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The Sily-Durst Chlorination of Hydroxy Sulfoxides

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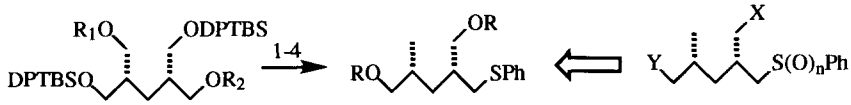
Abstract: *Treatment by sulfuryl chloride of the bis-O-TES derivative of a γ,ε-bis-hydroxy phenylsulfoxide resulted in the selective formation of the corresponding γ-chloro-ε-hydroxy phenylsulfone.* © 1997 Published by Elsevier Science Ltd.

In the course of an ongoing synthetic programme, we faced to the problem of preparing the chlorosulfone **1a** from the sulfide **2a**, a crystalline solid we obtained in fair yield (23%, overall) from the enantiomerically pure bis-acetate **3a**[1] by partial hydrolysis and hydrogenolysis of the hydroxy group in the ensuing monoacetate **3b** followed by exchange of the subsisting acetoxy group to a phenylthio residue, and, finally, desilylation of the resulting sulfide **2b**.



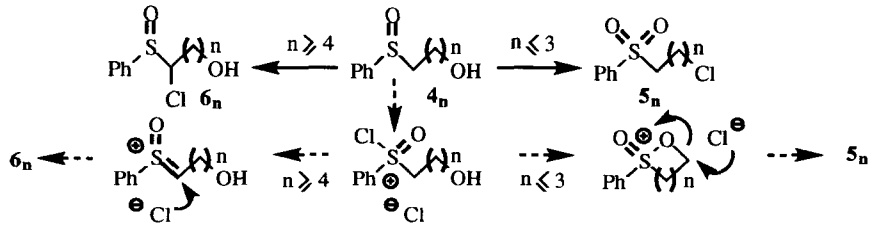
3a, R_1=R_2=Ac
3b, R_1=OH; R_2=Ac

2a, R=H
2b, R=DPTBS

1a, X=Cl; Y=OH; n=2
1b, X=OH; Y=Cl; n=2
1c, X=Y=Cl; n=2
1d, X=Y=OH; n=2
1e, X=Y=OH; n=1
1f, X=Y=OTES; n=1
1g, X=H; Y=OH; n=2

Reagents and Conditions: 1- K_2CO_3 (0.05 eq.), MeOH; -15 °C; 6 hours (39%); 2- *i*) Tosyl chloride (1eq.), DMAP (0.2 eq.), pyridine; 0 °C, 6 days (99%); *ii*)- PhSLi (2 eq.), DMF; r.t., 2 hours (72%); 3- *i*) reagent 1, *ii*) Ni-Raney (excess), EtOH; r.t., 6 hours (92%); 4- *i*) reagent 2; *ii*) TBAF (2..2 eq.), THF; r.t., 2 hours (89%).

Due to the close similarity of the hydroxy groups in the sulfide **2a**, the planned conversion of this sulfide into the sulfone **1a** was not a trivial task. To solve this problem, we went interested by an inviting Durst report on the reaction of hydroxyalkyl sulfoxides $\mathbf{4_n}$ with SO_2Cl_2.[2] As shown, depending on the distance between the remote hydroxy substituent and the sulfinyl group, the chlorination of sulfoxides $\mathbf{4_n}$ by sulfuryl chloride can give rise to the formation of either the chlorosulfones $\mathbf{5_n}$ or the α-chlorosulfoxides $\mathbf{6_n}$.



As suggested by Durst, that dichotomy in reactivity of sulfoxides $\mathbf{4_n}$ can be satisfactorily explained by assuming the initial formation of a chlorosulfoxonium cation. In that event, for the lower terms (n≤3), this ion can suffer an intramolecular, geometrically possible, nucleophilic displacement of the chlorine atom linked to the

sulfoxonium moiety by the hydroxy group to give an alcoxysulfonium, which, by nucleophilic attack of a chloride ion, delivers the observed chlorosulfone. For the higher terms (n≥4), participation of the remote hydroxy group is less favored and the preferred pathway is a Pummerer-like process, leading to an α-chlorosulfoxide.

