OXAZEPINES AND THIAZEPINES 35*
SYNTHESIS OF TETRACYCLIC BENZOTHIAZEPINES BY THE REACTION OF 2-AMINOTHIOPHENOL WITH EXOCYCLIC α,β-ENONES

Albert Lévai
Department of Organic Chemistry, Lajos Kossuth University, Egyetem tér 1, H-4010 Debrecen, Hungary

Dedicated to Prof. Dr. W. Wiegrebe on the occasion of his 65th birthday

Abstract: Tetracyclic chromeno- and 1-thiochromenobenzothiazepines **16-29** have been synthesized by the reaction of 2-aminothiophenol **1** and exocyclic α,β-unsaturated ketones **2-15** in hot toluene with trifluoroacetic acid catalyst.

Introduction

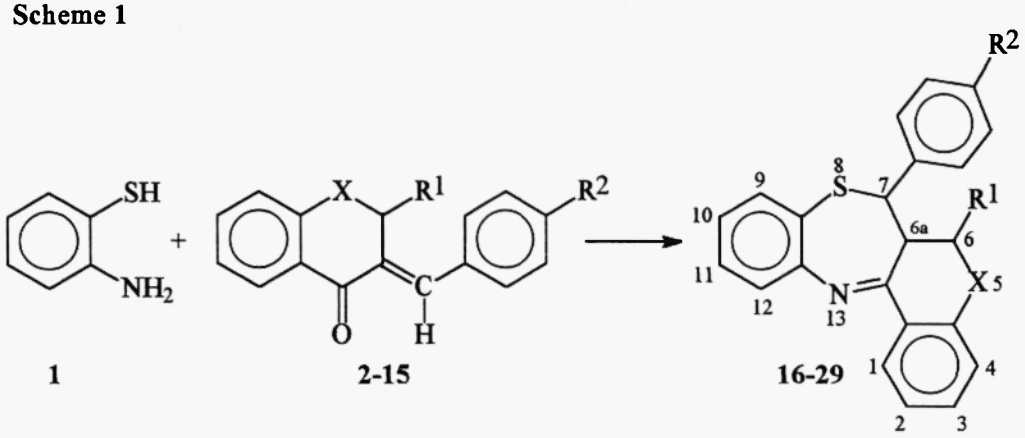
1,5-Benzothiazepines are well known seven-membered heterocyclic compounds and, owing to their diverse bioactivities (1-14), they are important substances in the drug research. Their synthesis has been extensively studied and numerous procedures have been described in the literature (15,16). Synthesis of 2,4-diaryl-2,3-dihydro-1,5-benzothiazepines by the reaction of 2-aminothiophenol with α,β-unsaturated ketones have been investigated in details and various relationships have been observed between the structure of the starting α,β-enones and the reaction products (17-26). However, the synthesis of related tetracyclic benzothiazepines has hitherto received less attention (27-31). The aim of this study was, therefore, to work out a simple and convenient procedure for the preparation of tetracyclic chromeno- and 1-thiochromenobenzothiazepines by the reaction of 2-aminothiophenol **1** with 3-arylidenechromanones **2-6**, -1-thiochromanones **7-10** and -flavanones **11-15**.

Results and Discussion

In our previous papers (28,29) synthesis and detailed stereochemical studies of the unsubstituted parent compounds of substances **16-19** have been described. As a continuation, we planned to generalize the formerly introduced procedure by investigating the reaction of 2-aminothiophenol **1** with related α,β-enones substituted in their arylidene moiety. For this reason, 2-aminothiophenol **1** was allowed to react with 3-arylidenechromanones

2-6, -1-thiochromanones **7-10** and -flavanones **11-15** in hot toluene in the presence of trifluoroacetic acid and tetracyclic benzothiazepines **16-29** have been obtained in good yields (Scheme 1 and Table 1).

Scheme 1



2,16: X = O, R^1 = H, R^2 = Me
3,17: X = O, R^1 = H, R^2 = iPr
4,18: X = O, R^1 = H, R^2 = MeO
5,19: X = O, R^1 = H, R^2 = F
6,20: X = O, R^1 = H, R^2 = Cl
7,21: X = S, R^1 = H, R^2 = Me
8,22: X = S, R^1 = H, R^2 = iPr
9,23: X = S, R^1 = H, R^2 = MeO
10,24: X = S, R^1 = H, R^2 = F
11,25: X = O, R^1 = Ph, R^2 = Me
12,26: X = O, R^1 = Ph, R^2 = iPr
13,27: X = O, R^1 = Ph, R^2 = MeO
14,28: X = O, R^1 = Ph, R^2 = F
15,29: X = O, R^1 = Ph, R^2 = Cl

