroscopic data (^{1}H NMR, ^{13}C NMR, IR) and confirmed by single crystal X-ray diffraction in the case of compound **2b** (scheme 3).

Produits	Rdt* %	^{1}H NMR (ppm)	^{13}C NMR(ppm)
1	94	7.133 (s, 3H, 3C*H*$_{arom}$), 11.97 (d, 2H, 2 N*H*)	114.88-123.09 (CH_{arom})
2a	85	3.52 (s, 3H, N-C*H*$_3$), 3.53 (s, 3H, N-C*H*$_3$)	30.47 (N-CH_3), 30.47 (N-CH_3).
2b	89	1.30-1.47 (m, 6H, 2C*H*$_3$), 4.15-4.34 (m, 4H, 2C*H*$_2$)	38.47 (CH_2), 38.46 (CH_2), 12.06 (CH_3), 12.02 (CH_3).
2c	85	0.85-1.09 (m, 6H, 2C*H*$_3$), 4.14-4.20 (m, 4H, 2C*H*$_2$-*N*)	43.15 ($2CH_2$), 28.80 (CH_2), 28.74 (CH_2), 20.14 ($2CH_2$), 13.76 ($2CH_3$).
2d	83	0.81-1.03 (m, 6H, 2CH_3), 1.28-1.44 (m, 20H, 10CH_2), 1.66-1.88 (m, 4H, 2CH_2-CH_2-N)	43.40 (CH_2), 43.39 (CH_2), 31.75($2CH_2$), 29.24(CH_2), 29.18(CH_2), 29.13($2CH_2$), 26.87(CH_2), 26.83(CH_2), 26.78(CH_2), 26.67(CH_2), 22.62($2CH_2$), 14.09($2CH_3$).
2e	87	0.90-1.03 (m, 6H, 2CH_3), 1.28-1.44 (m, 24H, 12CH_2), 1.68-1.80 (m, 4H, 2CH_2-CH_2-N)	43.40 (CH_2), 43.39 (CH_2), 31.83($2CH_2$), 29.24($6CH_2$), 26.87(CH_2), 26.83(CH_2), 26.78(CH_2), 26.68(CH_2), 22.66($2CH_2$), 14.09($2CH_3$).

Single-crystal X-ray analysis



Scheme3: Ortep of compound **2b** with atom numbering.

A plate-like specimen of $C_{12}H_{13}ClN_2O_2$, approximate dimensions 0.22mm x 0.18mm x 0.12mm, was used for the X-ray crystallographic analysis. Instrument description X-ray intensity data were measured on a Bruker D8 VENTURE PHOTON 100 CMOS system equipped with a mirror monochromator and a Cu INCOATEC IμS micro-focus source (λ = 1.54178 Å) [13].

Chemical formula	$C_{12}H_{13}ClN_2O_2$	
Formula weight	252.69g/mol	
Temperature	293 K	
Wavelength	1.54184 Å	
Crystal size	0.22 x 0.18 x 0.12 mm	
Crystal system	Monoclinic, I2/a	
Space group	I 2/a	
Unit cell dimensions	a = 14.6454 (8) Å	α = 90°
	b = 12.0415 (5) Å	β = 115.621 (7)°
	c = 15.1149 (9) Å	γ = 90°
Volume	2403.5 (3) $Å^3$	
Z	8	
Density (calculated)	1.392 g/cm^3	
Absorption coefficient	2.756 mm^{-1}	
F(000)	1056.0	

Conclusion

In this work, we have been able to develop reaction conditions for the preparation of new 2,3-quinoxaline(1H,4H)-dione. These newheterocyclic compounds were prepared for N-alkylations under phase transfer catalysis conditions using potassium carbonate as base and tetra-n-butylammonium bromide as catalyst. The compounds, thus synthesized, can be employed in 1,3-dipolar cycloaddition reactions and can be evaluated for their biological properties.The structures of the compounds were confirmed by single crystal X-ray diffraction in the case of compound **2b**.

Experimental

The uncorrected melting points were taken in capillary tube on a Buchi apparatus. ^1H and ^{13}C NMR spectra were recorded on a Brucker AC-300 instrument. The chemical shifts were expressed in parts per million of the inductor field, and measured with an accuracy of ± 0.1 for ^{13}C and ± 0.05 for ^1H. Tetramethylsilane (TMS) served as a reference.

1. Synthesis of 6-chloroquinoxaline-2,3(1H,4H)-dione

To 1g (7.01 mmol) of 4-Chloro-*o*-phenylenediamine was added 0.63g (7 mmol) of oxalic acid and 20 ml of HCl 4N, the mixture was refluxed for 5 hours and cooled. The black solid formed was filtered, washed with distilled water, dried and recovered in good yield.

2. Synthesis of compounds **2a-2e**

To a solution of 0.2 g (1.02 mmol) of 6-chloroquinoxaline-2,3(1H,4H)-dione **1** in 25 ml of DMF was added 0.35 g (2.54 mmol) of potassium carbonate K_2CO_3. The mixture is stirred for 5 minutes.Before addition of 0.01 equivalents of tetra-n-butylammonium bromide (BTBA) and 2.5 equivalents of the monohalogenated reagent. The mixture was then stirred at room temperature for 12 hours. After filtration of salts, the DMF was evaporated under reduced pressure. The obtained residue was dissolved in dichloromethane. The organic phase was dried over Na_2SO_4 and then concentrated. The obtained residue was chromatographed on Silica gel column (eluent: hexane/ethyl acetate (3/1)).

