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A Convenient Synthesis of β-Lactams from Alkylthioimidates

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Abstract: Stereoselective syntheses of trans-3,4,4-substituted--azetidin-2-ones from alkylthioimidates are described. Reduction of these compounds gave stereoselectively cis-4-alkyl-azetidin--2-ones which could be useful intermediates for preparation of biologically active B-lactams.

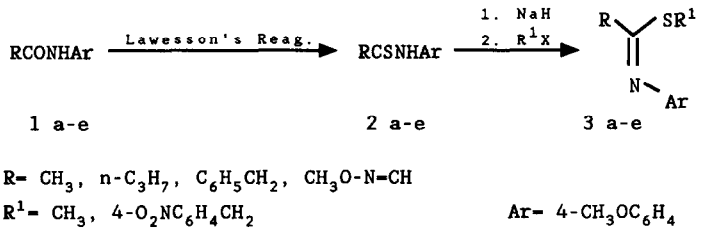
INTRODUCTION

At present, stereocontrolled syntheses of 3,4-substituted-azetidin--2-ones attract increasingly greater attention as they may serve as efficient intermediates for the synthesis of mono- and bicyclic β-lactam antibiotics[2a] and for a variety of other products[2bc]. It is well known that the annelation of formyl, cyclic, and arylthioimidates with activated acetic acid derivatives in the presence of triethylamine gives the β-lactams. In almost all known cases, these [2+2] cycloadditions proceed completely stereoselectively to give single *trans*-β-lactams[3]. In only one case, in the reaction with isocyanoacetyl chloride, thioimidate forms a mixture of *trans*- and *cis*- isomers[4]. Likewise, the annelation of a Schiff base with thiobenzyloxy- or with thiophenoxyacetic acid derivatives results in the *trans*- configuration of β-lactams. However, Van der Veen *et al.*[5] have reported the formation of *cis*-β-lactams as single isomers in the reaction of thiophenoxyacetyl chloride with imino compounds derived from phenylglyoxal. According to the literature, in the absence of a thio group in the imine or ketene components, *cis*-β-lactams are formed as a rule. Stereospecific formation of *trans*-β-lactams containing a thio group at C3 or C4, has not as yet been elucidated. There are no reports, however, on the same reaction performed with acyclic alkylthioimidates. Subsequently desulfurization seems to be an alternative way to stereoselective synthesis of *cis*-4-alkyl β-lactams instead of direct annelation of unstable alkylaldimines with ketenes[6].

In this paper we describe the synthesis of 3,4,4-substituted-azetidin--2-ones **5** and **6**, justified by the easy availability of acyclic alkylthioimidates **3**. Desulfurization of representative β-lactams **5** led to *cis*-4-alkyl-azetidin-2-ones **7**.

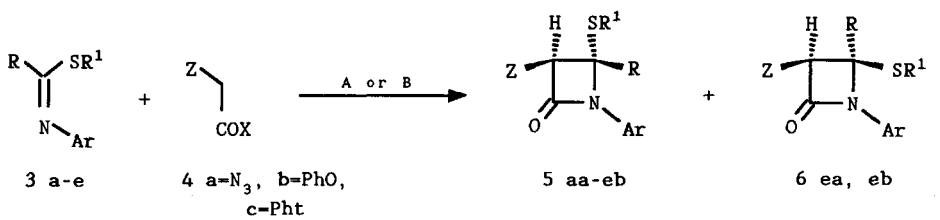
RESULTS AND DISCUSSION

Synthesis of acyclic alkylthioimidate. The acyclic alkylthioimidates 3a-e were prepared by thionation of appropriate carboxamides with Lawesson's reagent[7], followed by S-alkylation of the sodium salt of thiocarboxamides[8]. This method afforded high purity and good yield of the obtained thioimidates (Scheme 1).



Scheme 1. Preparation of alkylthioimidates 3.

Cycloaddition of ketenes to alkylthioimidates. Alkylthioimidates 3 were condensed with appropriate acid chlorides 4 (X=Cl) in the presence of triethylamine in a methylene chloride solution to give 3,4-(R^1S)-*trans*-β-lactams 5 as the sole product in yields from 10% to 82% (Method A). β-Lactams 5 were more conveniently prepared by the reaction of thioimidates 3 with the potassium salt of carboxylic acids 4 (X=OK), in the presence of phenyl dichlorophosphate for activation of the carboxyl group (Method B)[9].



Scheme 2. Preparation of 3,4,4-substituted β-lactams 5 and 6.

Only in the case of the reaction of thioimidate **3e** with appropriate ketene precursors, mixtures of *trans*- and *cis*- isomers were formed. The ratio of isomers was 6:4 to 9:1 in favor of the *trans*-isomer (Scheme 2 and Table 1).

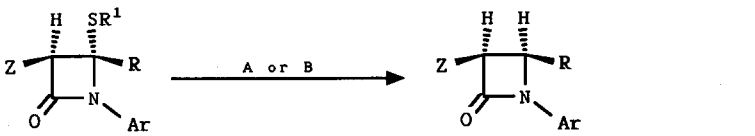
Desulfurization of β-lactams 5. Desulfurization of β-lactams **5ab** and **5db** with tributyltinhydride[10] in the presence of catalytic amount of AIBN in boiling toluene provided two *cis*-3,4-substituted β-lactams **7ab** and **7db**

Table 1. β-Lactams 5 and 6 Prepared.

