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A NEW AND CONVENIENT REDUCTION OF CEPHALOSPORIN SULPHOXIDES

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Abstract: A new, convenient and good yield reduction of cephalosporin S(β)-sulphoxides to the corresponding sulphides was achieved upon treatment with iodotrimethylsilane (TMSI) in dichloromethane.

Cephalosporin S(β)-sulphoxides (**1**) are very useful and widely used intermediates in synthesizing novel derivatives of these important antibacterial agents. However, to regain the

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biological activity of these compounds reduction of the sulphoxide moiety is necessary in every cases.

Of the several reduction methods available the PBr_3-method[1] and the AcCl-KI-method[2] are the most often chosen ones. Unfortunately, these reductions must be carried out in N,N-dimethylformamide or N,N-dimethylacetamide solutions. The yields are extremely dependant upon the dryness and purity of the solvents. However, it is very cumbersome to prepare good quality of these solvents.

Hence iodotrimethylsilane, an already known reducing agent was selected for our experiments. The reduction is carried out in easily available abs. dichloromethane and the reaction time is not too much longer than those of the other methods. Though a watereal work-up also cannot be avoided but it is much easier to handle with a dichloromethane solution than with DMF what is soluble in water.

Our results are summarized in the Table. The reactions were allowed to proceed for only an hour (see Experimental) in each case because longer reaction times resulted in decomposition of the cephalosporin β-lactam skeleton. Despite the

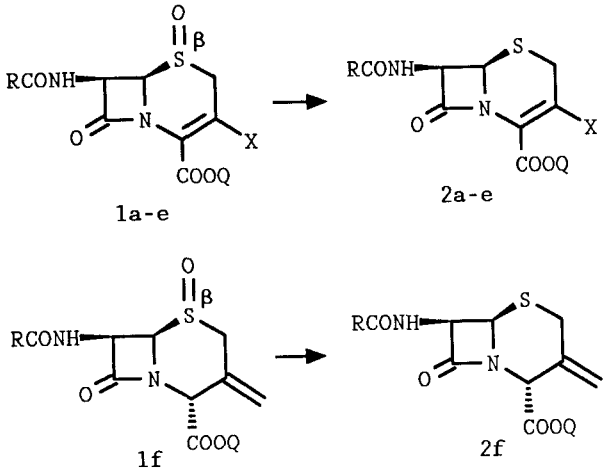

Table: Reduction of cephalosporin sulphoxides with TMSI

(2)	R	Q	X	Yield (%)*
a	$PhCH_2$	CH_3	CH_2OAc	65
b	$PhOCH_2$	CH_3	CH_2OAc	75
c	$PhCH_2$	CH_2CCl_3	CH_3	72
d	$PhCH_2O$	pNO_2-C_6H_4	CH_3	81
e	$PhCH_2$	pNO_2-C_6H_4	Cl	77
f	$PhOCH_2$	pNO_2-C_6H_4	-	68

*c.a. 80 % conversions were achieved. The yields are calculated for recovered starting material.

reported deacylation of acetoxymethylcephalosporins with TMSI under the same reaction conditions[3,4] we could also achieve the reduction of these derivatives (**1a, 1b**) when only 1.2 equivalents of the reagent was used. Only traces of the iodomethyl products were detected by TLC. Hence the affinity of the sulphoxide dipol towards TMSI is superior to that of the acetoxy side chain. Use of benzhydryl and p-methoxybenzyl esters are not preferred.[3] Other protecting and functional groups are virtually not affected by the reagent.

In summary, we have developed a new, convenient and good yield reduction method for cephalosporin S(β)-sulphoxides in dichloromethane solutions. As most of the protecting and finctional groups are not affected by the reagent the method is generally applicable.

EXPERIMENTAL

The infrared spectra were recorded in potassium bromide discs with a Perkin Elmer 283B instrument. The ^{1}H NMR spectra were recorded at 200 MHz on a Bruker VD 200SY spectrometer in deuteriochloroform with tetramethylsilane as

internal standard. For TLS purposes Merck DC Alurolle Kieselgel 60F 254 was used (UV light, ammonium molybdate/heat visualization). For column chromatography Kieselgel 60 silica gel was used.

General procedure for the reduction of cephalosporin sulphoxides with iodotrimethylsilane:

The cephalosporin sulphoxide (1 mmol) was dissolved in abs. dichloromethane (20 ml). TMSI (1.2 eq., 1.2 mmol, 300 mg, 214 µl) was added in one portion under an atmosphere of nitrogen. The reaction mixture was vigorously stirred for an hour at room temperature. Then the reaction mixture was diluted with dichloromethane (100 ml) and extracted with saturated $Na_2S_2O_3$ solution (3x100 ml), 10 % $NaHCO_3$ solution (100 ml) and brine (100 ml). The organic phase was dried over anhydrous $MgSO_4$. The solvent was then removed and the residue column chromatographed. The products were identified by TLC, IR and ^1H NMR when compared with authentic samples.

