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Staudinger Reaction of *Schiff* Bases of Acetylthiophene and Acetylpyridine with Ketenes. Diastereoselective Synthesis of 4-Heterosubstituted β-Lactams and their Conversion to β-Thiolactams

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Summary. Arylimines of 2-acetylthiophene and 2-, 3-, and 4-acetylpyridines react with ketenes yielding 4-heterosubstituted β-lactams. Reactions of imines with ketenes were proved to be diastereoselective. The stereochemistry of the products was confirmed by X-ray analysis. β-Lactams treated with *Lawesson*'s reagent gave β-thiolactams.

Keywords. β-Lactams; β-Thiolactams; *Staudinger* reaction; *Schiff* bases; Ketenes.

Introduction

The 2-azetidinone ring is the key structural unit of the most widely employed β-lactam antibiotics [1]. The need for new drugs displaying broader antibacterial activity has motivated organic chemists to design new functionalized azetidinones. There are numerous methods used for the construction of this heterocyclic ring. Among them ketene-imine cycloaddition, known as *Staudinger* reaction is the most often employed [2–4]. The stereochemical result of the *Staudinger* reaction depends on a structure of imine, on the ketene precursor, the sequence of reagent addition, and the solvent. Many diastereoselective variants of this reaction have been described by *Palomo et al*. [5]. The presence on the β-lactam ring of various substituents influences their potential biological activity. For example, *Carr et al*. [6] observed that lipase-catalysed resolution of β-lactams was dependent on the steric and electronic nature of the substituents. Introduction of heterocyclic substituents at the C-3 and C-4 carbon atoms of the β-lactam ring makes these compounds interesting for the study. Recently, *Troisi et al.* [7] reported stereoselective synthesis of 4-heterosubstituted β-lactams bearing benzothiazole, thiazole, or pyridine moiety *via* metal catalysed carbonylative cycloaddition of imines, derivatives of appropriates aldehydes with allyl bromide.

Apart from the chemical modification of the substituents attached to the β-lactam ring, the synthesis of β-thiolactams has found considerable interest [8–10]. The thioanalogous of penicillins and cephalosporins were shown to possess antibiotic activity [11]. One of synthesis strategies for thiolactams is thionation of the corresponding azetidinones by *Lawesson*'s or *Davy*'s reagents.

Continuing our study on the synthesis of β-lactams [12, 13], we were interested in the construction of azetidinones, which were substituted with a methyl group and thiophene, or pyridine ring at the carbon atom C-3. Next we focused our attention on the thionation reaction of thus synthesized azetidinones by *Lawesson*'s reagent.

Results and Discussion

Our approach to the synthesis of 4-heterosubstituted β-lactams consisted in the cycloaddition of ketenes

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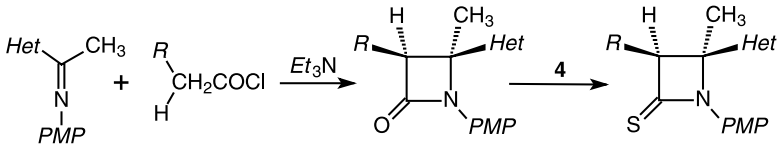

1a–1d **2a–2d** **3a–3m** **5a–5d**

			Het	*R*				*Het*	*R*
1a	**2a**	**3a**	Thienyl	OC_6H_5	**1c**	**2b**	**3i**	3-*py*	$OCH_2C_6H_5$
1a	**2b**	**3b**	Thienyl	$OCH_2C_6H_5$	**1c**	**2c**	**3j**	3-*py*	OCH_3
1a	**2c**	**3c**	Thienyl	OCH_3	**1d**	**2a**	**3k**	4-*py*	OC_6H_5
1a	**2d**	**3d**	Thienyl	*Pht*N	**1d**	**2b**	**3l**	4-*py*	$OCH_2C_6H_5$
1b	**2a**	**3e**	2-*py*	OC_6H_5	**1d**	**2c**	**3m**	4-*py*	OCH_3
1b	**2b**	**3f**	2-*py*	$OCH_2C_6H_5$		**3a**	**5a**	Thienyl	OC_6H_5
1b	**2c**	**3g**	2-*py*	OCH_3		**3e**	**5b**	2-*py*	OC_6H_5
1c	**2a**	**3h**	3-*py*	OC_6H_5		**3h**	**5c**	3-*py*	OC_6H_5

Scheme 1

to imines **1**. Ketenes were generated *in situ* from appropriate acid chlorides **2a**–**2d** in the presence of triethylamine. As imine substrates for the *Staudinger* reaction we used the *Schiff* bases of 2-acetylthiophene and 2-, 3-, and 4-acetylpyridines. Reactions of imines **1a**–**1d** with acid chlorides **2a**–**2d** were carried out in methylene chloride in the presence of triethylamine (Scheme 1). The obtained products **3a**–**3m** were separated and purified by column chromatography.