Comp. No	R	R^1	Z	5 / 6	Yield/Method
5ab	CH_3	CH_3	N_3	100/0	10/A, 16/B
5ab	CH_3	CH_3	PhO	100/0	82/A, 86/B
5ac	CH_3	CH_3	Pht	100/0	88/B
5bb	CH_3	$4\text{-}O_2NC_6H_4CH_2$	PhO	100/0	81/B
5cb	$n\text{-}C_3H_7$	CH_3	PhO	100/0	86/B
5cc	$n\text{-}C_3H_7$	CH_3	Pht	100/0	84/B
5da	$C_6H_5CH_2$	CH_3	N_3	100/0	42/A, 46/B
5db	$C_6H_5CH_2$	CH_3	PhO	100/0	92/B
5dc	$C_6H_5CH_2$	CH_3	Pht	100/0	89/B
5ea and 6ea	$CH_3O\text{-}N{=}CH$	CH_3	N_3	60/40	45*/B
5eb and 6eb	$CH_3O\text{-}N{=}CH$	CH_3	PhO	90/10	86*/B

*summarized yield of both isomers

in moderate yields. Treatment of the same β-lactams **5ab** and **5db** with activated Raney-Nickel[11] catalyst under hydrogen in ethyl acetate gave the desulfurized *cis*-β-lactams in 64% and 70% yields, respectively (Scheme 3).



5ab 7ab 35%(A), 64%(B)
5db 7db 55%(A), 70%(B)

Scheme 3. Desulfurization of β-lactams 5.

Structural investigations. In the case of 3,4-substituted azetidin--2-ones containing a hydrogen atoms at C3 and C4, the 3,4-configuration may be easily confirmed by ^1H NMR spectroscopy. On the other hand, in the present case involving the use of acyclic alkylthioimidates as imino components, simple ^1H NMR analysis could not confirm the configuration, because of the absence of hydrogen at C4. Therefore, in the present studies the structural elucidation of the β-lactams was mainly based on a series of $^1H\{^1H\}$ NOE experiments (see experimental part). The results show

that the proton at carbon C3 and the methylthio group at carbon C4 are on the same side of the β-lactam ring in isomers **5**. There was no effect on the methylthio group when the H-C3 proton was irradiated in isomers **6**. This authorized us to assign the expected *trans*-3,4-(R^1S)- configuration to isomers **5** and *cis*-3,4-(R^1S)- configuration to isomers **6**. To confirm the assumed configuration of 3,4,4-substituted β-lactams, X-ray structural investigations were performed for compounds **5dc** and **5eb**[12,13].

Summing up, *trans*-3,4,4-substituted-azetidin-2-ones are efficiently prepared in the reaction of alkylthioimidates with ketene precursors. Reductive removing of the 4-methylthio group gave stereoselectivelly *cis*-4-alkyl-azetidin-2-ones, which could be useful substrates for the synthesis of biologically active monobactams[14].

EXPERIMENTAL

General: ^1H and ^{13}C NMR spectra were measured with a Bruker AM-500 spectrometer at 500 MHz and 125 MHz, respectively, in a $CDCl_3$ solution; they are reported in ppm from internal TMS. The standard Bruker program was used to perform the NOE experiments. The IR spectra were measured with a Beckman AccuLab 1 spectrophotometer. The mass spectra were recorded with an AMD 604 spectrometer; peaks lower than 10% were not listed. Melting points were measured in an open capillary tube and are uncorrected. The progress of the reactions and purity of the products were tested by TLC on silica gel (Merck, Kieselgel $60F_{254}$, No.5554). The plates were developed with an appropriate mixture of hexane-ethyl acetate, and visualization was effected with UV light or by spraying with a phosphomolybdic acid solution. Column chromatography was carried out on silica gel (Merck, Kieselgel 60, No.60738). Elemental analysis was obtained from the Microanalytical Laboratory, Institute of Organic Chemistry of the Polish Academy of Sciences. Solvents and commercially available reagents were purified by literature procedures.

Carboxamides were prepared by the standard method: **1a**[15], **1c**[16], **1d**[17].

