A Practical Method for Synthesis of Penicillin and Cephalosporin Sulfoxides

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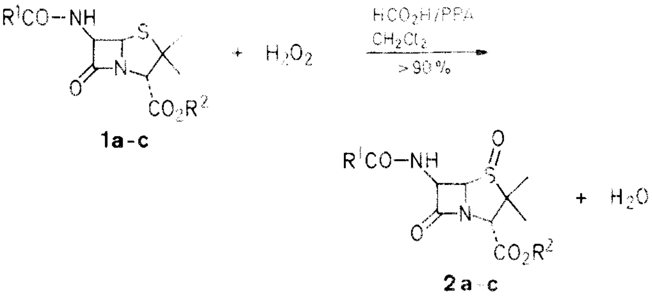
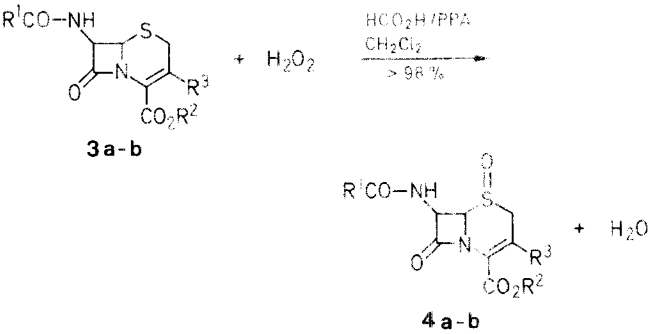
Penicillin and cephalosporin esters **1** and **3** are oxidized to the corresponding sulfoxides **2** and **4** by a safe and inexpensive method using a reagent mixture of hydrogen peroxide (35%), formic acid, and polyphosphoric acid.

For the industrial production of 1-oxacephalosporins[1] and 3-nor-type cephalosporins[2] possessing characteristic and marked antibacterial activity, we needed a safe and inexpensive method for the oxidation of penicillin esters to the corresponding sulfoxides. They are also key intermediates for production of 3-methylcephalosporins by ring expansion.[3] Of a number of known methods[4] for the synthesis of penicillin and cephalosporin sulfoxides, hydrogen peroxide oxidation in the presence of excess formic or acetic acid in dichloromethane[4] was most attractive.

Thus, penicillin diphenylmethyl esters **1a–b** were subjected to oxidation according to the method of Micetich et al.[4] However, the required sulfoxides **2a–b** were obtained in unsatisfactory yields, the most likely causes of which are the requirement of highly acid conditions and a long reaction time at room temperature for complete oxidation (Table 1, entries 1, 2, and 7). Apparently, decomposition of the sensitive substrates **1a–b** and formation of further oxidized sulfones occurred.

It was thought that decomposition of the substrates could be avoided by activating the oxidant, hydrogen peroxide. In such an attempt, a dehydrating agent such as acetic anhydride, an acid chloride, magnesium sulfate, or a phosphorus agent was added to the reaction mixture in order to remove water generated from hydrogen peroxide and hence increase the concentration of the oxidant. Among the additives employed, the most striking acceleration of oxidation was found with a mixture of polyphosphoric acid (116T)[5] and formic acid (Table 1, entries 3 and 8). In the corresponding reaction with acetic acid, cleavage of the substrates predominated (Table 1, entries 5 and 9). Maximization of the conditions in this oxidation method using formic and polyphosphoric acids resulted in drastic reduction of the molar ratio of reagents, especially formic acid (from 3 to 0.78 molar equivalent) and polyphosphoric acid (from 1 to 0.27 molar equivalent) (Table 1, entries 6 and 10). Thus, sulfoxides **2a–b** can be safely and inexpensively produced on industrial scale by oxidizing **1a–b** with a reagent mixture of hydrogen peroxide (35%), formic acid (88–95%), and polyphosphoric acid (116T) in a molar ratio of 1.05 : 0.78 : 0.27 in dichloromethane at 0–25 °C for 3–4 hours.[6] Similarly, penicillin ester **1c** and cephalosporin esters **3a–b** were oxidized to the corresponding sulfoxides **2c** and **4a–b** in essentially quantitative yields (Table 1, entries 11–13).





Substrate	Product	R¹	R²	R³
1a	**2a**	4-$CH_3C_6H_4$	$CHPh_2$	–
1b	**2b**	$PhCH_2$	$CHPh_2$	–
1c	**2c**	$PhOCH_2$	4-$O_2NC_6H_4CH_2$	–
3a	**4a**	$PhCH_2$	$CHPh_2$	H
3b	**4b**	4-$CH_3C_6H_4$	$CHPh_2$	CH_2OAc

Table 1. Syntheses of Sulfoxides **2** and **4**

Entry	Product	Acid	Molar Ratio Substrate/H_2O_2/Acid/PPA	Volume[a] CH_2Cl_2 (mL)	Conditions: Temp. (°C)/Time (h)	Yield[b] (%)
1	**2a**	AcOH	1 : 1.2 : 4 : 0	20	20–25/17	83
2	**2a**	HCO_2H	1 : 1.2 : 3 : 0	20	20–25/6	71
3	**2a**	HCO_2H	1 : 1.2 : 3 : 1	20	20–25/0.5	80
4	**2a**	HCO_2H	1 : 1.2 : 0 : 1	20	20–25/5	2
5	**2a**	AcOH	1 : 1.2 : 4 : 1	20	20–25/6	15
6	**2a**	HCO_2H	1 : 1.05 : 0.78 : 0.27	7	0–25/4	93
7	**2b**	HCO_2H	1 : 1.2 : 3 : 0	7	20–25/6	70
8	**2b**	HCO_2H	1 : 1.2 : 3 : 1	20	20–25/0.5	91
9	**2b**	AcOH	1 : 1.2 : 3 : 1	7	20–25/3	52
10	**2b**	HCO_2H	1 : 1.05 : 0.78 : 0.27	7	0–5/4	94
11	**2c**	HCO_2H	1 : 1.05 : 0.78 : 0.27	7	0–5/3	96
12	**4a**	HCO_2H	1 : 1.05 : 0.78 : 0.27	7	0–5/3	98
13	**4b**	HCO_2H	1 : 1.05 : 0.78 : 0.27	7	0–5/3	98