The β-lactam structure of **3a**–**3m** was established on the basis of analytical and spectral data. For example the IR spectrum of **3a** revealed the intensive band at 1746 cm^{-1} characteristic for the carbonyl group of azetidinone ring. In the ^1H NMR spectrum of **3a** the singlet at $\delta = 2.18$ ppm corresponding to methyl protons was observed. The protons of the methoxy group appeared as singlet at $\delta = 3.77$ ppm. Aromatic protons resonated as multiplet in the range of 6.82–7.34 ppm. The presence of one signal at $\delta = 5.23$ ppm of H-3 proton indicates that in the reaction of **1a** with phenoxyacetic acid chloride (**2a**) only one diastereoisomer **3a** was produced (Scheme 1). Inspecting the ^1H NMR spectrum of the crude reaction mixture displayed traces of the second diastereoisomer. The ^{13}C NMR spectrum of **3a** revealed the signal of the carbonyl carbon atom (C=O) at $\delta = 161.8$ ppm. The MS spectrum showed the molecular peak at $m/z = 365$.

To assign the relative configuration at carbon C3 of **3a**, a N*O*ESY experiment was performed. The significant cross peak correlating the two signals at $\delta = 5.23$ and 2.18 ppm indicates that the proton H-3 and methyl group are positioned on the same side of the azetidinone ring. The structure of β-lactam **3a** was finally confirmed by X-ray analysis. A perspective view of the molecule with the atomic numbering scheme is given in Fig. 1.

The reaction of **1a**–**1d** with **2a**–**2d** carried out under similar conditions afforded compounds **3b**–**3j** as single diastereoisomers in good yields (43–74%) (Scheme 1). Their spectral features were similar to those of **3a**.

Comparison of the above reactions showed, that the yields of products were influenced by the character of substrates. The *Schiff* base **1a** containing the thiophene ring was more reactive towards ketenes than **1b**–**1d** possessing the 2-, 3-, and 4-pyridyl unit because the reactions of imine **1a** with appropriate acid chlorides **2a**–**2d** yielded **3a**–**3d** in good yield (47–81%), whereas yields of **3e**–**3k** were significantly lower (34–74%).

To compare the selectivity of β-lactam synthesis and yields of products we applied another procedure [14]. It involves the reaction of imines with carbon acids in the presence of chlorosulphinylmethy-

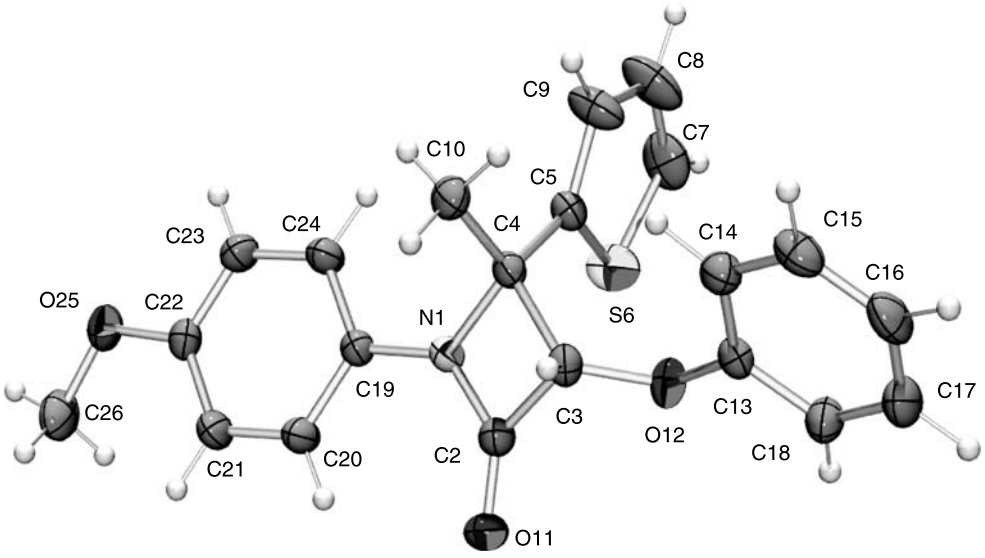

Fig. 1. A perspective view of the molecule of **3a** with the crystallographic atom numbering

lene-*N*,*N*-dimethylammonium chloride, formed by the reaction of thionyl chloride with *DMF* (see Experimental, *method b*). We used imines **1a**–**1d** and phenoxy- or methoxyacetic acids. The products (*method b*) were found to be identical in all respects with those prepared in the reaction of imines and acid chlorides (*method a*), but yields of products prepared *via b* were lower than those *via a* (see Experimental).

