Malose J. Mphahlele, Sebayitseng M. Hlatshwayo, Stephen M. Ndlovu and Manuel A. Fernandes, *S. Afr. J. Chem.,* 2001, **54**, 60-68, <http://journals.sabinet.co.za/sajchem/>, <http://ejour.sabinet.co.za/images/ejour/chem/chem_v54_a3.pdf>.
[formerly: Malose J. Mphahlele, Sebayitseng M. Hlatshwayo, Stephen M. Ndlovu and Manuel A. Fernandes, *S. Afr. J. Chem.,* 2001, **54**, 3. (9 pp.), <http://ejour.sabinet.co.za/images/ejour/chem/chem_v54_a3.pdf>.]

RESEARCH ARTICLE

Regio- and Stereoselective α-Halogenation of 2-Aryl-1-methylsulfonyl-2,3-dihydroquinolin-4(1*H*)-ones

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Received 12 January 2000; revised 14 November 2000; accepted 28 February 2001

Abstract

*2-Aryl-1-methylsulfonyl-2,3-dihydroquinolin-4(1*H*)-ones are readily converted into the corresponding 2-aryl-3-iodo- and 2-aryl-3-bromo-1-methylsulfonyl-2,3-dihydro-quinolin-4(1*H*)-ones using iodine in methanol and pyridinium perbromide in acetic acid, respectively. The reactions were found to be regioselective and stereoselective by ^{1}H NMR spectroscopy, affording in all cases the 2,3-*trans *isomers. X-ray crystallography was also used to investigate the relative stereochemistry of these 3-halo derivatives.*

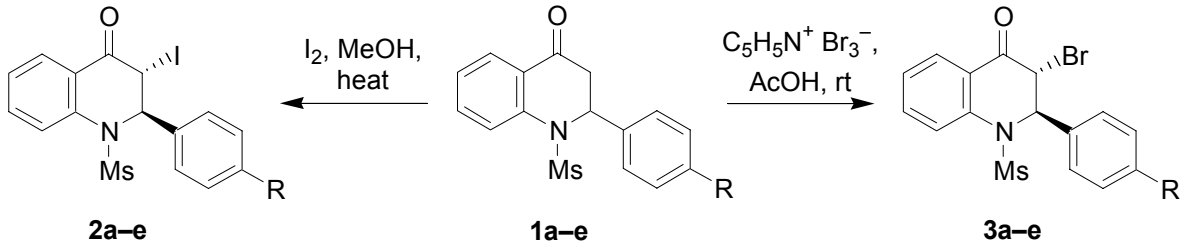
Keywords: Quinolones, halogenation, X-ray crystallography, stereochemistry

1. Introduction

Selective halogenation of heterocyclic systems continues to attract considerable attention because of the profound effect the introduction of a halogen atom into the heterocyclic ring can have on the physical, chemical and biological properties of such substrates.[1] In the course of our studies on the design and synthesis of 4-quinolone derivatives, we required an expedient, regio- and stereoselective method for introducing a halogen atom at C-3 of 2-aryl-1-methylsulfonyl-2,3-dihydroquinolin-4(1*H*)-ones. The *N*-substituted 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones substituted with a bromine or hydroxyl group at C-3 of the heterocyclic ring have been prepared before as inseparable mixtures of *cis* and *trans* isomers from side-chain brominated or bromo-methoxylated chalcones or chalcone epoxides, respectively.[3,4] A recently reported procedure involving the reaction of $BF_3.OEt_2$-activated 4-quinolone with phenylmagnesium halide in dichloromethane followed by halogenation using *N*-halosuccinimide affords the 2,3-*trans* 1-ethoxycarbonyl- and 1-benzyloxycarbonyl-substituted 3-halo-2-phenyl-2,3-dihydroquinolin-4(1*H*)-ones stereoselectively.[5] This procedure, however, is not regioselective because in some cases mixtures of halogenated and non-halogenated products are isolated depending on the nature of the *N*-halosuccinimides used. In this work, we have explored the C-3 halogenation of the 2-aryl-1-methylsulfonyl-2,3-dihydroquinolin-4(1*H*)-ones **1** using iodine in refluxing methanol and pyridinium perbromide in acetic acid, respectively.

