Chemistry of Heterocyclic Compounds, Vol. 44, No. 3, 2008

QUINAZOLINES

1. SYNTHESIS AND CHEMICAL REACTIONS OF 6-CHLOROSULFONYL-QUINAZOLINE-2,4-DIONES

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Treatment of quinazoline-2,4-dione and its symmetrical 1,3-dialkyl derivatives with chlorosulfonic acid gave the corresponding 6-chlorosulfonylquinazoline-2,4-diones. Reaction of the compounds obtained with nucleophilic agents (water, ammonia, aliphatic and cyclic amines) gave the corresponding free 2,4-dioxoquinazoline-6-sulfonic acids, 6-sulfamidoquinazoline-2,4-diones, and 2,4-dioxoquinazoline-6-sulfonic acid amides.

Keywords: 2,4-dioxoquinazoline-6-sulfonic acid amides, 2,4-dioxoquinazoline-6-sulfonic acids, symmetrical 1,3-dialkylquinazoline-2,4-diones, 6-chlorosulfonylquinazoline-2,4-diones, nucleophilic and electrophilic substitution.

Within the series of quinazoline derivatives there are found fungicides, bactericides, insecticides, and plant growth regulators [1]. Amongst them there are also found substances having anticholinesterase, soporific, antispasmodic, sedative, tranquilizing, muscle relaxing, antirheumatic, hypotensive, bronchodilating, diuretic, antimalarial, and other activities [1-8].

We have previously studied the chlorosulfonylation of benzoxazolin-2-ones [9] and benzothiazolin-2-ones [10] and synthesized the corresponding 6-chlorosulfonylbenzazolin-2-ones. In continuing investigation of electrophilic substitution in a series of nitrogen-containing heterocyclic compounds [9-13] it was of interest to study the chlorosulfonylation of quinazoline-2,4-dione and its symmetrical 1,3-dialkyl derivatives and to carry out chemical reactions of the compounds obtained.

It was found that the reaction of the quinazoline-2,4-diones **1a-d** with chlorosulfonic acid (CSA) forms the corresponding 6-chlorosulfonylquinazoline-2,4-diones **2a-d** regardless of the reagent ratio. The best yields are obtained with a molar ratio of the reagents **1a-d** to CSA of 1:5. This is likely due to the ease of the nucleophilic substitution reaction of the hydroxyl group of the intermediate sulfonic acids **3a-d** for the chlorine atom of the CSA due to the increased positive charge of the sulfur atom of the sulfo group.

The free 2,4-dioxoquinazoline-6-sulfonic acids **3a-d** could be synthesized in quantitative yields (Table 1) by hydrolysis of the corresponding 6-chlorosulfonylquinazoline-2,4-diones **2a-d**. It should be noted that the rate of the hydrolysis decreases with lengthening of the alkyl chain in the 1,3-dialkyl-6-chlorosulfonyl-quinazoline-2,4-diones **2c,d**. Thus if the conversion of the sulfochlorides **2a,b** to the corresponding sulfonic acids **3a,b** needs heating for 2 h the hydrolysis of compounds **2c,d** requires 6 and 10 h respectively.