Subsequently, we were interested in synthesis of β-thiolactams. Thionation of **3a** with *Lawesson*'s reagent (**4**) in dry *THF* yielded the corresponding 2-azetidinethione **5a** (Scheme 1). Its structure was consistent with analytical and spectra data. The ^{13}C NMR spectrum showed a signal at $\delta = 192$ ppm assigned to the carbon atom of C=S group. The MS spectrum of **5a** revealed the molecular ion at $m/z = 381$. The reaction of **3e** and **3h** with **4** carried out in *THF* yielded the appropriate azetidinethiones **5b** and **5c**. Analytical and spectral data of the obtained products confirm the β-thiolactam structure. The β-lactam **3k** bearing the 4-pyridinyl substituent did not undergo thionation with *Lawesson*'s reagent.

In conclusion, we synthesized novel β-lactams and β-thiolactams functionalized with heterocycles. The presence of thiophene and pyridine moieties at the β-lactam ring makes this class of compounds interesting for the study of their potential biological and pharmacological activities.

Experimental

Melting points were determined on a *Boetius* hot stage apparatus. IR spectra: Bruker IFS 48 in KBr pellets. NMR spectra: Bruker AMX 500 (^1H: 500.14 MHz, ^{13}C: 125.76 MHz), Bruker Avance II 300 (^1H: 300.18 MHz, ^{13}C: 75.48 MHz), in $CDCl_3$ with *TMS* as an internal standard. Mass spectra: Finningan Mat 95 (EI, 70 eV). Microanalyses were performed with Euro EA 3000 Elemental Analyzer; their results agreed satisfactorily with the calculated values.

Compounds **1a**–**1d** were prepared from 2-, 3-, 4-acetylpyridines, or 2-acetylthiophene and *p*-methoxyaniline, in the presence of a catalytic amount of *Para*-toluenesulfonic acid according to the procedure of Ref. [15].

*General Procedure of the Preparation of β-Lactams **3***

Method a: To a stirred and cooled (0–5°C) solution of 0.01 mol imine **1** and 0.03 mol triethylamine in dry CH_2Cl_2, a solution of 0.01 mol **2** in dry CH_2Cl_2 was added dropwise. The reaction mixture was allowed to come to room temperature and stirred overnight. After washing with water and 1 *N* HCl, the organic layer was dried ($MgSO_4$). The solvent was evaporated to leave an oily product which was purified by column chromatography on silica gel using $CHCl_3$ as eluent. Recrystallization from methanol furnished the pure products as colourless prisms.

Method b: A mixture of toluene (1.2 cm^3, 0.011 mol), *DMF* (1 cm^3, 0.012 mol), and thionyl chloride (0.8 cm^3, 0.011 mol) was placed in a dropping funnel. After 5 min two phases appeared and the lower layer was separated (chlorosulphinylmethylene *N*,*N*-dimethylammonium chloride). This reagent (0.01 mol) was added dropwise to a cooled and stirred solution or suspension of carboxylic acid (0.01 mol) in CH_2Cl_2. After 10 min 0.01 mol **1** and subsequently 0.03 mol triethylamine in CH_2Cl_2 were added. The reaction mixture was stirred overnight at room temperature. After washing with H_2O and dry-

ing ($MgSO_4$), the crude product was purified in similar way as described in *Method a*.

(3RS,4RS)-1-(4-Methoxyphenyl)-4-methyl-3-phenoxy-4-(2-thienyl)azetidin-2-one (**3a**, $C_{21}H_{19}NO_3S$)
Colourless prisms; mp 106–108°C; yield 81% (a), 39% (b); IR (KBr): $\bar{\nu} = 1746$ (C=O) cm^{-1}; ^1H NMR (500.14 MHz, $CDCl_3$): $\delta = 2.18$ (s, CH_3), 3.77 (s, OCH_3), 5.23 (s, H-3), 6.82 (m, 3CH arom, 1CH thienyl), 6.93 (m, 2CH arom), 7.06 (dd, $J = 3.6$, 1.2 Hz, 1CH thienyl), 7.16–7.21 (m, 2CH arom), 7.25 (dd, $J = 5.0$, 1.2 Hz, 1CH thienyl), 7.34 (m, 2CH arom) ppm; ^{13}C NMR (125.76 MHz, $CDCl_3$): $\delta = 22.8$ (CH_3), 55.4 (OCH_3), 66.1 (C-4), 88.3 (C-3), 114.4, 115.8, 120.1, 122.2, 126.5, 126.9, 127.3, 129.3, 140.9, 156.7, 157.1 (C arom), 161.8 (C=O) ppm; MS (EI, 70 eV): m/z (%) = 365 (5) $[M]^{+\bullet}$, 216 (100).

