OXAZEPINES AND THIAZEPINES 39*
SYNTHESIS OF TETRACYCLIC 1,5-BENZOTHIAZEPINES BY THE REACTION OF (*Z*)-3-ARYLIDENE-1-THIOFLAVANONES WITH 2-AMINOTHIOPHENOL

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Dedicated to Prof. Dr. András Messmer on the occasion of his 80th birthday

Abstract: Tetracyclic benzothiazepines **3a-j** have been synthesized by the reaction of 2-aminothiophenol (**1**) and (*Z*)-3-arylidene-1-thioflavanones **2a-j** in hot toluene by using trifluoroacetic acid catalyst. Structures of all new compounds have been elucidated by IR, ^{1}H and ^{13}C NMR spectroscopic measurements.

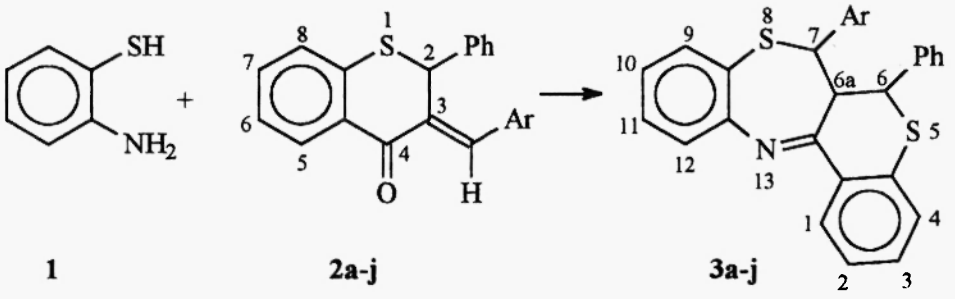
Introduction

Owing to their diverse bioactivities (1-10), 1,5-benzothiazepines are important compounds in the drug research. For this reason, numerous representatives have been published in the literature and different methods were introduced for their synthesis. A thoroughly investigated procedure is the preparation of 2,3-dihydro-1,5-benzothiazepines by the reaction of α,β-enones with 2-aminothiophenol (11-20). Their syntheses have also been summarized and discussed in several reviews (21-24). However, only few examples have hitherto been published for the synthesis of tetracyclic 1,5-benzothiazepines (25-30). This fact prompted us to study the synthesis of the tetracyclic 1,5-benzothiazepines in detail and herein we report on the preparation of such compounds by the reaction of (*Z*)-3-arylidene-1-thioflavanones with 2-aminothiophenol.

Results and Discussion

The 3-arylidene-1-thioflavanones belong to the exocyclic α,β-unsaturated ketones and their (*Z*)-isomers, where the carbonyl and aryl moieties are on the opposite sides of the carbon-carbon double bond, were synthesized by acid- (31-33) and base-catalyzed (34) condensation of 1-thioflavanones and aromatic aldehydes. The diastereomeric (*E*)-isomers were obtained by the photoisomerization of the appropriate (*Z*)-isomers (35,36). Formerly, we have investigated not only the synthesis, but also some chemical transformations of the 3-arylidene-1-thioflavanones. These studies comprised their rearrangement into 3-benzyl-1-thioflavones (37), 1,3-dipolar cycloaddition with diazomethane (38-40) and their oxidative transformations (41-43). As a continuation, now we have performed their reaction with 2-aminothiophenol to afford tetracyclic 1,5-benzothiazepines.

Scheme 1



1 **2a-j** **3a-j**

2a, 3a: Ar = C_6H_5
2b, 3b: Ar = 2-Me-C_6H_4
2c, 3c: Ar = 3-Me-C_6H_4
2d, 3d: Ar = 4-Me-C_6H_4
2e, 3e: Ar = 4-iPr-C_6H_4
2f, 3f: Ar = 4-MeO-C_6H_4
2g, 3g: Ar = 4-F-C_6H_4
2h, 3h: Ar = 2-Cl-C_6H_4
2i, 3i: Ar = 2-thienyl
2j, 3j: Ar = 2-naphthyl

2-Aminothiophenol **1** was allowed to react with (*Z*)-3-arylidene-1-thioflavanones **2a-j** in hot toluene by using trifluoroacetic acid as catalyst and tetracyclic 1,5-benzothiazepines **3a-j** were obtained in high (76-93%) yields (Scheme 1). The appropriate 1,5-benzothiazepine derivative was the sole isolable product in each case.

