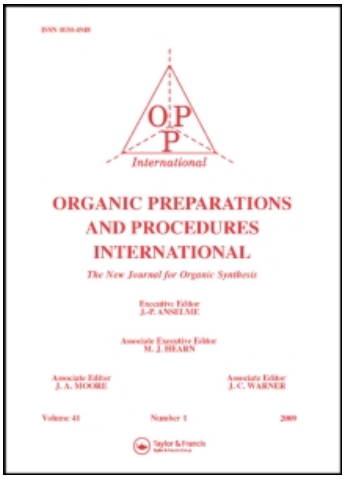

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TRANSFORMATION OF 6-HALOPENICILLANATES INTO 3-HALO-4-OXOAZETIDINE DERIVATIVES

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TRANSFORMATION OF 6-HALOPENICILLANATES INTO 3-HALO-4-OXOAZETIDINE DERIVATIVES

Submitted by Irena Lukić
(04/27/99)

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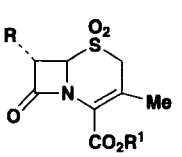
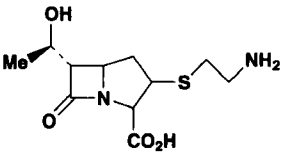
Azetidin-2-ones are of interest as precursors for the elaboration of new β-lactam analogues **A**[1] or for the stereocontrolled synthesis of thienamycin **B**.[2] Since readily obtained[3] penicillanic acid 1,1-dioxides may be degraded to azetidin-2-ones by reaction with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN),[4] we became interested in studying this reaction with 6,6-dibromo- and 6-bromopenicillanate 1,1-dioxides **1, 4** and **5** as substrates.