Structures of the reaction products **16-29** have been elucidated by elemental analyses, IR and ^{1}H-NMR spectroscopy. A C=N band characteristic for such and related 1,5-benzothiazepines (19-31) has been observed between 1600 and 1614 cm^{-1}. Presence of C=O and NH_2 bands could not be detected in the IR spectra. The absence of NH_2 signal in the ^{1}H-NMR spectra corroborates that not only the Michael addition of the mercapto group to the C-β atom of the α,β-enones but also the ring closure of the adducts take place under the applied reaction conditions affording tetracyclic benzothiazepines. In the ^{1}H-NMR spectra a doublet signal found at 4.89-4.91 ppm for the chromenobenzothiazepines **16-20** and around 5.17-5.21 ppm in the case of 1-thio-chromenobenzothiazepines **21-24** can be assigned to the hydrogen connected to the C-7 atom. While a doublet-doublet signal at 3.01-3.08 ppm and 3.40-3.43 ppm, respectively, belong to the hydrogen at the C-6a atom of these tetracyclic benzothiazepines (cf. Table 1). The ca. 12 Hz coupling constant values between these two protons reveal their *trans*-orientation indicating the formation of one diastereomer of these benzothiazepines with two centres of chirahty originating from the reaction of 2-aminothiophenol **1** with α,β-unsaturated ketones **2-10**.

Since there is a centre of chirality in 3-arylideneflavanones **11-15**, tetracyclic benzothiazepines obtained by their reaction with 2-aminothiophenol **1** possess three centres of chirahty giving rise to the formation of four diastereomeric structures. Therefore, it is especially important to determine the relative configuration of the

centres of chirality to get information concerning the stereoselectivity of the reaction. Utilizing the ^{1}H-NMR data of the tetracyclic benzothiazepine (28,29) prepared by the reaction of 3-benzylideneflavanone with 2-aminothiophenol as reference, signals of the aliphatic protons of compounds **25-29** (cf. Table 1) can easily be assigned to the particular atom. Doublets between 4.95 and 4.99 ppm belong to H-7 and those at 4.89-4.94 ppm to the H-6 proton. However, a doublet-doublet signal at 3.59-3.68 ppm can be assigned to the H-6a hydrogen. The ca. 12 Hz $J_{H\text{-}7,H\text{-}6a}$ coupling constant values reveal an *antiperiplanar*-orientation of these two protons. While the $J_{H\text{-}6,H\text{-}6a}$ = 1.1-1.3 Hz coupling constants refer to a *gauche*-arrangement of these latter protons. These ^{1}H-NMR data prove that the reaction of 3-aryhdeneflavanones **11-15** with 2-aminothiophenol **1** provides only one of the theoretically possible four diastereomers.

Conclusion

In summary, it can be concluded that we managed to generalize the procedure used previously only for the synthesis of heterocyclic benzothiazepines by the reaction of unsubstituted 3-benzylidenechromanone, -1-thiochromanone and -1-flavanone with 2-aminothiophenol (28,29). It has turned out that the presence of an electron donor or acceptor substituent at the *para*-position of the arylidene moiety is without influence on the course and stereoselectivity of the reaction.

Experimental

Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a Bruker WP 200 SY spectrometer at 200 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. TLC was performed on Kieselgel 60 F_{254} (Merck) layers using hexane:acetone (7:3 v/v) as eluent. Starting materials **2-15** were synthesized according to known procedures (32-33).

General procedure for the synthesis of compounds **16-29**

A mixture of 2-aminothiophenol (**1**, 12.0 mmol), α,β-unsaturated ketone (**2-15**, 10.0 mmol), trifluoroacetic acid (1.0 ml) and toluene (50.0 ml) was refluxed for 3 h. The solvent was evaporated under reduced pressure and the residue crystallized from methanol to obtain compounds **16-29** (cf. Table 1).

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Table 1. Yields, Physical and Spectral Data of Compounds **16-29**