Structures of all new compounds **3a-j** have been elucidated by elemental analyses, IR , ^{1}H- and ^{13}C-NMR spectroscopic measurements. Absence of C=O and NH_2 bands in the IR spectra reveals that not only the Michael addition of the thiol group to the β-carbon atoms of the α,β-unsaturated ketones but also the ring closure took place under these reaction conditions providing 1,5-benzothiazepines **3a-j** which was corroborated by the presence of a characteristic C=N band at ca. 1600 cm^{-1}. In the ^{1}H-NMR spectra a doublet signal between 3.60 and 3.83 ppm belongs to the 6-H hydrogen, while a doublet-doublet signal of the 6a-H proton is found between 3.57 and 3.90 ppm. The $J_{6\text{-H},6a\text{-H}}$ = 1.7-2.5 Hz coupling constant values refer to a *gauche*-orientation of these two neighbouring hydrogen atoms. A doublet signal of the 7-H proton is between 5.14 and 5.85 ppm and the ca. 12 Hz $J_{7\text{-H},6a\text{-H}}$ coupling constant values reveal an *antiperiplanar*-arrangement of these two protons. ^{13}C-NMR spectra of compounds **3a-j** corroborate the structures deduced from the IR and ^{1}H-NMR spectra by the assignment of the aliphatic and the imine carbon atoms (*cf.* Experimental). All these spectroscopic measurements unequivocally prove that 1,5-benzothiazepines **3a-j** were formed

as stereohomogeneous products and no other diastereomers were obtained even as minor components.

In summary, it can be concluded that this simple and convenient procedure can be advantageously utilized for a completelity stereoselective preparation of these tetracyclic 1,5-benzothiazepines with three centres of chirality.

Experimental

Melting points were determined with a Koffler hot-stage apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 200 spectrometer at 200/50 MHz in $CDCl_3$ (internal standard TMS, δ = 0.0 ppm) at room temperature. The IR spectra (KBr discs) were measured with a Perkin-Elmer 16 PC instrument. Elemental analyses were performed in-house with a Carlo Erba 1106 EA instrument. TLC was performed on Kieselgel 60 F_{254} (Merck) layer using hexane:acetone (7:3 v/v) as eluent. Starting materials **2a-j** were synthesized by the piperidine-catalyzed reaction 1-thioflavanone and aromatic aldehydes as described earlier by us (34).

General procedure for the synthesis of compounds **3a-j**

A mixture of 2-aminothiophenol (**1**, 6.0 mmol), (*Z*)-3-arylidene-1-thioflavanone **(2a-j**, 5.0 mmol), trifluoroacetic acid (0.5 ml) and toluene (30 ml) was refluxed for 3 h. The solvent was evaporated under reduced pressure and the residue was crystallized from methanol to afford tetracyclic benzothiazepines **3a-j**.

6a,7-Dihydro-6,7-diphenyl-6*H*-[1]benzothiopyrano[3,4-*c*][1,5]benzonthiazepine (3a): Yield 89%, m.p. 174-175 °C; IR: νC=N 1596 cm^{-1}; ^{1}H-NMR (δ): 3.62 (1H, d, J = 2.3 Hz, 6-H), 3.78 (1H, dd, J = 12.0, 2.4 Hz, 6a-H), 5.16 (1H, d, J = 12.0 Hz, 7-H), 6.97-8.62 (18 arom. H, m); ^{13}C-NMR (δ): 44.6 (C-6a), 47.1 (C-6), 61.5 (C-7), 164.1 (C-14).

Anal. Calcd. for $C_{28}H_{21}NS_2$: C, 77.22; H, 4.86; N, 3.21. Found: C, 77.28; H, 4.84; N, 3.23.