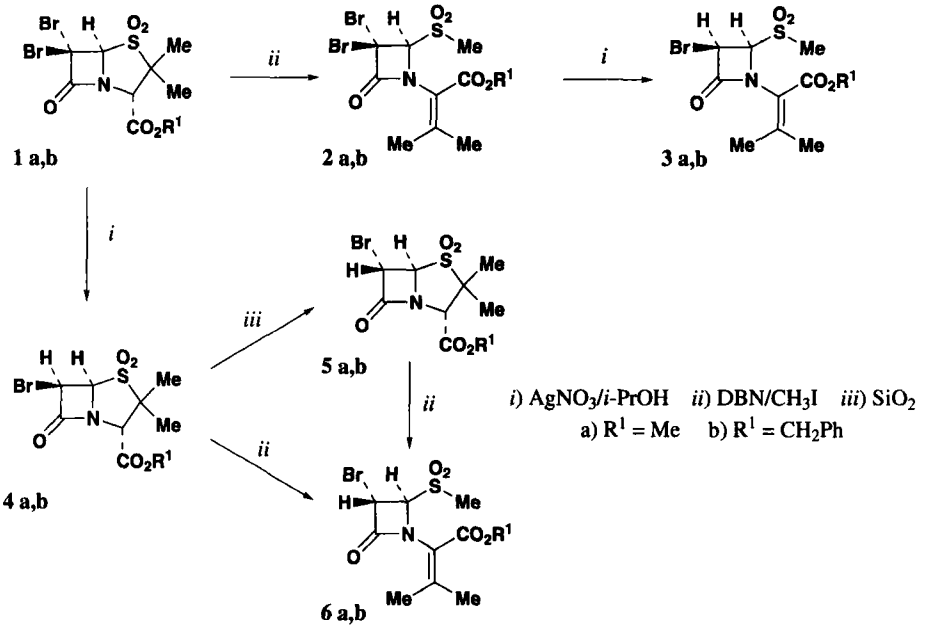


A



B

Reaction of 6, 6-dibromopenicillanate 1,1-dioxides (**1**) with DBN and iodomethane afforded esters of 2-[(2*R*)-3,3-dibromo-2-methanesulfonyl-4-oxo-azetidin-1-yl]-3-methyl-but-2-enoic acid (**2**). Under the same reaction conditions, 6α-bromopenicillanate 1,1-dioxides (**5**) were converted into esters of 2-[(2*R*,3*S*)-3-bromo-2-methanesulfonyl-4-oxo-azetidin-1-yl]-3-methyl-but-2-enoic acid (**6**). However, starting from 6β-bromopenicillanate 1,1-dioxides (**4**), the preparation of 2-[(2*R*,3*R*)-3-bromo-2-methanesulfonyl-4-oxo-azetidin-1-yl]-3-methyl-but-2-enoic acid (**3**) failed; instead of product **3**, again esters of 2-[(2*R*,3*S*)-3-bromo-2-methanesulfonyl-4-oxo-azetidin-1-yl]-3-methyl-but-2-enoic acid (**6**) were isolated. Evidently, inversion of configuration in the reaction of the 6β-bromopenicillanate 1,1-dioxide with DBN and iodomethane occurred; epimerization at the C-6 position of 6-phenylacetamidopenicillanate 1,1-dioxide in the presence of a trace of DBN had been previously noted.[4]



Scheme 1

There are several methods described for the hydrodehalogenation which could be applied for the preparation of 2-[(2*R*, 3*R*)-3-bromo-2-methanesulfonyl-4-oxo-azetidin-1-yl]-3-methyl-but-2-enoic acid derivatives. Hydrogenolysis of carbon-bromine bond with expensive tin hydride[5] leads to large amounts of organotin residues which can be difficult to remove cleanly from reaction mixtures. On the other hand, palladium-catalyzed hydrogenolysis[6] suffers from the drawback, that two competing reactions could occurr, namely cleavage of the ester group (*e. g.* benzyl or allyl) and of the carbon-bromine bond; moreover it requires relatively large amounts of expensive catalysts due to deactivation by the penicillin sulfide group. In addition, both of these procedures lead to the mixtures of completely and partially dehalogenated products in our case and in the example cited. 2-[(2*R*,*R*,3*R*)-3-

Bromo-2-methanesulfonyl-4-oxo-azetidin-1-yl]-3-methyl-2-but-2-enoic acid derivatives (**3**) were obtained stereoselectively by a method reported for the preparation 6β-bromopenicillanic acid 1,1-dioxides,[7] involving treatment of 2-[(2*R*)-3,3-dibromo-2-methanesulfonyl-4-oxo-azetidin-1-yl]-3-methyl-but-2-enoic acid esters (**2**) with silver nitrate or zinc chloride in 2-propanol. This reaction confirmed that the method could be applied not only to bicyclic systems such as penicillanates but also to azetidin-2-ones. The structures of new compounds were assigned using ^{1}H NMR on the basis of coupling constants differences.[8] The structure of 2-[(2*R*,33*S*)-3-bromo-2-methanesulfonyl-4-oxo-azetidin-1-yl]-3-methyl-2-but-2-enoic acid methyl ester was assigned to compound **6a** since its spectrum contains two two doublets (δ 5.11 and 5.21, J = 1.8 Hz) typical for 2-H and 3-H protons. For compound **6b**, the characteristic coupling was missing and only one singlet for the 2-H and 3-H protons appeared at δ 5.05. Missing of characteristic coupling was also observed for compounds **3a** and **3b**. Compound **3a** spectrum contains only one singlet for 2-H and 3-H protons at δ 5.21, and for compound **3b** at δ 5.14, respectively. Characteristic coupling for compounds **3a**, **3b** and **6b** (Table 1) was achieved by taking ^{1}H NMR spectra in DMSO-d_6. Compounds **3a** and **3b** showed two doublets at δ 5.52 and 5.87 (J = 5.2 Hz) and at δ 5.53 and 5.84 (J = 5.2 Hz) respectively, which is characteristic for a *cis* configuration. According to the obtained results these compounds were identified as the methyl and benzyl esters of 2-[(2*R*,3*R*)-3-bromo-2-methanesulfonyl-4-oxo-azetidin-1-yl]-3-methyl-2-butenoic acid. Compound **6b** also showed two doublets at δ 5.45 and 5.64 (J = 1.8 Hz) and the structure of 2-[(2*R*,3*S*)-3-bromo-2-methanesulfonyl-4-oxo-azetidin-1-yl]-3-methyl-2-butenoic acid benzyl ester could be assigned.