Crystal structure analysis: Compound **3a** with formula $C_{21}H_{19}NO_3S$ crystallizes in the monoclinic system, space group $P2_1/n$, with unit cell parameters $a = 13.7323(2)$, $b = 10.2084(1)$, $c = 13.8834(2)$ Å, $\beta = 106.78(1)°$, $V = 1863.4(1)$ $Å^3$, $Z = 4$. A total of 4252 independent reflections (R(int) = 0.0215) were collected up to theta angle 27.48° with 99.6% completeness on a sample (size $0.3 \times 0.25 \times 0.15$ mm^3) using a KappaCCD diffractometer and MoKα radiation. The structure was solved by direct methods with SHELXS97 [16] and refined by the full-matrix least-squares method on F^2 using SHELXL97 [17] program. Final discrepancy indices for $I > 2\sigma(I)$ were equal $R1 = 0.0492$, w$R2 = 0.1275$ and $R1 = 0.0639$, w$R2 = 0.1400$ for all data. The final difference *Fourier* map of electron density was featureless with the largest peak and hole of 0.343 and -0.507 e.$Å^{-3}$. All calculations and molecular graphics were done using the WinGX package [18]. The structural data were deposited at the Cambridge Crystallographic Data Centre. These data can be obtained free of charge *via* www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk) under reference number CCDC 614292.

(3RS,4RS)-3-Benzyloxy-1-(4-methoxyphenyl)-4-methyl-4-(2-thienyl)azetidin-2-one (**3b**, $C_{22}H_{21}NO_3S$)
Colourless prisms; mp 135–136°C; yield 59% (a); IR (KBr): $\bar{\nu} = 1753$ (C=O) cm^{-1}; ^1H NMR (300.18 MHz, $CDCl_3$): $\delta = 1.99$ (s, CH_3), 3.74 (s, OCH_3), 4.38 (d, 1H, $J = 11.3$ Hz, CH_2), 4.43 (d, 1H, $J = 11.3$ Hz, CH_2), 4.66 (s, H-3), 6.78 (m, 2CH arom), 7.07 (m, 3CH arom), 7.10 (dd, $J = 3.6$, 1.3 Hz, 1CH thienyl), 7.28–7.34 (m, 5CH arom), 7.37 (dd, $J = 5.0$, 1.3 Hz, 1CH thienyl) ppm; ^{13}C NMR (75.48 MHz, $CDCl_3$): $\delta = 22.9$ (CH_3), 55.4 (OCH_3), 65.1 (C-4), 72.9 (CH_2OPh), 89.9 (C-3), 114.4, 119.8, 126.4, 127.1, 127.3, 128.0, 128.2, 128.3, 129.5, 136.4, 141.7, 156.5 (C arom), 162.9 (C=O) ppm; MS (EI, 70 eV): m/z (%) = 379 (8) $[M]^{+\bullet}$, 230 (100).

(3RS,4RS)-3-Methoxy-1-(4-methoxyphenyl)-4-methyl-4-(2-thienyl)azetidin-2-one (**3c**, $C_{16}H_{17}NO_3S$)
Colourless prisms; mp 123–125°C; yield 64% (a), 38% (b); IR (KBr): $\bar{\nu} = 1746$ (C=O) cm^{-1}; ^1H NMR (300.18 MHz, $CDCl_3$): $\delta = 2.06$ (s, CH_3), 3.25 (s, OCH_3), 3.75 (s, OCH_3), 4.44 (s, H-3), 6.78 (m, 2CH arom), 7.05 (dd, $J = 5.0$, 3.6 Hz, 1CH thienyl), 7.11 (dd, $J = 3.6$, 1.3 Hz, 1CH thienyl), 7.25–7.30 (m, 3 CH arom), 7.37 (dd, $J = 5.0$, 1.3 Hz, 1CH thienyl) ppm; ^{13}C NMR (75.48 MHz, $CDCl_3$): $\delta = 23.0$ (CH_3), 55.4 (OCH_3), 58.7 (OCH_3) 65.6 (C-4), 92.1 (C-3), 114.4, 119.8, 126.4, 126.8, 127.3, 129.4, 141.5, 156.5 (C arom), 162.8 (C=O) ppm; MS (EI, 70 eV): m/z (%) = 303 (4) $[M]^{+\bullet}$, 154 (100).

(3RS,4RS)-1-(4-Methoxyphenyl)-4-methyl-3-phtalimide-4-(2-thienyl)azetidin-2-one (**3d**, $C_{23}H_{18}N_2O_4S$)
Colourless prisms; mp 233–235°C; yield 47% (b); IR (KBr): $\bar{\nu} = 1718$ (C=O), 1758 (C=O) 1781 (C=O) cm^{-1}; ^1H NMR (500.14 MHz, $CDCl_3$): $\delta = 1.96$ (s, CH_3), 3.77 (s, OCH_3), 5.35 (s, H-3), 6.84 (m, 2CH arom), 7.01 (dd, $J = 5.0$, 3.6 Hz, 1CH thienyl), 7.05 (dd, $J = 3.6$, 1.2 Hz, 1CH thienyl), 7.32 (dd, $J = 5.0$, 1.2 Hz, 1CH thienyl), 7.40 (m, 2CH arom), 7.77 (dd, $J = 5.6$, 3.0 Hz, 2CH arom), 7.89 (dd, $J = 5.6$, 3.0 Hz, 2CH arom) ppm; ^{13}C NMR (125.76 MHz, $CDCl_3$): $\delta = 18.9$ (CH_3), 55.4 (OCH_3), 65.1 (C-4), 67.6 (C-3), 114.4, 120.0, 123.9, 124.9, 125.9, 127.5, 129.8, 131.7, 134.6, 145.7, 156.7 (C arom) 160.4 (C=O), 167.0 (C=O) ppm; MS (EI, 70 eV): m/z (%) = 418 (8) $[M]^{+\bullet}$, 269 (100).