Compound 2a: R_f= 0.66 (30 % hexane in ethyl acetate); -IR(cm^{-1}): 1784, 1738, 1716, 1654, 1530,

1384, 1266, 1248, 1234; -^{1}H NMR(δ): 2.08 (s, 3H, Ac), 3.3 (d, 1H, J=17 Hz, 2-CH_2), 3.52 (d, 1H, J=17 Hz, 2-CH_2), 3.6 (d, 1H, J=10 Hz, 7-CH_2), 3.7 (d, 1H, J=10 Hz, 7-CH_2), 3.85 (s, 3H, OCH_3), 4.8 (d, 1H, J=12.5 Hz, CH_2O), 4.95 (d, 1H, J=5 Hz, H6), 5.05 (d, 1H, J=12.5 Hz, CH_2O), 5.85 (dd, 1H, J_1=5 Hz, J_2=9.5 Hz, H7), 6.08 (d, 1H, J=9.5 Hz, NH), 7.3 (m, 5H, aromatic).

Compound 2b: R_f=0.68 (30 % hexane in ethyl acetate); -IR(cm^{-1}): 1770, 1720, 1688, 1598, 1525, 1490, 1435, 1375, 1240, 1225, 750; -^{1}H NMR(δ): 2.1 (s, 3H, Ac), 3.35 (d, 1H, J=18.5 Hz, 2-CH_2), 3.6 (d, 1H, J=18.5 Hz, 2-CH_2), 3.9 (s, 3H, OCH_3), 4.55 (s, 2H, 7-CH_2), 4.85 (d, 1H, J=12.5 Hz, CH_2O), 5.03 (d, 1H, J=5 Hz, H6), 5.1 (d, 1H, J=12.5 Hz, CH_2O), 5.9 (dd, 1H, J_1=5 Hz, J_2= 10 Hz, H7), 6.9 - 7.4 (m, 6H, NH + aromatic).

Compound 2c: R_f=0.79 (30 % hexane in ethyl acetate); -IR(cm^{-1}): 1770, 1738, 1732, 1674, 1652, 1538, 1382, 1214, 1154, 1108; -^{1}H NMR(δ): 2.15 (s, 3H, CH_3), 3.2 (d, 1H, J=20 Hz, 2-CH_2), 3.48 (d, 1H, J=20 Hz, 2-CH_2), 3.6 (s, 2H, 7-CH_2), 4.78 (d, 1H, J=10 Hz, OCH_2), 4.9 (m, 3H, H6 + OCH_2), 5.78 (dd,

1H, J_1=5 Hz, J_2=9 Hz, H7), 6.75 (d, 1H, J=9 Hz, NH), 7.3 (m, 5H, aromatic).

Compound 2d: R_f=0.61 (50 % hexane in ethyl acetate); -IR(cm^{-1}): 1775, 1724, 1632, 1607, 1521, 1455, 1384, 1348, 1244, 1109, 1050; -^{1}H NMR(δ): 2.15 (s, 3H, CH_3), 3.23 (d, 1H, J=15.5 Hz, 2-CH_2), 3.55 (d, 1H, J=15.5 Hz, 2-CH_2), 4.98 (d, 1H, J=5 Hz, H6), 5.15 (s, 2H, 7-CH_2), 5.27 (d, 1H, J=11 Hz, OCH_2), 5.39 (d, 1H, J=11 Hz, OCH_2), 5.7 (m, 2H, H7 + NH), 7.25 - 8.3 (m, 9H, aromatic).

Compound 2e: R_f=0.58 (50 % hexane in ethyl acetate); -IR(cm^{-1}): 1772, 1724, 1654, 1610, 1524, 1494, 1388, 1346, 1318, 1280, 1254, 1230, 1174, 1164, 1114, 1092; -^{1}H NMR(δ): 3.48 (d, 1H, J=17.5 Hz, 2-CH_2), 3.63 (s, 2H, 7-CH_2), 3.8 (d, 1H, J=17.5 Hz, 2-CH_2), 5.0 (d, 1H, J=5 Hz, H6), 5.35 (d, 1H, J=10 Hz, OCH_2), 5.4 (d, 1H, J=10 Hz, OCH_2), 5.85 (dd, 1H, J_1=5 Hz, J_2=9 Hz, H7), 6.4 (d, 1H, J=9 Hz, NH), 7.2 - 8.3 (m, 9H, aromatic).

Compound 2f: R_f=0.54 (40 % hexane in ethyl acetate); -IR(cm^{-1}): 1774, 1747, 1688, 1601, 1521, 1495, 1374, 1349, 1323, 1231, 1178, 756, 737; -^{1}H

NMR(δ): 3.2 (d, 1H, J=15 Hz, 2-CH_2), 3.65 (d, 1H, J=15 Hz, 2-CH_2), 4.53 (s, 2H, 7-CH_2), 5.35 (m, 5H, H4 + $=CH_2$ + OCH_2), 5.43 (d, 1H, J=5 Hz, H6), 5.78 (dd, 1H, J_1=5 Hz, J_2=10 Hz, H7), 6.9 - 8.3 (m, 9H, aromatic).

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