Methoxyiminoacet-*p*-anisidide 1e was prepared from isonitroso--*p*-anisidide[18] according to the standard method: To a vigorously stirred solution of isonitroso-*p*-anisidide (3.9 g, 0.02 mole) in methylene chloride (40 cm^3), a 5% aqueous solution of sodium hydroxide (80 cm^3) was added, followed by an addition of dimethyl sulfate (3.8 g, 0.03 mole) in one portion. The reaction mixture was stirred until the starting oxime was consumed (TLC). The organic layer was separated and washed twice with water, whereupon the solvent was removed under reduced pressure. The residue crystallized from an ethanol-water mixture consisted of pure methoxyiminoacet-*p*-anisidide **1e**: 3.4 g; yield 82%; m.p. 99-101 °C; IR (nujol): 3350, 1660, 1600, 1520 cm^{-1}; ^1H NMR: 3.79 (s, 3H, CH_3O-Ar), 4.02 (s, 3H, CH_3O-N), 6.86-6.88 (m, 2H, Ar), 7.47 (s, 1H, CH=N), 7.49-7.51 (m, 2H, Ar), 8.21 (s, 1H, NH); ^{13}C NMR: 55.38 (CH_3O-Ar), 63.14 (CH_3O-N), 114.15, 121.55, 130.09 (Ar), 143.19 (CH=N), 156.55 (Ar), 159.16 (CO); Anal. calc. for $C_{10}H_{12}N_2O_3$: C 57.69, H 5.81, N 13.45 %, Found: C 57.44, H 5.70, N 13.34 %.

Thiocarboxamides 2 were obtained according to Lawesson et al.[6]:

Carboxamides (0.01 mol) and 2,4-bis-(p-methoxyphenyl)-1,3-dithia--diphosphetane-2,4-disulfide (Lawesson's reagent) (0.005 mol) in HMPA (10 cm^3) were jointly heated at 100 °C. The progress of the reaction was controlled by TLC. After disappearance of the carboxamide, the reaction mixture was allowed to cool to room temperature and then was poured into water. The mixture was extracted several times with diethyl ether. The combined ether layers were washed with saturated sodium hydrogen carbonate and dried over $MgSO_4$, whereupon ether was stripped off. The residue was purified by flash chromatography on Florisil® eluted with toluene.

Thioacet-*p*-anisidide 2a: Yield 92%; m.p. 115-117 °C (m.p. 118 °C)[19].

Butanethio-*p*-anisidide 2c: Yield 93%; m.p. 59-61 °C (m.p. 60 °C)[20].

Phenylthioacet-*p*-anisidide 2d: Yield 88%; m.p. 76-78 °C; Ir(nujol) : 3200, 1235, 1140 cm^{-1}; ^1H NMR: 3.76 (s, 3H, CH_3O), 4.23 (s, 2H, CH_2), 6.83-6.86, 7.33-7.35, 7.38-7.42 (m, 9H, Ar), 8.52 (s, 1H, NH); ^{13}C NMR: 46.98 (CH_2), 55.36 (CH_3O), 113.91, 125.42, 127.90, 129.26, 129.46, 131.41, 135.01, 158.15 (Ar), 201.14 (CS); Anal. calc. for $C_{15}H_{15}NOS$: C 70.01, H 5.87, N 5.44, S 12.46 %, Found: C 69.75, H 5.65, N 5.61, S 12.37 %.

Methoxyiminothioacet-*p*-anisidide 2d: Yield 76%; m.p. 71-72 °C; Ir(nujol): 3220, 1610, 1190, 1125 cm^{-1}; ^1H NMR: 3.79 (s, 3H, CH_3O-Ar), 4.01 (s, 3H, CH_3O-N), 6.88-6.91, 7.68-7.71 (Ar), 7.79 (s, 1H, CH=N), 9.72 (s, 1H, NH); ^{13}C NMR: 55.33 (CH_3O-Ar), 66.11 (CH_3O-N), 113.89, 124.33, 130.96 (Ar), 147.82 (CH=N), 157.83 (Ar), 184.18 (CS); Anal calc. for $C_{10}H_{12}N_2O_2S$: C 53.55, H 5.39, N 12.49, S 14.30%, Found: C 53.81, H 5.33, N 12.35, S 14.23 %.

General Procedure for the Preparation of Thioimidate 3: A solution of thiocarboxamide 2 (5 mmol) in tetrahydrofuran (5 cm^3) was added during 15 min to a suspension of sodium hydride (0.125 g, 50% in oil) in tetrahydrofuran (5 cm^3) at room temperature. The mixture was stirred for 1 h and then either methyl iodide (0.9 g, 6.3 mmol) or 4-nitrobenzyl chloride (1.0 g, 6 mmole) in case of 3b in tetrahydrofuran (5 cm^3) was added. After stirring for several hours, acetic acid (1 cm^3) was added to the reaction mixture which was filtered through Celite and evaporated. A solution of the residue in diethyl ether (15 cm^3) was washed successively with saturated sodium hydrogen carbonate and brine. Crude thioimidate 3 obtained after removal of ether was used directly in the next step without further purification.

S-methyl N-(4-methoxyphenyl)-acetthioimidate 3a: Yield 86%; m.p. 37-38°C; IR (nujol): 1630 cm^{-1}; ^1H NMR: 2.01 (s, 3H, CH_3), 2.41 (s, 3H, CH_3S), 3.78 (s, 3H, CH_3O), 6.62-6.64, 6.82-6.84 (m, 4H, Ar); ^{13}C NMR: 12.99 (CH_3S), 21.41 (CH_3), 55.38 (CH_3O), 114.19, 121.10, 143.86, 155.78 (Ar), 166.31 (C=N).