2. Results and Discussion

A series of 2-aryl-1-methylsulfonyl-2,3-dihydroquinolin-4(1*H*)-ones **1**, prepared as described in our previous communication,[6] was treated with one equivalent of iodine in methanol under reflux, or two equivalents of pyridinium perbromide in glacial acetic acid (Scheme), respectively. In both cases, we isolated the corresponding 2-aryl-3-halo-1-methylsulfonyl-2,3-dihydroquinolin-4(1*H*)-ones **2** and **3** regioselectively and stereoselectively. No nuclear halogenated derivatives were detected or isolated. The structures of products **2** and **3** were unambiguously determined with the aid of NMR (^{1}H and ^{13}C) and IR spectroscopy and mass spectrometry (see Table 1).



2a–e **1a–e** **3a–e**

Scheme **a**, R = H; **b**, R = F; **c**, R = Cl; **d**, R = Br; **e**, R = OCH_3; Ms = SO_2CH_3.

Table 1 ^{1}H NMR and mass spectral data of 2-aryl-3-halo-1-methylsulfonyl-2,3-dihydroquinolin-4(1*H*)-ones **2** and **3**.

Product	R	X	Yield (%)	m.p., ºC (solvent)	^{1}H NMR[a]	MS
2a	H	I	60	183–186 (MeOH)	5.30 (1H, d, *J* 2.6, 3-H), 6.06 (1H, d, *J* 2.6, 2-H)	Found: M^+, 426.9743. $C_{16}H_{14}INO_3S$ requires *M*, 426.9739
2b	F	I	50	193–194 (MeOH)	4.50 (1H, d, *J* 2.4, 3-H), 6.01 (1H, d, *J* 2.4, 2-H)	Found: M^+, 444.9651. $C_{16}H_{13}FINO_3S$ requires *M*, 444.9645
2c	Cl	I	58	207–210 (MeOH)	5.26 (1H, d, *J* 2.4, 3-H), 6.03 (1H, d, *J* 2.2, 2-H)	Found: M^+, 460.9353. $C_{16}H_{13}{}^{35}ClINO_3S$ requires *M*, 460.9349
2d	Br	I	55	198–200 (MeOH)	5.25 (1H, d, *J* 2.6, 3-H), 6.00 (1H, d, *J* 2.6, 2-H)	Found: M^+, 504.8849. $C_{16}H_{13}{}^{79}BrINO_3S$ requires *M*, 504.8845
2e	OMe	I	90	200–201 (MeOH)	5.24 (1H, d, *J* 2.6, 3-H), 6.00 (1H, d, *J* 2.6, 2-H)	Found: M^+, 456.9850. $C_{17}H_{16}INO_4S$ requires *M*, 456.9845
3a	H	Br	80	186–189 (EtOH–EtOAc)	4.96 (1H, d, *J* 2.4, 3-H), 6.21 (1H, d, *J* 2.6, 2-H)	Found: M^+, 378.9884. $C_{16}H_{14}{}^{79}BrNO_3S$ requires *M*, 378.9878
3b	F	Br	75	214–215 (EtOH)	4.92 (1H, d, *J* 2.6, 3-H), 6.19 (1H, d, *J* 2.6, 2-H)	Found: M^+, 396.9791. $C_{16}H_{13}{}^{79}BrFNO_3S$ requires *M*, 396.9784
3c	Cl	Br	85	200–203 (EtOH–EtOAc)	4.92 (1H, d, *J* 2.6, 3-H), 6.18 (1H, d, *J* 2.6, 2-H)	Found: M^+, 412.9473. $C_{16}H_{13}{}^{79}Br{}^{35}ClNO_3S$ requires *M*, 412.9488
3d	Br	Br	88	207–210 (EtOH–EtOAc)	4.92 (1H, d, *J* 2.6, 3-H), 6.16 (1H, d, *J* 2.6, 2-H)	Found: M^+, 456.8979. $C_{16}H_{13}{}^{79}Br_2NO_3S$ requires *M*, 456.8983
3e	OMe	Br	75	193–195 (EtOH–EtOAc)	4.91 (1H, d, *J* 2.6, 3-H), 6.15 (1H, d, *J* 2.6, 2-H)	Found: M^+, 408.9978. $C_{17}H_{16}{}^{79}BrNO_4S$ requires *M*, 408.9983

[a] For the sake of clarity, the ^{1}H NMR signals of the methyl and aromatic groups are not included. In all cases these groups resonate in the region δ_H 3.35–3.50 ($MeSO_2$), 3.71 (OMe) and 7.00-8.20 (Ar).

