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Selective Oxidation of Penicillin Derivatives to Penicillin (1R) and (1S)-Sulfoxides using Dimethyldioxirane

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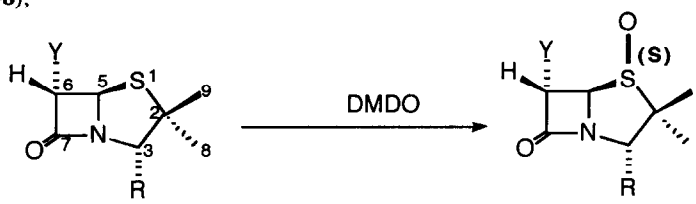
Abstract: We describe a convenient procedure for preparing (1R)-6,6-dihalo-, 6β-halo-penicillanates, 6,6-dihalopenam derivatives and (1S)-6-α-halopenicillanates sulfoxides by dimethyldioxirane asymmetric oxidation of the corresponding penicillanates and penam derivatives This method is characterized by mild reactions conditions, short reaction times, excellent selectivity, very high yield, ease of reaction workup and complete avoidance of overoxidation products

Enantiomerically pure (1R) and (1S)-penicillin sulfoxides having β-carbons bearing hydrogens can undergo thermal rearrangement via a concerted pseudopericyclic process to sulfenic acids that have been widely exploited to trap either intermolecularly for the preparation of 3-methyl or 3-exomethylene cephalosporin nucleus[1] or intramolecularly with heteroaromatic thiols for preparing 2-halomethyl-penams derivatives.[2] These modified cephalosporins and penicillins have already proved to be key intermediates in the manufacture of therapeutically important cephalosporin antibiotics,[3] and 2-β-triazolylmethylpenicillanic acids, as β-lactamase inhibitors.[4]

We have found that the oxidation of (pivaloyloxy)methyl (Pom) 6,6-dihalo- and the 6-β-halopenicillanates using *m*-chloroperbenzoic acid (*m*-CPBA) afforded the pure (R)-sulfoxides isomers [5] We also had reported that 6,6-dibromo-3α-cyano-2,2-dimethylpenam reacts with oxone in aqueous methanol to give the corresponding pure (1R)-sulfoxide in good yield.[6] In these cases the oxidation occured at the sterically more accesible α-face of the penam nucleus, while with the Pom 6-α-halopenicillanates and 6,6-dihydropenicillanate, the reaction with *m*-CPBA proceeded with a remarkable degree of stereocontrol producing the (1S)-sulfoxides [5]

Now, we wish to report a mild, facile and high-yielding method for the preparation of diastereomerically pure (R) and (S) sulfoxides of a series of 6,6-dihalo- and 6-halo-penicillanates and other penam derivatives using 2,2-dimethyldioxirane (DMDO).[7] In terms of operational simplicity and efficiency, this approach offers significant advantages over existing methods for the oxidation of penicillin derivatives with non-6-β-acylamido

substituents. The stereospecificity of the reaction is illustrated by the conversion of penicillanates (**I-4**) into the (1S)-sulfoxides (**5-8**),[8]



1	Y=Br R=-$CH_2C_6H_5$	**5**
2	Y=Cl R=-$CH_2C_6H_5$	**6**
3	Y=F R=-$CH_2C_6H_5$	**7**
4	Y=F R=-$CH_2OCOC(CH_3)_3$	**8**

and penicillanates (**9-14**), 6,6-dibromopenicillanic acid (**15**) and 6,6-dibromo-3α-hydroxymethyl-2,2-dimethylpenam (**16**) into the corresponding (1R) sulfoxides (**17-24**).

9	X=Br	Y=H	R=-$CO_2CH_2C_6H_5$	**17**
10	X=F	Y=H	R=-$CO_2CH_2C_6H_5$	**18**
11	X=Br	Y=F	R=-$CO_2CH_2C_6H_5$	**19**
12	X=Br	Y=Br	R=-$CO_2CH_2C_6H_5$	**20**
13	X=Br	Y=Br	R=-$CO_2CH_2OCOC(CH_3)_3$	**21**
14	X=Br	Y=Br	R=-$CO_2CH(C_6H_5)_2$	**22**
15	X=Br	Y=Br	R=-CO_2H	**23**
16	X=Br	Y=Br	R=-CH_2OH	**24**

The yield for these transformations was quantitative and the enantiomeric purities were 100%, as determined by ^1H NMR. The absolute configuration of (1R) and (1S) penicillin sulfoxides has been adequately established by ^{13}C NMR chemical shifts correlations [5,9] Table 1 summarizes ^{13}C NMR spectra.

