Unexpected Formation of Thiophene-annulated Tetrahydro-3-benzazepines by Alkylation of Thiolactams with Ethyl Bromoacetate

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In order to synthesize enantiomerically pure tetrahydro-3-benzazepines with diverse substitution patterns, the lactams 3 were converted into thiolactams 4 upon treatment with Lawesson’s reagent. Instead of an Eschenmoser sulfide contraction a thiophene annulation reaction occurred, when the thiolactams 4 were reacted with ethyl bromoacetate. Altogether, enantiomerically pure thiophene-annulated 3-benzazepines 7 were prepared in a very short reaction sequence (five reaction steps) starting from commercially available 0-phenylenediacetic acid.

Key words: Tetrahydro-3-benzazepines, Enantiomerically Pure Compounds, Thiophene Annulation, Thiolactams, Lawesson’s Reagent, Eschenmoser Sulfide Contraction, X-Ray Crystal Structure Analysis

Introduction

The tetrahydro-3-benzazepine scaffold (Fig. 1) is a privileged structure in Medicinal Chemistry [1, 2] because it contains the 2-arylethylamine substructure of several neurotransmitters, e. g. noradrenaline, dopamine and serotonin. Therefore compounds comprising the 3-benzazepine ring can be used for the activation or inhibition of the corresponding neurotransmitter receptors. Prominent examples are the prototypical dopamine D1 receptor antagonist SCH23360 [3, 4], the D1 receptor agonist fenoldopam [3, 4], and the 5-HT2C receptor agonist lorcaserin which is used for the treatment of obesity [5]. Moreover, the tetrahydro-3-benzazepine ring system can be regarded as a homolog of the tetrahydroisoquinoline system, which is also a privileged structure and thus found in several pharmacologically active compounds.

Due to the promising pharmacological potential of tetrahydro-3-benzazepines, our interest has been focused on the development of synthetic methods allowing the stereoselective introduction of different substituents at all positions of the saturated part of the ring system (positions 1 – 5). Recently we have published the asymmetric synthesis of 1-monosubstituted [6, 7], 2-monosubstituted [8, 9], 2,3-disubstituted [10], 1,4-disubstituted [11, 12], and 1,3,4-trisubstituted tetrahydro-3-benzazepines of type 1 [13] (Fig. 1). Some of the prepared compounds showed promising affinity toward σ1 or NMDA receptors [6, 7, 11, 13]. Therefore, it was planned to expand our synthetic strategy to get access to 2,4-disubstituted and 2,3,4-trisubstituted tetrahydro-3-benzazepines 2.

Results and Discussion

For the introduction of an additional substituent in 2-position of the 3-benzazepine scaffold, the use of an Eschenmoser sulfide contraction [14] was planned. For this purpose the lactams 3 were prepared by reaction of 0-phenylenediacetic acid with an excess of methylolithium [15] followed by reductive amination and ring closure [13]. At first the lactams 3 were converted into thiolactams 4 upon treatment with Lawesson’s reagent [16, 17] in refluxing toluene. After 2 h the thiolactams 4 were isolated in 81% – 86% yields (Scheme 1).
In order to perform the Eschenmoser sulfide contraction [14] the thiolactam 4a was reacted with ethyl bromoacetate and subsequently with PPh₃ to obtain the enamino ester 6a. However, instead of expected 6a the thio-phenyl-substituted 3-benzazepine 7a was formed.

Repeating the same reaction in refluxing CHCl₃ without addition of PPh₃ provided the tricyclic compound 7a in 48% yield. The same transformation took place upon reaction of the phenylethyl-substituted enantiomerically pure thiolactams 4b and 4c with ethyl bromoacetate. The thieno[3,2-a]-[3]benzazepines 7b and 7c were isolated in 65% and 68% yield, respectively.

The ¹H NMR spectrum of the tricyclic compound 7c displays signals for the aliphatic Ph-CH₂CHCH₃ part of the 3-benzazepine scaffold, i.e. a doublet of doublets at 2.47 ppm and a doublet at 2.65 ppm (6-CH₃), a multiplet at 3.77–3.84 ppm (5-CH) and a doublet at 0.66 ppm (CH₃). Signals for the ethoxy group of the original ester moiety are missing. Two doublets at 3.68 and 3.74 ppm with a coupling constant of 16.9 Hz represent the protons of the methylene moiety in 2-position. In the ¹³C NMR spectrum two signals at 105.5 and 173.1 ppm indicate the presence of two additional olefinic carbon atoms (C-3a and C-10b) and the signal at 195.5 ppm indicates the presence of a ketone carbonyl moiety.

