CROATICA CHEMICA ACTA CCACAA 62 (3) 521—527 (1989)

CCA-1882

YU ISSN 0011-1643
UDC 547.718
Original Scientific Paper

Preparation of Chiral Oxoazetidinesulfinates

Jure J. Herak, Miće Kovačević, and Branimir Gašpert

Research Institute PLIVA, Zagreb, Croatia, Yugoslavia

Received May 5, 1988

Diastereomeric oxoazetidinesulfinates *IV* were prepared from penicillanate *S,S*-dioxide (Sulbactam) *via* sulfinic acid *I* and sulfinyl chlorides *II*. Both epimers *IVa* and *IVb* gave the same oxoazetidinesulfonate *V* upon oxidation.

The ^{1}H NMR spectra of *IVa* and *IVb* correspond to those of alfa- and beta-*S*-oxide of penicillanates.

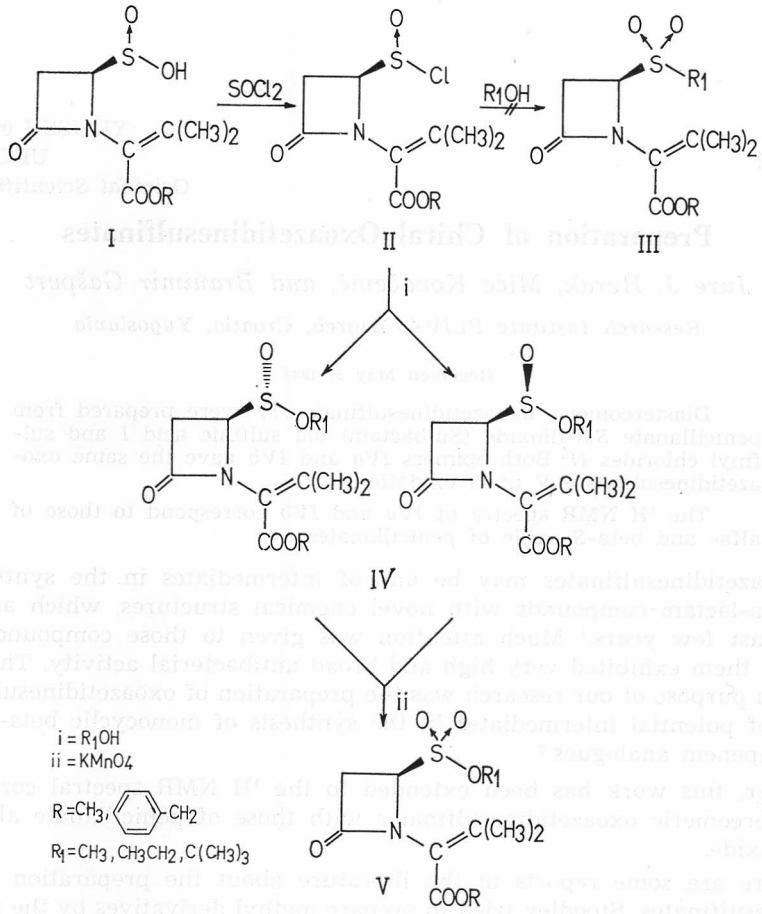
Oxoazetidinesulfinates may be one of intermediates in the synthesis of new beta-lactam compounds with novel chemical structures, which appeared in the last few years.[1] Much attention was given to those compounds since many of them exhibited very high and broad antibacterial activity. Therefore, the main purpose of our research was the preparation of oxoazetidinesulfinates, as one of potential intermediates in the synthesis of monocyclic beta-lactams or carbapenem analogues.[2]

Later, this work has been extended to the ^{1}H NMR spectral correlation of diastereomeric oxoazetidinesulfinates with those of penicillanate alfa- and beta-*S*-oxide.