Thus, it could be hoped that treatment by SO_2Cl_2 of the sulfoxide **1e**, obtained efficiently (96%) by $NaIO_4$ oxidation[3] of the sulfide **2a**, would result in the selective formation of the target chlorosulfone **1a**.

Slow addition of sulfuryl chloride to a 2.4 M solution of **1e** in CH_2Cl_2 at -78°C led to a mixture, which, by flash-chromatography (silica gel; hexane/AcOEt), afforded successively: *i*) the dichloro sulfone **1c**; *ii*) the tetrahydropyranyl derivative **7**; *iii*) the chlorosulfone **1a**; *iv*) the bis-hydroxy sulfone **1d** (Table 1, entry 1).[4,5]

Table 1: SO_2Cl_2 chlorination of sulfoxide **1e***

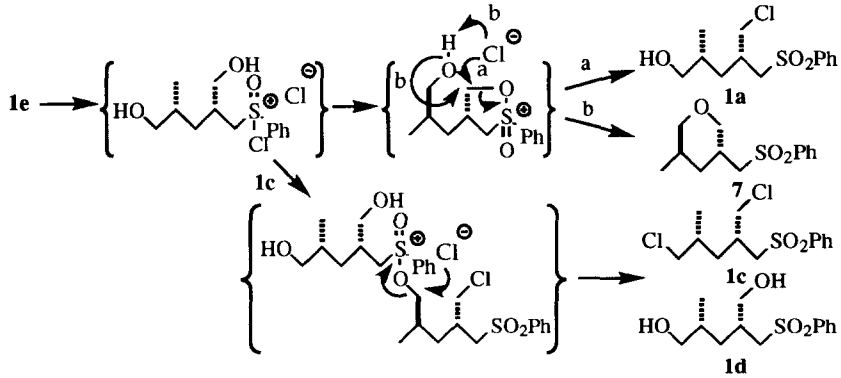
Entry	$[1e]_0$	Products (%)**			
		1a	**7**	**1c**	**1d**
1	2.4 M	10	44	23	23
2	0.14 M	34	66	traces	traces
3	0.005 M	30	70	0	0
4	0.11 M***	traces	80	10	10

* SO_2Cl_2 (1.2 eq.) added to **1e** as a diluted (ca 0.1M) CH_2Cl_2 solution

** ratio determined by NMR of the crude reaction product

*** with added $(n\text{-Hept})_4NCl$ (10 eq.)

Lowering the initial concentration of **1e** suppressed the formation of compounds **1c** and **1d** whereas the yield in sulfone **7** increased (entries 1-3, table 1). A plausible scenario, consonant with these results and homogeneous with Durst scheme (*vide supra*), is depicted below.



The initially-formed chlorosulfoxonium cation would evolute to a cyclic alcoxysulfoxonium species, which would react with a chloride ion, acting either as a base or a nucleophile, to give competitively the sulfone **7** and the chlorosulfone **1a**. Subsidiarily, nucleophilic attack of the chlorosulfone **1a** onto the former cationic species would led to both sulfones **1c** and **1d**.

Accordingly, the SO_2Cl_2 chlorination of **1e** was conducted in presence of tetrakis-N-heptylammonium chloride with the hope that the a pathway would be favoured, but, deceptively, adding SO_2Cl_2 to a CH_2Cl_2 solution of **1e** with excess $(Hept)_4NCl$ resulted in the almost-exclusive formation of the sulfone **7** (entry 4 of table 1).