S-(4-nitrophenyl)methyl N-(4-methoxyphenyl)-acetthioimidate 3b: Yield 70%; m.p. 59-60 °C; IR (nujol): 1610 cm^{-1}; ^1H NMR: 2.03 (s, 3H, CH_3), 3.80 (s, 3H, CH_3O), 4.33 (s, 2H, CH_2), 6.64-6.66, 6.86-6.88, 7.55-7.57, 8.14-8.16 (m, 8H, Ar).

S-methyl N-(4-methoxyphenyl)-butanethioimidate 3c: Yield 89%; m.p. 85-87 °C; IR (nujol): 1625 cm^{-1}; ^1H NMR: 0.83 (t, 3H, J=7.3, CH_3), 1.51-1.58 (m, 2H, CH_2), 2.29 (t, 2H, J=7.6, CH_2), 2.38 (s, 3H, CH_3S), 3.79 (s, 3H, CH_3O), 6.64-6.66, 6.83-6.85 (m, 4H, Ar); ^{13}C NMR: 12.71 (CH_3S),

13.71 (CH_3), 21.22 (CH_2), 36.65 (CH_2), 55.36 (CH_3O), 114.15, 120.81, 143.94, 155.56 (Ar), 170.86 (C=N).

S-methyl N-(4-methoxyphenyl)-phenylacetthioimidate 3d: Yield 85%; m.p. 83-85 °C; IR (nujol): 1610 cm^{-1}; ^1H NMR: 2.38 (s, 3H, CH_3S), 3.71 (s, 2H, CH_2), 3.80 (s, 3H, CH_3O), 6.66-6.68, 6.83-6.85 (m, 4H, Ar), 7.07-7.10, 7.21-7.26 (m, 5H, Ar); ^{13}C NMR: 13.22 (CH_3S), 40.87 (CH_2), 55.48 (CH_3O), 114.33, 121.07, 126.80, 128.40, 129.21, 136.01, 143.75, 155.88 (Ar), 168.61 (C=N).

S-methyl N-(4-methoxyphenyl)-metoxyiminoacetthioimidate 3e: Yield 80%; m.p. 60-62 °C; IR (nujol): 1625, 1605 cm^{-1}; ^1H NMR: 2.34 (s, 3H, CH_3 S), 3.79 (s, 3H, CH_3OAr), 3.98 (s, 3H, CH_3O-N), 6.73-6.75, 6.84-6.86 (m, 4H, Ar), 7.70 (s, 1H, CH=N); ^{13}C NMR: 12.43 (CH_3S), 55.47 (CH_3OAr), 62.92 (CH_3O-N), 114.25, 121.88, 142.72, 156.81 (Ar), 141.99 (CH=N), 159.75 (C=N).

General Procedure for the Preparation of β-Lactams 5 and 6.

Method A: A solution of the acid chloride **4** (15 mmol) in methylene chloride (10 cm^3) was slowly added at 0°C to a stirred solution of thioimidate **3** (10 mmol) and triethylamine (4.2 ml, 30 mmol) in methylene chloride (40 cm^3). The cooling bath was removed and the resulting mixture was stirred overnight at room temperature. The mixture was treated with diluted hydrochloric acid and next with saturated sodium hydrogen carbonate. The organic layer was separated and dried over $MgSO_4$; the solvent was evaporated. The crude β-lactam **5** was crystallized from ethanol or purified by column chromatography.

Method B: To a vigorously stirred suspension of the potassium salt of the corresponding carboxylic acid **4** (20 mmol), triethylamine (4.2 ml, 30 mmol), and thioimidate **3** (10 mmol) in methylene chloride (40 cm^3), at 0°C a solution of phenyl dichlorophosphate (3.0 ml, 20 mmol) in methylene chloride (10 cm^3) was added dropwise. After 2 h the mixture was heated to room temperature and stirred overnight. The reaction mixture was worked-up as above to afford **5** or/and **6**.

***trans*-1-(4-methoxyphenyl)-3-azido-4-methyl-4-methylthio-azetidin-2-one 5aa:** Yield 10% (A), 16% (B); m.p. 85-87 °C; IR(KBr): 2110, 1750 cm^{-1}; ^1H NMR: 1.80 (s, 3H, CH_3), 2.03 (s, 3H, CH_3S), 3.80 (s, 3H, CH_3O), 4.85 (s, 1H, H-C3), 6.88-6.90, 7.67-7.69 (m, 4H, Ar); ^{13}C NMR: 10.99 (CH_3S), 20.24 (CH_3), 55.41 (CH_3O), 70.53 (C4), 72.22 (C3), 114.50, 119.50, 129.15,, 157.10 (Ar), 159.66 (CO); MS m/z, (%): 278 M^+(24), 250 (18), 203 (44), 148 (100), 134 (17), 129 (44), 107 (14), 100 (35), 77 (18), 74 (19), 59 (35); Anal. calc. for $C_{12}H_{14}N_4O_2S$: C 51.78, H 5.07, N 20.13 S 11.52 %, Found C 51.88, H 4.90, N 19.94 S 11.60 %.

1D $^1H\{^1H\}$ NOEDIFF experiment: H-C3⇄CH_3S (1.9, 1.0), CH_3-C4→ortho-Anis (1.3).