6a,7-Dihydro-7-(2-methylphenyl)-6-phenyl-6*H*-[1]benzothiopyrano[3,4-*c*][1,5]benzothiazepine (3b): Yield 88%, m.p. 192-193 °C; IR: νC=N 1598 cm^{-1}; ^{1}H-NMR (δ): 2.58 (3H, s, CH_3), 3.78 (1H, d, J = 2.3 Hz, 6-H), 3.80 (1H, dd, J = 11.8, 2.5 Hz, 6a-H), 5.54 (1H, d, J = 12.0 Hz, 7-H), 7.02-8.61 (17 arom. H, m); ^{13}C-NMR (δ): 20.1 (CH_3), 44.8 (C-6a), 46.7 (C-6), 55.8 (C-7), 164.0 (C-14).

Anal. Calcd. for $C_{29}H_{23}NS_2$: C, 77.48; H, 5.16; N, 3.11. Found: C, 77.53; H, 5.14; N, 3.09.

6a,7-Dihydro-7-(3-methylphenyl)-6-phenyl-6*H*-[1]benzothiopyrano[3,4-*c*][1,5]benzothiazepine (3c): Yield 84%, m.p. 165-166 °C; IR: νC=N 1600 cm^{-1}; ^{1}H-NMR (δ): 2.34 (3H, s, CH_3), 3.68 (1H, d, J = 2.2 Hz, 6-H), 3.80 (1H, dd, J = 11.8, 2.6 Hz, 6a-H), 5.55 (1H, d, J = 12.1 Hz, 7-H), 6.94-8.61 (17 arom. H, m); ^{13}C-NMR (δ): 21.3 (CH_3), 44.7 (C-6a), 46.9 (C-6), 61.5 (C-7), 164.2 (C-14).

Anal. Calcd. for $C_{29}H_{23}NS_2$: C, 77.48; H, 5.16; N, 3.11. Found: C, 77.44; H, 5.17; N, 3.13.

6a,7-Dihydro-7-(4-methylphenyl)-6-phenyl-6*H*-[1]benzothiopyrano[3,4-*c*][1,5]benzothiazepine (3d): Yield 93%, m.p. 126-127 °C; IR: νC=N 1604 cm^{-1}; ^{1}H-NMR (δ): 2.37 (3H, s,

CH_3), 3.68 (1H, d, J = 2.3 Hz, 6-H), 3.78 (1H, dd, J = 12.0, 2.4 Hz, 6a-H), 5.17 (1H, d, J = 11.9 Hz, 7-H), 7.02-8.64 (17 arom. H, m); ^{13}C-NMR (δ): 21.0 (CH_3), 44.8 (C-6a), 47.1 (C-6), 61.4 (C-7), 164.2 (C-14).

Anal. Calcd. for $C_{29}H_{23}NS_2$: C, 77.48; H, 5.16; N, 3.11. Found: C, 77.52; H, 5.18; N, 3.12.

6a,7-Dihydro-7-(4-isopropylphenyl)-6-phenyl-6*H*-[1]benzothiopyrano[3,4-*c*][1,5]benzothiazepine (3e): Yield 85%, m.p. 160-161 °C; IR. νC=N 1602 cm^{-1}; ^{1}NMR (δ): (6H, d, $CH(CH_3)_2$), 2.90 (1H, m, $CH(CH_3)_2$), 3.66 (1H, d, J = 2.5 Hz, 6-H), 3.78 (1H, dd, J = 11.9, 2.4 Hz, 6a-H), 5.17 (1H, d, J = 11.9 Hz, 7-H), 7.02-8.61 (17 arom. H, m); ^{13}C-NMR (δ): 23.6 (2 CH_3), 33.6 ($CH(CH_3)_2$), 44.8 (C-6a), 47.2 (C-6), 61.4 (C-7), 164.2 (C-14).

Anal. Calcd. for $C_{31}H_{27}NS_2$: C, 77.96; H, 5.70; N, 2.93. Found: C, 77.91; H, 5.72; N, 2.94.

6a,7-Dihydro-7-(4-methoxyphenyl)-6-phenyl-6*H*-[1]benzothiopyrano[3,4-*c*][1,5]benzothiazepine (3f): Yield 81%, m.p. 177-178 °C; IR: νC=N 1604 cm^{-1}; ^{1}H-NMR (δ): 3.66 (1H, d, J = 2.5 Hz, 6-H), 3.78 (1H, dd, J = 12.1, 2.8 Hz, 6a-H), 3.83 (3H, s, OCH_3), 5.14 (1H, d, J = 11.8 Hz, 7-H), 6.83-8.62 (17 arom. H, m); ^{13}C-NMR (δ): 44.8 (C-6a), 47.3 (C-6), 55.2 (OCH_3), 61.1 (C-7), 164.3 (C-14).

