OXAZEPINES AND THIAZEPINES 38*
SYNTHESIS OF 2,4-DIARYL-2,3-DIHYDRO-1,5-BENZOTHIAZEPINES BY THE REACTION OF 2'-HYDROXYCHALCONES WITH 2-AMINOTHIOPHENOL

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Dedicated to Prof. Dr. Lajos Papp on the occasion of his 70th birthday

Abstract: Simple and convenient procedures have been developed for the synthesis of 2,4-diaryl-2,3-dihydro-1,5-benzothiazepines by the reaction of 2'-hydroxychalcones **1-22** with 2-aminothiophenol either in hot ethanol in the presence of piperidine or in hot toluene in the presence of trifluoroacetic acid.

Introduction

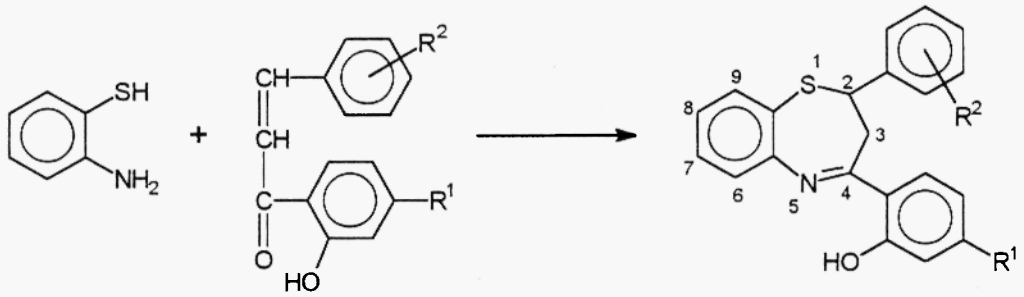
Owing to their well known bioactivities (1-10), 1,5-benzothiazepines are useful and important heterocyclic compounds utilized in the drug research. Synthesis of this group of benzothiazepines has been intensely studied and numerous procedures are described in the literature (11,12). Because of their easy availability, the 2,4-diaryl-2,3-dihydro-1,5-benzothiazepines received especially much attention. Their synthesis can be conveniently performed by the reaction of α,β-unsaturated ketones with 2-aminothiophenol. Although this reaction has been investigated by several research groups (13-25), modification of the known reaction conditions or the development of new procedures are important to get newer insight into the formation of these 1,5-benzothiazepines. The aim of this study was, therefore, to introduce simple and convenient procedures for the synthesis of 2,4-diaryl-2,3-dihydro-1,5-benzothiazepines by the reaction of 2'-hydroxychalcones with 2-aminothiophenol.

Results and Discussion

Previously we investigated the reaction of chalcones variously substituted in their rings *A* or *B* with 2-aminothiophenol under neutral reaction conditions (16,17). It has turned out that, depending on the substitution pattern of the aromatic rings of the chalcones, either β-phenyl-β-(2-aminophenylmercapto)propiophenones or 2,4-diaryl-2,3-dihydro-1,5-benzothiazepines are obtained under neutral reaction conditions. 2'-Hydroxychalcones usually gave 1,5-benzothiazepines or a mixture of the Michael adduct and the seven-membered product of the subsequent ring closure. For

this reason, it seemed expedient to investigate the reaction of these compounds under alkaline and acidic reaction conditions as well.

