Synthesis and Ring Transformation of Substituted *S*-(1-Phenylpyrrolidine-2-ones-3-yl)isothiuronium Salts to Substituted 2-Imino-5-[2-(Phenylamino)ethyl]thiazolidin-4-ones

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Dedicated to Professor Jaromír Kaválek on the occasion of his 65th birthday

Substituted *S*-(1-phenylpyrrolidin-2-on-3-yl)isothiuronium salts in weakly basic media undergo intramolecular recyclisation reaction in which the γ-lactam cycle is split and a thiazolidine cycle is formed. A series of six substituted 2-imino-5-[2-(phenylamino)ethyl]-thiazolidin-4-ones have been prepared by this reaction.

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Introduction.

Cyclic amides such as β-lactams or γ-lactams can represent basic structural units of antibiotics [1]. On the other hand, thiazolidine [2] cycle also belongs among pharmaceutically significant heterocycles representing an important group of per oral antidiabetics [3]. We have found that substituted *S*-(1-phenylpyrrolidin-2-on-3-yl)isothiuronium salts (**1a-f**) in weakly basic media (pH about 9) undergo an intramolecular recyclisation reaction. In this particular case, the γ-lactam ring is split and a thiazolidine cycle is formed, *i.e*. substituted 2-imino-5-[2-(phenylamino)ethyl]-thiazolidin-4-ones (**2a-f**) are obtained (Scheme 1). Rearrangements of heterocyclic rings in which a ring is opened and subsequently another ring is closed are of particular interest both synthetically and theoretically. Such processes may provide fascinating routes to derivatives that can be obtained only with great difficulties – or not at all – by other procedures. Our system is classifiable [4] as a "classical ring transformation", where the starting and the final systems are of the same size but the heteroatoms and/or their positions have been changed. Ring transformations of five-membered heterocycles dealt with over the past ten years were discussed and reviewed [4,5].

Scheme 1

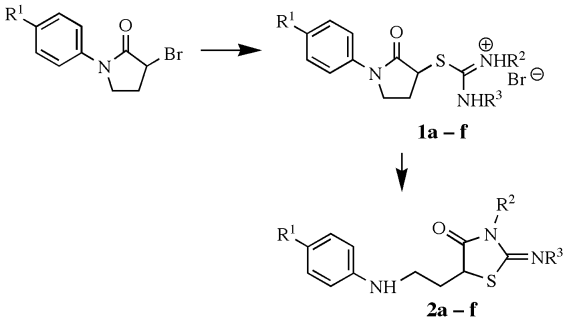


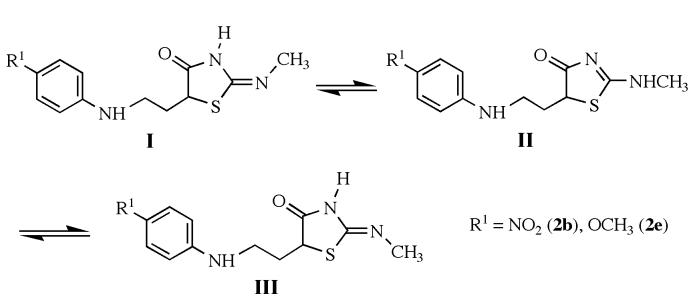
Table 1

1,2	a	b	c	d	e	f
R1	NO_2	NO_2	NO_2	OCH_3	OCH_3	OCH_3
R2	H	H	CH_3	H	H	CH_3
R3	H	CH_3	CH_3	H	CH_3	CH_3

Results and Discussion.