We went then to consider that initial silylation of the two hydroxy groups in the sulfoxide **1e** could sterically hindered the undesirable participation of the more distant hydroxy without preventing the formation of the aforementionned cyclic alcoxysulfoxonium species but, obviously, it was safe to verify first that a γ-silyloxyalkyl sulfoxide would be transformed into the corresponding chlorosulfone by treatment with SO_2Cl_2.

Accordingly, a series of O-silyl derivatives -*i.e.* $\mathbf{7_n a\text{-}d}$ (n=2-4)- of the sulfoxides $\mathbf{4_n}$ were tested in the above chlorination conditions, the extraction process being followed by methanolysis of silyl protecting-groups.[6]

Table 2: $PhS(O)CH_2\text{-}(CH_2)_n\text{-}OR \xrightarrow[\text{then, MeOH/HCl}]{SO_2Cl_2,\ -78\ °C} PhSO_2\text{-}CH_2\text{-}(CH_2)_n\text{-}Cl + PhS(O)CH(Cl)\text{-}(CH_2)_n\text{-}OH$

$\mathbf{7_n a\text{-}d}$ $\mathbf{5_n}$ $\mathbf{6_n}$

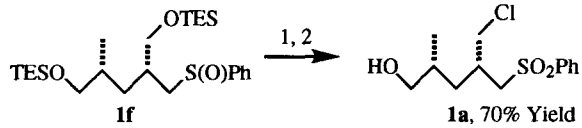
Starting sulfoxide	Product, Yield (%)*	
$\mathbf{4_2}$, n=2; R=H	$\mathbf{5_2}$, 96**	—
$\mathbf{7_2 a}$, n=2; R=TMS	" , 75	—
$\mathbf{7_2 b}$, n=2; R=TES	" , 76	—
$\mathbf{7_2 c}$, n=2; R=TBDMS	" , 73	—
$\mathbf{7_2 d}$, n=2; R=DPTBS	—	$\mathbf{6_2}$, 70
$\mathbf{4_3}$, n=3; R=H	$\mathbf{5_3}$, 88**	—
$\mathbf{7_3 b}$, n=3; R=TES	" , 78	—
$\mathbf{4_4}$, n=4; R=H	—	$\mathbf{6_4}$, 90**
$\mathbf{7_4 b}$, n=4; R=TES	—	" , 45***

* after methanolysis of the crude chlorination mixture and chromatography

** taken from ref. 2

*** decomposition products were also formed

As it can be seen (Table 2), excepted for the DPTBS derivative $\mathbf{7_2 d}$, the results obtained with these O-protected sulfoxides parallel that registered with the parent hydroxy sulfoxides. Subsequent treatment by SO_2Cl_2 of the bis-O-TES derivative of the sulfoxide **1a** (*i.e.* **1f**) in solvent and temperature conditions as above resulted, as expected, in the formation of the desired chlorosulfone **2a** in a satisfactory 70% yield, after purification.[7]



1f **1a**, 70% Yield

Reagents and conditions: 1- SO_2Cl_2 (1.2 eq.), CH_2Cl_2 (150 ml/mmol): -78 °C, 20 mn; 2- MeOH (40 ml/mmol), conc. HCl (1 drop); r.t., 12 hours.

In conclusion, O-silyloxyalkyl sulfoxides have been shown to react with SO_2Cl_2 likewise the corresponding hydroxyalkyl sulfoxides. A distinct advantage of that sily-Durst chlorination process, with respect to the original procedure, lies to the possibility to obtain, from the same sulfoxide, either a chlorosulfone or an α-chloro sulfoxide by selecting the appropriate silyl group (compare entries 2-4 and 5 of table 2). Moreover, it allowed to convert selectively the γ,ε-bis-hydroxy sulfide **2a** into the corresponding γ-chloro-ε-hydroxy sulfone **1a**, which was the major goal of this study.

