OXAZEPINES AND THIAZEPINES 40*
SYNTHESIS OF 4-ARYL-2-(3-CHROMONYL)-2,3-DIHYDRO-1,5-BENZOTHIAZEPINES AND THEIR CONVERSION INTO 3-ACETYL-2,3-DIHYDROBENZOTHIAZOLES

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

Abstract: 4-Aryl-2-(3-chromonyl)-2,3-dihydro-1,5-benzothiazepines **3a-g** have been synthesized by the reaction of 2-aminothiophenol (**1**) and 3-(3-oxo-3-arylpropenyl)chromen-4-ones **2a-g** in hot toluene in the presence of acetic acid. 1,5-Benzothiazepines **3a,b,d,e** have been converted into 3-acetyl-2,3-dihydrobenzothiazoles **4a,b,d,e** under acetylating conditions.

Introduction

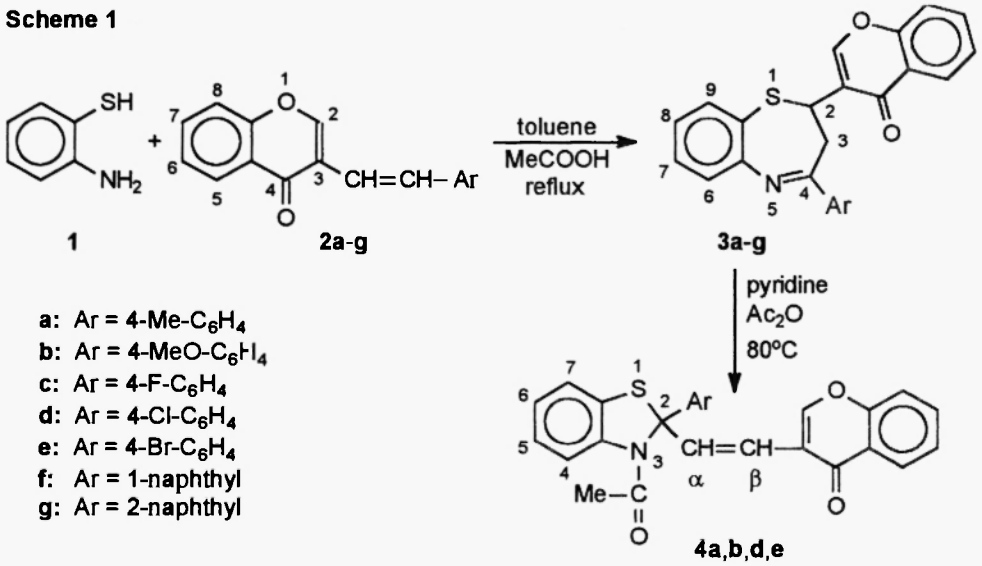
1,5-Benzothiazepines possess well known bioactivities (1-10) and are especially important nitrogen- and sulfur-containing heterocyclic compounds in the drug research. Synthesis of such benzothiazepines has been investigated in numerous laboratories and the invented procedures have also been compiled in several review articles (11-14). Owing to their easy availability, 2,4-disubstituted 2,3-dihydro-1,5-benzothiazepines received considerable attention. Procedures utilized for their synthesis are mainly based on the reaction of 2-aminothiophenol with α,β-unsaturated ketones (15-27). Related tetracyclic benzothiazepines have also been synthesized by the reaction of exocyclic α,β-enones and 2-aminothiophenol (17, 28-33). Although numerous representatives of this group of 1,5-benzothiazepines have already been synthesized and described in the literature, because of the potential bioactivities of their new derivatives, a continuous attention is paid to the synthesis of new 2,4-disubstituted 2,3-dihydro-1,5-benzothiazepines. This fact prompted us to continue our study in this field and herein we report on the synthesis of 4-aryl-2-(3-chromonyl)-2,3-dihydro-1,5-benzothiazepines and their conversion into 3-acetyl-2,3-dihydrobenzothiazoles. Introduction of a 3-chromonyl group into the benzothiazepine and benzothiazole molecules may result in new bioactivities.

