

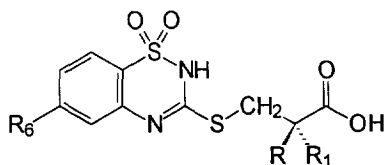
Stereospecific Synthesis of 3-[(2*H*-1,2,4-Benzothiadiazine-1,1-dioxide-3-yl)thio]-2-methylpropanoic Acids

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Abstract: 3-[(2*H*-1,2,4-Benzothiadiazine-1,1-dioxide-3-yl)thio]-2-methylpropanoic acids were synthesized from the corresponding 3-mercaptoderivatives by alkylation with (+) (R)- and (-) (S)-3-bromo-2-methylpropanoic acid methyl ester. The nucleophilic substitution takes place with complete maintenance of the enantiomeric purity. Copyright © 1996 Elsevier Science Ltd

Cyclooxygenase is an asymmetric target which preferentially binds the S (+) isomer of α -arylpropanoic acids. Moreover the absolute stereochemistry of such compounds influences their metabolic processes such as oxidation of the aryl or aryl-alkyl groups, glucuronidation and plasma protein binding¹⁻³. As part of an ongoing program aimed at gaining more information on the structural features enhancing inhibitory potency and specificity of arylalkanoic acids and of their isomers^{4,7}, the stereospecific synthesis of 3-[(2*H*-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)thio]-2-methylpropanoic acids of general formula **A** was performed.



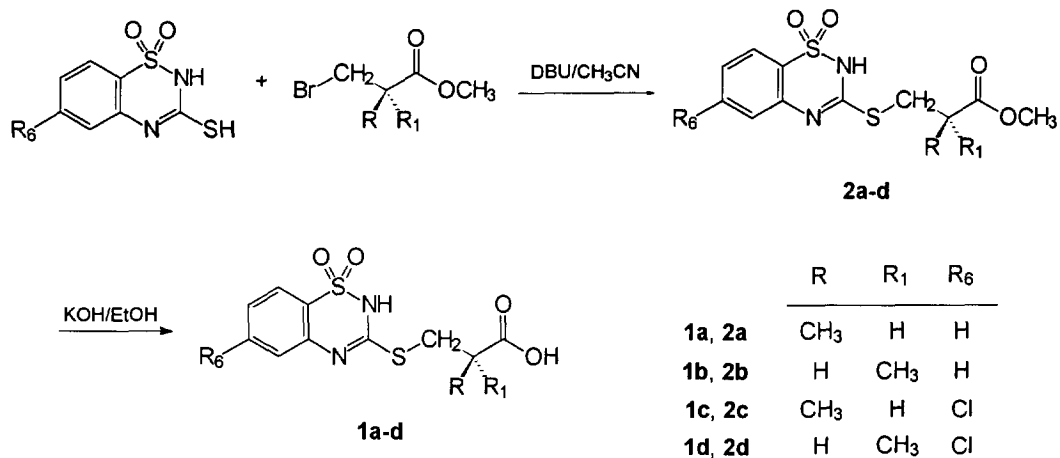
R, R₁ = H, CH₃; R₆ = H, Cl

A

Compounds **1a-d** were synthesized from the corresponding 3-mercaptoderivatives by alkylation with (+) (R)- and (-) (S)-3-bromo-2-methylpropanoic acid methyl ester using 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) as dehydrohalogenating agent in acetonitrile at 80°C and following hydrolysis of the **2a-d** esters with KOH in ethanol (Scheme 1). The nucleophilic substitution does not involve the stereogenic carbon and takes place with retention of the enantiomeric purity as confirmed by measurements of ¹H NMR spectra in the presence of the chiral shift reagent (CSR) tris[3-(2,2,3,3,4,4,4-heptafluoro-1-oxobutyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-onato-O,O']europium [Eu(hfc)₃]⁸.

Enantiomeric excess evaluation was carried out on the esters **2a-d** owing to their CDCl₃ solubility. CDCl₃ solutions (0.01 M) of the racemic mixtures⁹ of **2a** - **2b** and of **2c** - **2d** in the presence of shift reagent (0.24 CSR/compound molar ratio) show a large shift of the methoxyl resonance with signal splitting ($\Delta\Delta\delta$ = 5.0 and 7.0 Hz respectively). Accuracy of e.e. evaluation was within (\pm) 2%. To assess if the subsequent hydrolysis of **2a-d** to **1a-d** involves racemization, the (S)-3-[(6-chloro-2*H*-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)thio]-2-

methyl propanoic acid **1d** was submitted to esterification with methanol and BF_3 . The enantiomeric excess of the obtained ester (> 98%) is comparable with that of the same compound obtained by nucleophilic substitution indicating racemization is not occurring.