(3RS,4RS)-1-(4-Methoxyphenyl)-4-methyl-3-phenoxy-4-(2-pyridinyl)azetidin-2-one (**3e**, $C_{22}H_{20}N_2O_3$)
Colourless prisms; mp 108–110°C; yield 68% (a), 42% (b); IR (KBr): $\bar{\nu} = 1751$ (C=O) cm^{-1}; ^1H NMR (500.14 MHz, $CDCl_3$): $\delta = 2.23$ (s, CH_3), 3.76 (s, OCH_3), 5.19 (s, H-3), 6.73–6.82 (m, 4CH arom), 6.89 (t, $J = 7.4$ Hz, 1CH py), 7.28 (m, 2CH arom), 7.51 (d, $J = 7.8$ Hz, 1CH py), 7.60 (dd, $J = 7.8$, 1.8 Hz, 1CH py), 8.51 (dd, $J = 4.9$, 0.9 Hz, 1CH py) ppm, ^{13}C NMR (125.76 MHz, $CDCl_3$): $\delta = 20.1$ (CH_3), 55.4 (OCH_3), 76.5 (C-4), 88.6 (C-3), 114.4, 115.8, 119.6, 122.2, 122.8, 129.2, 129.3, 135.9, 148.9, 156.1, 156.9 (C arom), 162.1 (C=O) ppm; MS (EI, 70 eV): m/z (%) = 360 (12) $[M]^{+\bullet}$, 267 (100).

(3RS,4RS)-3-Benzyloxy-1-(4-methoxyphenyl)-4-methyl-4-(2-pyridinyl)azetidin-2-one (**3f**, $C_{23}H_{22}N_2O_3$)
Colourless prisms; mp 128–129°C; yield 49% (a); IR (KBr): $\bar{\nu} = 1745$ (C=O) cm^{-1}; ^1H NMR (300.18 MHz, $CDCl_3$): $\delta =$ 2.09 (s, CH_3), 3.75 (s, OCH_3), 4.31 (d, 1H, $J = 11.4$ Hz, CH_2), 4.37 (d, 1H, $J = 11.4$ Hz, CH_2), 4.65 (s, H-3), 6.78 (m, 2CH arom), 6.95 (m, 1CH py), 7.21–7.28 (m, 6CH arom), 7.48 (d, $J = 8.0$ Hz, 1CH py), 7.66 (td, $J = 7.8$, 1.8 Hz, 1CH py) 8.68 (m, 1CH py) ppm; ^{13}C NMR (75.48 MHz, $CDCl_3$): $\delta = 20.4$ (CH_3), 55.4 (OCH_3), 69.6 (C-4), 72.5 (CH_2OPh), 90.2 (C-3), 114.4, 119.5, 122.7, 123.0, 127.8, 127.9, 128.2, 129.5, 136.3, 149.1, 156.3, 157.3 (C arom), 163.2 (C=O) ppm; MS (EI, 70 eV): m/z (%) = 374 (100) $[M]^{+\bullet}$.

(3RS,4RS)-3-Methoxy-1-(4-methoxyphenyl)-4-methyl-4-(2-pyridinyl)azetidin-2-one (**3g**, $C_{17}H_{18}N_2O_3$)
Colourless prisms; mp 85–87°C; yield 53% (a), 38% (b); IR (KBr): $\bar{\nu} = 1743$ (C=O) cm^{-1}; ^1H NMR (300.18 MHz, $CDCl_3$): $\delta = 2.11$ (s, 3H, CH_3), 3.17 (s, OCH_3), 3.75 (s, OCH_3), 4.47 (s, H-3), 6.80 (m, 2CH arom), 7.28–7.30 (m,

3CH arom, 1CH py), 7.44 (d, $J = 8.0$ Hz, 1CH py), 7.66 (td, $J = 7.8$, 1.8 Hz, 1CH py) 8.68 (m, 1CH py) ppm; ^{13}C NMR (75.48 MHz, $CDCl_3$): $\delta = 20.5$ (CH_3), 55.4 (OCH_3), 58.7 (OCH_3) 65.9 (C-4), 92.4 (C-3), 114.2, 119.5, 121.5, 122.8, 129.5, 137.0, 156.3 (C arom), 163.2 (C=O) ppm; MS (EI, 70 eV): m/z (%) = 298 (28) $[M]^{+\bullet}$, 149 (100).