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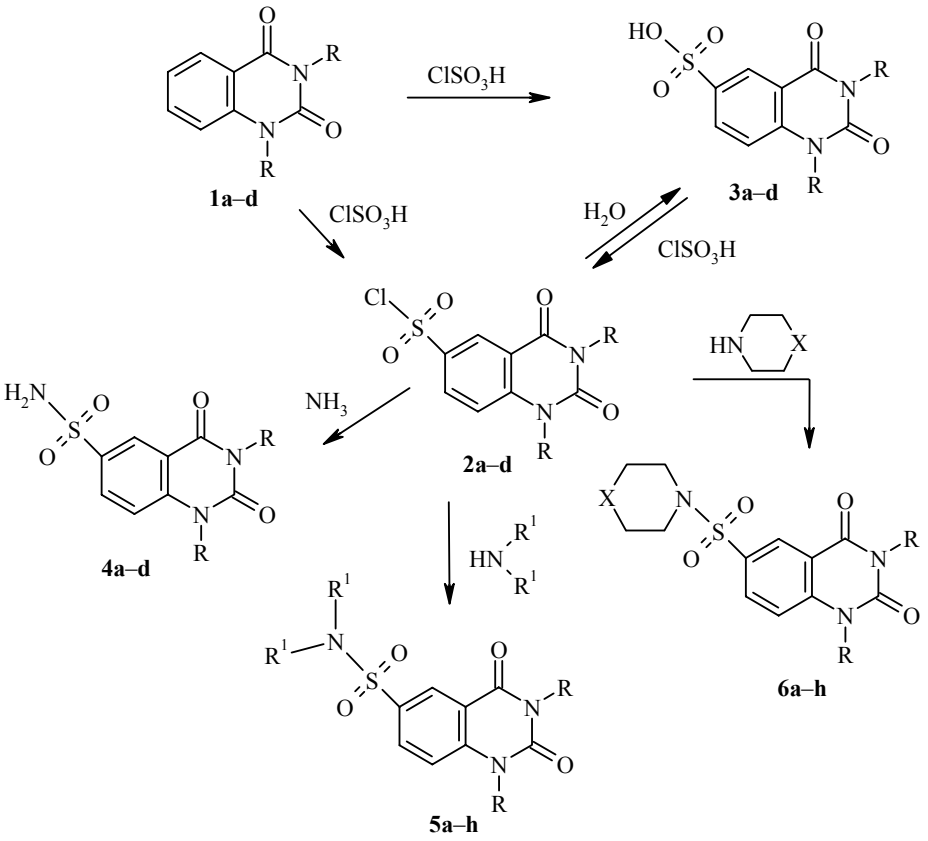


1–**4 a** R = H, **b** R = Me, **c** R = *n*-Pr; **d** R = *n*-Bu; **5**, **6 a**, **e** R = H, **b**, **f** R = Me, **c**, **g** R = *n*-Pr, **d**, **h** R = *n*-Bu; **5 a**–**d** R^1 = Et, **e**–**h** R^1 = *n*-Bu; **6 a**–**d** X = CH_2, **e**–**h** X = O

It should also be noted that the sulfonic acids **3a-d** react smoothly with CSA in quantitative yields to give the corresponding 6-chlorosulfonylquinazoline-2,4-diones **2a-d**.

The reactions of compounds **2a-d** with ammonia and with aliphatic and heterocyclic amines takes place smoothly independently of the length of the alkyl groups in positions 1 and 3. Refluxing compounds **2a-d** with concentrated ammonia solution gave the corresponding 6-sulfamidoquinazoline-2,4-diones **4a-d**. Reaction of compounds **2a-d** with aliphatic amines in the presence of triethylamine at room temperature gives high yields of the corresponding N,N-dialkylamides of 2,4-dioxoquinazoline-6-sulfonic acids **5a-h** and with heterocyclic amines the 2,4-dioxoquinazoline-6-sulfonic acid morpholide and piperidide (Table 1). It is likely that the basicity of the amine used is a determining factor in these reactions.

The structure of the synthesized compounds **2-6** was identified by IR and ^{1}H NMR spectroscopy, mass spectrometry, and was confirmed by elemental analytical data.

The IR spectra of compounds **2-6** show characteristic absorption bands for the asymmetric and symmetric stretching vibrations of the SO_2 groups in the region 1100-1400 cm^{-1}. The free 2,4-dioxoquinazoline-6-sulfonic acids **3a-d** in addition show stretching absorptions for the S–O group at 600-700 cm^{-1} (Table 2).

The mass spectra of compounds **2-6** show molcular ions and fragments fully confirming the proposed structures. The mass spectra of compounds **4-6** show a common fragmentation with fission of the SO_2–NR^1_2 bond to give the fragments **A** [M^+–NR^1_2] and **B** [NR^1_2] independently of the nature of the R and R^1 substituent.

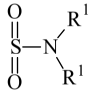
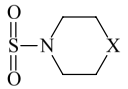
It was found that the M^+ molcular ion peaks in compounds **4a-d** have maximum intensity whereas in compounds **5a-h, 6a-h** the fragment **A** peaks are a maximum. Hence the first fragmentation act in compound **2a** is fission of the S–Cl bond whereas in the sulfochlorides **2b-d** the 1,3-dialkyl substituents separate. The fragmentation route associated with elimination of the quinazoline-2,4-dione ring is expressed weakly.