The reactions of 3-bromo-1-(4-nitrophenyl)pyrrolidin-2-one and 3-bromo-1-(4-methoxyphenyl)pyrrolidin-2-one [6] with thiourea, *N*-methylthiourea and *N,N'*-dimethylthiourea give practically pure, crystalline isothiuronium salts **1a-b** and **1d-f**, respectively. It was not possible to isolate *S*-[1-(4-nitrophenyl)pyrrolidin-2-on-3-yl]- *N,N'*-dimethyl-isothiuronium bromide (**1c**): hydrobromide **2c** separated from the reaction mixture instead. The other substituted thiazolidines **2a-b** and **2d-f** were prepared by transformation of the corresponding isothiuronium salts **1a-f**. From the ^{1}H nmr spectra of 2-methylimino-5-[2-(4-nitrophenylamino)ethyl]thiazolidin-4-one (**2b**) and 2-methylimino-5-[2-(4-methoxyphenylamino)ethyl]-thiazolidin-4-one (**2e**) it is obvious that these substances dissolved in dimethyl sulphoxide exist in the form of two tautomers differing in the position of C=N double bond. The tautomers with exocyclic bond exist in the form of two geometrical isomers differing in the configuration of methyl group (Scheme 2).

Scheme 2



In the ^{1}H nmr spectrum of compound **2b** (R^1: NO_2) one can clearly see the presence of three isomers **I**, **II**, **III** (Scheme 2) whose proportions change with time. In a freshly prepared solution (in dimethyl sulphoxide) the major component is the isomer with endocyclic double bond (**II**). The minor isomer **2b** (**I** or **III**) can only be characterised by the following chemical shifts: for =N~CH_3 δ 2.93 (s, 3H), and for CO–NH δ 9.6 (vbs, 1H). The following chemical shifts were measured for the second more populated exocyclic minor isomer **2b** (**III** or **I**): for =N~CH_3 δ 3.03 (s, 3H), –CH– δ 4.45 (m, 1H), –NH–Ar δ 7.41 (t, 1H, ^3J 5.5 Hz), –CO–NH δ 9.34 (s, 1H). After a week's standing of **2b** solution at room temperature the proportions of individual isomers changed, and the originally more populated exo-isomer became the major component of the mixture to the detriment of the endo-isomer. The observed rate constant of reaction **1a** → **2a** at 25 °C (k_{obs} = 1.6x10^{-2} s^{-1}) was determined spectrophotometrically in 0.01 *M* tris(hydroxymethyl)amine buffer with initial concentration 1·10^{-4} *M* **1a**, at pH = 7.1 and ionic strength equal to 1. The spectral record of the reaction **1a** → **2a** is characterised by decreasing maximum of **1a** at 316 nm and increasing maximum of **2a** at 410 nm, with isosbestic points at 269 and 352 nm.

EXPERIMENTAL

The results of elemental analyses of the individual compounds agreed with the calculated values. The ^{1}H and ^{13}C nmr spectra were measured on a Bruker AMX 360 apparatus or Bruker Avance 500 apparatus. For the measurements, the substances were dissolved in hexadeuteriodimethyl sulphoxide (DMSO-d_6). The chemical shifts δ_H and δ_C are referenced to the middle signal of multiplet of the solvent (δ_H = 2.55 ppm, δ_C = 39.6 ppm). The spectrophotometric kinetic measurement were carried out on an HP UV/VIS 8453 Diode Array apparatus in a 1 cm quartz cell with lid.

General Procedure for Preparation of Substituted *S*-(1-Phenylpyrrolidin-2-on-3-yl)isothiuronium Salts (**1a-b, 1d-f**).

A solution of 3-bromo-1-(4-nitrophenyl)pyrrolidin-2-one [6] or 3-bromo-1-(4-methoxyphenyl)pyrrolidin-2-one [6] (1.75 mmol) in 10 ml dry acetone was treated with a solution of thiourea or *N*-methylthiourea or *N*,*N'*-dimethylthiourea (1.75 mmol) dissolved in 10 ml dry acetone. The mixture was left to stand at room temperature overnight. The precipitated crystalline solid (isothiuronium salts **1a-f**, respectively) was collected by suction on a sintered-glass filter and dried.

S-[1-(4-Nitrophenyl)pyrrolidine-2-one-3-yl]isothiuronium Bromide (**1a**).