The following is a typical procedure for the preparation of benzyl 6,6-dibromo penicillanate 1(R)-sulfoxide (**20**) A solution of DMDO (0 08 M sol in acetone, 1 8 mL, 0 144 mmol) was added to a stirred solution of benzyl 6,6-dibromopenicillanate (**12**) (43 mg., 0.096 mmol) in dry dichloromethane (4 mL) at room

temperature, under nitrogen. The reaction was completed within 10 minutes (monitored by TLC). After that, solvent was evaporated to yield the title compound (**20**)[5] (44.5 mg., 100%), as a colourless solid.

Table 1. ^{13}C NMR chemical shifts of penicillin sulfoxides.[a]

Compound	C-2	C-3	C-5	C-6	C-7	C-8	C-9
5	73.9	65.1	78 9	38 6	165.8	17.8	19.5
6	73.5	65.1	79.1	53.3	165.3	17.9	19.6
7	73.9	64.7	76.8	89.5	164 2	17.9	19.4
8	73.8	64.6	76.9	89.6	164.2	17.9	19.2
17	70.7	66.1	79.9	42.9	165.7	16.0	24.1
18	69.4	65 2	79.0	91.5	166 0	15.6	23.9
19	72.7	66.6	91.0	98 5	160.3	16.7	24.5
20	72.2	66 6	92.6	47 6	162.0	16.6	24.5
21	72 0	66.2	92.4	47.5	162.1	16.6	24 3
22	72 3	66 6	92.5	47 6	162.0	16.4	24.6
23[b]	73.4	67.6	89.9	51.0	166.7	19.7	26.8
24	73.8	60.3	97.3	48.8	163.7	17.6	24.3

a) Shifts in ppm downfield from internal TMS in $CDCl_3$ b) in DMSO-d_6

The mechanism of these oxidation has not been established at present. To explain the high degree of diastereoselectivity of these reactions we have taken into account the nature of the C-6 halogen substituents and the stereochemistry at sulfur in the conformation of penam nucleus. As is shown in compounds **1**, **2** and **9** they are attacked by DMDO exclusively from the opposite orientation (α or β) of the bulky C-6 substituents. Interestingly, 6-α-fluoropenicillanates (**3**) and (**4**) also give the corresponding 1(S)-sulfoxides even though there is not a significant steric effect It is possible that an intramolecular polar directing effect of the fluorine atom can explain this result. An electrostatic effect of a polar substituent can favor a transition state leading to the isomer with the sulfoxide and the polar substituent in a trans relationship. It has been reported that this effect can influence the stereochemistry of the olefin-peracid reaction.[10] A similar explanation can be used in the case of the synthesis of benzyl 6-β-fluoropenicillanate (1R)-sulfoxide (**18**). Experimental results in 6,6-dibromopenicillanates (**12-14**) and 6,6-dibromopenicillanic acid (**15**), as well as, in 6,6-dibromo-3α-hydroxymethyl-2,2-dimethylpenam (**16**), shows that steric effects predominate giving the 1(R)-sulfoxides exclusively, as a result of the attack on the less hindered face. The possibility of a 1,3-diaxial electrostatic

interaction between the C-6 substituents in the β-orientation and the oxygen atom of the β-sulfoxide, which may favor the transition state leading to the α-sulfoxides, can not be ruled out.

In summary, the oxidation of penicillin sulfides with non-6-β-acylamido substituents[11] have several outstanding characteristics. (a) yields are quantitative; (b) the oxidation is stereospecific and mild, yielding only sulfoxides but no sulfones; (c) the reaction is complete within a few minutes, (d) the procedure is very simple and the isolation of penicillin sulfoxides can be carried out readily

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