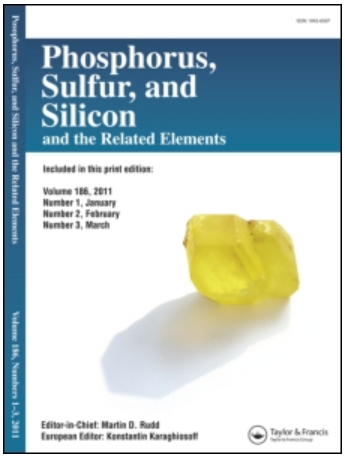

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Communication

REACTION OF CYCLOPROPYLBENZENE AND CYCLOPROPYL PHENYL KETONE WITH SULFUR TRIOXIDE[1–3]

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The sulfonation of cyclopropylbenzene (**1a**) and cyclopropyl phenyl ketone (**5**) with sulfur trioxide in both nitromethane and 1,4-dioxane as solvent has been studied. Sulfonation of cyclopropylbenzene (**1a**) with up to 2.0 mol-equiv. of SO_3 in dioxane leads to the initial formation of 3-phenyl-1,3-propanesultone (**2a**) which product subsequently slowly isomerizes to 3-phenyl-2-propene-1-sulfonic acid (**4a**). Sulfonation of **1a** with 4.0 mol-equiv. of SO_3 in nitromethane gives the corresponding 4-sulfo derivatives **2b** and **4b**, of which the former product also slowly isomerizes to give the latter. Reaction of cyclopropyl phenyl ketone (**5**) with SO_3 in nitromethane yields quantitatively 1-benzoyl-1,3-propanesultone (**6**). Upon aqueous alkaline work-up of the reaction mixtures, the γ-sultones **2a** and **6** are quantitatively converted into the corresponding potassium hydroxypropanesulfonates **3** and **7**, respectively. Mechanisms for the formation of the various products from the starting cyclopropyl substrates are proposed.

Key words: Sulfur trioxide sulfonation, cyclopropylbenzene, cyclopropyl phenyl ketone, γ-sultone, 1,2-oxathiolane dioxide, γ-hydroxypropanesulfonic acid, potassium γ-hydroxypropanesulfonate.

INTRODUCTION

Recently we have shown that the type of product formed on sulfonation of alkylidenecyclopropanes with sulfur trioxide depends on the substituents at the methylene carbon.[2,4] The products resulting from methylene- and cyclopropylidenecyclopropane are the corresponding 2-methylene-1,3-propanesultones, whereas diphenylmethylidene- and adamantylidene-cyclopropane afforded 1-(diphenylmethylidene)- and 1-adamantylidene-1,3-propanesultone, respectively. These observations, in combination with our general interest in aliphatic and aromatic sulfonation, prompted us to study the reaction of cyclopropylbenzene (**1a**) and cyclopropyl phenyl ketone (**5**) with SO_3 in the complex forming solvents 1,4-dioxane and nitromethane.

It has been established[5,6] that the SO_3 sulfonation of mixed aliphatic-aromatic ketones, typically aceto- and propiophenone, initially leads exclusively to aliphatic sulfonation at the α-carbon of the alkyl group, and only subsequently to sulfonation of the phenyl moiety. We have confirmed these observations for aceto-, propio-, and butyrophenone, for cyclopentyl and cyclohexyl phenyl ketone, for the 1-oxo derivatives of indane and 1,2,3,4-tetrahydronaphthalene,[7] and for 1,3-dioxo-indane.[7,8]

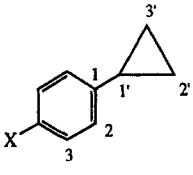
Levina and Shabarov have reported that reaction of cyclopropylbenzene (**1a**) with SO_3-pyridine, followed by aqueous alkaline work-up, gave 3-phenyl-2-propene-1-sulfonate in a yield of 65%.[9] Extensive studies on the reaction of cyclopropylbenzene with various electrophiles have shown that in general mainly *ortho* and *para* substitution of the phenyl group takes place, in addition to reactions in which the cyclopropyl moiety is involved.[10]

RESULTS AND DISCUSSION

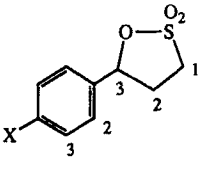
The sulfonation of cyclopropylbenzene (**1a**) and cyclopropyl phenyl ketone (**5**) has been studied, using SO_3 in either nitromethane or 1,4-dioxane as solvent. The results are collected in Table I.