[a] Volume based on the substrate weight (1.0 g).
[b] Yield of isolated crystalline product

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Table 2. Penicillin Sulfoxides **2** and Cephalosporin Sulfoxides **4** Prepared

Product[a]	mp (°C)[b]		Molecular Formula[c]	^{1}H-NMR (TMS)[d] δ, J(Hz)
	found	reported		
2a	177–179		$C_{29}H_{28}N_2O_5S$ (516.6)	($CDCl_3$) 0.94 (s, 3H); 1.72 (s, 3H); 2.39 (s, 3H); 4.82 (s, 1H); 5.10 (d, 1H, J = 4.6); 6.30 (dd, 1H, J = 4.6, 10.2); 7.01 (s, 1H); 7.2–7.7 (m, 14H); 7.82 (br d, 1H, J = 10.2)
2b	146–148	146[7]	$C_{29}H_{28}N_2O_5S$ (516.6)	($CDCl_3$) 0.87 (s, 3H); 1.65 (s, 3H); 3.56, 3.59 (ABq, 2H, J = 15.6); 4.72 (s, 1H); 4.94 (d, 1H, J = 4.6); 6.04 (dd, 1H, J = 4.6, 10.4); 6.98 (s, 1H); 7.07 (br d, 1H, J = 10.4); 7.2–7.4 (m, 15H)
2c	180–181	180–181[8]	$C_{23}H_{23}N_3O_8S$ (501.5)	($CDCl_3$) 1.16 (s, 3H); 1.72 (s, 3H); 4.55 (s, 2H); 4.74 (s, 1H); 5.05 (d, 1H, J = 4.8); 5.31, 5.35 (ABq, 2H, J = 10.6); 6.12 (dd, 1H, J = 4.8, 10.6); 6.9–8.3 (m, 9H); 8.25 (br d, 1H, J = 10.6)
4a	203–204		$C_{28}H_{24}N_2O_5S$ (500.6)	(DMSO-d_6) 3.57, 3.70 (ABq, 2H, J = 14); 3.61, 3.95 (ABq, d, 2H, J = 19, 6.4, 2.2, 1.4[e]); 4.89 (dd, 1H, J = 4.8, 1.4[e]); 5.89 (dd, 1H, J = 8.4, 4.8); 6.56 (dd, 1H, J = 6.4, 2.2); 6.95 (s, 1H); 7.2–7.6 (m, 15H); 8.45 (d, 1H, J = 8.4)
4b	184–185		$C_{30}H_{28}N_2O_7S$ (560.6)	($CDCl_3$) 2.03 (s, 3H); 2.41 (s, 3H); 3.27, 3.85 (ABq, 2H, J = 18.8, 1.4[e]); 4.59 (dd, 1H, J = 4.8, 1.4[e]); 4.77, 5.33 (ABq, 2H, J = 14.2); 6.36 (dd, 1H, J = 9.8, 4.8); 6.98 (s, 1H); 7.35 (br d, 1H, J = 9.8); 7.2–7.7 (m, 14H)

[a] Recrystallized from MeOH.
[b] Uncorrected, measured with a Yanagimoto micro melting point apparatus.
[c] Satisfactory microanalyses obtained: C ± 0.4, H ± 0.2, N ± 0.2, S ± 0.2.
[d] Recorded on a Varian VXR-200 spectrometer.
[e] Long range coupling.

Replacement of polyphosphoric acid by phosphoric acid (85%) in the above method was effective for enhancement of the reactivity, but the yields of sulfoxides were lower. Decomposition of the substrates predominated in the absence of formic acid (Table 1, entry 4). These results lead to the conclusion that the significance of polyphosphoric acid is to make the reaction medium appropriately more acidic and facilitate formation of performic acid, which is the actual oxidant.

Preparation of Sulfoxides 2a–c and 4a, b; General Procedure:

To viscous polyphosphoric acid (116T) (5.4 mmol) are added a cooled solution (0°C) of **1a–c** or **3a, b** (20 mmol) in CH_2Cl_2 (70–200 mL), 35% aq. H_2O_2 (21 mmol), and 95% formic acid (15.6 mmol). The mixture is stirred for 3–4 hours at 0–5°C until oxidation is complete (TLC: Kieselgel 60 F_{254}, Merck, developed with benzene/EtOAc, 2:1 or 1:1). The organic layer is washed with an aq. solution containing 2.8% $NaHCO_3$, 1.7% $NaHSO_3$, and a small amount of n-$Bu_4N^+Br^-$ and then with water, and the solvent is evaporated *in vacuo* to give **2a–c** or **4a, b** as a crystalline or syrupy product. The crude sulfoxide thus obtained, when recrystallized from MeOH or i-PrOH, is sufficiently pure for subsequent reactions.

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