***trans*-1-(4-methoxyphenyl)-3-phenoxy-4-methyl-4-methylthio-azetidin-2-one 5ab:** Yield 82% (A), 86% (B); m.p. 106.0-107.5 °C; IR(KBr): 1755 cm^{-1}; ^1H NMR: 1.77 (s, 3H, CH_3), 2.10 (s, 3H, CH_3S), 3.80 (s, 3H, CH_3O), 5.32 (s, 1H, H-C3), 6.90-6.92, 7.03-7.07 7.12-7.14, 7.32-7.35, 7.78-7.80 (m, 9H, Ar), ^{13}C NMR: 10.85 (CH_3S), 18.98 (CH_3), 55.39 (CH_3O), 71.14 (C4), 85.87 (C3), 114.47, 115.59, 119.54, 122.40, 123.41, 129.69, 157.00, 157.30 (Ar), 160.80 (CO) ; MS m/z, (%): 329 M^+(76), 180 (100), 160 (16), 148

(23), 87 (19); Anal. calc. for $C_{18}H_{19}NO_3S$: C 65.63, H 5.81, N 4.25, S 9.73 %, Found C 65.81, H 5.62, N 4.11, S 9.74 %.
1D $^1H\{^1H\}$ NOEDIFF experiment: H-C3⇄CH_3S (2.2, 1.5), H-C3→ortho-PhO (5.6), CH_3-C4→ortho-PhO (1.0), CH_3-C4→ortho-Anis (1.2).

trans-**1-(4-methoxyphenyl)-3-phthalimido-4-methyl-4-methylthio-azetidin-2-one 5ac**: Yield 88% (B); m.p. 167-169 °C; IR(KBr): 1730, 1765, 1785 cm^{-1}; ^1H NMR: 1.78 (s, 3H, CH_3), 2.19 (s, 3H, CH_3S), 3.82 (s, 3H, CH_3S), 5.55 (s, 1H, H-C3), 6.92-6.94, 7.75-7.79, 7.87-7.91 (m, 8H, Ar); ^{13}C NMR: 11.43 (CH_3S), 19.82 (CH_3), 55.40 (CH_3O), 63.24 (C3), 71.06 (C4), 114.42, 119.92, 123.82, 129.46, 131.50, 134.59, 157.02 (Ar), 159.42 (CO), 167.00 (CO) ; MS m/z, (%): 382 M^+(26), 233 (100), 186 (62), 160 (31), 148 (33), 104 (21); Anal. calc. for $C_{20}H_{18}N_2O_4S$: C 62.81, H 4.74, N 7.32, S 8.38 %, Found C 62.64, H 4.43, N 7.66, S 8.12 %.
1D $^1H\{^1H\}$ NOEDIFF experiment: H-C3⇄CH_3S (4.2, 1.5), CH_3-C4→ortho-Anis (1.0).

trans-**1-(4-methoxyphenyl)-3-phenoxy-4-methyl-4-(4-nitrophenylmethyl)-thio-azetidin-2-one 5bb**: Yield 81% (B); m.p. 99-101 °C; IR(KBr): 1775 cm^{-1}; ^1H NMR: 1.79 (s, 3H, CH_3), 3.81 (s, 3H, CH_3O), 3.81, 3.91 (AB, 2H, J=13.7), 5.21 (s, 1H, H-C), 6.85-6.87, 7.03-7.06, 7.32-7.34, 7.67-7.69, 8.01-8.03 (m, 13H, Ar), ^{13}C NMR 19.13 (CH_3), 33.04 ($-CH_2S$), 55.49 (CH_3O), 72.14 (C4), 86.60 (C3), 114.43, 115.55, 119.33, 122.65, 123.84, 129.23, 129.61, 129.77, 144.24, 147.20, 157.11, 157.21 (Ar), 160.41 (CO) ; MS m/z, (%): 450 M^+(13), 301 (100), 165 (43), 148 (20), 137 (16); Anal. calc. for $C_{24}H_{22}N_2O_5S$: C 63.99, H 4.92, N 6.22, S 7.12 %, Found C 63.70, H 4.68, N 6.91, S 7.12 %.

trans-**1-(4-methoxyphenyl)-3-phenoxy-4-(n-propyl)-4-methylthio-azetidin-2-one 5cb**: Yield 86% (B); m.p. 111-113 °C; IR(KBr): 1775 cm^{-1}; ^1H NMR: 0.83 (t, 3H, CH_3, J=7.3), 1.39-1.46 (m, 1H, 1/2 CH_2), 1.64-1.69 (m, 1H, 1/2 CH_2), 2.07 (s, 3H, CH_3S), 2.10-2.16 (m, 2H, CH_2), 3.80 (s, 3H, CH_3O), 5.33 (s, 1H, H-C3), 6.90-6.92, 7.05-7.07, 7.14-7.16, 7.32-7.35, 7.78-7.80 (m, 9H, Ar); ^{13}C NMR: 10.51 (CH_3S, 14.22 (CH_3), 18.31 (CH_2), 36.23 (CH_2), 55.39 (CH_3O), 74.31 (C4), 85.70 (C3), 114.44, 115.80, 119.48, 122.47, 129.68, 130.17, 156.92, 157.67 (Ar), 161.59 (CO); MS m/z, (%): 357 M^+(42), 310 (9), 264 (16), 67 (13); Anal. calc. for $C_{20}H_{23}NO_3S$: C 67.20, H 6.49, N 3.92, S 8.97 %, Found: C 67.13, H 6.46, N 3.91, S 9.01 %.