Reaction of cyclopropylbenzene (**1a**) with 1.0 mol-equiv. of SO_3 in dioxane-d_8 gives 3-phenyl-1,3-propanesultone (**2a**) as the only product in a yield of 75%. Aqueous alkaline work-up of the reaction mixture containing the γ-sultone **2a** led to the quantitative conversion of **2a** into potassium 3-hydroxy-3-phenylpropane-1-sulfonate (**3**). On using 2.0 mol-equiv. of SO_3, **1a** is fully converted into the γ-sultone **2a**, which subsequently slowly isomerizes to give 3-phenyl-2-propene-1-sulfonic acid (**4a**), *i.e.* the product observed by Levina and Shabarov.[9]

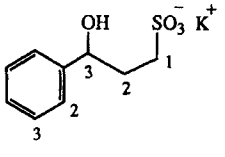
Upon performing the sulfonation of **1a** with 4.0 mol-equiv. of SO_3 in nitromethane-d_3 as solvent, the products are 3-(4-sulfophenyl)-1,3-propanesultone (**2b**) and 3-(4-sulfophenyl)-2-propene-1-sulfonic acid (**4b**), the latter resulting from the former by isomerization. The formation of 3-(4-sulfophenyl)-1,3-propanesultone (**2b**) from cyclopropylbenzene (**1a**) may proceed in two ways. First by initial sulfonation of cyclopropylbenzene at the *para* position to give cyclopropylbenzene-4-sulfonic acid (**1b**), followed by conversion of the cyclopropyl into the 1,3-propanesultone moiety, and second by initial conversion of **1a** into 3-phenyl-1,3-propanesultone (**2a**) and subsequent sulfonation of the phenyl at the *para* position. The observations of direct electrophilic phenyl substitution of cyclopropylbenzene on using various other electrophiles[10] indicate that the first sequence is at least of some importance.



1a X = H
1b X = SO_3H



2a X = H
2b X = SO_3H



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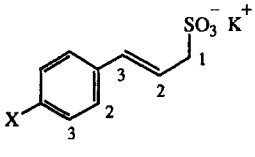
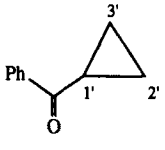


4a X = H
4b X = SO_3H



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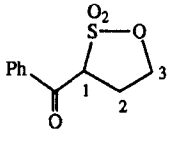

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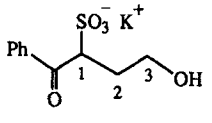

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TABLE I

Sulfonation of cyclopropylbenzene (**1a**) and cyclopropyl phenyl ketone (**5**) with SO_3

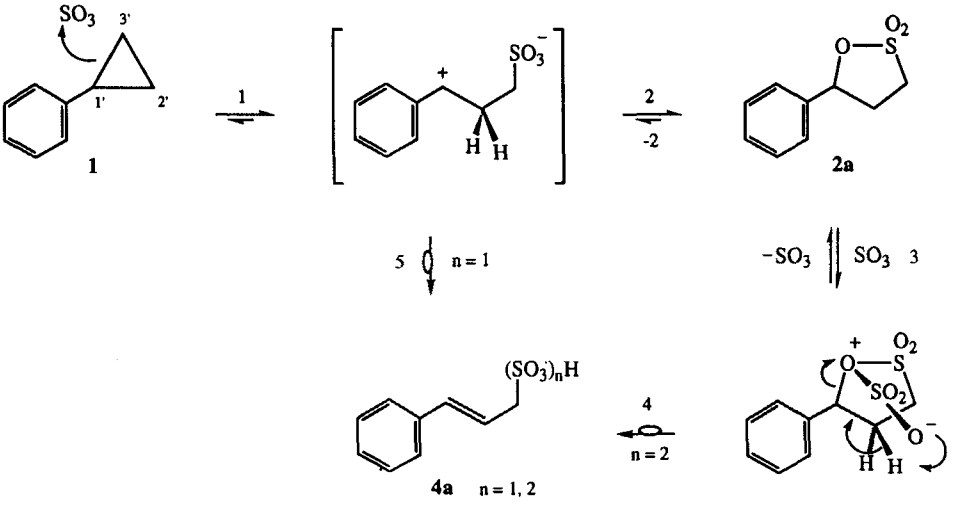
Substrate	SO_3 (mol-equiv. ± 0.1)	Solvent[a]	Temp. (°C)	React. time (min)	Reaction mixture composition (%, ± 2)						
					substrate	**2a**	**4a**	**2b**	**4b**	**6**	**7**
1a	1.0	D	15	10	43	57					
				25	33	67					
				215	27	73					
				1440	25	75					
	2.0	D	15	20	14	86					
				32	7	93					
				130	-	>98					
				1210		90	10				
				2600		84	16				
				18700		38	62				
1a	1.0	N	25	[b]							
	4.0	N	25	10[c]	-			70	20		
				70				45	45		
				150				15	75		
				340				8	86		
5	1.0	N	25	165	50					50	
				[d]	[e]						>98
	2.0	N	25	60	-					>98	