Compound **1a** was obtained in 76% yield, mp 218-220 °C; ^{1}H nmr: δ 2.24 and 2.82 (2×m, 2×1H), 4.06 (m, 2H), 5.11 (t, 1H, ^3J 9.2 Hz), 8.00 (m, 2H), 8.33 (m, 2H), 9.28 (bs, 2H), 9.43 (bs, 2H); ^{13}C nmr: δ 24.4, 46.0, 46.6, 119.7, 124.8, 143.4, 144.3, 168.4, 171.1.

Anal. Calcd. for $C_{11}H_{13}BrN_4O_3S$: (361.2): C, 36.58, H, 3.63, Br, 22.12, N, 15.51, S, 8.88. Found: C, 36.63, H, 3.74, Br, 22.15, N, 15.58, S, 8.92.

S-[1-(4-Nitrophenyl)pyrrolidine-2-one-3-yl]-*N*-methylisothiuronium Bromide (**1b**).

Compound **1b** was obtained in 81% yield, mp 227-230 °C; ^{1}H nmr: δ 2.22 and 2.81 (2×m, 2×1H), 3.00 (d, 3H, ^3J 4.7 Hz), 4.06 (m, 2H), 5.16 (t, 1H, ^3J 9.1 Hz), 7.99 (m, 2H), 8.31 (m, 2H), 9.38 and 9.66 (2×bs, 2×1H), 9.99 (bm, 1H); ^{13}C nmr: δ 24.4, 31.0, 46.4, 46.7, 119.7, 124.8, 143.4, 144.3, 164.8, 171.3.

Anal. Calcd. for $C_{12}H_{15}BrN_4O_3S$: (375.2): C, 38.41, H, 4.03, Br, 21.29, N, 14.93, S, 8.54. Found: C, 38.51, H, 4.06, Br, 21.35, N, 15.00, S, 8.53.

S-[1-(4-Methoxyphenyl)pyrrolidine-2-one-3-yl]isothiuronium Bromide (**1d**).

Compound **1d** was obtained in 79 % yield, mp 222-225 °C; ^{1}H nmr: δ 2.16 and 2.76 (2×m, 2×1H), 3.81 (s, 3H), 3.96 (m, 2H), 4.92 (t, 1H, ^3J 8.8 Hz), 7.04 (m, 2H), 7.60 (m, 2H), 9.22 and 9.46 (2×bs, 4H); ^{13}C nmr: δ 24.3, 45.6, 47.2, 55.4, 114.1, 122.1, 131.6, 156.8, 168.7, 170.0.

Anal. Calcd. for $C_{12}H_{16}BrN_3O_2S$: (346.2): C, 41.63, H, 4.66, Br, 23.08, N, 12.14, S, 9.26. Found: C, 41.58, H, 4.61, Br, 23.10, N, 12.18, S, 9.31.

S-[1-(4-Methoxyphenyl)pyrrolidine-2-one-3-yl]-*N*-methylisothiuronium Bromide (**1e**).

Compound **1e** was obtained in 75 % yield, mp 186-188 °C; ^{1}H nmr: δ 2.15 and 2.75 (2×m, 2×1H), 3.00 (s, 3H), 3.80 (s, 3H), 3.95 (m, 2H), 5.02 (t, 1H, ^3J 8.8 Hz), 7.02 (m, 2H), 7.60 (m, 2H), 9.34 (bs, 1H), 9.75 (bs, 1H), 10.05 (bs, 1H); ^{13}C nmr: δ 24.2, 30.8, 46.0, 47.2, 55.4, 114.1, 122.2, 131.5, 156.9, 165.3, 170.1.

Anal. Calcd. for $C_{13}H_{18}BrN_3O_2S$: (360.3): C, 43.34, H, 5.04, Br, 22.18, N, 11.66, S, 8.90. Found: C, 43.29, H, 5.07, Br, 22.21, N, 11.71, S, 9.01.

S-[1-(4-Methoxyphenyl)pyrrolidin-2-one-3-yl]-*N*,*N'*-dimethylisothiuronium Bromide (**1f**).