Scheme 1



1 - 22 **23 - 44**

1, 23 : $R^1 = H$, $R^2 = 2$–Me

2, 24 : $R^1 = H$, $R^2 = 4$–Me

3, 25 : $R^1 = H$, $R^2 = 4$–iPr

4, 26 : $R^1 = H$, $R^2 = 2$–OMe

5, 27 : $R^1 = H$, $R^2 = 3$–OMe

6, 28 : $R^1 = H$, $R^2 = 4$–OMe

7, 29 : $R^1 = H$, $R^2 = 2,3$–$(OMe)_2$

8, 30 : $R^1 = H$, $R^2 = 3,4$–$(OMe)_2$

9, 31 : $R^1 = H$, $R^2 = 3,4,5$–$(OMe)_3$

10, 32 : $R^1 = H$, $R^2 = 4$–OH

11, 33 : $R^1 = H$, $R^2 = 2$–Cl

12, 34 : $R^1 = H$, $R^2 = 3$–Cl

13, 35 : $R^1 = H$, $R^2 = 4$–Cl

14, 36 : $R^1 = H$, $R^2 = 2,4$–Cl_2

15, 37 : $R^1 = H$, $R^2 = 3,4$–Cl_2

16, 38 : $R^1 = H$, $R^2 = 3$–NO_2

17, 39 : $R^1 = H$, $R^2 = 4$–NO_2

18, 40 : $R^1 = OMe$, $R^2 = 2$–OMe

19, 41 : $R^1 = OMe$, $R^2 = 3$–OH

20, 42 : $R^1 = OMe$, $R^2 = OCH_2O$

21, 43 : $R^1 = OMe$, $R^2 = (3$–OH, 4–OMe)

22, 44 : $R^1 = OMe$, $R^2 = 3,4$–$(OMe)_2$

Stephens and Field (14) found that the reaction of the unsubstituted chalcone and 2-aminothiophenol provided β-phenyl-β-(2-aminophenylmercapto)propiophenone in hot methanol in the presence of piperidine. We came to similar conclusion in the case of several α,β-unsaturated ketones. However, if 2'-hydroxychalcones were allowed to react with 2-aminothiophenol in hot ethanol in the presence of piperidine (*Method i*) 2,4-diaryl-2,3-dihydro-1,5-benzothiazepines were obtained in each case (*cf.* Experimental). This fact can be explained by a quasi-protonation of the carbonyl group *via* the chelation with the *ortho* hydroxyl group promoting the condensation step and thus the formation of the seven-membered hetero ring. In case the two starting materials were refluxed in toluene in the presence of trifluoroacetic acid (*Method ii*) benzothiazepines **23-44** were obtained in good yields (*cf.* Experimental). Structures of compounds synthesized have been

elucidated by elemental analyses, IR and ^{1}H-NMR measurements. A C=N band characteristic for such 2,3-dihydro-1,5-benzothiazepines has been observed between 1595 and 1611 cm^{-1}. Chemical shift, coupling constant values and multiplicity of protons attached to carbon atoms C-2 and C-3 unequivocally prove the structure of all reaction products.

In summary, it can be concluded that we managed to introduce efficient procedures for the preparation of 1,5-benzothiazepines starting from 2'-hydroxychalcones.

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 measured with a Perkin-Elmer 16 PC instrument. TLC was performed on Kieselgel 60 F_{254} (Merck) layer using hexane:acetone (7:3 v/v) as eluent. Starting materials **1-22** were synthesized from the appropriate acetophenones and aromatic aldehydes according to known procedures (26).

General procedures for the preparation of compounds **23-44**

Method i: A mixture of chalcone (**4-6**, **11-14**, 20.0 mmol), 2-aminothiophenol (24.0 mmol), piperidine (5.0 ml) and ethanol (100.0 ml) was refluxed for 2 h, then the solvent was evaporated under reduced pressure and the residue was crystallized from methanol to afford compounds **26-28** and **33-36** as pale yellow crystals.

Method ii: A mixture of chalcone (**1-22**, 10.0 mmol), 2-aminothiophenol (12.0 mmol), trifluoroacetic acid (1.0 ml) and toluene (50.0 ml) was refluxed for 3 h, then the solvent was evaporated under reduced pressure and the residue was crystallized from methanol to obtain benzothiazepines **23-44**.

2,3-Dihydro-4-(2-hydroxyphenyl)-2-(2-methylphenyl)-1,5-benzothiazepine (23): Yield (Method ii) 60%, m.p. 167-168 °C; IR: νC=N 1608 cm^{-1}; ^{1}H-NMR (δ): 2.46 (3H, s, CH_3), 3.12 (1H, t, J = 12.4 Hz, 3-H), 3.41 (1H, dd, J = 12.3, 4.6 Hz, 3-H), 5.39 (1H, dd, J = 12.3, 4.6 Hz, 2-H), 6.89-7.68 (12 arom. H, m).