TABLE 1. ^{1}H NMR Data for 3-Halo-4-Oxoazetidine Derivatives

Compd	R^1	2-H	3-H	OCH_2Ph	OCH_3
2a	CH_3	5.54			3.82
2b	CH_2Ph	5.36		5.12 and 5.37	
3a	CH_3	5.21 5.52 (J = 5.2)[a]	5.21 5.87 (J = 5.2)[a]		3.81 3.74[a]
3b	CH_2Ph	5.14 5.53 (J = 5.2)[a]	5.14 5.84 (J = 5.2)[a]	5.12 and 5.33 5.24[a]	
6a	CH_3	5.11, (J = 1.8)	5.21 (J = 1.8)		3.84
6b	CH_2Ph	5.05 5.45 (J = 1.8)[a]	5.05 5.64 (J = 1.8)[a]	5.14 and 5.37 5.25[a]	

a) DMSO-d_6

In conclusion, new derivatives of 2-[(2*R*)-3,3-dibromo-2-methanesulfonyl-4-oxo-azetidin-1-yl]-, and 2-[(2*R*,3*R*)-3-bromo-2-methanesulfonyl-4-oxo-azetidin-1-yl]-, and 2-[(2*R*,3*S*)-3-bromo-2-methanesulfonyl-4-oxo-azetidin-1-yl]-3-methyl-2-but-2-enoic acid were prepared. Furthermore, 2-[(2*R*,3*R*)-3-bromo-2-methanesulfonyl-4-oxo-azetidin-1-yl]-3-methyl-2-but-2-enoic acid derivatives were prepared by hydrodehalogenation whose stereoselectivity was established. It was shown to be

applicable not only to bicyclic systems such as penicillanates, but also to azetidin-2-ones. This method complements other procedures to prepare the desired azetidin-2-ones.

EXPERIMENTAL SECTION

Melting points were determined on a Fisher micro melting apparatus and are uncorrected. The IR spectra were recorded in KBr pellets or in methylene chloride solution on a Perkin Elmer Infracord 257 and are reported in wavelengths followed by relative intensities in brackets. The ^{1}H NMR spectra were recorded in $CDCl_3$ unless otherwise stated, with tetramethylsilane (TMS) as internal standard, on a JEOL FX 90 Q spectrometer and all chemical shifts are given in ppm downfield from TMS. TLC was performed on precoated Silicagel 60 F_{254} plates (Merck) and the spots were visualized using UV lamp or iodine vapor.

2-[(2*R*)-3,3-Dibromo-2-methanesulfonyl-4-oxo-azetidin-1-yl]-3-methyl-but-2-enoic acid Methyl Ester (2a).- To a solution of methyl ester of 6,6-dibromopenicillanic acid 1,1-dioxide (**1a**) (1.62 g, 0.004 mol), in methylene chloride (20 mL) was added DBN (0.66 mL, 0.0055 mol) and the solution was stirred at room temperature for 30 min. Iodomethane (2.5 mL; 0.04 mol) was added and the solution was stirred at room temperature for 2 h. The reaction mixture was washed with 1N hydrochloric acid and brine and the separated organic layer was dried ($MgSO_4$), filtered and evaporated. Crude reaction product was crystallized from a mixture of methylene chloride and diisopropylether to yield product (1.01 g; 78%) mp. 161-164°. Spectroscopic data correspond to described data.[1]

Anal. Calcd. for $C_{10}H_{13}Br_2NO_5S$: C, 28.66; H, 3.13; N, : 3.34; S, 7.65

Found: C, 28.56; H, 3.18; N:, 3.42; S, 7.83

2-[(2*R*)-3,3-Dibromo-2-methanesulfonyl-4-oxo-azetidin-1-yl]-3-methyl-but-2-enoic acid Benzyl Ester (2b).- To a solution of benzyl ester of 6,6-dibromopenicillanic acid l,l-dioxide (**1b**) (4.81 g, 0.01 mol) in methylene chloride (50 mL) was added DBN (1.65 mL, 0.0138 mol) and the solution was stirred at room temperature for 15 min. Iodomethane (6.25 mL, 0.10 mol) was added and the solution was stirred at room temperature for 24 h. The reaction solution was washed with 1N hydrochloric acid and brine and the organic layer was dried ($MgSO_4$), filtered and evaporated to give a dark residue, which was purified by column chromatography on silica gel 60 (Merck 0.063-0.200 mm) with benzene-acetone (95:5) as eluent to yield (2.2 g; 44%) oily colorless product. This crude product was crystallized from 2-propanol to give 1.98 g (40%), mp. 80-82°; R_f = 0.51 [benzene-acetone (95:5)]. IR (CH_2Cl_2): 1800 (vs), 1725 (s), 1215 (s), 690 (vs) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.12 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.81 (s, 3H, SO_2CH_3), 5.36 (s, 1H, 2-H), 5.12 and 5.37 (each 1H, d, *J* = 12 Hz, CH_2Ph) and 7.38 (5H, Ar).