[a] D and N stand for dioxane-d_8 and nitromethane-d_3, respectively. [b] The making-up of the reaction mixture led to the formation of a precipitate, possibly containing (in part) *p*-sulfophenylcyclopropane. [c] In the homogeneous reaction mixture other products than those listed are present to an extent of ~10%. [d] Product mixture composition after aqueous alkaline work-up of the nitromethane reaction mixture using 1.0 mol-equiv. of SO_3. [e] Not determined.

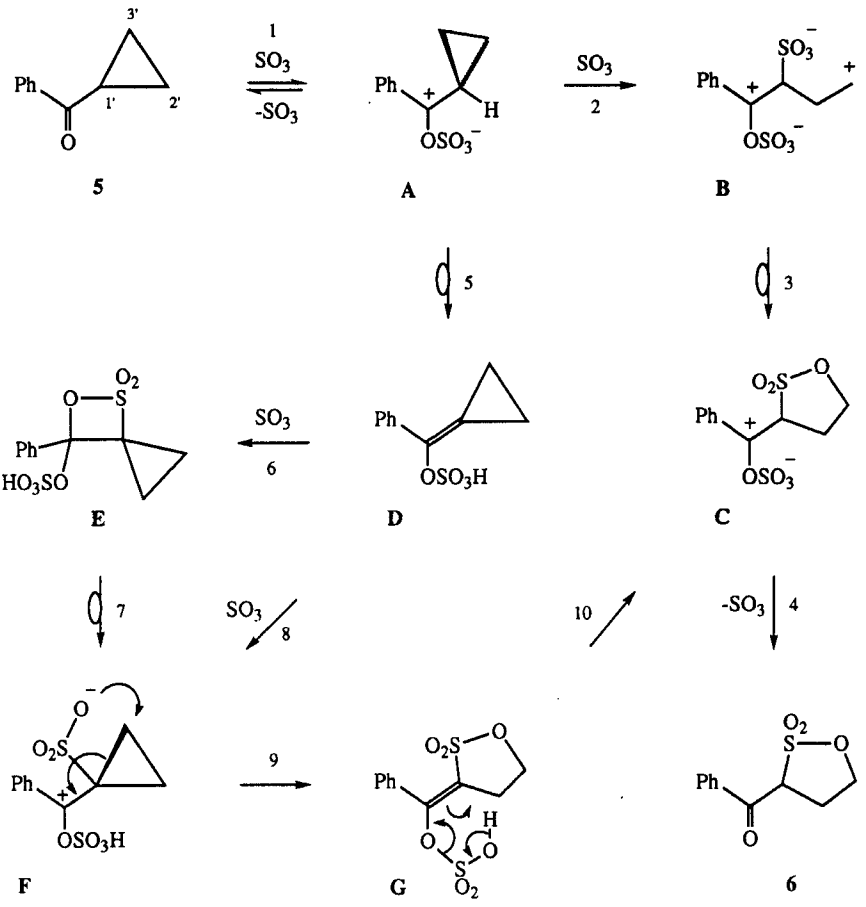
The absence of *ortho* sulfonation beyond the limit of detection, which is 2–3%, may be ascribed to steric hindrance between the cyclopropyl and sulfo groups in the σ-complex for *ortho* sulfonation. The conjugative stabilization of the σ-complexes leading to *ortho* and *para* substitution will be maximal when the cyclopropyl substituent is in the bisected conformation.[17] For the *ortho* sulfonation, because of steric hindrance with the incoming bulky sulfo group, tordation of the cyclopropyl group from the bisected orientation will occur. This will very significantly reduce the mesomeric conjugation between the cyclopropyl substituent and the cationic cyclohexadienyl structure in the transition state that leads to *ortho* sulfonation, and thus to a substantial reduction in the degree of *ortho* sulfonation.