trans-**1-(4-methoxyphenyl)-3-phthalimido-4-(n-propyl)-4-methylthio--azetidin-2-one 5cc**: Yield 84% (B); m.p. 165-166 °C; IR(KBr): 1800, 1765, 1735 cm^{-1}; ^1H NMR: 0.72 (t, 3H, CH_3, J=7.4), 1.15-1.25 (m, 1H, 1/2 CH_2) , 1.42-1.52 (m, 1H, 1/2 CH_2), 2.05-2.15 (m, 1H, 1/2 CH_2) , 2.23-2.33 (m, 1H, 1/2 CH_2), 2.19 (s, 3H, CH_3S), 3.82 (s, 3H, CH_3O), 5.53 (s, 1H, H-C3), 6.92-6.94, 7.79-7.81, 7.91-7.93 (m, 8H, Ar); ^{13}C NMR: 10.53 (CH_3S), 14.44 (CH_3), 18.18 (CH_2), 35.90 (CH_2), 55.40 (CH_3O), 62.93 (C3), 75.45 (C4), 114.36, 120.78, 123.86, 129.56, 131.42, 134.64, 157.24 (Ar), 160.02 (CO), 167.10 (CO) ; MS m/z, (%): 410 M^+(14), 363 (15), 213 (43), 198 (18), 176 (18), 101 (14); Anal. calc. for $C_{22}H_{22}N_2O_4$ S: C 64.37, H 5.40, N 6.82, S 7.81 %, Found: C 64.40, H 5.27, N 7.11, S 7.90 %.

trans-**1-(4-methoxyphenyl)-3-azido-4-phenylmethyl-4-methylthio-azetidin-2-one 5da**: Yield 42 % (A), 46 % (B); m.p. 78.5-80.0 °C; IR(KBr): 2130, 1750 cm^{-1}; ^1H NMR: 1.97 (s, 3H, CH_3S), 3.46 and 3.50 (AB, 2H, J=14.7,

$\underline{CH_2}Ph$), 3.79 (s, 3H, CH_3O), 4.91 (s, 1H, H-C3), 6.83-6.85, 7.25-7.27, 7.31-7.33, 7.67-7.69 (m, 9H, Ar); ^{13}C NMR: 10.71 (CH_3S), 39.41 ($\underline{CH_2}Ph$), 55.39 (CH_3O), 72.44 (C3), 74.42 (C4), 114.34, 119.63, 127.35, 128.13, 129.46, 130.85, 133.98, 157.06 (Ar), 160.03 (CO); MS m/z, (%): 354 M^+(15), 326 (26), 279 (100), 235 (24), 224 (37), 176 (21), 151 (67), 130 (36), 119 (19), 91 (100); Anal. calc. for $C_{18}H_{18}N_4O_2S$: C 61.00, H 5.12, N 15.81, S 9.05 %, Found: C 61.00, H 4.90, N 15.90, S 8.97 %.

***trans*-1-(4-methoxyphenyl)-3-phenoxy-4-phenylmethyl-4-methylthio-azetidin-2-one 5db:** Yield 92 % (B); m.p. 124.5-126.0 °C; IR(KBr): 1750 cm^{-1}; ^1H NMR: 2.04 (s, 3H, CH_3S), 3.47 and 3.53 (AB, 2H, J=14.7, $\underline{CH_2}Ph$), 3.77 (s, 3H, CH_3O), 5.38 (s, 1H, H-C3), 6.78-6.80, 7.11-7.13, 7.17-7.19, 7.33-7.35, 7.66-7.68 (m, 14H, Ar); ^{13}C NMR: 10.69 (CH_3S), 39.44 ($\underline{CH_2}Ph$), 55.36 (CH_3O), 74.95 (C4), 86.22 (C3), 114.12, 116.01, 119.57, 122.59, 127.09, 127.82, 129.72, 130.12, 131.09, 134.20, 156.80, 157.37 (Ar), 161.50 (CO); MS m/z, (%): 405 M^+(21), 278 (13), 256 (100), 149 (15), 115 (19), 91 (24), 70 (13), 57 (16), 43 (17); Anal. calc. for $C_{24}H_{23}NO_3S$: C 71.09, H 5.72, N 3.45, S 7.91 %, Found: C 70.91, H 5.52, N 3.12, S 7.81 %.