Anal. Calcd. for $C_{22}H_{19}NOS$: C, 76.50; H, 5.54. Found: C, 76.57; H, 5.51.

2,3-Dihydro-4-(2-hydroxyphenyl)-2-(4-methylphenyl)-1,5-benzothiazepine (24): Yield (Method ii) 89%, m.p. 158-159 °C; IR: νC=N 1598 cm^{-1}; ^{1}H-NMR (δ): 2.36 (3H, s, CH_3), 3.09 (1H, t, J = 12.1 Hz, 3-H), 3.41 (1H, dd, J = 12.2, 4.4 Hz, 3-H), 5.03 (1H, dd, J = 12.2, 4.4 Hz, 2-H), 6.87-7.56 (12 arom. H, m)

Anal. Calcd. for $C_{22}H_{19}NOS$: C, 76.50; H, 5.54. Found: C, 76.44; 5.56.

2,3-Dihydro-4-(2-hydroxyphenyl)-2-(4-isopropylphenyl)-1,5-benzothiazepine (25): Yield (Method ii) 64%, m.p. 124-125 °C; IR: νC=N 1605 cm^{-1}; ^{1}H-NMR (δ): 1.24 (6H, d, J = 6.9 Hz, $CH(CH_3)_2$), 2.90 (1H, m, $CH(CH_3)_2$), 3.09 (1H, t, J = 12.4, 3-H), 3.44 (1H, dd, J = 13.2, 4.7 Hz, 3-H), 5.07 (1H, dd, J = 12.4, 4.7 Hz, 2-H), 6.86-7.69 (12 arom. H, m).

Anal. Calcd. for $C_{24}H_{23}NOS$: C, 77.19; H, 6.21. Found: C, 77.24; H, 6.24.

2,3-Dihydro-4-(2-hydroxyphenyl)-2-(2-methoxyphenyl)-1,5-benzothiazepine (26): Yield (Method i) 85% and (Method ii) 64%, m.p. 195-196 °C; IR: νC=N 1608 cm^{-1}; ^{1}H-NMR (δ): 2.89 (1H, t, J = 12.9 Hz, 3-H), 3.47 (1H, dd, J = 12.8, 4.4 Hz, 3-H), 3.90 (3H, s, OCH_3), 5.69 (1H, dd, J = 12.9, 4.4 Hz, 2-H), 6.86-7.84 (12 arom. H, m).

Anal. Calcd. for $C_{22}H_{19}NO_2S$: C, 71.12; H, 5.30. Found: C, 72.16; H, 5.32.

2,3-Dihydro-4-(2-hydroxyphenyl)-2-(3-methoxyphenyl)-1,5-benzothiazepine (27): Yield (Method i) 67% and (Method ii) 69%, m.p. 132-133 °C; IR: νC=N 1606 cm^{-1}; ^{1}H-NMR (δ): 3.10 (1H, t, J = 12.5 Hz, 3-H), 3.42 (1H, dd, J = 13.1, 4.8 Hz, 3-H), 3.80 (3H, s, OCH_3), 5.04 (1H, dd, J = 12.1, 4.7 Hz, 2-H), 6.81-7.71 (12 arom. H, m).

Anal. Calcd. for $C_{22}H_{19}NO_2S$: C, 71.12; H, 5.30. Found: C, 71.18; H, 5.27.

2,3-Dihydro-4-(2-hydroxyphenyl)-2-(4-methoxyphenyl)-1,5-benzothiazepine (28): Yield (Method i) 74% and (Method ii) 78%, m.p. 193-194 °C; IR: νC=N 1608 cm^{-1}; ^{1}H-NMR (δ): 3.08 (1H, t, J = 12.5 Hz, 3-H), 3.40 (1H, dd, J = 13.2, 4.6 Hz, 3-H), 3.81 (3H, s, OCH_3), 5.06 (1H, dd, J = 12.4, 4.6 Hz, 2-H), 6.84-7.69 (12 arom. H, m).