In order to prove the structure of the thio-phenyl-annulated 3-benzazepines 7 unequivocally, the enantiomerically pure compound 7c was recrystallized from a CH₂Cl₂-­n-hexane mixture resulting in crystals which were suitable for X-ray crystal structure analysis. The molecular structure of 7c in the crystal is displayed in Fig. 2. It clearly shows the annulated thio-phenyl moiety with the carbonyl group in 1-position. Moreover, the (S)-configuration of both the chiral center in 5-position and the N-substituent is clearly proved by the structure determination.

![Molecular structure of 7c in the crystal](image)

**Table 1. Synthesis of thio-phenyl-annulated 3-benzazepines 7 from lactams 3.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Educt R¹</th>
<th>Configuration</th>
<th>Product 4 (yield)</th>
<th>Product 7 (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>benzyl¹</td>
<td>4a (81%)</td>
<td>7a (68%)</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>(R)-1-phenylethyl</td>
<td>4b (86%)</td>
<td>7b (65%)</td>
</tr>
<tr>
<td>3</td>
<td>3c</td>
<td>(S)-1-phenylethyl</td>
<td>4c (83%)</td>
<td>7c (68%)</td>
</tr>
</tbody>
</table>

*a Racemic mixture; b configuration in 4-position of the 3-benzazepine ring is (R); c configuration in 4-position of the 3-benzazepine ring is (S).
It is assumed that the thiophene annulation proceeded via the following reaction pathway (Scheme 1): At first ethyl bromoacetate reacted with the thiolactams 4 to produce S-alkythioiminium salts 5. Instead of deprotonation in α-position of the ester moiety, it was argued that the ring size of the α-thiolactam (6-, 7-membered) and the substituent in the position of the bromoacetates were responsible for the bromine atom in β-position of ethyl 3-bromopropionate less reactive than the bromine atom in α-position of ethyl 2-bromoacetate. The nucleophilic substitution at the secondary C atom of ethyl 2-bromopropionate is sterically inhibited.

A similar thiophene annihilation reaction has been reported by G. Lhommet et al. [19]. Whereas five-, six-, and seven-membered thiolactams reacted with ethyl bromoacetate to afford the expected enamino esters, the transformation of piperidine-2-thiones and azepane-2-thiones with α-substituted bromoacetates afforded exclusively thiophene-annulated pyridines and azepines. It was argued that the ring size of the thiolactam (6-, 7-membered) and the substituent in the α-position of the bromoacetates were responsible for the thiophene annihilation. The reaction of secondary β-ketothioamides with ethyl bromoacetate also led to heterocyclic systems instead of enamino esters. In this case the NH moiety of the secondary ketene N,S-acetal intermediates reacted with the ester moiety to give 1,3-thiazolidin-4-ones [20]. In the total synthesis of the natural products (±)-lythrancepine II and III a similar thiophene annihilation was observed, when a thiolactam reacted with an α-bromoketone [21].

In conclusion, the unexpected formation of thiophene-annulated 3-benzazepines 7 by alkylation of thiolactams 4 with ethyl bromoacetate allows a very facile access to enantiomerically pure tetrasubstituted 3-benzazepines. Together with the three reaction steps required for the synthesis of lactams 3 starting from commercially available o-phenylenediacetic acid (reaction with MeLi, reductive amination, cyclization with CDI), the complete reaction sequence comprises only five reaction steps.

**Experimental Section**

**Chemistry, general**

Unless otherwise mentioned, THF was dried with sodium/benzophenone and was freshly distilled before use. Thin layer chromatography (tlc): Silica gel 60 F254 plates (Merck). Flash chromatography: Silica gel 60, 40 – 64 µm (Merck); parentheses include: diameter of the column, length of column, fraction size, eluent, Rf value. Melting point: Melting point apparatus SMP 3 (Stuart Scientific), uncorrected. IR: IR spectrophotometer 480Plus FT-ATR-IR (Jasco). 1H NMR (400 MHz), 13C NMR (100 MHz): Mercury plus 400 spectrometer (Varian); δ = ppm relative to tetramethylsilane; coupling constants are given with 0.5 Hz resolution. Where necessary, the assignment of the signals in the 1H NMR and 13C NMR spectra was performed using 1H-1H and 1H-13C COSY NMR spectra. Optical rotation α (deg) was determined with a Polarimeter 341 (Perkin Elmer); length 1 dm, wavelength 589 nm (sodium D line); the unit of the specific rotation [α]d (deg mL dm−1 g−1) is omitted; concentration of the sample c (g per 100 mL) and the solvents used are given in brackets. MS: EI = electron impact, ESI = electrospray ionization: MicroTof (BrukerDaltronics, Bremen), calibration with sodium formate clusters before measurement. HPLC method for determination of the product purity: Merck Hitachi Equipment; UV detector: L-7400; autosampler: L-7200; pump: L-7100; degasser: L-7614; Method: column: LiChrospher® 60 RP-select B (5 µm), 250 – 4 mm cartridge; flow rate: 1.00 mLmin−1; injection volume: 5.0 µL; detection at λ = 210 nm; solvents: A: water with 0.05% (v/v) trifluoroacetic acid; B: acetonitrile with 0.05% (v/v) trifluoroacetic acid: gradient elution: (A %): 0–4 min: 90%; 4–29 min: gradient from 90% to 0%; 29–31 min: 0%; 31–31.5 min: gradient from 0% to 90%; 31.5–40 min: 90%.