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References and Notes

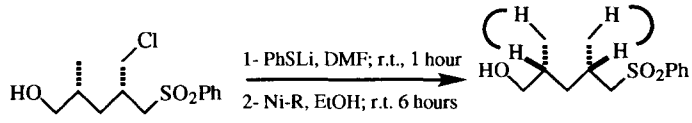
1- Breuilles, P.; Schmittberger, T.; Uguen, D. *Tetrahedron Lett.* **1993**, *34*, 4205-4208.

2- Durst, T.; Tin, K.- C.; Marcil, M. J. V. *Can. J. Chem.* **1973**, *51*, 1704-1712.

3- The sulfone **1d**, which also formed (ca 4%), was eliminated by column chromatography (hexane/AcOEt).

4- Selected data: **2a**: m. p. 69 °C; ^{1}H NMR: 0.86 (d, J=6.4 Hz, 3H), 1.1-1.3 (m, 1H), 1.45-1.65 (m, 1H), 1.73 (o, J=6.7 Hz, 1H); 1.91 (ht, J=6.4 Hz, 1H), 2.31 (m, 1H, O*H*), 2.54 (m, 1H, O*H*), 2.96 (d, J=6.2 Hz, 2H), 3.41 (d, J=6 Hz, 2H), 3.66 (d, J=5.1 Hz, 1H), 7.1-7.4 (m, 5H); ^{13}C NMR: 17.07, 32.99, 34.51, 35.77, 37.72, 65.22, 68.21, 126.11, 129.04, 129.26, 136.74; $[\alpha]_D$ +16 (c=1.3, CH_2Cl_2); **1a**: ^{1}H NMR: 0.87 (d, J=6.5 Hz, 3H), 1.3-1.5 (m, 1H), 1.5-1.7 (m, 2H), 2.47-2.65 (m, 1H), 3.17 (ddd (AB part of an ABX system), J_{AB}=14.4 Hz, J_{AX}=4.4 Hz, J_{BX}=7.2 Hz ($\Delta\nu$=63.9 Hz), 2H); 3.4-3.6 (m, 2H), 3.76 (ddd (AB part of an ABX system), J_{AB}=11.2 Hz, J_{AX}=4.1 Hz, J_{BX}=4 Hz ($\Delta\nu$=35.2 Hz), 2H), 7.55-7.75 (m, 3H), 7.9-8 (m, 2H); ^{13}C NMR: 17.02, 32.79, 33.16, 36.02, 48.38, 57.32, 67.53, 127.92, 129.54, 134.01, 139.62; $[\alpha]_D$ +14 (c=0.1, CH_2Cl_2); **1b**: ^{1}H NMR: 0.92 (d, J=6.6 Hz, 3H), 1.22-1.4 (m, 1H), 1.5-1.69 (m, 1H), 1.72-1.9 (m, 1H), 2.15-2.4 (m, 1H + O*H*), 3.15 (ddd (AB part of an ABX system), J_{AB}=14.3 Hz, J_{AX}=3.9 Hz, J_{BX}=7.9 Hz ($\Delta\nu$=57.3 Hz), 2H), 3.39 (d, J=5.5 Hz, 2H), 3.74 (ddd (AB part of an ABX system), J_{AB}=11.2 Hz, J_{AX}=5.1 Hz, J_{BX}=4.4 Hz ($\Delta\nu$=46.9 Hz), 2H), 7.5-7.75 (m, 3H), 7.9-8 (m, 2H); ^{13}C: 17.86, 32.93, 33.83, 35.93, 50.77, 57.33, 64.48, 127.92, 129.52, 133.98, 139.63; $[\alpha]_D$ +11 (c=1, CH_2Cl_2); **1c**: ^{1}H NMR: 0.95 (d, J=6.5 Hz, 3H), 1.3-1.5 (m, 1H), 1.5-1.65 (m, 2H), 1.7-1.9 (m, 1H), 2.45-2.6 (m, 1H), 3.16 (ddd (AB part of an ABX system), J_{AB}=14.5 Hz, J_{AX}=3.3 Hz, J_{BX}=8 Hz ($\Delta\nu$=71.4 Hz), 2H), 3.41 (d, J=5.4 Hz, 2H), 3.78 (ddd (AB part of an ABX system), J_{AB}=11.2 Hz, J_{AX}=3.6 Hz, J_{BX}=4.1 Hz ($\Delta\nu$=41.2 Hz), 2H), 7.55-7.75 (m, 3H), 7.9-8 (m, 2H); ^{13}C NMR: 18, 32.76, 32.92, 36.56, 48.16, 50.4, 56.97, 