Anal. Calcd. for $C_{22}H_{19}NO_2S$: C, 71.12; H, 5.30. Found: 71.07; H, 5.33.

2,3-Dihydro-2-(2,3-dimethoxyphenyl)-4-(2-hydroxyphenyl)-1,5-benzothiazepine (29): Yield (Method ii) 79%, m.p. 173-174 °C; IR: νC=N 1601 cm^{-1}; ^{1}H-NMR (δ): 2.89 (1H, t, J = 12.9 Hz, 3-H), 3.46 (1H, dd, J = 13.1, 4.5 Hz, 3-H), 3.89 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 5.56 (1H, dd, J = 12.9, 4.4 Hz, 2-H), 6.85-7.89 (11 arom. H, m).

Anal. Calcd. for $C_{23}H_{21}NO_3S$: C, 70.57; H, 5.41. Found: C, 70.62; H, 5.39.

2,3-Dihydro-2-(3,4-dimethoxyphenyl)-4-(2-hydroxyphenyl)-1,5-benzothiazepine (30): Yield (Method ii) 72%, m.p. 146-147 °C; IR: νC=N 1598 cm^{-1}; ^{1}H-NMR (δ): 3.10 (1H, t, J = 13.0 Hz, 3-H), 3.41 (1H, dd, J = 13.0, 4.6 Hz, 3-H), 3.78 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 5.08 (1H, dd, J = 13.0, 4.4 Hz, 2-H), 6.81-7.71 (11 arom. H, m).

Anal. Calcd. for $C_{23}H_{21}NO_3S$: C, 70.57; H, 5.41. Found: C, 70.54; H, 5.43.

2,3-Dihydro-4-(2-hydroxyphenyl)-2-(3,4,5-trimethoxyphenyl)-1,5-benzothiazepine (31): Yield (Method ii) 71%, m.p. 196-197 °C; IR: νC=N 1602 cm^{-1}; ^{1}H-NMR (δ): 3.10 (1H, t, J = 12.7 Hz, 3-H), 3.41 (1H, dd, J = 12.9, 4.5 Hz, 3-H), 3.78 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 5.06 (1H, dd, J = 11.9, 5.1 Hz, 2-H), 6.54-7.70 (10 arom. H, m).

Anal. Cacld. for $C_{24}H_{23}NO_4S$: C, 68.39; H, 5.50. Found: C, 68.33; H, 5.52.

2,3-Dihydro-4-(2-hydroxyphenyl)-2-(4-hydroxyphenyl)-1,5-benzothiazepine (32): Yield (Method ii) 65%, m.p. 207-208 °C; IR: νC=N 1598 cm^{-1}; ^{1}H-NMR (δ): 3.07 (1H, t, J = 13.1 Hz, 3-H), 3.41 (1H, dd, J = 12.8, 4.4 Hz, 3-H), 5.01 (1H, dd, J = 12.9, 4.6 Hz, 2-H), 6.74-7.69 (12 arom. H, m).

Anal. Calcd. for $C_{21}H_{17}NO_2S$: C, 72.61; H, 4.93. Found: C, 72.66; H, 4.96.

2-(2-Chlorophenyl)-2,3-dihydro-4-(2-hydroxyphenyl)-1,5-benzothiazepine (33): Yield (Method i) 79% and (Method ii) 87%, m.p. 184-185 °C; IR: νC=N 1606 cm^{-1}; ^{1}H-NMR (δ): 2.90 (1H, t, J = 12.8 Hz, 3-H), 3.47 (1H, dd, J = 13.1, 4.6 Hz, 3-H), 5.62 (1H, dd, J = 12.6, 4.6 Hz, 2-H), 6.90-7.93 (12 arom. H, m).

Anal. Calcd. for $C_{21}H_{16}ClNOS$: C, 68.95; H, 4.41. Found: 68.90; H, 4.43.

2-(3-Chlorophenyl)-2,3-dihydro-4-(2-hydroxyphenyl)-1,5-benzothiazepine (34): Yield (Method i) 75% and (Method ii) 90%, m.p. 153-154 °C; νC=N 1611 cm^{-1}; ^{1}H-NMR (δ): 3.04 (1H, t, J = 12.9 Hz, 3-H), 3.41 (1H, J = 13.1, 4.7 Hz, 3-H), 5.01 (1H, dd, J = 12.4, 4.5 Hz, 2-H), 6.89-7.70 (12 arom. H, m).