Compound **1f** was obtained in 77 % yield, mp 129-131 °C; ^{1}H nmr: δ 2.20 and 2.78 (2×m, 2×1H), 3.03 (d, 3H, ^3J 4,2), 3.09 (s, 3H), 3,80 (s, 3H), 3.97 (m, 2H), 5.01 (t, 1H, ^3J 8.8), 7.03 (m, 2H), 7.60 (m, 2H), 9.46 (bs, 1H), 9.75 (bs, 1H); ^{13}C nmr: δ 24.7, 31.1, 31.5, 46.8, 47.7, 55.4, 114.1, 122.1, 131.6, 156.8, 165.7, 169.6.

Anal. Calcd. for $C_{14}H_{20}BrN_3O_2S$: (374.3): C, 44.93, H, 5.39, Br, 21.35, N, 11.23, S, 8.57. Found: C, 44.98, H, 5.35, Br, 21.41, N, 11.31, S, 8.55.

General Procedure of Preparation of Substituted 2-Imino-5-[2-(phenylamino)ethyl]thiazolidin-4-ones (**2a-b, 2d-f**).

Isothiuronium salt **1a-b**, **1d-f** (1.39 mmol) was stirred in 10 ml 5% aqueous ammonia with addition of 10 mg of ammonium acetate at room temperature for 3 hours. The oil, primarily formed, gradually changed into a suspension. The solid was collected by suction on a sintered-glass filter and dried. Recrystallisation from aqueous methanol (1:1) gave products **2a-b**, **2d-f**.

2-Imino-5-[2-(4-nitrophenylamino)ethyl]thiazolidine-4-one (**2a**).

Compound **2a** was obtained in 60 % yield, mp 239-240 °C; ^{1}H nmr: δ 1.93 and 2.36 (2×m, 2×1H), 3.28 (m, 2H), 4.33 (dd, 1H, ^3J 9.4, 4.0 Hz), 6.65 (m, 2H), 7.39 (t, 1H, ^3J 5.4), 8.02 (m, 2H), 8.85 (bs, 1H), 9.05 (bs, 1H); ^{13}C nmr: δ 32.5, 41.1, 54.1, 111.0, 126.4, 136.0, 154.4, 181.7, 189.7.

Anal. Calcd. for $C_{11}H_{12}N_4O_3S$: (281.3): C, 47.14, H, 4.32, N, 19.99, S, 11.44. Found: C, 47.21, H, 4.33, N, 19.95, S, 11.56.

2-Methylimino-5-[2-(4-nitrophenylamino)ethyl]thiazolidine-4-one (**2b**).

Compound **2b** was obtained in 50 % yield, mp 183-185 °C; **2b** (**II**) ^{1}H nmr (500 MHz): δ 1.95 and 2.04 (2×m, 2×1H), 2.38 (m, 2H), 2.99 (d, 3H, ^3J 4.6), 4.35 (m, 1H), 6.69 (m, 2H), 7.44 (t, 1H, ^3J 5.5), 8.07 (m, 2H), 9.2 (q, 1H, ^3J 4.6); ^{13}C nmr: δ 30.1, 31.3, 39.9, 52.3, 109.6, 124.9, 135.4, 152.9, 178.5, 188.1.

Anal. Calcd. for $C_{12}H_{14}N_4O_3S$: (294.3): C, 48.97, H, 4.79, N, 19.04, S, 10.89. Found: C, 48.87, H, 4.82, N, 19.11, S, 11.10.

2-Methylimino-3-methyl-5-[2-(4-nitrophenylamino)ethyl]thiazolidine-4-one Hydrobromide (**2c**).

This compound was prepared by the method described for isothiuronium salts: 67 % yield, mp 225-227 °C; ^{1}H nmr (500 MHz): δ 2.33 and 2.42 (2×m, 2×1H), 3.18 (s, 3H), 3.19 (s, 3H), 3.42 (t, 2H, ^3J .6), 4.78 (m, 1H), 6.72 (m, 2H), 8.05 (m, 2H); ^{13}C nmr (500MHz): δ 28.9, 29.4, 29.6, 38.3, 46.1, 109.7, 124.7, 135.6, 152.5, 167.4, 171.6.