**General procedure for the synthesis of thiolactams 4**

Lawesson’s reagent (1 equiv) was added to a solution of lactam 3 (1 equiv) in toluene (10 mL). The mixture was stirred under reflux for 2 h. The solvent was evaporated in vacuo to obtain a viscous oil, which was purified by flash chromatography.

3-Benzyl-4-methyl-1,3,4,5-tetrahydro-3-benzazepine-2-thione (4a)

Following the General Procedure, Lawesson’s reagent (73 mg, 0.18 mmol) was added to a solution of lactam 3a (49 mg, 0.18 mmol) in toluene (10 mL). The mixture was...
stirred under reflux for 2 h. The solvent was evaporated in vacuo to obtain a viscous oil, which was purified by flash chromatography (d = 2 cm, l = 10 cm, V = 10 mL, cyclohexane-EtOAc 80 : 20, Rf = 0.60 (cyclohexane-EtOAc 60 : 40)). – Colorless viscous oil, yield 42 mg (81%). – C_{18}H_{19}NS (281.4 g mol^{-1}). – FT-IR (ATR, film): ν (cm^{-1}) = 3026 (aliphatic C–H), 1175 (C = S). – ^1H NMR (CDCl_3): δ (ppm) = 1.33 (d, J = 6.7 Hz, 3H, CH_3), 2.84 (dd, d = 16.4/10.6 Hz, 1H, 5-H), 2.94 (dd, d = 16.4/5.0 Hz, 1H, 5-H), 4.33 (d, J = 14.7 Hz, 1H, 1-H), 4.43 – 4.52 (m, 1H, 4-H), 4.64 (d, J = 14.6 Hz, 1H, 1-H), 4.94 (d, J = 15.4 Hz, 1H, N(CH_2)Ph), 5.64 (d, J = 15.4 Hz, 1H, N(CH_2)Ph), 6.86 – 7.23 (m, 9H, arom). – ^13C NMR (CDCl_3): δ (ppm) = 20.5 (1C, CH_3), 39.7 (1C, C-5), 51.2 (1C, C-1), 54.6 (1C, C-4), 56.3 (1C, N(CH_2)Ph), 126.8, 127.1, 127.2, 127.6, 128.5, 129.5 (9C, Ph-CH), 134.0, 134.9, 136.3 (3C, Ph-C), 203.6 (1C, C = S). – Exact mass (ESI): m/z = 282.1319 (calcd. 282.1311 for C_{18}H_{19}NSH, [M+H]^+). – Purity (HPLC): 95.1% (Rt = 21.3 min).

(R)-4-Methyl-3-[(R)-1-phenylethyl]-1,3,4,5-tetrahydro-3-benzazepin-2-thione (4b)

Following the General Procedure, Lawesson’s reagent (87 mg, 0.21 mmol) was added to a solution of lactam 3b (60 mg, 0.21 mmol) in toluene (10 mL). The mixture was stirred under reflux for 2 h. The solvent was evaporated in vacuo to obtain a viscous oil, which was purified by flash chromatography (d = 2 cm, l = 10 cm, V = 10 mL, cyclohexane-EtOAc 90 : 10, Rf = 0.60 (cyclohexane-EtOAc 60 : 40)). – Colorless solid, m. p. 108 – 110 °C, yield 44 mg (83%). – [α]_{D}^{20} = −7.5 (c = 1.00, CH_2Cl_2). – Exact mass (ESI): m/z = 318.1279 (calcd. 318.1287 for C_{19}H_{21}NSNa, [MNa]^+). – Purity (HPLC): 98.4% (Rt = 22.1 min).