Anal. Calcd. for $C_{21}H_{16}ClNOS$: C, 68.95; H, 4.41. Found: C, 68.98; H, 4.39.

2-(4-Chlorophenyl)-2,3-dihydro-4-(2-hydroxyphenyl)-1,5-benzothiazepine (35): Yield (Method i) 66% and (Method ii) 87%, m.p. 172-173 °C; IR: νC=N 1601 cm^{-1}; ^{1}H-NMR (δ): 3.03 (1H, t, J = 12.4 Hz, 3-H), 3.39 (1H, dd, J = 12.4, 4.7 Hz, 3-H), 5.03 (1H, dd, J = 12.4, 4.6 Hz, 2-H), 6.88-7.65 (12 arom. H, m).

Anal. Calcd. for $C_{21}H_{16}ClNOS$: C, 68.95; H, 4.41. Found: C, 68.99; H, 4.38.

2-(2,4-Dichlorophenyl)-2,3-dihydro-4-(2-hydroxyphenyl)-1,5-benzothiazepine (36): Yield (Method i) 77% and (Method ii) 92%, m.p. 186-187 °C; IR: νC=N 1610 cm^{-1}; ^{1}H-NMR (δ): 2.88

(1H, t, J = 12.8 Hz, 3-H), 3.45 (1H, dd, J = 13.1, 4.7 Hz, 3-H), 5.55 (1H, dd, J = 12.7, 4.5 Hz, 2-H), 6.90-7.79 (11 arom. H, m).

Anal. Calcd. for $C_{21}H_{15}Cl_2NOS$: C, 63.01; H. 3.78. Found: C, 63.05; H, 3.75.

2-(3,4-Dichlorophenyl)-2,3-dihydro-4-(2-hydroxyphenyl)-1,5-benzothiazepine (37): Yield (Method ii) 85%, m.p. 203-204 °C; IR: νC=N 1609 cm^{-1}; ^{1}H-NMR (δ): 3.04 (1H, t, J = 12.5 Hz, 3-H), 3.44 (1H, dd, J = 13.1, 4.8 Hz, 3-H), 5.02 (1H, dd, J = 12.4, 4.7 Hz, 2-H), 6.91-7.68 (11 arom. H, m).

Anal. Calcd. for $C_{21}H_{15}Cl_2NOS$: C, 63.01; H, 3.78. Found: C, 63.06; H, 3.81.

2,3-Dihydro-4-(2-hydroxyphenyl)-2-(3-nitrophenyl)-1,5-benzothiazepine (38): Yield (Method ii) 71%, m.p. 206-207 °C; IR: νC=N 1611 cm^{-1}; ^{1}H-NMR (δ): 3.08 (1H, t, J = 12.6 Hz, 3-H), 3.48 (1H, dd, J = 12.9, 4.7 Hz, 3-H), 5.14 (1H, dd, J = 12.5, 4.7 Hz, 2.H), 6.92-8.21 (12 arom. H, m).

Anal. Cacld. for $C_{21}H_{16}N_2O_3S$: C, 67.02; H, 4.29. Found: C, 67.06; H, 4.31.

2,3-Dihydro-4-(2-hydroxyphenyl)-2-(4-nitropbenyl)-1,5-benzothiazepine (39): Yield (Method ii) 72%, m.p. 205-206 °C; IR: νC=N 1595 cm^{-1}; ^{1}H-NMR (δ): 3.09 (1H, t, J = 12.7 Hz, 3-H), 3.48 (1H, dd, J = 13.0, 4.6 Hz, 3-H), 5.01 (IH, dd, J = 12.6, 4.7 Hz, 2-H), 6.89-8.23 (12 arom. H, m).

Anal. Cacld. for $C_{21}H_{16}N_2O_3S$: C, 67.02; H, 4.29. Found: 67.07; H, 4.26.