***trans*-1-(4-methoxyphenyl)-3-phthalimido-4-phenylmethyl-4-methylthio--azetidin-2-one 5dc:** Yield 89 % (B); m.p. 157-159 °C; IR(KBr): 1790, 1765, 1725cm^{-1}; ^1H NMR: 2.21 (s, 3H, CH_3S), 3.48 and 3.71 (AB, 2H, J=15.6, $\underline{CH_2}Ph$), 3.80 (s, 3H, CH_3O), 5.60 (s, 1H, H-C3), 6.86-6.88, 6.90-6.95, 7.14-7.16, 7.68-7.71, 7.72-7.75 (m, 13H, Ar); ^{13}C NMR: 11.34 (CH_3S), 40.82 ($\underline{CH_2}Ph$), 55.40 (CH_3O), 62.60 (C3), 74.51 (C4), 114.26, 120.43, 123.48, 126.58, 127.93, 128.25, 129.57, 131.43, 134.06, 134.28, 157.09 (Ar), 160.05 (CO), 167.12 (CO); MS m/z, (%): 458 M^+(16), 410 (27), 309 (100), 261 (79), 233 (27), 104 (16), 91 (48); Anal. calc. for $C_{26}H_{22}N_2O_4S$: C 68.10, H 4.84, N 6.11, S 6.99 %, Found: C 68.31, H 4.92, N 6.06, S 6.85.

1D $^1H\{^1H\}$ NOEDIFF experiment: H-C3⇄CH_3S (3.1, 1.5), Ph$\underline{CH_2}$-C4→ no response

***trans*-1-(4-methoxyphenyl)-3-azido-4-methoxyiminomethyl-4-methylthio--azetidin-2-one 5ea:** Yield 27 % (B); m.p. 73-75 °C; IR(nujol): 2180, 1780, 1600 cm^{-1}; ^1H NMR: 2.02 (s, 3H, CH_3S), 3.80 (s, 3H, CH_3OAr), 3.95 (s, 3H, CH_3O-N), 4.96 (s, 1H, H-C3), 7.59 (s, 1H, CH=N), 6.87-6.89, 7.61-7.63 (m, 4H, Ar); ^{13}C NMR: 10.52 (CH_3S), 55.42 (CH_3OAr), 62.77 (CH_3O-N), 71.22 (C4), 73.81 (C3), 114.37, 120.09, 128.90, 145.00 (CH=N), 157.40 (Ar), 159.07 (CO); MS m/z, (%): 321 M^+(35), 246 (20), 215 (25), 191 (52), 149 (28), 144 (100), 134 (37), 113 (44), 102 (62); Anal. calc. for $C_{13}H_{15}N_5O_3S$: C 48.59, H 4.70, N 21.79, S 9.98 %, Found: C 48.55, H 4.40, N 21.90, S 10.00 %

1D $^1H\{^1H\}$ NOEDIFF experiment: H-C3⇄CH_3S (3.2, 1.3)

***cis*-1-(4-methoxyphenyl)-3-azido-4-methoxyiminomethyl-4-methylthio--azetidin-2-one 6ea:** Yield 18% (B); oil; IR ($CHCl_3$): 2100, 1765, 1610 cm^{-1}; ^1H NMR: 2.13 (s, 3H, CH_3S), 3.80 (s, 3H, CH_3OAr), 3.91 (s, 3H, CH_3O-N), 5.23 (s, 1H, H-C3), 7.72 (s, 1H, CH=N), 6.87-6.89, 7.61-7.63 (m, 4H, Ar); ^{13}C NMR: 11.59 (CH_3S), 54.47 (CH_3OAr), 61.73 (CH_3O-N), 71.78 (C3), 72.21 (C4), 113.59, 118.89, 127.94, 143.81 (CH=N), 156.36 (Ar), 159.00 (CO); Anal. calc. for $C_{13}H_{15}N_5O_3S$: C 48.59, H 4.70, N 21.79, S 9.98 %, Found: C 48.73, H 4.81, N 21.63, S 9.76 %

1D $^1H\{^1H\}$ NOEDIFF experiment: H-C3→ no response, CH_3S→ no response.

***trans*-1-(4-methoxyphenyl)-3-phenoxy-4-methoxyiminomethyl-4-methylthio-**

-azetidin-2-one 5eb: Yield 77 % (B); m.p. 110.0-111.5 °C; IK(nujol): 1770, 1610 cm^{-1}; ^1H NMR: 2.06 (s, 3H, CH_3S), 3.81 (s, 3H, CH_3OAr), 3.84 (s, 3H, CH_3O-N), 5.43 (s, 1H, H-C3), 7.60 (s, 1H, CH=N), 6.89-6.91, 7.06-7.08, 7.10-7.12, 7.32-7.35, 7.72-7.74 (m, 9H, Ar); ^{13}C NMR: 10.17 (CH_3S), 55.43 (CH_3OAr), 62.57 (CH_3O-N), 71.71 (C4), 87.65 (C3), 114.38, 116.00, 120.02, 122.87, 129.29, 129.70, 144.95 (CH=N), 156.90, 157.34 (Ar), 160.26 (CO) ; MS m/z,(%): 372 M^+,(36), 278 (46), 248 (23), 232 (19), 223 (100), 191 (16), 149 (14), 103 (14), 77 (10);; Anal. calc. for $C_{19}H_{20}N_2O_4S$: C 61.27, H 5.41, N 7.52, S 8.61 %, Found: C 61.27, H 5.60, N 7.82, S 8.86 %.