TABLE 1. Physicochemical Characteristics for the Compounds Prepared **2-6**

Compound	Empirical formula	Found N, % / Calculated N, %	mp., °C (Solvent for recrystallization)	Yield, % (method)
2a	$C_8H_5ClN_2O_4S$	11.02 / 10.74	307-309 (Heptane)	77 (A) 95 (B)
2b	$C_{10}H_9ClN_2O_4S$	9.51 / 9.70	146-14 (Hexane)	74
2c	$C_{14}H_{17}ClN_2O_4S$	7.83 / 8.12	96-97 (Benzene)	72
2d	$C_{16}H_{21}ClN_2O_4S$	7.80 / 7.51	84-85 (Chloroform)	67
3a	$C_8H_6N_2O_5S$	11.21 / 11.57	365-367 (Water)	95
3b	$C_{10}H_{10}N_2O_5S$	10.01 / 10.37	236-238 (Water)	91
3c	$C_{14}H_{18}N_2O_5S$	8.89 / 8.58	182-184 (Water)	96
3d	$C_{16}H_{22}N_2O_5S$	8.21 / 7.90	72–73 (Water)	91
4a	$C_8H_7N_3O_4S$	17.08 / 17.42	334-336 (Ethanol)	86
4b	$C_{10}H_{11}N_3O_4S$	15.87 / 15.61	270-271 (Aqueous ethanol)	96
4c	$C_{14}H_{19}N_3O_4S$	13.04 / 12.32	230-232 (Aqueous ethanol)	97
4d	$C_{16}H_{23}N_3O_4S$	11.67 / 11.89	206-208 (Aqueous ethanol)	95
5a	$C_{12}H_{15}N_3O_4S$	13.86 / 14.14	300-302 (Methanol)	80
5b	$C_{14}H_{19}N_3O_4S$	12.61 / 12.92	214-216 (Methanol)	87
5c	$C_{18}H_{27}N_3O_4S$	10.86 / 11.02	146-148 (Aqueous methanol)	92
5d	$C_{20}H_{31}N_3O_4S$	10.61 / 10.26	112-113 (Aqueous methanol)	89
5e	$C_{16}H_{23}N_3O_4S$	12.21 / 11.89	225-227 (Ethanol)	80
5f	$C_{18}H_{27}N_3O_4S$	10.77 / 11.02	138-140 (Aqueous ethanol)	97
5g	$C_{22}H_{35}N_3O_4S$	10.02 / 9.61	86-88 (Aqueous ethanol)	95
5h	$C_{24}H_{39}N_3O_4S$	8.74 / 9.03	82-83 (Aqueous ethanol)	79
6a	$C_{13}H_{15}N_3O_4S$	13.21 / 13.59	304-306 (Ethanol)	85
6b	$C_{15}H_{19}N_3O_4S$	12.09 / 12.46	246-248 (Aqueous ethanol)	89
6c	$C_{19}H_{27}N_3O_4S$	10.89 / 10.68	164-166 (Aqueous ethanol)	92
6d	$C_{21}H_{31}N_3O_4S$	10.28 / 9.97	138-140 (Benzene)	89
6e	$C_{12}H_{13}N_3O_5S$	13.82 / 13.50	302-303 (Ethanol)	87
6f	$C_{14}H_{17}N_3O_5S$	12.09 / 12.38	244-246 (Aqueous ethanol)	90
6g	$C_{18}H_{25}N_3O_5S$	10.21 / 10.63	142-144 (Aqueous ethanol)	96

The ^{1}H NMR spectra of compounds **2-6** (Table 2) also confirm the proposed structures. The quinazoline-2,4-dione ring region of the spectrum shows a doublet for proton H-5 at 8.25-8.47 ppm (^mJ = 2.3 Hz), a double doublet for protons H-7 at 7.80-7.93 ppm (^oJ = 8.8-9.2 and ^mJ = ~2.3 Hz), and a double