(3RS,4RS)-1-(4-Methoxyphenyl)-4-methyl-3-phenoxy-4-(3-pyridinyl)azetidin-2-one (**3h**, $C_{22}H_{20}N_2O_3$)
Colourless prisms; mp 150–152°C; yield 67% (a), 32% (b); IR (KBr): $\bar{\nu} = 1744$ (C=O) cm^{-1}; ^{1}H NMR (500.14 MHz, $CDCl_3$): $\delta = 2.11$ (s, CH_3), 3.69 (s, OCH_3), 5.16 (s, H-3), 6.65 (m, 2CH arom), 6.74 (m, 2CH arom), 6.85 (t, $J = 7.4$ Hz, 1CH arom), 7.09 (m, 2CH arom), 7.15 (ddd, $J = 8.1$, 4.9, 0.7 Hz, 1CH py), 7.20 (m, 2CH arom), 7.66 (m, 1CH py), 8.45 (dd, $J = 4.6$, 1.4 Hz, 1CH py), 8.58 (d, $J = 2.3$ Hz, 1CH py) ppm; ^{13}C NMR (125.76 MHz, $CDCl_3$): $\delta = 21.2$ (CH_3), 55.4 (OCH_3), 66.4 (C-4), 87.8 (C-3), 114.6, 115.5, 119.7, 122.4, 122.8, 129.4, 132.4, 135.2, 148.5, 149.5 156.5, 156.7 (C arom), 161.7 (C=O) ppm; MS (EI, 70 eV): m/z (%) = 360 (18) $[M]^{+\bullet}$, 211 (100).

(3RS,4RS)-3-Benzyloxy-1-(4-methoxyphenyl)-4-methyl-4-(3-pyridinyl)azetidin-2-one (**3i**, $C_{23}H_{22}N_2O_3$)
Colourless prisms; mp 143–145°C; yield 74% (a); IR (KBr): $\bar{\nu} = 1747$ (C=O) cm^{-1}; ^{1}H NMR (300.18 MHz, $CDCl_3$): $\delta = 1.98$ (s, CH_3), 3.74 (s, OCH_3), 4.29 (d, 1H, $J = 11.6$. Hz, CH_2), 4.47 (d, 1H, $J = 11.6$. Hz, CH_2), 4.62 (s, H-3), 6.77 (m, 2CH arom), 6.96 (m, 2CH arom) 7.19–7.27 (m, 5CH arom, 1CH py), 7.73 (m, 1CH py), 8.62 (d, $J = 4.8$, 1.5 Hz, 1CH py), 8.68 (d, $J = 2.1$ Hz, 1CH py) ppm; ^{13}C NMR (75.48 MHz, $CDCl_3$): $\delta = 21.1$ (CH_3), 55.4 (OCH_3), 66.1 (C-4), 72.9 (CH_2), 89.8 (C-3), 114.5, 119.5, 123.1, 128.1, 128.2, 128.4, 129.2, 133.2, 135.6, 136.1, 148.4, 149.4, 156.5 (C arom), 163.1 (C=O) ppm; MS (EI, 70 eV): m/z (%) = 374 (100) $[M]^{+\bullet}$.

(3RS,4RS)-3-Methoxy-1-(4-methoxyphenyl)-4-methyl-4-(3-pyridinyl)azetidin-2-one (**3j**, $C_{17}H_{18}N_2O_3$)
Colourless prisms; mp 93–95°C; yield 47% (a), 34% (b); IR (KBr): $\bar{\nu} = 1747$ (C=O) cm^{-1}; ^{1}H NMR (300.18 MHz, $CDCl_3$): $\delta = 2.09$ (s, CH_3), 3.19 (s, OCH_3), 3.74 (s, OCH_3), 4.45 (s, H-3), 6.79 (m, 2CH arom), 7.22 (m, 2CH arom), 7.33 (m, 1CH py), 7.77 (ddd, $J = 8.0$, 2.4, 1.6 Hz, 1CH py), 8.60 (dd, $J = 4.8$, 1.6 Hz, 1CH py), 8.72 (d, $J = 1.9$ Hz, 1CH py) ppm; ^{13}C NMR (75.48 MHz, $CDCl_3$): $\delta = 21.4$ (CH_3), 55.4 (OCH_3), 58.4 (OCH_3), 65.9 (C-4), 91.9 (C-3), 114.5, 119.5, 123.2, 129.1, 133.2, 135.6, 148.2, 149.2, 156.5 (C arom), 162.9 (C=O) ppm; MS (EI, 70 eV): m/z (%) = 298 (23) $[M]^{+\bullet}$, 149 (100).