Compound	Yield (%)	m.p. (°C)	$\nu_{C=N}$ (cm^{-1})	^{1}H-NMR δ (ppm), *J* (Hz)
16	84	164-165	1601	2.37 (3H, s), 3.08 (1H, dd, J_1 = 12.3, J_2 = 1.6), 3.81 (1H, dd, J_1 = 11.9, J_2 = 1.6), 4.09 (1H, dd, J_1 = 11.9, J_2 = 2.8), 4.89 (1H, d, J = 12.3), 6.99-7.19 (11 arom. H, m), 8.50 (1H, d, J = 7.7)
17	85	132-133	1602	1.26 (6H, d, J = 7.7), 2.89 (1H, m), 3.04 (1H, dd, J_1 = 12.3, J_2 = 1.6), 3.79 (1H, dd, J_1 = 11.8, J_2 = 1.0), 4.02 (1H, dd, J_1 = 11.8, J_2 = 2.8), 4.89 (1H, d, J = 12.3), 6.98-7.67 (11 arom. H, m), 8.38 (1H, dd, J_1 = 8.0, J_2 = 1.7)
18	73	191-192	1604	3.02 (1H, dd, J_1 = 12.3, J_2 = 1.7), 3.70 (1H, d, J = 11.8), 3.73 (3H, s), 4.03 (1H, dd, J_1 = 11.8, J_2 = 2.8), 4.91 (1H, d, J = 12.3), 6.83-7.68 (11 arom. H, m), 8.38 (1H, dd, J_1 = 8.0, J_2 = 1.6)
19	80	166-167	1601	3.02 (1H, dd, J_1 = 12.3, J_2 = 1.6), 3.80 (1H, d, J = 11.8), 4.09 (1H, dd, J_1 = 11.8, J_2 = 2.7), 4.91 (1H, d, J = 12.3), 7.00-7.71 (11 arom. H, m), 8.55 (1H, d, J = 7.6)
20	68	178-179	1602	3.01 (1H, dd, J_1 = 12.3, J_2 = 2.7), 3.75 (1H, dd, J_1 = 11.9, J_2 = 1.0), 4.05 (1H, dd, J_1 = 11.9, J_2 = 2.8), 4.87 (1H, d, J = 12.3), 6.98-7.68 (11 arom. H, m), 8.38 (1H, dd, J_1 = 8.0, J_2 = 1.7)
21	88	198-199	1603	2.25 (1H, dd, J_1 = 11.7, J_2 = 2.9), 2.36 (3H, s), 3.23 (1H, dd, J_1 = 12.0, J_2 = 3.3), 3.43 (1H, m), 5.17 (1H, d, J = 12.0), 7.09-7.62 (11 arom. H, m), 8.67 (1H, dd, J_1 = 7.0, J_2 = 1.3)
22	82	212-213	1600	1.25 (6H, d, J = 7.0), 2.25 (1H, dd, J_1 = 13.8, J_2 = 2.9), 2.90 (1H, m), 3.23 (1H, dd, J_1 = 13.8, J_2 = 3.3), 3.42 (1H, m), 5.18 (1H, d, J = 12.0), 7.11-7.65 (11 arom. H, m), 8.64 (1H, dd, J_1 = 6.9, J_2 = 1.3)
23	77	202-203	1601	2.24 (1H, dd, J_1 = 13.8, J_2 = 2.8), 3.23 (1H, dd, J_1 = 13.8, J_2 = 2.8), 3.39 (1H, m), 3.80 (3H, s), 5.18 (1H, d, J = 11.9), 6.81-7.64 (11 arom. H, m), 8.64 (1H, d, J = 8.0)
24	85	200-201	1601	2.25 (1H, dd, J_1 = 13.5, J_2 = 2.3), 3.21 (1H, dd, J_1 = 13.5, J_2 = 2.3), 3.40 (1H, m), 5.21 (1H, d, J = 11.6), 6.97-7.66 (11 arom. H, m), 8.84 (1H, dd, J_1 = 7.7, J_2 = 1.5)
25	65	166-167	1616	2.38 (3H, s), 3.67 (1H, dd, J_1 = 12.2, J_2 = 1.1), 4.94 (1H, d, J = 1.1), 4.98 (1H, d, J = 12.2), 6.97-7.68 (16 arom. H, m), 8.22 (1H, dd, J_1 = 7.8, J_2 = 1.6)

Table 1. Continued

Compound	Yield (%)	m.p. (°C)	$\nu_{C=N}$ (cm^{-1})	^{1}H-NMR δ (ppm), *J* (Hz)
26	72	160-161	1608	1.28 (6H, d, J = 6.9), 2.93 (1H, m), 3.68 (1H, dd, J_1 = 12.2, J_2 = 1.1), 4.89 (1H, d, J = 1.1), 4.95 (1H, d, J = 12.2), 7.01-7.73 (16 arom. H, m), 8.26 (1H, dd, J_1 = 7.7, J_2 = 1.6)
27	61	183-184	1603	3.62 (1H, dd, J_1 = 12.3, J_2 = 1.1), 3.81 (3H, s), 4.94 (1H, d, J = 1.1), 4.99 (1H, d, J = 12.3), 6.84-7.69 (16 arom. H, m), 8.21 (1H, d, J = 7.9)
28	71	162-163	1614	3.59 (1H, dd, J_1 = 12.2, J_2 = 1.2), 4.91 (1H, d, J = 1.2), 4.98 (1H, d, J = 12.2), 6.98-7.69 (16 arom. H, m), 8.23 (1H, dd, J_1 = 7.5, J_2 = 1.8)
29	77	182-183	1614	3.60 (1H, dd, J_1 = 12.2, J_2 = 1.3), 4.91 (1H, d, J = 1.3), 4.96 (1H, d, J = 12.2), 6.90-7.70 (16 arom. H, m), 8.22 (1H, dd, J_1 = 8.5, J_2 = 1.8)

The elemental analyses for C, H and N were within ±0.4 % of the theoretical values.

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* For Part 34, see G. Tóth, J. Halász, A. Levai, and B. Rezessy, *Monatsh. Chem.*, submitted.

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