The 200 MHz ^{1}H NMR spectra of compounds **2** and **3** obtained in chloroform-*d* are characterized by two sets of doublets at *ca*. δ 4.9–5.2 ppm and *ca*. δ 6.0–6.2 ppm, with vicinal coupling constants $J_{2,3}$ in the range 2.3–2.6 Hz, which correspond to 2-H and 3-H, respectively (Table 1). This value for the coupling constant is comparable to the literature values reported by Donnelly and Farrell[4b] for 3-bromo-2-phenyl-1-phenylsulfonyl-2,3-dihydroquinolin-4(1*H*)-ones ($J_{2,3}$ 3.0 Hz, in $CDCl_3$ at 60 MHz) and by Beifuss and coworkers[5] for the analogous 2-alkyl- and 2-aryl-1-ethoxycarbonyl-3-halo-2,3-dihydroquinolin-4(1*H*)-one derivatives ($J_{2,3}$ 2.5 Hz, in C_6D_6 at 200 MHz). Donnelly and Farrell also reported the detection in the crude product mixture of an isomer having two sets of doublets at δ 5.21 ppm and δ 6.23 ppm with a vicinal coupling constant of 6 Hz, however, this isomer could not be isolated.[4] On the basis of the magnitude of the observed coupling constants, these authors assigned the 2,3-*cis* geometry to the major isomer ($J_{2,3}$ 3.0 Hz), and the minor isomer was assigned the *trans* configuration. On the other hand, Beifuss and coworkers assigned the *trans* geometry to the analogous 1-benzyloxycarbonyl- and 1-ethoxycarbonyl-3-halo-2-methyl-2,3-dihydroquinolin-4(1*H*)-ones on the basis of information obtained from X-ray crystal structure data.[5]

Single crystal X-ray structure determinations (Table 2) were carried out in this investigation on 3-iodo-2-(4-methoxyphenyl)-1-methylsulfonyl-2,3-dihydroquinolin-4(1*H*)-one **2e** (Fig. 1a) and 3-bromo-2-(4-bromophenyl)-1-methylsulfonyl-2,3-dihydroquinolin-4(1*H*)-one **3d** (Fig. 1b). The C-2 and C-3 substituents in both cases were shown to adopt a *trans* diaxial orientation, with torsion angles (Table 3) comparable to the values (65.5º) obtained by Beifuss and coworkers for analogous 1-benzyloxycarbonyl and 1-ethoxycarbonyl derivatives.[5] Our results thus contradict those reported by Donnelly and Farrell,[4] and support the *trans* geometry observed by Beifuss and coworkers.[5] The observed stereoselectivity of the reactions under discussion can be explained by attack of the electrophilic halogen atom on the enolic carbon–carbon double bond formed between C-3 and C-4. This attack would take place exclusively on the less hindered face of the enol *anti* to the bulky C-2 aryl group, leading to *trans* diaxial orientation of the substituents on C-2 and C-3.

Table 2 Crystal data and details of the X-ray data collections and refinements for **2e** and **3d**.