Results and Discussion

In our previous studies (18-22, 27), the reaction of variously substituted chalcones and related α,β-unsaturated ketones and 2-aminothiophenol was investigated in detail. It has been concluded that under neutral conditions, both the substitution pattern of the phenyl rings of the chalcones and the bulkiness of the substituents of the related α,β-enones, influence either the Michael adducts or the corresponding 2,3-dihydro-1,5-benzothiazepines are formed. If 3-

(3-oxo-3-phenylpropenyl)chromen-4-one (34-36) was allowed to react with 2-aminothiophenol in hot toluene 3-[1-(2-aminophenylmercapto)-3-oxo-3-phenylpropyl]-chromen-4-one was formed which was then converted into 2-(3-chromonyl)-2,3-dihydro-4-phenyl-1,5-benzothiazepine in refluxing methanol in the presence of acetic acid (22). Since this compound comprises both a chromone and a benzothiazepine moieties, bioactivities can be expected in the case of such a structure. For this reason, it seemed expedient to synthesize a series of 4-aryl-2-(3-chromonyl)-2,3-dihydro-1,5-benzothiazepines.

Scheme 1



1 **2a-g** **3a-g** **4a,b,d,e**

a: Ar = 4-Me-C_6H_4
b: Ar = 4-MeO-C_6H_4
c: Ar = 4-F-C_6H_4
d: Ar = 4-Cl-C_6H_4
e: Ar = 4-Br-C_6H_4
f: Ar = 1-naphthyl
g: Ar = 2-naphthyl

3-(3-Oxo-3-arylpropenyl)chromen-4-ones **2a-g** were allowed to react with 2-aminothiophenol (**1**) in hot toluene in the presence of acetic acid and 4-aryl-2-(3-chromonyl)-2,3-dihydro-1,5-benzothiazepines **3a-g** were obtained in good (63-81%) yields (Scheme 1). Acetic acid catalyzes the ring closure of the initially formed Michael adduct and, therefore, it proved to be a convenient catalyst for a one-pot synthesis of such 1,5-benzothiazepines (12,14). Structures of the 1,5-benzothiazepines synthesized have been elucidated by elemental analyses, IR and ^{1}H-NMR spectroscopic measurements. A C=O band indicating the presence of the chromonyl unit is found between 1630 and 1644 cm^{-1}. A C=N band characteristic for a 2,3-dihydro-1,5-benzothiazepine skeleton is around 1600 cm^{-1}. Chemical shifts, multiplicity and coupling constant values of protons attached to the C-2 and C-3 atoms unequivocally prove the 2,3-dihydro-1,5-benzothiazepine structure.

Previously we have found that 2,4-diaryl-2,3-dihydro-1,5-benzothiazepines undergo a ring contraction under acetylating conditions providing 3-acetyl-2,3-dihydrobenzothiazoles (37,38). To get new insights into this transformation invented by us, 1,5-benzothiazepines

3a,b,d,e were heated at 80 °C in a mixture of anhydrous pyridine and acetic anhydride to obtain 3-acetyl-2,3-dihydrobenzothiazoles **4a,b,d,e** in moderate or good (53-72%) yields. Structure elucidation of these new compounds has been performed by elemental analyses, IR and ^{1}H-NMR spectroscopic measurements. In the IR spectra two C=O bands (*cf.* Experimental) were observed which prove the presence of an acetyl and a chromonyl groups. In their ^{1}H-NMR spectra, a broad singlet signal of an acetyl group is at ca. 2.30 ppm, while the doublet signals of the vinylic protons are overlapped by those of the aromatic protons.

In summary, it can be concluded that we managed to introduce a simple and general procedure for the preparation of 4-aryl-2-(3-chromonyl)-2,3-dihydro-1,5-benzothiazepines. It has also turned out that this kind of 2,3-dihydro-1,5-benzothiazepines can be easily converted into 3-acetyl-2,3-dihydrobenzothiazoles under reaction conditions used for this ring contraction of 2,4-diaryl-2,3-dihydro-1,5-benzothiazepines.

Experimental

Melting points were determined with a Koffler hot-stage apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian Gemini 200 spectrometer at 200 MHz in $CDCl_3$ (internal standard TMS, δ = 0.0 ppm) at room temperature. The IR spectra (KBr discs) were obtained with a Perkin-Elmer 16 PC instrument. Elemental analyses were measured 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-g** were synthesized according to known procedures (34-36).

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

A mixture of 2-aminothiophenol (**1**, 6.0 mmol), 3-(3-oxo-3-arylpropenyl)chromen-4-one (**2a-g**, 5.0 mmol), acetic acid (5.0 ml) and toluene (50 ml) was refluxed for 6 h. The solvent was evaporated under reduced pressure and the residue was crystallized from methanol to obtain 4-aryl-2-(3-chromonyl)-2,3-dihydro-1,5-benzothiazepines **3a-g**.