TABLE 2. Spectral Characteristics of Compounds **2-6**

Compound	IR spectrum, ν, cm^{-1}			^{1}H NMR spectrum, δ, ppm (*J*, Hz)							Mass-spectrum, $[M]^+$ *m/z* (I_{rel}, %)
	$\nu_{as}SO_2$	ν_sSO_2	$\nu_sS–O$	H-5 (1H, d)	H-7 (1H, dd)	H-8 (1H, d)	1-CH_3 (3H, s)	3-CH_3 (3H, s)			
2a	1370	1180	—	8.32 ($J_{5,7}$ = 2.3)	7.86 ($J_{7,8}$ = 9.2, $J_{7,5}$ = 2.3)	7.23 ($J_{8,7}$ = 9.2)	—	—	—	—	260 (37) (for ^{35}Cl)
2b	1375	1170	—	8.35 ($J_{5,7}$ = 2.3)	7.84 ($J_{7,8}$ = 9.2, $J_{7,5}$ = 2.3)	7.30 ($J_{8,7}$ = 9.2)	3.38	3.22	—	—	288 (42)
3a	1170	1150	700	8.34 ($J_{5,7}$ = 2.3)	7.89 ($J_{7,8}$ = 9.2, $J_{7,5}$ = 2.3)	7.26 ($J_{8,7}$ = 9.2)	—	—	—	—	242 (51)
3b	1180	1155	690	8.36 ($J_{5,7}$ = 2.3)	7.85 ($J_{7,8}$ = 9.2, $J_{7,5}$ =2.3)	7.28 ($J_{8,7}$ = 9.2)	3.37	3.20	—	—	270 (49)
4a	1390	1160	—	8.42 ($J_{5,7}$ = 2.3)	7.88 ($J_{7,8}$ = 9.2, $J_{7,5}$ = 2.3)	7.28 ($J_{8,7}$ = 9.2)	—	—	—	—	241 (100)
4b	1380	1170	—	8.47 ($J_{5,7}$ = 2.3)	7.93 ($J_{7,8}$ = 9.2, $J_{7,5}$ = 2.3)	7.20 ($J_{8,7}$ = 9.2)	3.36	3.20	—	—	269 (100)
5b	1330	1180	—	8.31 ($J_{5,7}$ = 2.3)	7.87 ($J_{7,8}$ = 8.8, $J_{7,5}$ = 2.3)	7.23 ($J_{8,7}$ = 8.8)	3.36	3.20	2.94 (4H, q, J = 6.7, CH_2–N–CH_2); 0.77 (6H, t, J = 6.9, $2CH_3$)	—	325 (38)
5f	1340	1170	—	8.32 ($J_{5,7}$ = 2.3)	7.86 ($J_{7,8}$ = 9.2, $J_{7,5}$ = 2.3)	7.22 ($J_{8,7}$ = 9.2)	3.36	3.21	2.86-2.89 (4H, t, J = 7.5, α-$2CH_2$); 1.15-1.89 (4H, dt, J_1 = 8.2, J_2 = 7.9, J_3 = 7.2, β-$2CH_2$); 0.87-0.93 (4H, tt, J_1 = 7.5, J_2 = 7.2, γ-$2CH_2$); 0.48 (6H, s, $2CH_3$)	—	381 (35)
6b	1350	1165	—	8.25 ($J_{5,7}$ = 2.3)	7.81 ($J_{7,8}$ = 8.8, $J_{7,5}$ = 2.3)	7.25 ($J_{8,7}$ = 8.8)	3.36	3.21	—	2.70-2.72 (4H, t, J = 5.6, α-CH_2); 1.24-1.27 (4H, dt, J_1 = 6.2, J_2 = 4.7, β-$2CH_2$) 1.08-1.09 (2H, br. d, γ-CH_2)	337 (41)
6f	1360	1170	—	8.28 ($J_{5,7}$ = 2.3)	7.80 ($J_{7,8}$ = 9.2, $J_{7,5}$ = 2.3)	7.26 ($J_{8,7}$ = 9.2)	3.37	3.21	—	3.57-3.60 (4H, t, J = 4.9, α-$2CH_2$); 2.82-2.85 (4H, t, J = 4.6, β-$2CH_2$)	339 (39)

for proton H-8 at 7.20-7.30 ppm (^{o}J = 8.8-9.2 Hz). The NH group protons are seen at low field (9.20-10.10 ppm). The protons of the 1,3-dialkyl and alkyl residues in the amide groups are seen at high field (0.46-3.57 ppm) (Table 2).