There are some reports in the literature about the preparation of oxoazetidinesulfinates. Stoodley tried to prepare methyl derivatives by the reaction of methyl iodide with sodium salt of sulfinic acid (*I*).[3] Instead of ester (*IV*) he isolated methyl sulfone (*III*), which is in agreement with the assumption that sulfur in sulfinic acid reacts like nucleophile towards alkyl halides.[4] In a similar experiment, starting with the DBU salt of sulfinic acid, a mixture of sulfone (*III*) and sulfinate (*IV*) was obtained, indicating that the product of the reaction depends on the reaction conditions.[2] Another preparation of sulfinates was reported by Spry, who treated cephem-*S,S*-dioxide with thiourea and diazomethane.[5]

Some oxoazetidinesulfinyl chlorides were used as intermediates in the oxidative ring expansion of penicillin into 3-methylenecepham. They were prepared by treating penicillin sulfoxide with NCS, which resulted in the diastereomeric mixture of sulfinyl chlorides.[6]

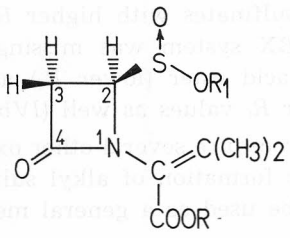
We started with penicillanate sulfinic acids *I*, obtained by the opening of thiazolidine ring of penicillanate *S,S*-dioxide (Sulbactam ester) according to the procedure of R. J. Stoodley *et al.*[3] Thus prepared sulfinic acid *I* was transformed into the corresponding sulfinyl chloride *II* by thionyl chloride.



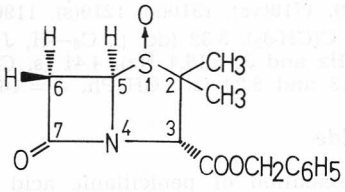
^{1}H NMR spectra of crude product indicated a mixture of diastereomers, which was in accordance with the report about the mixture of sulfinyl chlorides obtained from penicillins.[6] Since the obtained sulfinyl chlorides were very reactive, it was not possible to purify them. Evidence for structure *II* was obtained by hydrolysis, which yielded the starting sulfinic acid *I*. Treatment of *II* with methanol yielded a mixture of two compounds, detected by TLC and separated by column chromatography. Both isolated compounds had the same elemental analysis, different spectra from methyl sulfone *III*, and by oxidation with $KMnO_4$ gave the same sulfonate *V*. Since the reaction of penicillanate *S,S*-dioxide with DBN was shown to be stereochemically controlled,[3,8] it follows that the separated compounds should be epimeric at sulfur, and have been assigned as *IVa* and *IVb*.

The chiral nature of sulfinate group was demonstrated also by NMR spectroscopy. ^{1}H NMR spectra of diastereomeric pairs of all prepared oxo-

azetidinesulfinates revealed significant differences in splitting the signals of the protons at C_2 and C_3 atoms. Spectra of isomers with higher R_f values on TLC (*IVa*), showed the typical pattern of the ABX system with clear geminal splitting of the protons at C_3 atom. In contrast, in the spectra of isomers with lower R_f values (*IVb*) such splitting was missing.



R	R1	Rf	δ (ppm)		IV
			C2 ···· H	H ▬ C3 ···· H	
CH3	CH3	0.37	4.77 (dd)	3.19 (dd – α) 3.49 (dd – β)	a
		0.32	4.80 (dd)	3.18 (d) 3.21 (d)	b
$CH_2C_6H_5$	CH3	0.47	4.69 (dd)	3.09 (dd – α) 3.43 (dd – β)	a
		0.42	4.72 (d) 4.76 (d)	3.10 (d) 3.11 (d)	b
$CH_2C_6H_5$	CH_2CH_3	0.52	4.67 (dd)	3.11 (dd – α) 3.42 (dd – β)	a
		0.49	4.75 (dd)	3.09 (d) 4.00 (d)	b
$CH_2C_6H_5$	$C(CH_3)_3$	0.57	4.72 (dd)	3.13 (dd – α) 3.40 (dd – β)	a
		0.54	4.68 (2d)	3.02 (d) 3.04 (d)	b



Epimer	Rf	δ (ppm)	
		C5 ···· H	H ▬ C6 ···· H
1 – α ox. ide	0.18	4.61 (dd)	3.32 (dd – β) 3.62 (dd – α)
1 – β ox. ide	0.12	4.93 (t)	3.33 (d)

These marked differences in ^{1}H NMR spectra are very similar to those of the penicillanic acid *S*-oxides which we prepared according to the method reported.[9]

It can be seen from the table that alfa-*S*-oxide of penicillanic acid ester (higher R_f) showed the same characteristic pattern of the ABX system as diastereomer of oxoazetidinesulfinates with higher R_f values (*IVa*). This characteristic pattern of the ABX system was missing in ^{1}H NMR spectra of beta-*S*-oxide of penicillanic acid ester (lower R_f) and in those of the oxoazetidinesulfinates with lower R_f values as well (*IVb*).