Anal. Calcd. for $C_{13}H_{17}BrN_4O_3S$: (389.3): C, 40.11, H, 4.04, Br, 20.53, N, 14.39, S, 8.24. Found: C, 40.16, H, 4.37, Br, 20.62, N, 14.43, S, 8.32.

2-Imino-5-[2-(4-methoxyphenylamino)ethyl]thiazolidine-4-one (**2d**).

Compound **2d** was obtained in 62 % yield, mp 161-163 °C; ^{1}H nmr: δ 1.85 and 2.35 (2×m, 2×1H), 3.10 (m, 2H), 3,68 (s, 3H), 4.33 (dd, 1H, ^3J 9.9, 3.8 Hz), 5.30 (t, 1H, ^3J 5.4 Hz), 6.56 (m, 2H), 6.75 (m, 2H), 8.83 and 9.03 (bs, 1H); ^{13}C nmr: δ 33.1, 42.5, 54.5, 55.4, 113.3, 114.8, 142.9, 150.9, 181.8, 189.9.

Anal. Calcd. for $C_{12}H_{15}N_3O_2S$: (265.3): C, 54.32, H, 5.70, N, 15.84, S, 12.08. Found: C, 54.40, H, 5.62, N, 15.81, S, 12.12.

Methylimino-5-[2-(4-methoxyphenylamino)ethyl]thiazolidine-4-one (**2e**).

Compound **2e** was obtained in 52 % yield, mp 103-104 °C; **2e** (**I** or **III**) ^{1}H nmr: δ 1.86 and 2.37 (2×m, 2×1H), 2.93 (s, 3H), 3.09 (m, 2H), 3.68 (s, 3H), 4.34 (m, 1H), 5.33 (bs, 1H), 6.56 (m, 2H), 6.76 (m, 2H), 9.60 (vbs, 1H); ^{13}C nmr: δ 31.0, 33.1, 42.5, 53.9, 55.4, 113.3, 114.7, 142.9, 150.9, 179.5, 189.0; **2e** (**II**) ^{1}H nmr: δ 1.86 and 2.37 (2×m, 2×1H), 2.99 (d, 3H, ^3J 4.4), 3.09 (m, 2H), 3.68 (s, 3H), 4.34 (m, 1H), 5.33 (bs, 1H), 6.56 (m, 2H), 6.76 (m, 2H), 9.19 (bq, 1H); ^{13}C nmr: δ 31.0, 33.1, 42.5, 53.9, 55.4, 113.3, 114.7, 142.9, 150.9, 179.5, 189.0.

Anal. Calcd. for $C_{12}H_{17}N_3O_2S$: (279.4): C, 55.89, H, 6.13, N, 15.04, S, 11.48. Found: C, 56.01, H, 6.15, N, 15.11, S, 11.53.

2-Methylimino-3-methyl-5-[2-(4-methoxyphenylamino)-ethyl]thiazolidine-4-one (**2f**).

Compound **2f** was obtained in 63 % yield, mp 85-86 °C; ^{1}H nmr: δ 1.94 and 2.38 (2×m, 2×1H), 3.06 (s, 3H), 3.09 (s, 3H), 3.14 (m, 2H), 3.68 (s, 3H), 4.45 (dd, 1H, ^3J 9.5, 4.1), 5.30 (t, 1H, ^3J 5.8), 6.57 (m, 2H), 6.76 (m, 2H); ^{13}C nmr: δ 29.0, 32.7, 38.1, 41.5, 45.8, 55.4, 113.4, 114.8, 142.8, 151.0, 153.2, 174.1.

Anal. Calcd. for $C_{14}H_{19}N_3O_2S$: (293.4): C, 57.32, H, 6.53, N, 14.32, S, 10.93. Found: C, 57.35, H, 6.67, N, 14.43, S, 10.96.

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