(3RS,4RS)-1-(4-Methoxyphenyl)-4-methyl-3-phenoxy-4-(4-pyridinyl)azetidin-2-one (**3k**, $C_{22}H_{20}N_2O_3$)
Colourless prisms; mp 145–147°C; yield 53% (a), 38% (b); IR (KBr): $\bar{\nu} = 1751$ (C=O) cm^{-1}; ^{1}H NMR (500.14 MHz, $CDCl_3$): $\delta = 2.13$ (s, CH_3), 3.76 (s, OCH_3), 5.23 (s, H-3), 6.72 (m, 2CH arom), 6.93 (m, 2CH arom), 6.93 (m, 1CH arom), 7.17 (m, 2CH), 7.24–7.30 (m, 2CH arom, 2CH py), 8.55 (d, $J = 4.6$, 1.5 Hz, 2CH py) ppm; ^{13}C NMR (125.76 MHz, $CDCl_3$): $\delta = 20.9$ (CH_3), 55.4 (OCH_3), 67.1 (C-4), 87.8 (C-3), 114.6, 115.5, 119.6, 122.2, 122.5, 129.4, 145.9, 149.8, 156.5, 156.7 (C arom), 161.6 (C=O) ppm; MS (EI, 70 eV): m/z (%) = 360 (90) $[M]^{+\bullet}$, 211 (100).

(3RS,4RS)-3-Benzyloxy-1-(4-methoxyphenyl)-4-methyl-4-(4-pyridinyl)azetidin-2-one (**3l**, $C_{23}H_{22}N_2O_3$)
Colourless prisms; mp 148–150°C; yield 67% (a); IR (KBr): $\bar{\nu} = 1747$ (C=O) cm^{-1}; ^{1}H NMR (300.18 MHz, $CDCl_3$): $\delta =$ 1.91 (s, CH_3), 3.72 (s, OCH_3), 4.30 (d, 1H, $J = 11.5$ Hz, CH_2), 4.46 (d, 1H, $J = 11.5$ Hz, CH_2), 4.60 (s, H-3), 6.75 (m, 2CH arom), 6.92 (m, 2CH py), 7.16–7.28 (m, 7CH arom, py), 8.60 (dd, $J = 4.6$, 1.5 Hz, 2CH py) ppm; ^{13}C NMR (75.48 MHz, $CDCl_3$): $\delta = 20.9$ (CH_3), 55.4 (OCH_3), 66.8 (OCH_3) 73.1 (C-4), 90.0 (C-3), 114.5, 119.5, 122.4, 128.1, 128.2, 128.5, 129.2, 136.1, 149.9, 156.5 (C arom), 162.9 (C=O) ppm; MS (EI, 70 eV): m/z (%) = 374 (25) $[M]^{+\bullet}$, 91 (100).

(3RS,4RS)-3-Methoxy-1-(4-methoxyphenyl)-4-methyl-4-(4-pyridinyl)azetidin-2-one (**3m**, $C_{17}H_{18}N_2O_3$)
Colourless prisms; mp 94–96°C; yield 43% (a); IR (KBr): $\bar{\nu} = 1734$ (C=O) cm^{-1}; ^{1}H NMR (500.14 MHz, $CDCl_3$): $\delta = 2.03$ (s, CH_3), 3.21 (s, OCH_3), 3.76 (s, OCH_3), 4.44 (s, H-3), 6.80 (m, 2CH arom), 7.21 (m, 2CH arom), 7.34 (dd, $J = 4.5$, 1.6 Hz, 2CH py), 8.64 (dd, $J = 4.5$, 1.6 Hz, 2CH py) ppm; ^{13}C NMR (125.76 MHz, $CDCl_3$): $\delta = 21.1$ (CH_3), 55.4 (OCH_3), 58.7 (OCH_3), 66.7 (C-4), 92.0 (C-3), 114.5, 119.5, 122.2, 129.2, 146.7, 150.0, 156.6 (C arom), 162.8 (C=O) ppm; MS (EI, 70 eV): m/z (%) = 298 (26) $[M]^{+\bullet}$, 149 (100).

General Procedure of the Preparation of β-Thiolactams ***5*** *by Thionation with Lawesson's Reagent*
To 0.0028 mol **3** dissolved in 10 cm^3 dry *THF*, 0.6 g *Lawesson*'s reagent (**4**, 0.0014 mol, 0.5 equivalent) were added in small portions. The reaction mixture was refluxed for 10 h. After evaporation of the solvent the crude product was purified by column chromatography on silica gel using chloroform as eluent. Recrystallization from methanol furnished the pure products **5** as pale yellow prisms.

(3RS,4RS)-1-(4-Methoxyphenyl)-4-methyl-3-phenoxy-4-(2-thienyl)azetidin-2-thione (**5a**, $C_{21}H_{19}NO_2S_2$)
Pale yellow prisms; mp 93–95°C; yield 82%; ^{1}H NMR (500.14 MHz, $CDCl_3$): $\delta = 2.18$ (s, CH_3), 3.78 (s, OCH_3), 5.04 (s, H-3), 6.82–6.85 (m, 4CH arom), 6.93–6.97 (m, 1CH arom, 1CH thienyl), 7.10 (dd, $J = 3.6$, 1.2 Hz, 1CH thienyl), 7.18 (m, 1CH thienyl), 7.30 (dd, $J = 5.0$, 1.2 Hz, 1CH thienyl), 7.80 (m, 2CH arom) ppm; ^{13}C NMR (125.76 MHz, $CDCl_3$): $\delta = 22.4$ (CH_3), 55.4 (OCH_3), 74.4 (C-4), 86.5 (C-3), 114.1, 116.1, 121.6, 122.3, 126.8, 126.9, 127.0, 127.6, 129.2, 139.7, 157.1, 157.8 (C arom), 192.4 (C=S) ppm; MS (EI, 70 eV): m/z (%) = 381 (13) $[M]^{+\bullet}$, 216 (100).