Anal. Calcd. for $C_{29}H_{23}NOS_2$: C, 74.82; H, 4.98; N, 3.01. Found: C, 74.78; H, 4.96; N, 3.02.

6a,7-Dihydro-7-(4-fluorophenyl)-6-phenyl-6*H*-[1]benzothiopyrano[3,4-*c*][1,5]benzothiazepine (3g): Yield 84%, m.p. 169-170 °C; IR: νC=N 1600 cm^{-1}; ^{1}H-NMR (δ): 3.60 (1H, d, J = 2.5 Hz, 6-H), 3.71 (1H, dd, J = 12.0, 2.4 Hz, 6a-H), 5.15 (1H, d, J = 12.0 Hz, 7-H), 6.97-8.60 (17 arom. H, m); ^{13}C-NMR (δ): 44.7 (C-6a), 47.2 (C-6), 60.7 (C-7), 163.9 (C-14).

Anal. Calcd. for $C_{28}H_{20}FNS_2$: C, 74.16; H, 4.45; N, 3.09. Found: C, 74.19; H, 4.47; N, 3.07.

6a,7-Dihydro-7-(2-chlorophenyl)-6-phenyl-6*H*-[1]benzothiopyrano[3,4-*c*][1,5]benzothiazepine (3h): Yield 80%, m.p. 169-170 °C; IR: νC=N 1598 cm^{-1}; ^{1}H-NMR (δ): 3.70 (1H, d, J = 1.7 Hz, 6-H), 3.86 (1H, dd, J = 12.0 Hz, 2.2 Hz, 6a-H), 5.85 (1H, d, J = 12.1 Hz, 7-H), 6.98-8.63 (17 arom. H, m); ^{13}C-NMR (δ): 44.7 (C-6a), 46.8 (C-6), 55.6 (C-7), 163.8 (C-14).

Anal. Calcd. for $C_{28}H_{20}ClNS_2$: C, 71.56; H, 4.29; N, 2.98. Found: C, 71.59; H, 4.31; N, 2.97.

6,7-Dihydro-6-phenyl-7-(2-thienyl)-6*H*-[1]benzothiopyrano[3,4-*c*][1,5]benzothiazepine (3i): Yield 76%, m.p. 166-167 °C; IR: νC=N 1598 cm^{-1}; ^{1}H-NMR (δ): 3.57 (1H, dd, J = 11.8, 2.4 Hz, 6a-H), 3.83 (1H, d, J = 2.3 Hz, 6-H), 5.49 (1H, d, J = 12.0 Hz, 7-H), 6.90-8.57 (16 arom. H, m); ^{13}C-NMR (δ): 44.9 (C-6a), 48.7 (C-6), 57.1 (C-7, 163.6 (C-14).

Anal. Calcd. for $C_{26}H_{19}NS_3$: C, 70.74; H, 4.34; N, 3.17. Found: C, 70.77; H, 4.36; N, 3.18.

6a,7-Dihydro-7-(2-naphthyl)-6-phenyl-6*H*-[1]benzothiopyrano[3,4-*c*][1,5]benzothiazepine (3j): Yield 78%, m.p. 177-178 °C; IR: νC=N 1600 cm^{-1}; ^{1}H-NMR (δ): 3.64 (1H, d, J = 2.4 Hz, 6-H), 3.90 (1H, dd, J = 12.0, 2.5 Hz, 6a-H), 5.35 (1H, d, J = 12.1 Hz, 7-H), 6.98-8.64 (20 arom. H, m); ^{13}C-NMR (δ): 45.3 (C-6a), 47.0 (C-6), 62.3 (C-7), 164.6 (C-14).

Anal. Calcd. for $C_{32}H_{23}NS_2$: C, 79.17; H, 4.77; N, 2.88. Found: C, 79.14; H, 4.75; N, 2.87.

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*For Part 38, see A. Levai, *Heterocycl. Commun.* **5**, 359 (1999)

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