	2e	**3d**
Empirical formula	$C_{17}H_{16}INO_4S$	$C_{16}H_{13}Br_2NO_3S$
CCDC-code number	CCDC 160785	CCDC 160784
Formula weight	457.27	459.15
Temperature	293(2) K	293(2) K
Wavelength	0.71073 Å	0.71073 Å
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/c$
Unit cell dimensions	a = 11.375(3) Å	a = 10.8648(18) Å
	b = 9.315(2) Å	b = 9.2952(15) Å
	c = 16.731(4) Å	c = 16.920(3) Å
	$\alpha = \gamma = 90°$	$\alpha = \gamma = 90°$
	β = 105.606(5)°	β = 104.497(3)°
Volume	1707.4(8) Å^3	1654.3(5) Å^3
Z	4	4
Density (calculated)	1.779 g cm^{-3}	1.844 g cm^{-3}
Absorption coefficient μ	2.019 mm^{-1}	5.039 mm^{-1}
F(000)	904	904
Crystal size (mm)	0.40 × 0.32 × 0.12	0.50 x 0.50 x 0.42
θ range for data collection	1.86–28.34°	1.94–26.37°
Index ranges	$-15 \le h \le 15$	$-12 \le h \le 13$
	$-12 \le k \le 11$	$-11 \le k \le 11$
	$-17 \le l \le 22$	$-20 \le l \le 21$
Reflections collected	11547	9710
Independent reflections	4218 (R_{int} = 0.0329)	3361 (R_{int} = 0.0291)
Completeness to θ	98.7% (to θ = 28.34°)	99.4% (to θ = 26.37°)
Absorption correction	Empirical	Empirical
Max. and min. transmission	0.7937 and 0.4990	0.2260 and 0.1872
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data / restraints / parameters	4218 / 0 / 219	3361 / 0 / 210
Goodness-of-fit on F^2	1.044	0.903
Final R indices [$I>2\sigma(I)$]	$R1$ = 0.0349, $wR2$ = 0.0916	$R1$ = 0.0262, $wR2$ = 0.0586
R indices (all data)	$R1$ = 0.0468, $wR2$ = 0.0978	$R1$ = 0.0396, $wR2$ = 0.0598
Extinction coefficient	—	0.0101(4)
Largest diff. peak and hole	1.117 and –0.811 e Å^{-3}	0.411 and –0.355 e Å^{-3}

Several methods for the α-halogenation of cyclic ketones have been reported.[7] However, the results described in Scheme 1 represent simple high yielding, regio- and stereoselective routes to hitherto unknown 2,3-*trans* 2-aryl-3-halo-1-methylsulfonyl-2,3-dihydroquinolin-4(1*H*)-ones. These reactions occur under relatively mild conditions, and the isolation of the products does not involve tedious

chromatographic separations. Systems **2** and **3** are suitable substrates for further studies of chemical transformation; for example, they can serve as intermediates in the synthesis of C_3-linked biflavanoid derivatives. The antimalarial activity of quinolone derivatives is well documented,[8] thus systems **2** and **3** are suitable candidates for the screening of antimalarial activity to establish the effect of structure on biological activity.

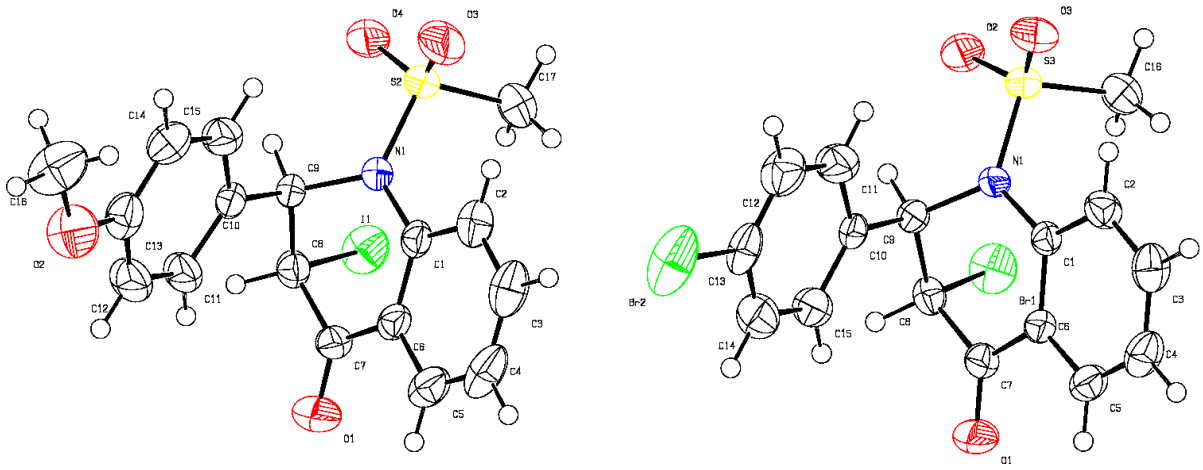


Figure 1 (a) X-ray crystal structure of 3-iodo-2-(4-methoxyphenyl)-1-methylsulfonyl-2,3-dihydroquinolin-4(1*H*)-one **2e** showing crystallographic numbering. (b) X-ray crystal structure of 3-bromo-2-(4-bromophenyl)-1-methylsulfonyl-2,3-dihydroquinolin-4(1*H*)-one **3d** showing crystallographic numbering. For clarity, hydrogen atoms are not labelled.