(3RS,4RS)-1-(4-Methoxyphenyl)-4-methyl-3-phenoxy-4-(2-pyridinyl)azetidin-2-thione (**5b**, $C_{22}H_{20}NO_2S$)
Pale yellow prisms; mp 95–97°C; yield 52%; ^{1}H NMR (500.14 MHz, $CDCl_3$): $\delta = 2.28$ (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 5.03 (s, H-3), 6.80–6.86 (m, 4CH arom), 6.94 (t,

$J = 7.4$ Hz, 1CH py), 7.16–7.22 (m, 3CH arom), 7.55 (d, $J = 7.9$ Hz, 1CH py), 7.66 (m, 1CH py) 7.83 (m, 2CH arom), 8.57 (m, 1CH py) ppm; ^{13}C NMR (125.76 MHz, $CDCl_3$): $\delta = 19.8$ (CH_3), 55.5 (OCH_3), 78.3 (C-4), 86.4 (C-3), 114.2, 114.5, 116.3, 121.2, 122.4, 123.2, 129.2, 130.0, 136.2, 149.1, 155.4, 157.1, 157.8 (C arom), 192.6 (C=S) ppm; MS (EI, 70 eV): m/z (%) = 376 (11) $[M]^{+\bullet}$, 283 (100).

(3RS,4RS)-1-(4-Methoxyphenyl)-4-methyl-3-phenoxy-4-(3-pyridinyl)azetidin-2-thione (**5c**, $C_{22}H_{20}NO_2S$)
Pale yellow prisms; mp 95–97°C; yield 36%; ^{1}H NMR (500.14 MHz, $CDCl_3$): $\delta = 2.14$ (s, CH_3), 3.71 (s, OCH_3), 4.98 (s, H-3), 6.64 (m, 2CH arom), 6.75 (m, 2CH arom), 6.86 (t, $J = 7.7$ Hz, 1CH arom), 7.09–7.19 (m, 2CH arom, 1CH py), 7.21 (m, 2CH arom), 7.70 (m, 1CH py), 8.45 (m, 1CH py), 8.58 (d, $J = 2.3$ Hz, 1CH py) ppm; ^{13}C NMR (125.76 MHz, $CDCl_3$): $\delta = 20.7$ (CH_3), 55.5 (OCH_3), 66.5 (C-4), 85.6 (C-3), 114.3, 115.9, 121.2, 122.6, 122.8, 129.1, 132.9, 135.4, 148.7, 149.6 156.6, 156.9 (C arom), 192.2 (C=S) ppm; MS (EI, 70 eV): m/z (%) = 376 (17) $[M]^{+\bullet}$, 283 (100).

References

[1] Issacs NS (1976) Chem Soc Rev 181
[2] Staudinger H (1907) Justus Liebigs Ann Chem **356**: 51
[3] Bose AK, Anjameyulu B (1966) Chem Ind (London) 903
[4] Hart D, Ha DC (1989) Chem Rev 1447
[5] Palomo C, Aizpurua JM, Ganboa I, Oiabide M (1999) Eur Org Chem 3223
[6] Carr JA, Al-Azemi TF, Long TE, Shim JY, Coates CM, Turos E, Bisht KS (2003) Tetrahedron **59**: 9147
[7] Troisi L, Ronzini L, Granito C, De Vitis L, Pindinelli E (2006) Tetrahedron **62**: 1564
[8] Nieschalk J, Spanka C, Schaumann E (1996) Liebigs Ann 135
[9] Nieschalk J, Schaumann E (1996) Liebigs Ann 141
[10] Creary X, Zhu C (1996) J Am Chem Soc **118**: 12331
[11] Wojtkowski PW, Dolfini JE, Kocy C, Cimarusti CM (1975) J Am Chem Soc **97**: 5628
[12] Bogdanowicz-Szwed K, Krasodomska M (1994) Monatsh Chem **125**: 1247
[13] Bogdanowicz-Szwed K, Krasodomska M (1998) Monatsh Chem **129**: 81
[14] Arrieta A, Aizpurua JM, Palomo C (1984) Tetrahedron Lett **25**: 3365
[15] Bogdanowicz-Szwed K (1977) Roczniki Chem **51**: 267
[16] Sheldrick GM (1997) SHELXS97 – Program for crystal structure solution, Univ Göttingen, Germany
[17] Sheldrick GM (1997) SHELXL97 – Program for crystal structure refinement, Univ Göttingen, Germany
[18] Farrugia LJ (1997) J Appl Cryst **32**: 837