2-(3-Chromonyl)-2,3-dihydro-4-(4-methylphenyl)-1,5-benzothiazepine (3a): Yield 63%, m.p. 191-192 °C; IR: νC=N 1606, νC=O 1640 cm^{-1}; ^{1}H-NMR (δ): 2.40 (3H, s, Me), 2.42 (1H, J = 12.5 Hz, 3-H), 3.62 (1H, dd, J = 12.5, 4.7 Hz, 3-H), 5.28 (1H, dd, J = 12.4, 4.6 Hz, 2-H), 7.03-8.28 (12 arom. H+H, m).

Anal. Calcd. for $C_{25}H_{19}NO_2S$: C, 75.55; H, 4.82; N, 3.52. Found: C, 75.51; H, 4.84; N, 3.51.

2-(3-Chromonyl)-2,3-dihydro-4-(4-methoxyphenyl)-1,5-benzothiazepine (3b): Yield 68%, m.p. 229-230 °C; IR: νC=N 1606, νC=O 1634 cm^{-1}; ^{1}H-NMR (δ): 2.80 (1H, t, J = 12.5 Hz, 3-H), 3.24 (1H, dd, J = 12.7, 5.4 Hz, 3-H), 3.78 (1H, dd, J = 12.5, 5.7 Hz, 2-H), 4.82 (3H, s, OMe), 6.59-7.82 (12 arom. H+H, m).

Anal. Calcd. for $C_{25}H_{19}NO_3S$: C, 72.63; H, 4.63; N, 3.39. Found: C, 72.59; H, 4.65; N, 3.37.

2-(3-Chromonyl)-2,3-dihydro-4-(4-fluorophenyl)-1,5-benzothiazepine (3c): Yield 76%, m.p. 233-234 °C; IR: νC=N 1598, νC=O 1630 cm^{-1}; ^{1}H-NMR (δ): 2.82 (1H, **t**, J = 12.5 Hz, 3-H), 3.04 (1H, dd, J = 12.8, 5.2 Hz, 3-H), 3.80 (1H, dd, J = 12.4, 4.6 Hz, 2-H), 6.78-7.74 (12 arom. H+H, m).

Anal. Calcd. for $C_{24}H_{16}FNO_2S$: C, 71.81; H, 4.02; N, 3.49. Found C, 71.84; H, 4.03; N, 3.51.

4-(4-Chlorophenyl)-2-(3-chromonyl)-2,3-dihydro-1,5-benzothiazepine (3d): Yield 71%, m.p. 188-189 °C; IR: νC=N 1608, νC=O 1644 cm^{-1}; ^{1}H-NMR (δ): 2.52 (1H, t, J = 12.4, 3-H), 3.60 (1H, dd, J = 12.5, 4.6 Hz, 3-H), 5.28 (1H, dd, J = 12.6, 4.6 Hz, 2-H), 7.11-8.38 (12 arom. H+H, m).

Anal. Calcd. for $C_{24}H_{16}ClNO_2S$: C, 68.98; H, 3.86; N, 3.35. Found: C, 68.94; H, 3.88; N, 3.34.

4-(4-Bromophenyl)-2-(3-chromonyl)-2,3-dihydro-1,5-benzothiazepine (3e): Yield 81%, m.p. 235-236 °C; IR: νC=N 1598, νC=O 1634 cm^{-1}; ^{1}H-NMR (δ): 2.81 (1H, t, J = 12.4 Hz, 3-H), 3.02 (1H, dd, J = 12.4, 4.5 Hz, 3-H), 3.81 (1H, dd, J = 12.5, 4.6 Hz, 2-H), 6.60-7.64 (12 arom. H+H, m).

Anal. Calcd. for $C_{24}H_{16}BrNO_2S$: C, 62.35; H, 3.49; N, 3.03. Found: C, 62.38; H, 3.51; N, 3.02.

2-(3-Chromonyl)-2,3-dihydro-4-(1-naphthyl)-1,5-benzothiazepine (3f): Yield, 70%, m.p. 254-255 °C; IR: νC=N 1600, νC=O 1630 cm^{-1}; ^{1}H-NMR (δ): 3.02 (1H, t, J = 12.4 Hz, 3-H), 3.17 (1H, dd, J = 12.5, 4.6 Hz, 3-H), 5.26 (1H, dd, J = 12.5, 4.5 Hz, 2-H), 6.62-8.36 (15 arom. H+H, m).