According to the above procedure several other oxoazetidinesulfinates were prepared. In no case was the formation of alkyl sulfones (*III*) detected, indicating that this method can be used as a general method for the preparation of oxoazetidinesulfinates.

EXPERIMENTAL

Melting points are uncorrected.

The IR spectra were recorded in methylenechloride 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 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 original plates (Merck, Kieselgel HF_{254}) followed by detection with iodine vapors and UV absorption in the solvent system: benzene-ethylacetate 3 : 1.

Penicillanic Acid 1-α-Oxide

It was prepared from 6,6-dibromopenicillanic acid 1-α-oxide,[9] which was obtained by oxidation of 6,6-dibromopenicillanic acid,[10] according to the method reported.

Penicillanic Acid 1-α-Oxide Benzyl Ester

It was prepared by the method reported for the preparation of benzylester of 6,6-dibromopenicillanic acid.[9].

Yield: 69%; *m. p.* 85—87 °C; R_f 0.18.

IR spectrum (KBr): 1750(vs), 1710(vs), 1310(s), 1210(s), 1190(s) cm^{-1}.

^{1}H NMR: 1.26 and 1.54 (2s, $C(CH_3)_2$), 3.32 (dd, β, C_6—H, J = 2.3 Hz and J = 16.4 Hz), 3.62 (dd, α, C_6—H, J = 4.4 Hz and J = 16.4 Hz), 4.41 (s, C_3—H), 4.60 (dd, C_5—H, J = 2.3 Hz and J = 4.4 Hz), 5.13 and 5.29 (2d, CH_2Ph, J = 16 Hz), 7.37 (s, C_6H_5).

Penicillanic Acid 1-β-Oxide

It was prepared by oxidation of penicillanic acid with 3-chlorobenzoic acid according to the method reported.[9]

Penicillanic Acid 1-β-Oxide Benzyl Ester

It was prepared according to the above procedure.[9]

Yield: 58%; *M. p.* 116—8 °C; R_f 0.12.

IR Spectrum (KBr): 1760(vs), 1710(vs), 1270(s), 1210(s), 1050(s) cm^{-1}.

^{1}H NMR: 1.10 and 1.65 (2s, $C(CH_3)_2$), 3.33 (d, C_6—H, J = 4 Hz), 4.54 (s, C_3—H), 4.93 (t, C_5—H, J = 4 Hz), 5.13 and 5.31 (2 d, CH_2Ph, J = 13 Hz) and 7.37 (s, C_6H_5).

Preparation of Oxoazetidinesulfinates (IV)

Oxoazetidinesulfinic acid (10 g) was dissolved in $SOCl_2$ (50 ml), or methylene-chloride (50 ml) and $SOCl_2$ (8 g) were added. The solution was mixed for 1 hour at 25 °C. The solvent and excess of $SOCl_2$ was evaporated under reduced pressure to oily residue. Alcohol (50 ml) was added with cooling to keep the temperature of solution at 25 °C. The reaction solution was stirred for 30 minutes and solvent evaporated. The oily residue was dissolved in methylene chloride, washed with water, sat. solution of $NaHCO_3$, dried ($MgSO_4$), filtered and evaporated.

Yield: 70—80%. The crude product was chromatographed over silica gel using a benzene-ethylacetate gradient.

2R-1-(1-Methyloxycarbonyl-2-methylprop-1-enyl)-4-oxo azetidine-2-sulfinic Acid Methyl Ester

IR Spectrum: 1780(s), 1730(m), 1370(m), 1100(b, m), 990(m) cm^{-1}.

a) *Epimer (IVa; R, R_1=CH_3)*

M. p. 88—90 °C; R_f 0.37.

Anal. $C_{10}H_{15}NO_5S$ (261.28) calc'd.: C 45.97; H 5.97; N 5.36; S 12.26%
found: C 46.01; H 6.07; N 5.52; S 12.52%.

^1H NMR: 2.0 and 2.24 (2s, $C(CH_3)_2$), 3.19 (dd, α C_3—H, J = 5 Hz and J = 15.6 Hz), 3.49 (dd, β C_3—H, J = 2.6 Hz and J = 15.6 Hz), 3.78 (s, 2 OCH_3), 4.77 (dd, C_2—H, J = 2.6 Hz and J = 5 Hz).

b) *Epimer (IVb; R, R_1=CH_3)*

Viscous oil; R_f 0.32.