EXPERIMENTAL

The IR spectra of the compounds studied were obtained on a UR-20 spectrometer using vaseline oil. ^{1}H NMR spectra were taken on a UNITY 400^{+} instrument (400 MHz) using CD_3COOD and with TMS as internal standard. Mass spectra were registered on a Kratos MS-30 instrument with direct introduction of the sample into the ion source (ionization energy 70 eV). Monitoring of the reaction course and purity of the compounds prepared was carried out by TLC on Silufol UV-254 plates in a solvent system of benzene–acetone (10:1) and revealed using a solution of $KMnO_4$ (1 g), H_2SO_4 (4 ml), and water (96 ml).

The quinazoline-2,4-dione (**1a**) was prepared by cyclization of anthranilic acid with urea [14] and the symmetrical 1,3-dialkylquinazoline-2,4-diones **1b-d** by alkylation of compound **1a** with the corresponding alkyl halides under phase-transfer catalytic reaction conditions [15].

6-Chlorosulfonylquinazoline-2,4-dione (2a). A. Compound **1a** (1.62 g, 10 mmol) was added portionwise with stirring to chlorosulfonic acid (5.83 g, 50 mmol) cooled to 5-10ºC at such a rate that the reaction temperature did not exceed 15ºC.

The reaction mixture was heated to 50-60ºC, held at this temperature for 6 h, and poured into crushed ice. The precipitate formed was filtered off, washed with water, and recrystallized from heptane. Yield 2.0 g.

B. 2,4-Dioxoquinazoline-6-sulfonic acid (**3a)** (2.42 g, 10 mmol) was added portionwise to chlorosulfonic acid (2.33 g, 20 mmol) cooled to 0ºC at such a rate that the temperature did not exceed 10ºC. The mixture was heated to 50-60ºC, held at this temperature for 2 h, and poured onto crushed ice. The precipitate obtained was filtered off, washed with water, and recrystallized from heptane. Yield 2.47 g.

6-Chlorosulfonylquinazoline-2,4-diones 2b-d were prepared similarly.

2,4-Dioxoquinazoline-6-sulfonic Acid (3a). A mixture of compound **2a** (2.6 g, 10 mmol) in water (20 ml) was refluxed for 2 h and the solvent was partially distilled off. The precipitate obtained was filtered off and recrystallized from water. Yield 2.29 g.

2,4-Dioxoquinazoline-6-sulfonic Acids 3b-d were synthesized similarly.

6-Sulfonamidoquinazoline-2,4-dione (4a). A mixture of compound **2a** (2.6 g, 10 mmol) in concentrated ammonia (100 ml) was heated for 2 h with stirring and left overnight. The precipitate obtained was filtered off and recrystallized from ethanol. Yield 2.07 g.

6-Sulfonamidoquinazoline-2,4-diones 4b-d were prepared similarly (Table 1).

2,4-Dioxoquinazoline-6-sulfonic Acid N,N-diethylamide (5a). A mixture of diethylamine (0.73 g, 10 mmol) and triethylamine (1.01 g, 10 mmol) in acetone (15 ml) was added dropwise to a solution of compound **2a** (2.6 g, 10 mmol) in acetone (30 ml). The product was stirred at room temperature for 2 h, acetone evaporated off, and water (100 ml) was added to the residue. The precipitate obtained was filtered off and recrystallized from methanol. Yield 2.37 g.

2,4-Dioxoquinazoline-6-sulfonic Acid N,N-diethyl- and N,N-di-*n*-butylamides 5b-h were prepared similarly.

2,4-Dioxoquinazoline-2,4-sulfonic Acid N-piperidide (6a) was prepared similarly to compound **5a** from compound **2a** (2.6 g, 10 mmol), piperidine (0.85 g, 10 mmol), and triethylamine (1.01 g, 10 mmol). Yield 2.62 g.

2,4-Dioxoquinazoline-6-sulfonic Acid N-piperidide and N-morpholide 6b-h were synthesized similarly.

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