Table 3 Selected torsion angles (º) for **2e** and **3d**. For atom labelling see Figures 1a and 1b, respectively.

Compound **2e**		Compound **3d**	
I(1)-C(8)-C(7)-C(6)	97.5(2)	C(6)-C(7)-C(8)-Br(1)	93.2(2)
C(7)-C(8)-C(9)-N(1)	52.9(3)	C(7)-C(8)-C(9)-C(10)	–69.3(2)
I(1)-C(8)-C(9)-N(1)	–65.8(2)	C(7)-C(8)-C(9)-N(1)	53.3(2)
C(7)-C(8)-C(9)-C(10)	–68.9(3)	Br(1)-C(8)-C(9)-N(1)	–65.56(19)
I(1)-C(8)-C(9)-C(10)	172.50(15)	Br(1)-C(8)-C(9)-C(10)	171.77(14)

3. Experimental

Melting points were recorded on a Thermocouple digital melting point apparatus and are uncorrected. NMR spectra were obtained for $CDCl_3$ solutions on a Varian Gemini 200 MHz spectrometer and the chemical shifts are quoted relative to the solvent peak (^{1}H: 7.25 ppm). *J* values are given in Hz. High-resolution mass spectra were recorded at Cape Technikon Mass Spectrometry Unit using a VG–70 SEQ MASPEC II[32] instrument (scanning at RP 10 000). The synthesis and characterization of systems **1a**–**e** used as substrates in this investigation have been reported elsewhere.[6]

3.1. α-Iodination of Systems 1. General Procedure

A stirred mixture of **1** (1 equiv.) and iodine (1 equiv.) in methanol (5 cm^3 $mmol^{-1}$ of **1**) was heated under reflux for 5 h. The mixture was allowed to cool and the crystalline product was filtered and washed with cold methanol to afford the corresponding 2-aryl-3-iodo-1-methylsulfonyl-2,3-dihydroquinolin-4(1*H*)-ones **2** (see Table 1).

3.2. α-Bromination of Systems 1. General Procedure

Pyridinium perbromide (2 equiv.) was added to a solution of **1** (1 equiv.) in glacial acetic acid (10 cm^3 $mmol^{-1}$ of **1**), and the mixture was stirred at room temperature for 1 h. Ice cold water (20 cm^3 $mmol^{-1}$ of **1**) was added to the precipitate, which was then filtered and recrystallized to afford the corresponding 2-aryl-3-bromo-1-methylsulfonyl-2,3-dihydroquinolin-4(1*H*)-ones **3** (see Table 1).

3.3. X-Ray Crystallographic Data Collection and Processing

Intensity data were collected on a Siemens (now Bruker AXS) SMART 1K CCD area detector diffractometer with graphite monochromated Mo *K*α radiation (50kV, 30mA).[9a] The collection method involved ω-scans of width 0.3°. Data reduction and absorption corrections were carried out using SAINT[9b] and SADABS[9c] programs, respectively.

3.4. Structure Analysis and Refinement

The crystal structure was solved using SHELXS-97.[9d] Non-hydrogen atoms were first refined isotropically, followed by anisotropic refinement by full-matrix least-squares

calculation based on F^2 using SHELXL-97.[9d] Hydrogen atoms were geometrically fixed and allowed to ride on the respective atoms.

Acknowledgements

We thank Dr P. Boshoff (Cape Technikon Mass Spectrometry Unit) and Mr R.M. Mampa (University of the North) for MS and NMR data, respectively. Financial assistance from the National Research Foundation is gratefully acknowledged.

Supplementary material

Tables of atomic coordinates and equivalent isotropic displacement parameters, bond lengths and angles, anisotropic displacement parameters, and hydrogen atomic coordinates and their isotropic displacement parameters for compounds **2e** and **3d**, as well as torsion angles for **2e**, may be found by following the hyperlink or from *Sabinet Online* on request.

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