^1H NMR: 2.06 and 2.23 (2s, $C(CH_3)_2$), 3.18 and 3.21 (2d, C_3—H, J = 3.2 Hz and J = 5.7 Hz), 3.78 and 3.79 (2s, 2 OCH_3), 4.80 (dd, C_2—H, J = 3.2 Hz and J = 5.7 Hz).

2R-1-(1-Benzyloxycarbonyl-2-methylprop-1-enyl)-4-oxo azetidine-2-sulfinic Acid Methyl Ester

IR Spectrum: 1780(s), 1730(m), 1360(m), 1200(m), 1100(b, m), 990(m) cm^{-1}.

Anal. $C_{16}H_{19}NO_5S$ (337.42) calc'd.: C 56.95; H 5.69; N 4.15; S 9.50%
found: C 57.07; H 5.85; N 4.11; S 9.94%.

a) *Epimer (IVa; R=$CH_2C_6H_5$; R_1=CH_3)*

Viscous oil; R_f 0.47.

^1H NMR: 2.0 and 2.24 (2s, $C(CH_3)_2$), 3.09 (dd, α C_3—H, J = 5.0 Hz and J = 15.6 Hz), 3.43 (dd, β C_3—H, J = 2.6 Hz and J = 15.6 Hz), 3.70 (s, OCH_3), 4.69 (dd, C_2—H, J = 2.6 Hz and J = 5 Hz), 5.3 and 5.29 (2d, CH_2Ph, J = 16 Hz), 7.35 (s, C_6H_5).

b) *Epimer (IVb; R=$CH_2C_6H_5$; R_1=CH_3)*

Viscous oil; R_f 0.42.

^1H NMR: 2.07 and 2.24 (2s, $C(CH_3)_2$), 3.10 and 3.11 (2d, C_3—H, J = 3.5 Hz and J = 4.7 Hz), 3.71 (s, OCH_3), 4.72 and 4.76 (2d, C_2—H, J = 3.5 Hz and J = 4.7 Hz), 5.12 and 5.30 (2d, CH_2Ph J = 12.3 Hz), 7.36 (s, C_6H_5).

2R-1-(1-Benzyloxycarbonyl-2-methyl-prop-1-enyl)-4-oxo azetidine-2-sulfinic Acid Ethyl Eester

IR Spectrum: 1780(s), 1715(b, m), 1160(m), 1200(m), 1070(m), 990(m) cm^{-1}.

Anal. $C_{17}H_{21}NO_5S$ (351.45) calc'd.: C 58.08; H 6.03; N 3.99; S 9.13%
found: C 57.86; H 5.90; N 4.43; S 8.71%.

a) *Epimer (IVa; R=$CH_2C_6H_5$; R_1=CH_2CH_3)*

Amorphous solid; R_f 0.52.

^1H NMR: 1.26 (t, CH_3, J = 7.1 Hz), 2.00 and 2.24 (2s, $C(CH_3)_2$), 3.11 (dd, α C_3—H, J = 5 Hz and J = 15.5 Hz), 3.42 (dd, β C_3—H, J = 2.7 Hz and J = 15.5 Hz), 4.03 and 4.05 (2q, OCH_2, J = 2 Hz and J = 7.1 Hz), 4.67 (dd, C_2—H, J = 2.7 Hz and J = 5 Hz), 5.13 and 5.30 (2d, CH_2Ph, J = 15.1 Hz), 7.36 (s, C_6H_5).

b) *Epimer (IVb; $R=CH_2C_6H_5$; $R_1=CH_2CH_3$)*

Viscous oil; R_f 0.49.

^{1}H NMR: 1.24 (t, CH_3, J = 6.7 Hz), 2.07 and 2.23 (2s, $C(CH_3)_2$), 3.09 and 4.00 (2d, C_3—H, J = 3.5 Hz and J = 4.4 Hz), 4.03 and 4.04 (2q, OCH_2, J = 22.3 Hz and J = 6.7 Hz), 4.75 (dd, C_2—H, J = 3.5 Hz and J = 4.4 Hz), 5.11 and 5.31 (2d, CH_2Ph, J = 12.3 Hz), 7.36 (s, C_6H_5).