Anal. Calcd. for $C_{16}H_{17}Br_2NO_5S$: C, 38.81; H, 3.46; N, : 2.83; S, 6.47

Found: C, 38.65; H, 3.50; N, : 2.73; S, 6.28

2-[(2*R*,3*R*)-3-Bromo-2-methanesulfonyl-4-oxo-azetidin-1-yl]-3-methyl-but-2-enoic acid Methyl Ester (3a).- To a solution of 2-[(2*R*)-3,3-dibromo-2-methanesulfonyl-4-oxo-azetidin-1-yl]-3-methyl-but-2-enoic acid methyl ester (**2a**) (0.104g, 0.25 mmol) in 2-propanol (5 mL) was added silver nitrate

(0.17 g, 1 mmol) and the reaction mixture refluxed for 30 min. The reaction mixture was cooled, precipitate filtered and the filtrate evaporated. Crude product was chromatographed on a column of silica gel 60 (Merck 0.063-0.200 mm) with methylene chloride-ethyl acetate (2:1) as eluent to yield oily product (0.063 g; 75%). R_f =0.63 [methylene chloride-ethyl acetate (2:1)]; IR (CH_2Cl_2): 1795 (vs), 1735 (s), 1700 (s), 1360 (s), 1330 (vs), 1215 (s), 1145 (vs) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.15 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 3.01 (s, 3H, SO_2CH_3), 3.81 (s, 3H, OCH_3), 5.27 (s, 2H, 2-H and 3-H). ^1H NMR (DMSO-d_6): δ 2.01 (s, 3H, CH_3) 2.19 (s, 3H, CH_3), 3.07 (s, 3H, SO_2CH_3), 3.74 (s, 3H, OCH_3), 5.52 and 5.87 (each 1H, d, J = 5.2 Hz, 2-H and 3-H).

Anal. Calcd. for $C_{10}H_{14}BrNO_5S$: C, 35.31; H, 4.15; N, 4.12; S, 9.42
Found: C, 35.19; H, 4.30; N, 4.07; S, 9.59

The product with identical spectroscopic data was also obtained according to the following procedure: To a solution of 2-[(2*R*)-3,3-dibromo-2-methanesulfonyl-4-oxo-azetidin-1-yl]-3-methyl-but-2-enoic acid methyl ester (**2a**) (0.104 g, 0.25 mmol) in 2-propanol (5 mL), was added zinc chloride (0.136 g; 1mmol) and the mixture refluxed for 4 h. Then reaction mixture was cooled, precipitate filtered and the filtrate evaporated. The crude reaction product was chromatographed on a column of silica gel 60 (Merck 0.063-0.200 mm) with methylene chloride-ethyl acetate (2:1) as eluent to yield oil (0.060 g; 72%).

2-[(2*R*,3*R*)-3-Bromo-2-methanesulfonyl-4-oxo-azetidin-1-yl]-3-methyl-but-2-enoic acid Benzyl Ester (3b).- To a solution of 2-[(2*R*)-3,3-dibromo-2-methanesulfonyl-4-oxo-azetidin-1-yl]-3-methyl-but-2-enoic acid benzyl ester (**2b**) (0.495g, 0.001 mol) in 2-propanol (20 mL) was added silver nitrate (0.676 g, 0.004 mol) and the reacton mixture was refluxed for 30 min. The reaction mixture was cooled, precipitate filtered and the filtrate evaporated. Crude residue was chromatographed on a column of silica gel 60 (Merck 0.063-0.200 mm) with benzene-acetone (95:5) as eluent to yield colorless oily product (0.333 g; 80%); R_f =0.35 [benzene-acetone (95:5)]. IR (100%): 1790 (vs), 1725 (s), 1700 (s), 1620 (m), 1480 (s), 1360 (s), 1335 (vs), 1290 (vs), 1215 (vs) 1150 (s), 680 (vs) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.14 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 2.84 (s, 3H, SO_2CH_3), 5.14 (s, 2H, 2-H and 3-H), 5.12 and 5.33 (each lH, d, J =12 Hz, CH_2Ph) and 7.36 (5H, Ar). ^1H NMR (DMSO-d_6): δ 2.01 (s, 3H, CH_3), 2.18 (s, 3H, CH_3), 3.05 (s, 3H, SO_2CH_3), 5.24 (s, 2H, CH_2Ph), 5.53 and 5.84 (each 1H, d, J = 5.2 Hz, 2-H and 3-H) and 7.39 (5H, Ar).