4-Benzyl-5-methyl-5,6-dihydro-2H-thieno[3,2-a][3]benzazepin-1(4H)-one (7a)

To a solution of thiolactam 4a (50 mg, 0.18 mmol) in CHCl_3 (10 mL), an excess of ethyl bromoacetate (199 µL, 1.8 mmol) was added. The mixture was stirred under reflux for 20 h. The solvent was evaporated in vacuo and the crude product was purified by flash chromatography (d = 2 cm, l = 20 cm, V = 10 mL, cyclohexane-EtOAc 80 : 20, Rf = 0.30 (cyclohexane-EtOAc 60 : 40)). – Colorless solid, m. p. 182 – 184 °C, yield 28 mg (48%). – C_{20}H_{24}NO_{3} (321.4 g mol^{-1}). – FT-IR (ATR, film): ν (cm^{-1}) = 2968 (aliphatic C–H), 1658 (C=O). – ^1H NMR (CDCl_3): δ (ppm) = 0.80 (d, J = 6.5 Hz, 3H, CH_3), 2.68 (dd, d = 14.6/6.0 Hz, 1H, 6-H), 3.18 (d, J = 14.7 Hz, 1H, 6-H), 3.68 – 3.74 (m, 2H, 2-H), 3.90 – 3.98 (m, 1H, 5-H), 4.60 (d, J = 17.0 Hz, 1H, N(CH_2)Ph), 4.90 (d, J = 17.0 Hz, 1H, N(CH_2)Ph), 6.89 – 7.41 (m, 8H, arom), 7.88 – 8.01 (m, 1H, arom). – ^13C NMR (CDCl_3): δ (ppm) = 18.5 (1C, CH_3), 36.8 (1C, C-6), 40.3 (1C, C-2), 57.4 (1C, C-5), 60.2 (1C, N(CH_2)Ph), 105.6 (1C, C-3a), 125.6, 126.6, 126.9, 128.1, 128.5, 129.1, 129.3 (9C, Ph-CH), 131.1, 134.5, 135.2 (3C, Ph-C), 174.7 (1C, C-10b), 194.8 (1C, C=O). – Exact mass (ESI): m/z = 322.1274 (calcd. 322.1260 for C_{20}H_{24}NO_{3}SH, [M+H]^+). – Purity (HPLC): 88.5% (Rt = 21.0 min).

(S)-4-Methyl-3-[(S)-1-phenylethyl]-1,3,4,5-tetrahydro-3-benzazepin-2-thione (4c)

Following the General Procedure, Lawesson’s reagent (73 mg, 0.18 mmol) was added to a solution of lactam 3c (50 mg, 0.18 mmol) in toluene (10 mL). The mixture was stirred under reflux for 2 h. The solvent was evaporated in vacuo to obtain a viscous oil, which was purified by flash chromatography (d = 2 cm, l = 10 cm, V = 10 mL, cyclohexane-EtOAc 90 : 10, Rf = 0.60 (cyclohexane-EtOAc 60 : 40)). – Colorless solid, m. p. 108 – 110 °C, yield 44 mg (83%). – [α]_{D}^{20} = −7.5 (c = 1.00, CH_2Cl_2). – Exact mass (ESI): m/z = 318.1279 (calcd. 318.1287 for C_{19}H_{21}NSNa, [MNa]^+). – Purity (HPLC): 98.4% (Rt = 22.1 min).

To a solution of thiolactam 4a (50 mg, 0.18 mmol) in CHCl_3 (10 mL), an excess of ethyl bromoacetate (199 µL, 1.8 mmol) was added. The mixture was stirred under reflux for 20 h. The solvent was evaporated in vacuo and the crude product was purified by flash chromatography (d = 2 cm, l = 20 cm, V = 10 mL, cyclohexane-EtOAc 80 : 20, Rf = 0.30 (cyclohexane-EtOAc 60 : 40)). – Colorless solid, m. p. 182 – 184 °C, yield 28 mg (48%). – C_{20}H_{24}NO_{3} (321.4 g mol^{-1}). – FT-IR (ATR, film): ν (cm^{-1}) = 2968 (aliphatic C–H), 1658 (C=O). – ^1H NMR (CDCl_3): δ (ppm) = 0.80 (d, J = 6.5 Hz, 3H, CH_3), 2.68 (dd, d = 14.6/6.0 Hz, 1H, 6-H), 3.18 (d, J = 14.7 Hz, 1H, 6-H), 3.68 – 3.74 (m, 2H, 2-H), 3.90 – 3.98 (m, 1H, 5-H), 4.60 (d, J = 17.0 Hz, 1H, N(CH_2)Ph), 4.90 (d, J = 17.0 Hz, 1H, N(CH_2)Ph), 6.89 – 7.41 (m, 8H, arom), 7.88 – 8.01 (m, 1H, arom). – ^13C NMR (CDCl_3): δ (ppm) = 18.5 (1C, CH_3), 36.8 (1C, C-6), 40.3 (1C, C-2), 57.4 (1C, C-5), 60.2 (1C, N(CH_2)Ph), 105.6 (1C, C-3a), 125.6, 126.6, 126.9, 128.1, 128.5, 129.1, 129.3 (9C, Ph-CH), 131.1, 134.5, 135.2 (3C, Ph-C), 174.7 (1C, C-10b), 194.8 (1C, C=O). – Exact mass (ESI): m/z = 322.1274 (calcd. 322.1260 for C_{20}H_{24}NO_{3}SH, [M+H]^+). – Purity (HPLC): 88.5% (Rt = 21.0 min).
C-3a), 125.4, 126.3, 127.4, 128.6, 128.8, 129.1, 129.4 (9C, Ph-CH), 133.7, 135.3, 138.3 (3C, Ph-C), 173.1 (1C, C=O). – \( \alpha = -71.2 \) (c = 0.20, CH\(_2\)Cl\(_2\)). – Exact mass (ESI): \( m/z = 336.1429 \) (calcd. 336.1422 for C\(_{21}\)H\(_{21}\)NOS, [M+H]+). – Purity (HPLC): 97.2% (\( \tau_R = 22.0 \) min).