Anal. Calcd. for $C_{28}H_{19}NO_2S$: C, 77.58; H, 4.42; N, 3.23. Found: C, 77.56; H, 4.40; N, 3.24.

2-(3-Chromonyl)-2,3-dihydro-4-(2-naphthyl)-1,5-benzothiazepine (3g): Yield 71%, m.p. 234-235 °C; IR: νC=N 1606, νC=O 1634 cm^{-1}; ^{1}H-NMR (δ): 2.90 (1H, t, J = 12.4 Hz, 3-H), 3.16 (1H, dd, J = 12.3, 5.3 Hz, 3-H), 3.74 (1H, dd, J = 12.6, 5.3 Hz, 2-H), 6.63-8.01 (15 arom. H+H, m).

Anal. Calcd. for $C_{28}H_{19}NO_2S$: C, 77.58; H, 4.42; N, 3.23. Found C, 77.61; H, 4.44; N, 3.21.

General procedure for the preparation of compounds **4a,b,d,e**

A mixture of 1,5-benzothiazepines **3a,b,d,e** (3.0 mmol), anhydrous pyridine (5.0 ml) and acetic anhydride (10.0 ml) was heated at 80 °C for 7 h, then poured onto crushed ice. The precipitate was separated by filtration, washed with water, dried and recrystallized from methanol to obtain pale yellow crystalline substances **4a,b,d,e**.

3-Acetyl-2-[β-(3-chromonyl)vinyl]-2,3-dihydro-2-(4-methylphenyl)benzothiazole (4a): Yield 72%, m.p. 198-199 °C; IR: νC=O 1688 and 1656 cm^{-1}; ^{1}H-NMR (δ): 2.30 (3H, s, MeCO), 2.36 (3H, s, Me), 6.72-7.74 (12 arom. H+2H, m).

Anal. Calcd. for $C_{27}H_{21}NO_3S$: C, 73.79; H, 4.82; N, 3.18. Found: C, 73.83; H, 4.80; N, 3.16.

3-Acetyl-2-[β-(3-chromonyl)vinyl]-2,3-dihydro-2-(4-methoxyphenyl)benzothiazole (4b): Yield 64%, m.p. 216-217 °C; IR: νC=O 1688 and 1648 cm^{-1}; ^{1}H-NMR (δ): 2.28 (3H, s, MeCO), 3.76 (3H, s, MeO), 6.74-7.72 (12 arom. H+2H, m).

Anal. Calcd. for $C_{27}H_{21}NO_4S$: C, 71.20; H, 4.65; N, 3.07. Found: C, 71.17; H, 4.66; N, 3.09.

3-Acetyl-2-(4-chlorophenyl)-2-[β-(3-chromonyl)vinyl]-2,3-dihydrobenzothiazole (4d): Yield 59%, m.p. 140-141 °C; IR: νC=O 1672 and 1654 cm $^{-1}$; ^{1}H-NMR (δ): 2.31 (3H, s, MeCO), 6.28-8.32 (12 arom. H+2H, m).

Anal. Calcd. for $C_{26}H_{18}ClNO_3S$: C, 67.90; H, 3.94; N, 3.04. Found. C, 67.92; H, 3.93; N, 3.06.

3-Acetyl-2-(4-bromophenyl)-2-[β-(3-chromonyl)vinyl]-2,3-dihydrobenzothiazole (4e): Yield 53%, m.p. 186-187 °C; IR: νC=O 1688 and 1652 cm^{-1}; ^{1}H-NMR (δ): 2.30 (3H, s, MeCO), 6.73-7.80 (12 arom. H+2H, m).

Anal. Calcd. for $C_{26}H_{18}BrNO_3S$: C, 61.92; H, 3.59; N, 2.78. Found: C, 61.94; H, 3.57; N, 2.79.

Acknowledgements

The present study was sponsored by the Hungarian National Research Foundation (Grant No. OTKA T034123) for which our gratitude is expressed. Technical assistance of Mrs. M. Nagy is highly appreciated.