*6-chloroquinoxaline-2,3(1H,4H)-dione :**1***
Yield (94%); Mp :>300 °C; ^{1}H NMR (DMSO-d_6) δ: 7.133 (s, 3H, 3CH_{arom}) ; 11.97 (d, 2H, 2 NH) ; ^{13}C NMR (DMSO-d6) δ : 155.47 (C=O) ; 155.27 (C=O) ; 127.34 (Cq) ; 127.00 (Cq) ; 125.22 (Cq) ; 123.09 (CH_{arom}) ; 117.02 (CH_{arom}) ; 114.88 (CH_{arom}).

*6-chloro-1,4-dimethylquinoxaline-2,3(1H,4H)-dione:**2a***

Yield (85%); Mp : 144 °C ; eluent of recrystallization (Dichloromethane/Hexane); ^{1}H NMR ($CDCl_3$) δ : 3.52 (s, 3H, N-CH_3) ; 3.53 (s, 3H, N-CH_3) ; 7.31-7.50 (m, 3H, CH_{arom}) ; ^{13}C NMR ($CDCl_3$) δ : 155.47 (C=O) ; 155.27 (C=O) ; 127.34 (Cq) ; 127.00 (Cq) ; 125.22 (Cq) ; 123.62 (CH_{arom}) ; 117.10 (CH_{arom}) ; 115.33 (CH_{arom}) ; 30.47 (N-CH_3) ; 30.47 (N-CH_3).

*6-chloro-1,4-diethylquinoxaline-2,3(1H,4H)-dione :**2b***

Yield (89%); Mp : 201 °C ; eluent of recrystallization (Dichloromethane/Hexane); ^{1}H NMR ($CDCl_3$) δ : 1.30-1.47 (m, 6H, 2CH_3) ; 4.15-4.34 (m, 4H, 2CH_2); 7.15-7.33 (m, 3H, CH_{arom}); ^{13}C NMR ($CDCl_3$) δ : 153.61 (C=O); 153.37 (C=O); 129.66 (Cq); 127.52 (Cq); 125.18 (Cq); 123.96 (CH_{arom}) ; 116.04 (CH_{arom}) ; 115.04 (CH_{arom}) ; 38.47 (CH_2) ; 38.46 (CH_2) ; 12.06 (CH_3) ; 12.02 (CH_3).

*1,4-dibutyl-6-chloroquinoxaline-2,3(1H,4H)-dione:**2c***
Yield (85%) ; Mp : 120 °C ; eluent of recrystallization (Dichloromethane/Hexane);^{1}H NMR ($CDCl_3$) δ : 0.85-1.09 (m, 6H, 2CH_3) ; 1.41-1.55 (m, 4H, 2CH_2-CH_3) ; 1.67-1.80 (m, 4H, 2CH_2-CH_2) ; 4.14-4.20 (m, 4H, 2CH_2-N) ; 7.16-7.28 (m, 3H, CH_{arom}) ; ^{13}C NMR ($CDCl_3$) δ : 153.80 (C=O) ; 153.54 (C=O) ; 129.51 (Cq) ; 127.76 (Cq) ; 125.41 (Cq); 123.83 (CH_{arom}) ; 116.14 (CH_{arom}) ; 115.14 (CH_{arom}) ; 43.15 (2CH_2) ; 28.80 (CH_2) ; 28.74 (CH_2) ; 20.14 (2CH_2) ; 13.76 (2CH_3).

*6-chloro-1,4-dioctylquinoxaline-2,3(1H,4H)-dione:**2d***

Yield (83%) ; Mp : 108 °C ; eluent of recrystallization (Dichloromethane/Ether);^{1}H NMR ($CDCl_3$) δ : 0.81-1.03 (m, 6H, $2CH_3$) ; 1.28-1.44 (m, 20H, $10CH_2$) ; 1.66-1.88 (m, 4H, $2CH_2$-CH_2-N) ; 4.14-4.27 (m, 4H, $2CH_2$-N) ; 7.11-7.36 (m, 3H, CH_{arom}) ; ^{13}C NMR ($CDCl_3$) δ : 153.79 (C=O) ; 153.53 (C=O) ; 129.51 (Cq) ; 127.76 (Cq) ; 125.41 (Cq); 123.82 (CH_{arom});116.13(CH_{arom}) ;115.15(CH_{arom}) ;43.40(CH_2) ;43.39(CH_2) ;31.75($2CH_2$) ;29.24(CH_2) ;29.18(CH_2) ;29.13($2CH_2$) ;26.87(CH_2) ;26.83(CH_2) ;26.78(CH_2) ;26.67(CH_2) ;22.62($2CH_2$) ; 14.09($2CH_3$).

*6-chloro-1,4-dinonylquinoxaline-2,3(1H,4H)-dione:**2e***

Yield (87%) ; Mp : 106 °C ; eluent of recrystallization (Dichloromethane/Ether);^{1}H NMR ($CDCl_3$) δ : 0.90-1.03 (m, 6H, $2CH_3$) ; 1.28-1.44 (m, 24H, $12CH_2$) ; 1.68-1.80 (m, 4H, $2CH_2$-CH_2-N) ; 4.13-4.27 (m, 4H, $2CH_2$-N) ; 7.07-7.36 (m, 3H, CH_{arom}) ; ^{13}C NMR ($CDCl_3$) δ : 153.79 (C=O) ; 153.53 (C=O) ; 129.51 (Cq) ; 127.76 (Cq) ; 125.41 (Cq); 123.82 (CH_{arom}); 116.13(CH_{arom}) ;115.15(CH_{arom}) ;43.40(CH_2) ;43.39(CH_2) ;31.83($2CH_2$) ;29.24($6CH_2$) ;26.87(CH_2) ;26.83(CH_2) ;26.78(CH_2) ;26.68(CH_2) ;22.66($2CH_2$) ;14.09($2CH_3$).

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