2,3-Dihydro-4-(2-hydroxy-4-methoxyphenyl)-2-(2-methoxyphenyl)-1,5-benzothiazepine (40): Yield (Method ii) 82%, m.p. 195-196 °C; IR: νC=N 1598 cm^{-1}; ^{1}H-NMR (δ): 2.88 (1H, t, J = 12.8 Hz, 3-H), 3.40 (1H, dd, J = 12.9, 4.3 Hz, 3-H), 3.87 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 5.54 (1H, dd, J = 12.8, 4.3 Hz, 2-H), 6.47-7.75 (11 arom. H, m).

Anal. Calcd. for $C_{23}H_{21}NO_3S$: C, 70.57; H, 5.41. Found: 70.61; H, 5.38.

2,3-Dihydro-2-(3-hydroxyphenyl)-4-(2-hydroxy-4-methoxyphenyl)-1,5-benzothiazepine (41): Yield (Method ii) 82%, m.p. 159-160 °C; IR: νC=N 1596 cm^{-1}; ^{1}H-NMR (δ): 3.06 (IH, t, J = 12.9 Hz, 3-H), 3.36 (IH, dd, J = 13.0, 4.4 Hz, 3-H), 3.90 (3H, s, OCH_3), 4.98 (1H, dd, J = 12.7, 4.5 Hz, 2-H), 6.46-7.69 (11 arom. H, m).

Anal. Calcd. for $C_{22}H_{19}NO_3S$: C, 70.02; H, 5.07. Found. C, 70.06; H, 5.04.

2,3-Dihydro-4-(2-hydroxy-4-methoxyphenyl)-2-(3,4-methylenedioxyphenyl)-1,5-benzothiazepine (42): Yield (Method ii) 67%, m.p. 200-201 °C; IR: νC=N 1602; ^{1}H-NMR (δ): 3.01 (1H, t, J = 12.9 Hz, 3-H), 3.32 (IH, dd, J = 12.8, 4.3 Hz, 3-H), 3.85 (3H, s, OCH_3), 4.96 (1H, dd, J = 12.7, 4.4 Hz, 2-H), 5.97 (2H, s, OCH_2O), 6.43-7.67 (10 arom. H, m).

Anal. Calcd. for $C_{23}H_{19}NO_4S$: C, 68.14; H, 4.72. Found: C, 68.18; H, 4.69.

2,3-Dihydro-2-(3-hydroxy-4-methoxyphenyl)-4-(2-hydroxy-4-methoxyphenyl)-1,5-benzothiazepine (43): Yield (Method ii) 82%, m.p. 186-187 °C; IR: νC=N 1601 cm^{-1}; ^{1}H-NMR (δ): 3.02 (1H, t, J = 12.4 Hz, 3-H), 3.31 (1H, dd, J = 12.4, 4.7 Hz, 3-H), 3.85 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 4.93 (IH, dd, J = 12.4, 4.7 Hz, 2-H), 6.43-7.68 (10 arom. H, m).

Anal. Calcd. for $C_{23}H_{21}NO_4S$: C, 67.80; H, 5.19. Found: C, 67.84; H, 5.17.

2,3-Dihydro-2-(3,4-dimethoxyphenyl)-4-(2-hydroxy-4-methoxyphenyl)-1,5-benzothiazepine (44): Yield (Method ii) 86%, m.p. 173-174 °C; IR: νC=N 1602 cm^{-1}; ^{1}H-NMR (δ): 3.04 (1H, t, J = 12.5 Hz, 3-H), 3.34 (1H, dd, J = 12.5, 4.6 Hz, 3-H), 3.79 (3H, s, OCH_3), 3.87 (3H, s, OCH_3) 3.92 (3H, s, OCH_3), 5.03 (1H, dd, J = 12.5, 4.6 Hz, 2-H), 6.42-7.70 (10 arom. H, m).

Anal. Calcd. for $C_{24}H_{23}NO_4S$: C, 68.39; H, 5.50. Found: C, 68.36; H, 5.46.

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*For Part 37, see A. Lévai, *Monatsh. Chem.* **129**, 909 (1998)
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