2R-1-(1-Benzyloxycarbonyl-2-methyl-prop-1-enyl)-4-oxo azetidine-2-sulfinic Acid t-*Butyl Ester*

IR Spectrum: 1760(s), 1700(m), 1360(m), 1210(s), 1120(m), 1070(m), 860(s) cm^{-1}.

Anal. $C_{19}H_{25}NO_5S$ (379.46) Calc'd: C 60.13; H 6.64; N 3.69; S 8.45%
found: C 60.77; H 7.05; N 3.98; S 8.35%.

a) *Epimer (IVa; $R=CH_2C_6H_5$; $R_1=C(CH_3)_3$)*
Amorphous solid; R_f 0.57.

^{1}H NMR: 1.36 (s, $C(CH_3)_3$), 1.98 and 2.2 (2s, $C(CH_3)_2$), 3.13 (dd, α C_3—H, J = 5.3 Hz and J = 15.8 Hz), 3.4 (dd, β C_3—H, J = 2.9 Hz and J = 15.8 Hz), 4.72 (dd, C_2—H, J = 2.9 Hz and J = 5.3 Hz), 5.11 and 5.32 (2d, CH_2Ph, J = 12.1 Hz), 7.36 (s, C_6H_5).

b) *Epimer (IVb; $R=CH_2C_6H_5$; $R_1=C(CH_3)_3$)*
Viscous oil; R_f 0.54.

^{1}H NMR: 1.34 (s, $C(CH_3)_3$), 2.10 and 2.22 (2s, $C(CH_3)_2$), 3.02 and 3.04 (2d, C_3—H, J = 3.5 Hz and J = 4.4 Hz), 4.68 (2d, C_2—H, J = 3.5 Hz and J = 4.4 Hz), 5.10 and 5.31 (2d, CH_2Ph, J = 12.4 Hz), 7.36 (s, C_6H_5).

Oxidation of Oxoazetidinesulfinates

Oxoazetidinesulfinate (*IVa* or *IVb* epimer) (1 g) was dissolved in 80% acetic acid (5 ml) or a mixture of acetic acid and ethylacetate (10 ml; 1 : 1), cooled to 0—5 °C and saturated aqueous solution of $KMnO_4$ was added with cooling and stirring as long as the rose colour persisted. After addition of water (20 ml), the colour of the solution was discharged by adding 30% solution of H_2O_2. Ethylacetate (20 ml) was added and organic layer washed with water, sat. solution of $NaHCO_3$, dried and filtered. Evaporation of solvent yielded the product in the form of viscous oil.

2R-1-(1-Methyloxycarbonyl-2-methylprop-1-enyl)-4-oxo -azetidine-2-sulfonic Acid Methyl Ester (V; $R=R_1=CH_3$)

Yield: 84%; R_f 0.44.

Anal. $C_{10}H_{15}NO_6S$ (277.29) Calc'd.: C 43.31; H 5.45; N 5.05; S 11.56%
found: C 42.96; H 5.56; N 5.52; S 11.40%.

IR Spectrum: 1850(s), 1725(b, m), 1365(s), 1210(m), 1180(s), 1080(m), 980(s) cm^{-1}.

^{1}H NMR: 2.08 and 2.27 (2s, $C(CH_3)_2$), 3.42 (d, C_3—H, J = 3.8 Hz), 3.80 and 3.90 (2s, 2 OCH_3), 5.21 (t, C_2—H, J = 3.8 Hz).

2R-1-(1-Benzyloxycarbonyl-2-methylprop-1-enyl)-4-oxo-azetidine-2-sulfonic Acid Methyl Ester (V; $R=CH_2C_6H_5$; $R_1=CH_3$)

Yield: 87%; R_f 0.62.

Anal. $C_{16}H_{19}NO_6S$ (353.42) Calc'd.: C 54.37; H 5.43; N 3.96; S 9.07%
found: C 53.98; H 5.34; N 3.98; S 8.81%.

IR Spectrum: 1780(s), 1730(m), 1350(s), 1180(m), 1000(m) cm^{-1}.

^{1}H NMR: 2.07 and 2.27 (2s, $C(CH_3)_2$), 3.36 (d, C_3—H, J = 4.1, Hz) 3.74 (s, OCH_3), 5.10 (t, C_2—H, J = 4.1 Hz), 5.13 and 5.33 (2d, CH_2Ph, J = 12 Hz), 7.36 (s, C_6H_5).