127.96, 129.59, 133.98, 139.52; **1d**: ^{1}H NMR: 0.8 (d, J=6.4 Hz, 3H), 1.15-1.3 (m, 1H), 1.5-1.7 (m, 2H), 2.15-2.4 (m, 1H), 2.45- (m, 1H, O*H*), 2.8 (m, 1H, O*H*), 3.15 (ddd (AB part of an ABX system), J_{AB}=14.3 Hz, J_{AX}=4.8 Hz, J_{BX}=7 Hz ($\Delta\nu$=56.5 Hz), 2H), 3.32-3.55 (m, 2H), 3.68 (ddd (AB part of an ABX system), J_{AB}=11.2 Hz, J_{AX}=5.6 Hz, J_{BX}=4.6 Hz ($\Delta\nu$=45.4 Hz), 2H), 7.5-7.7 (m, 3H), 7.85-7.95 (m, 2H); ^{13}C NMR: 16.97, 32.92, 33.89, 35.22, 57.48, 64.69, 67.65, 127.88, 129.49, 133.92, 139.68; $[\alpha]_D$ +13 (c=0.4, CH_2Cl_2); **7**: ^{1}H NMR: 0.81 (d, J=6.4 Hz, 3H), 1.35-1.5 (m, 1H), 1.6-1.85 (m, 2H), 2.35-2.46 (m, 1H), 2.95-3.1 (m, 1H), 3.24 (ddd (AB part of an ABX system), J_{AB}=14.2 Hz, J_{AX}=5.5 Hz, J_{BX}=6.9 Hz ($\Delta\nu$=47.6 Hz), 2H), 3.55-3.67 (m, 1H), 3.6-3.8 (m, 2H), 7.55-7.75 (m, 3H), 7.9-8 (m, 2H); ^{13}C NMR: 17.17, 26.68, 29.17, 36.53, 57.8, 70.95, 74.61, 127.89, 129.46, 133.82, 139.64. All NMR spectra have been recorded on $CDCl_3$ solutions. $[\alpha]_D$ values have been measured at 21 °C.

5- Clear distinction between structures **1a** and **1b** was not straightforward. Unambiguous structure assignement was secured as follows: sequential treatment of the chlorosulfone **1a** with LiSPh and Raney nickel afforded the sulfone **1g**, the structure of which was established by irradiation (^{1}H NMR) of the (CH_3)-C*H* protons, which resulted, in each case, in the decoupling of only one doublet, corresponding to the protons of the adjacent methyl group, in the ^{1}H NMR spectra.



1a **1g**

6- The small amount of sulfone **7** (ca 10%), which still formed, was easily eliminated by flash-chromatography on silica gel (hexane/AcOEt). On a larger scale (5-10 g), trace amount of the isomeric chlorosulfone **1b** was detected (NMR).

7- O-silyl derivatives $\mathbf{7_n}$ and **1f** were prepared (Yields in the range 90-100%) by stirring a few hours, at 0-10 °C, the corresponding sulfoxide with the appropriate trialkylsilyl chloride (1.1 eq.) in CH_2Cl_2, in presence of triethylamine (1.2 eq.) and DMAP (0.2 eq.), the work-up consisting in the evaporation of solvents, followed by filtration of the residue on a short column of silica gel (AcOEt).

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