The formation of 3-phenyl-1,3-propanesultone (**2a**) from cyclopropylbenzene (**1a**) may proceed (see Scheme I) by electrophilic attack[19] of the SO_3 sulfur at the cyclopropyl C(2′) or C(3′), with the ingrowing positive charge at the benzylic carbon being conjugatively stabilized by the adjacent phenyl group (step 1), followed by ring closure to give the γ-sultone **2a** (step 2). The subsequent slow conversion of **2a** into the isomeric unsaturated sulfonic acid **4a** may be explained in terms of SO_3 addition at the oxygen in the γ-sultone ring (step 3), followed by a synchronous rearrangement via a six-membered cyclic transition state, in which the O—C(3) and C(2)—H bonds are broken and the C(3)—C(2) π bond and the terminal O—H σ bond are formed (step 4). The alternative route for the isomerization of **2a** via the steps -2 and 5 is considered less likely, since the proton transfer then has to proceed via a five-membered ring type of transition state which generally is considered to be less attractive than via a six-membered cyclic transition state.

Sulfonation of cyclopropyl phenyl ketone (**5**) with 1.0 and 2.0 mol-equiv. of SO_3 in nitromethane-d_3 gives 1-benzoyl-1,3-propanesultone (**6**) in a yield of 50 and >98%, respectively.[20] These two observations may suggest that two moles of SO_3 are involved in the formation of the γ-sultone **6**. Upon aqueous alkaline work-up of the reaction mixture, the γ-sultone **6** was quantitatively converted into potassium



SCHEME I Mechanism of formation of 3-phenyl-1,3-propanesultone (**2a**) and 3-phenyl-2-propene-1-(pyro)sulfonic acid (**4a**, n = 1, 2) upon reaction of cyclopropylbenzene (**1a**) with SO_3 in dioxane.



SCHEME II Mechanism of formation of 1-benzoyl-1,3-propanesultone (**6**) upon reaction of cyclopropyl phenyl ketone (**5**) and SO_3 in nitromethane.

1-benzoyl-3-hydroxypropane-1-sulfonate (**7**).[21] The formation of the γ-sultone **6** from the cyclopropyl ketone **5** may be explained in two ways, as shown in Scheme II. The initial step in both cases is addition of SO_3 to the carbonyl oxygen with formation of complex **A** (step 1). Because of the positive charge of its carbonyl carbon, any direct addition of SO_3 to the cyclopropyl moiety of **A** will occur at C(1′) (step 2).[22] Ring closure of the resulting intermediate **B** (step 3) and subsequent loss of SO_3 (step 4) then afford the γ-sultone **6**. Alternatively, intramolecular proton transfer of the C(1′) hydrogen to one of the three sulfonate oxygens of **A** via a six-membered cyclic transition state may occur to give the (phenylmethylidene)cyclopropane hydrogen sulfate **D** (step 5). Electrophilic addition of another molecule of SO_3 to the carbon carbon double bond of **D** then will afford the dipolar species **F**, presumably via β-sultone **E** as intermediate (steps 6 and 7)[4,23] rather than by a one step monodentate type of addition (step 8). Subsequent intramolecular rearrangement of the species **F** may furnish the γ-sultone type of species **G**. Intramolecular proton transfer of **G** via a six-membered cyclic transition state (step

TABLE II

NMR data of cyclopropylbenzene (**1a**), cyclopropyl phenyl ketone (**5**) and their SO_3 sulfonation products