Anal. Calcd. for $C_{16}H_{18}BrNO_5S$: C, 46.16; H, 4.36; N, 3.36; S, 7.70
Found: C, 46.28; H, 4.30; N, 3.42; S, 7.92

2-[(2*R*,3*S*)-3-Bromo-2-methanesulfonyl-4-oxo-azetidin-1-yl]-3-methyl-but-2-enoic acid Methyl Ester (6a).- To a solution of methyl ester of 6α-bromopenicillanic acid 1,1-dioxide (**5a**) (1.63 g; 0.005 mol) in methylene chloride (30 mL) was added DBN (1 mL; 0.0084 mol) and the solution was stirred at room temperature for 15 min. Iodomethane (1.55 mL, 0.025 mol) was added and the solution was stirred at room temperature till the reaction ended (monitored by TLC). The reaction mixture was diluted with methylene chloride, washed with 1N hydrochloric acid and brine. The separated organic layer was dried ($MgSO_4$), filtered and evaporated to dryness to yield foam (1.12 g; 65.8%). R_f

=0.77 [methylene chloride-ethyl acetate (2:1)]; IR (CH_2Cl_2): 1795 (vs), 1735 (s), 1700 (s), 1360 (s), 1330 (vs), 1215 (s), 1145 (vs) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.10 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 2.91 (s, 3H, SO_2CH_3), 3.83 (s, 3H, OCH_3), 5.11 and 5.21 (each lH, d, J = 1.8 Hz, 2-H and 3-H).

Anal. Calcd. for $C_{10}H_{14}Br\ rNO_5S$: C, 35.31; H, 4.15; N,: 4.12; S, 9.42

Found: C, 35.19; H, 4.30; N,: 4.07; S, 9.59

2-[(2*R*,3*S*)-3-Bromo-2-methanesulfonyl-4-oxo-azetidin-1-yl]-3-methyl-but-2-enoic acid Benzyl Ester (6b).- To a solution of benzyl ester of 6β-bromopenicillanic acid 1,1-dioxide (**4b**) (3.22 g, 0.008 mol) in methylene chloride (40 mL) was added DBN (1.3 mL, 0.0108 mol) and the solution stirred at room temperature for 15 minutes. Iodomethane (5.0 mL; 0.08 mol) was added and the solution was stirred at room temperature for 8 h. The reaction mixture was washed with 1N hydrochloric acid and brine, and the separated organic layer was dried ($MgSO_4$), filtered and evaporated to yield colorless oily product (3.27 g; 98.3%). This crude residue was chromatographed on a column of silica gel 60 (Merck 0.063-0.200 mm) with benzene-acetone (95:5) as eluent. Rf =0.42 [benzene-acetone (95:5). IR (100%): 1795 (vs), 1725 (s), 1630 (m), 1360 (s), 1330 (vs), 1215 (vs), 1145 (vs), 965 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.09 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.69 (s, 3H, SO_2CH_3), 5.05 (s, 2H, 2-H and 3-H), 5.14 and 5.37 (each 1H, d, J = 12 Hz, CH_2Ph) and 7.39 (5H, Ar). ^1H NMR (DMSO-d_6): δ 1.98 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 3.12 (s, 3H, SO_2CH_3), 5.25 (s, 2H, CH_2Ph), 5.45 and 5.64 (each 1H, d, J = 1.8 Hz, 2-H and 3-H), and 7.40 (5H, Ar).

Anal. Calcd. for $C_{16}H_{18}BrNO_5S$: C, 46.16; H, 4.36; N,: 3.36; S, 7.70

Found: C, 46.28; H, 4.30; N,: 3.42; S, 7.92

The product with identical spectroscopic data was obtained using benzyl ester of 6α-bromopenicillanic acid 1,1-dioxide (**5b**) as starting material. Yield: 2.79 g (83.8%).

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