(S)-5-Methyl-4-[(S)-1-phenylethyl]-5,6-dihydro-2H-thieno[3,2-a][3]benzazepin-4(4H)-one (7e)

To a solution of thiocarbazot (S\(_\alpha\)-4S)-4\(_c\) (60 mg, 0.20 mmol) in CHCl\(_3\) (10 mL), an excess of ethyl bromoacetate (221 \( \mu \)L, 2.0 mmol) was added. The mixture was heated to reflux for 20 h. The solvent was evaporated in vacuo, and the crude product was purified by flash chromatography (\( d = 2 \) cm, \( l = 20 \) cm, \( V = 10 \) mL, cyclohexane-EtOAc 80:20, \( R_I = 0.32 \) (cyclohexane-EtOAc 60:40)). – Colorless solid, m.p. 143–144 °C, yield 46 mg (68%), – \( \alpha = -70.3 \) (c = 0.68, CH\(_2\)Cl\(_2\)). – Exact mass (ESI): \( m/z = 336.1420 \) (calcd. 336.1422 for C\(_{21}\)H\(_{21}\)NOS, [M+H]+). – Purity (HPLC): 96.9% (\( \tau_R = 21.9 \) min).

X-Ray crystal structure analysis of 7e

For the X-ray crystal structure analysis, a sample of 7e was recrystallized from CH\(_2\)Cl\(_2\)-n-hexane. A data set was collected with a Nonius KappaCCD diffractometer. Programs used: data collection: COLLECT (Nonius B.V., 1998); data reduction: DENZO-SMN [22]; absorption correction: DENZO [23]; structure solution: SHELXS-97 [24]; structure refinement: SHELXL-97 [25]; graphics: XP (Bruker Analytical X-Ray Instruments Inc., 2000).

Crystal structure data: Formula C\(_{21}\)H\(_{21}\)NOS; \( M_r = 335.45 \); colorless crystal, 0.30 × 0.27 × 0.15 mm\(^3\); orthorhombic; space group P2\(_1\)2\(_1\)2\(_1\) (no. 19), Z = 4; \( a = 8.7257(3) \), \( b = 10.2788(3) \), \( c = 19.4764(10) \) Å; \( V = 1746.83(12) \) Å\(^3\); \( \rho_{calc} = 1.28 \) g cm\(^{-3}\); \( \mu = 1.7 \) mm\(^{-1}\). Data collection: Radiation: CuK\(_\alpha\), \( \lambda = 1.54178 \) Å; \( T = 223 (2) \) K; \( \omega\)- and \( \varphi\)-scans, 9028 reflections collected (\( \pm h, \pm k, \pm l \)), \( \langle \sin \theta / \lambda \rangle = 0.60 \) Å\(^{-1}\), empirical absorption correction, \( T_{min} / max \) = 0.632/0.786, 2873 independent (\( R_{int} = 0.032 \)) and 2805 “observed” reflections \( I > 2 \sigma(I) \). Refinement: 219 refined parameters, \( R_1 \) \( [I > 2 \sigma(I)] \) = 0.031, \( wR_2 \) (all data) = 0.080, Flack parameter x 0.048 (17), max. \( \lambda \) min. residual electron density 0.12/−0.16 e Å\(^{-3}\). Hydrogen atoms calculated and refined as riding atoms.

CCDC 913691 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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