References

*For Part 39, see Ref. (33)

(1) T. Nagao, S. Sato, H. Nakijama and A. Kiyomoto, *Japan. J. Pharmacol.*, **22**, 1 (1972)

(2) K. Yamada, T. Shimamura and H. Nakajima, *Japan J. Pharmacol.*, **23**, 321 (1973)

(3) T. Nagao, M. Sato, H. Nakijama and A. Kiyomoto, *Chem. Pharm. Bull*, **21**, 92 (1973)

(4) J. Slade, J. L. Stanton, D. Ben-David and G. Mazzenga, *J. Med. Chem.*, **28**, 1517 (1986)

(5) H. Yamamoto and H. Asai, *Chem. Pharm. Bul.*, **34**, 3844 (1986)

(6) M. J. Kendall and J. V. Okopski, *J. Clin. Hospital Pharm.*, **11**, 159 (1986)

(7) T. Asano, T. Okumura, K. Hirano, T. Adachi and M. Sugiura, *Chem. Pharm. Bull.*, **34**, 4328 (1986)

(8) Y. Inada, K. Itoh, K. Kamiya, H. Sugihara and K. Nishikawa, *Japan J. Pharmacol.*, 47, 135 (1988)

(9) S. Murata, K. Kikkawa, H. Yabana and T. Nagao, *Arzneim-Forsch.*, **38**, 521 (1988)

(10) K. Kikkawa, S. Murata and T. Nagao, *Arzneim-Forsch.*, **38**, 526 (1988)

(11) A. Levai, *Trends Heterocycl. Chem.*, 4, 51 (1995)

(12) A. Chimirri, R. Gitto, S. Grasso, A. M. Monforte and M. Zappala, *Adv. Heterocycl. Chem.*, **63**, 61 (1995)

(13) A. Levai, *Pharmazie*, **54**, 719 (1999)

(14) A. Lévai, *J. Heterocycl. Chem.*, **37**, 199 (2000)

(15) W. Ried and W. Marx, *Chem. Ber.*, **90**, 2683 (1957)

(16) W. D. Stephens and L. Field, *J. Org. Chem.*, **24**, 1576 (1959)

(17) O. Hideg-Hankovszky and K. Hideg, *Acta Chim. Acad. Sci. Hung.*, **68**, 403 (1971)

(18) A. Lévai and R. Bognár, *Acta Chim. Acad. Sci. Hung.*, **88**, 293 (1976)

(19) A. Lévai and R. Bognár, *Acta Chim. Acad. Sci. Hung.*, **92**, 415 (1977)

(20) A. Lévai, *Pharmazie*, **34**, 439 (1979)

(21) A. Lévai, R. Bognár and J. Kajtár, *Acta Chim. Acad. Sci. Hung.*, **103**, 27 (1980)

(22) A. Lévai, *Pharmazie*, **36**, 449 (1981)

(23) A. K. Gupta, V. K. Singh and U. C. Pant, *Indian J. Chem.*, **22B**, 1057 (1983)

(24) U. C. Pant, B. S. Gaur and M. Chugh, *Indian J. Chem.*, **27**B, 189 (1988)

(25) U. C. Pant, B. S. Gaur and M. Chugh, *Indian J. Chem.*, **27B**, 752 (1988)

(26) S. Pant, A. Bhatia, A. Sharma and U. C. Pant, *Indian J. Chem.*, **33B**, 885 (1994)

(27) A. Lévai, *Heterocycl. Commun.*, **5**, 359 (1999)

(28) A. Lévai, G. Tóth, Á. Szöllősy, *Stud. Org. Chem. (Amsterdam)*, **11**, 41 (1982)

(29) G. Tóth, Á. Szöllősy, A. Lévai and H. Duddeck, *Org. Magn. Reson.*, **20**, 133 (1982)

(30) S. Pant, B. C. Joshi and U. C. Pant, *Indian J. Chem.*, **33B**, 869 (1994)

(31) A. Lévai, *Sci. Pharm.*, **64**, 523 (1996)

(32) A. Lévai, *Heterocycl. Commun.*, **3**, 211 (1997)

(33) A. Lévai, *Heterocycl. Commun.*, in press.

(34) V. K. Polyakov, V. M. Voronkin and C. V. Tsukerman, *Ukr. Khim. Zh.*, 388 (1976)

(35) M. S. S. Shankar, R. B. Reddy, G. V. P. C. Mouli and Y. D. Reddy, *J. Indian Chem. Soc.*, **66**, 30 (1989)

(36) D. L. M. Coutinho and P. S. Fernandes, *Indian J. Chem.*, **31B**, 573 (1992)

(37) G. Tóth, A. Lévai, B. Balázs and A. Simon, *Liebigs Ann./Recueil*, 995 (1997)

(38) A. Lévai, *Monatsh. Chem.*, **129**, 909 (1998)

Received on April 15, 2002