Compound	Solvent[a]	NMR	δ (ppm, ± 0.02)										
			C_3-moiety			phenyl						OH	CO
			1	2	3	1	2	3	4	5	6		
1a	D	^1H	2.10(m)	1.05(m)			<---------		7.25[c]		--------->		
2a	D	^1H	5.82	2.83	3.60		<---------		7.57(br.s)		--------->		
2b	N	^1H	5.80	2.80	3.55		7.75[d]	8.10[d]	-				
3	DMSO	^1H	4.50	1.90	2.40		<---------		7.08(br.s)		--------->	5.10	
4a	D	^1H	4.37	5.04	6.15				7.08(br.s)				
4b	D	^1H	4.10	4.80	6.00		7.90[e]	8.13[e]	-				
5	N	^1H	2.80(m)	1.10(m)			<--------		7.70[c]		-------->		
6	N	^1H	6.35	3.40	5.80				7.70[c]				
7	DMSO	^1H	4.75	2.11	3.22		8.00	<--------	7.51[c]	-------->			
	W	^{13}C	65.5	34.5	62.2	163.1							200.3

[a] D, N, DMSO and W stand for dioxane-d_8, nitromethane-d_3, DMSO-d_6 and D_2O, respectively. [b] δ relative to virtual TMS. [c] Centre of unresolved multiplet. [d,e] The $^3J_{H,H}$'s and $^4J_{H,H}$'s values are 7 - 8 and 1 - 2 Hz, respectively.

10) gives the dipolar complex **C**, which, upon loss of SO_3 (step 4), gives the actually observed product **6**.

EXPERIMENTAL

The applied chemicals were obtained commercially and used as such. The NMR spectra were recorded on Varian XL-100, and Bruker AC-200 and WM-250 spectrometers.

Sulfonation Procedures and Analysis

Method A. 0.5 ml of a solution of the substrate in the desired concentration in 1,4-dioxane-d_8 was added at 15°C under argon to a heterogeneous mixture of 0.5 ml of dioxane-d_8 and the appropriate amount of SO_3. A sample of the resulting homogeneous solution was then transferred into an NMR tube and ^1H NMR spectra were recorded after selected time intervals.

Method B. A solution of the desired amount of SO_3 in 0.5 ml of nitromethane-d_3 was added to a solution of 0.25 mmol of the substrate in 0.5 ml of nitromethane-d_3 at 25°C under an atmosphere of argon. A sample of the resulting homogeneous reaction mixture was then transferred into an NMR tube and ^1H and ^{13}C NMR spectra were recorded after selected time intervals, as appropriate.

Some of the sulfonation reaction mixtures were subjected to alkaline aqueous work-up. After the appropriate reaction time, 1.0 ml of H_2O or D_2O was added to the reaction mixture and the resulting mixture heated to 50°C for 30 min to hydrolyze the sultones. The aqueous layer was separated and extracted at room temperature three times with 1–2 ml of CH_2Cl_2 to remove any unconverted substrate and remaining solvent. Residual CH_2Cl_2 was removed by bubbling nitrogen through the aqueous solution for 30 min, which was then neutralized with dilute aqueous potassium hydroxide and the water removed by freeze drying. Subsequently, a ^1H NMR spectrum of the resulting potassium sulfonate mixture, dissolved in DMSO-d_6, was recorded for product analysis.

The structural assignments of the products of the SO_3 sulfonations were made on the basis of the observed NMR chemical shifts, absorption area ratios and coupling constants. The assignments are collected in Table II. The compositions of the sulfonation reaction mixtures and of the isolated sulfo product mixtures were determined by multicomponent ^1H NMR analysis on the basis of specific absorptions of the various components.[24]

ACKNOWLEDGEMENT

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20. Sulfonation of **5** does not take place upon using dioxane instead of nitromethane as solvent.
21. The structural assignment of **7** is based on ^{1}H and ^{13}C NMR (Table II), IR ($CHCl_3$, cm^{-1}): 3440 (OH), 1120 (SO_3^-), and MS (FAB^-) m/z: 243 ($M\text{-}K^-$).
22. The addition of SO_3 to the cyclopropyl moiety of cyclopropyl phenyl ketone (**5**) takes place preferentially at C(1′), because SO_3 addition at C(2′) or C(3′) would develop in the resulting intermediate a positive charge at C(1′), *i.e.* directly adjacent to the positive charge at the carbonyl carbon.
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