2R-1-(1-Benzyloxycarbonyl-2-methylprop-1-enyl)-4-oxo-azetidine-2-sulfonic Acid Ethyl Ester (V; $R=CH_2C_6H_5$; $R_1=CH_2CH_3$)
Yield: 82%; R_f 0.66.

Anal. $C_{17}H_{21}NO_6S$ (367.41) Calc'd: C 55.57; H 5.76; N 3.81; S 8.72%
found: C 55.80; H 6.11; N 4.26; S 8.65%.

IR Spectrum: 1790(s), 1730(m), 1370(s), 1220(m), 1180(s), 1080(m), 1000(m), 920(m) cm^{-1}. ^1H NMR: 1.26 (t, CH_3, $J = 7$ Hz), 2.08 and 2.27 (2s, $C(CH_3)_2$), 3.33 (d, C_3—H, $J = 4.1$ Hz), 4.13 and 4.15 (2q, OCH_2, $J = 2.6$ Hz and $J = 7$ Hz), 5.06 (t, C_2—H, $J = 4.1$ Hz), 5.12 and 5.33 (2d, CH_2Ph, $J = 12$ Hz), 7.36 (s, C_6H_5).

Hydrolysis of Oxoazetidinesulfinyl Chloride (II)

2R-1-(1-Benzyloxycarbonyl-2-methylprop-1-enyl)-4-oxo-azetidine-2-sulfinyl chloride (*II*; $R=CH_2C_6H_5$) (5 g), water (20 ml) and methylene chloride (20 ml) was stirred for 1 hour at 25 °C. The solution was neutralized with aqueous solution of $NaHCO_3$. The separated aqueous layer was acidified with dil. hydrochloric acid and extracted with methylene chloride. Evaporation of dried organic extract left 2R-1-(1-benzyloxycarbonyl-2-methylprop-1-enyl)-4-oxoazetidine-2-sulfinic acid (*I*; $R=CH_2C_6H_5$) in 70% yield.

Acknowledgement. — The authors thank the members of the Organic Chemistry Department of the PLIVA Research Institute for recording the IR spectra and for microanalyses.

The ^1H NMR spectra were recorded by the NMR Service of the Institute »Ruđer Bošković«.

REFERENCES

1. E. S. Hamanaka and M. S. Kellogg, *Annu. Rep. Med. Chem.* **18** (1983) 109; T. D. Gootz, *ibid.* **20** (1985) 137; G. L. Dunn, *ibid.* **21** (1986) 131.
2. H. Maruyama and T. Hiroaka, *J. Org. Chem.* **51** (1986) 339.
3. C. M. Paut, J. Steele, and R. J. Stoodley, *J. Chem. Soc. Perkin I* (1982) 595.
4. C. J. M. Stirling, *Int. J. Sulphur Chem. B* **6** (1971) 277.
5. D. O. Spry, *Tetrahedron Lett.* (1978) 4751.
6. S. Kukolja, S. R. Lammert, M. R. B. Gleissner, and A. I. Ellis, *J. Amer. Chem. Soc.* **98** (1976) 5040.
7. A. W. Chow, N. M. Hall, and J. R. E. Hoover, *J. Org. Chem.* **18** (1953) 3733.
8. J. Steel and R. J. Stoodley, *J. Chem. Soc. Perkin I* (1983) 2241; G. D. Amando and R. J. Stoodley, *Tetrahedron Lett.* **26** (1985) 497.
9. Pfizer Inc., *Ger. Offenlegungsschrift*, 28 24 535 (1978).
10. J. P. Clayton, *J. Chem. Soc. (C)* (1969) 2123.

SAŽETAK

Priprava kiralnih oksoazetidinsulfinata

Jure J. Herak, Miće Kovačević i Branimir Gašpert

Priređeni su oksoazetidinsulfinati *IV* polazeći od penicilat-*S*,*S*-dioksida (Sulbaktama), preko sulfinske kiseline *I* i sulfinilklorida *II*. Odvojeni diastereomeri *IVa* i *IVb* oksidacijom sa $KMnO_4$ daju isti produkt, oksoazetidin-sulfonat *V*. Ustanovljena je podudarnost ^1H NMR spektra spojeva *IVa* i *IVb* sa spektrima penicilat alfa- i beta-S-oksida.