1D $^1H\{^1H\}$ NOEDIFF experiment: H-C3⇄CH_3S (2.9, 1.2), H-C3→ortho-PhO (6.8).

cis-**1-(4-methoxyphenyl)-3-phenoxy-4-methoxyiminomethyl-4-methylthio--azetidin-2-one 6eb:** Yield 9% (B); m.p. 123-125 °C; IR(nujol): 1760, 1615 cm^{-1}; ^1H NMR: 2.16 (s, 3H, CH_3O), 3.81 (s, 3H, CH_3OAr), 3.95 (s, 3H, CH_3O-N), 5.62 (s, 1H, H-C3), 7.77 (s, 1H, CH=N), 6.90-6.92, 7.07-7.09, 7.09-7.11, 7.31-7.34, 7.72-7.74 (m, 9H, Ar); ^{13}C NMR: 12.32 (CH_3S), 55.47 (CH_3OAr), 62.72 (CH_3O-N), 73.47 (C4), 86.81 (C3), 114.54, 115.79, 119.82, 122.68, 129.20, 129.57, 145.68 (CH=N), 157.24, 157.27 (Ar), 161.50 (CO); MS m/z, (%): 372 M^+(16), 279 (19), 223 (100), 191 (26), 149 (27), 103 (23), 77 (24); Anal. calc. for $C_{19}H_{20}N_2O_4S$: C 61.27, H 5.41, N 7.52, S 8.61 %, Found: C 61.44, H 5.76, N 7.64, S 8.56 %.

1D $^1H\{^1H\}$ NOEDIFF experiment: H-C3→ortho-PhO (7.8), CH_3S→ no response.

Desulfurization of β-lactams 5.

Method A: A solution of **5ab** or **5db** (5 mmol), tributyltinhydride (1.45 g, 5 mmol), and AIBN (80 mg, 0.5 mmol) in toluene (20 cm^3) was boiled during 2 h. Tributyltinhydride (1.45 g, 5 mmol) and AIBN (80 mg, 0.5 mmol) were added to the reaction mixture which was additionally refluxed 2 h. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel to afford *cis*-3,4-substituted β-lactam **7ab** or **7db**, respectively.

Method B: A solution of **5ab** or **5db** (5 mmol) in ethyl acetate (15 cm^3), containing an activated Raney-Nickel (4 g), was stirred overnight at room temperature under hydrogen . The catalyst was filtered off and washed with ethyl acetate (15 cm^3). The combined solvent was removed under reduced pressure and the residue was purified as above.

cis-**N-(4-methoxyphenyl)-3-phenoxy-4-methyl-azetidin-2-one 7ab:** Yield 35% (A), 55% (B); m.p. 141-142 °C; IR (KBr): 1755 cm^{-1}; ^1H NMR: 1.47 (d, 3H, J=6.2, CH_3), 3.80 (s, 3H, CH_3O), 4.51 (qq, 1H, J=6.2, J=4.9, H-C4), 5.32 (d, 1H, J=4.9, H-C3), 6.89-6.91, 7.01-7.05, 7.30-7.33, 7.38-7.40 (m, 9H, Ar); ^{13}C NMR: 12.89 (CH_3), 54.20 (C4), 55.47 (CH_3O), 79.62 (C3), 162.25 (CO), 114.55, 115.38, 118.69, 122.14, 129.61, 130.30, 156.50, 157.54 (Ar); MS m/z, (%): 283 M^+(21), 149 (100), 134 (36), 111 (32), 97 (48), 83 (40), 71 (52), 57 (72), 43 (69); Anal. calc. for $C_{17}H_{17}NO_3$: C 72.07, H 6.05, N 4.94 %, Found: C 72.19, H 5.85, N 5.02 %.

cis-**N-(4-methoxyphenyl)-3-phenoxy-4-methylphenyl-azetidin-2-one 7db:** Yield 64% (A), 70% (B); m.p. 129-130 °C; IR (KBr): 1745 cm^{-1}; ^1H NMR: 3.26 and 3.29 (ABMX, 2H, J=14.5, J=8.1, J=4.7, CH_2Ph), 3.79 (s, 3H, CH_3O), 4.63 (ABMX, 1H, J=8.1, J=4.7, J=5.1, H-C4), 5.36 (ABMX, d, 1H, J=5.1, H-C3), 6.78-6.80, 7.11-7.13, 7.17-7.19, 7.33-7.35, 7.66-7.68 (m, 14H, Ar); ^{13}C NMR: 33.92 (CH_2Ph), 55.45 (CH_3O), 55.59 (C4), 80.10 (C3), 162.96 (CO),

114.40, 115.87, 119.10, 122.26, 126.65, 128.53, 129.31, 129.52, 130.11, 137.29, 156.52, 157.73 (Ar); MS m/z, (%): 359 M^+(100), 240 (18), 210 (33), 149 (94), 134 (28), 117 (90), 91 (27); Anal. calc. for $C_{23}H_{21}NO_3$: C 76.86, H 5.89, N 3.90 %, Found: C 76.95, H 5.76, N 3.68 %.

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