Scheme 1

The reported synthesis appears to be convenient for obtaining enantiomerically pure 3-[(2*H*-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)thio]-2-methylpropanoic acids in high yields.

EXPERIMENTAL

Melting points were determined with a Büchi 510 capillary apparatus and are uncorrected. ^1H NMR spectra were recorded with a Bruker DPX 200 and AMX-400 FT-NMR spectrometer using CDCl_3 and DMSO-d_6 as solvents and tetramethylsilane (TMS) as external standard. Chemical shifts are in ppm (δ) and coupling constants (*J*) in Hz. Multiplicities are abbreviated as follows: s, singlet; d, doublet; m, multiplet; *, D_2O changeable. IR spectra were recorded on a Perkin Elmer Model 1600 FT-IR spectrometer (Nujol mull) and were consistent with the assigned structures. Optical rotations were measured using a Perkin Elmer 241 polarimeter. The progress of the reaction was followed by thin-layer chromatography (TLC) on aluminium sheets silica gel 60 F₂₅₄, 0.2 mm thick: eluent chloroform-methanol 8:2. Elemental analyses were performed in Microanalysis Laboratory of Dipartimento di Scienze Farmaceutiche of Modena University on a Carlo Erba Elemental Analyzer 1106 apparatus.

3-[(2H-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)thio]-2-methylpropanoic acid methyl esters 2a-d

To a solution of the appropriate 3-mercaptoderivative (0,01 mol) in acetonitrile (20 ml per gram) 3-bromo-2-methylpropanoic acid methyl ester (0,012 mol) and DBU (0,012mol) were added dropwise under stirring at the temperature of 80°C. The reaction mixture was kept at the above conditions for 1 hour, then acetonitrile was evaporated under reduced pressure and the residue was treated with water; the insoluble was filtered, washed with water, dried in vacuo and crystallized from methanol and water.

(R)-3-[(2*H*-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)thio]-2-methylpropanoic acid methyl ester **2a**

Yield: 75%. m.p. 145°C. $[\alpha]_D^{20} = +86.0$ (c 0.5, methanol). >98% ee by NMR analysis with CSR. $^1\text{H NMR}$ (DMSO- d_6): δ 1.33 (d, $J=7.1$, 3H), 2.99 to 3.07 (m, 1H), 3.38 to 3.48 (m, 2H), 3.75 (s, 3H), 7.37 (dd, $J=1.1$, 8.2, 1H), 7.53 (ddd, $J=1.1$, 7.9, 7.6, 1H), 7.77 (ddd, $J=1.3$, 7.6, 8.2, 1H), 7.89 (dd, $J=1.3, 7.9$, 1H), 12.63 (s*, 1H). IR (Nujol) ν_{max} : 3222, 1729, 1164, 1377 cm^{-1} . Anal. Calcd. for $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}_4\text{S}_2$: C, 45.88; H, 4.48; N, 8.91. Found: C, 45.67, H, 4.52, N, 8.95.

(S)-3-[(2*H*-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)thio]-2-methylpropanoic acid methyl ester **2b**

Yield: 81%. m.p.: 145°C. $[\alpha]_D^{20} = -86.0$ (c 0.5, methanol). >98% ee by NMR analysis with CSR. $^1\text{H NMR}$ (DMSO- d_6): δ 1.33 (d, $J=7.1$, 3H), 2.99 to 3.07 (m, 1H), 3.38 to 3.48 (m, 2H), 3.75 (s, 3H), 7.37 (dd, $J=1.0$, 7.9, 1H), 7.53 (ddd, $J=1.0$, 7.8, 7.6, 1H), 7.77 (ddd, $J=1.4$, 7.6, 7.9, 1H), 7.89 (dd, $J=1.4$, 7.8, 1H), 12.63 (s*, 1H). IR (Nujol) ν_{max} : 3222, 1728, 1163, 1377 cm^{-1} . Anal. Calcd. for $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}_4\text{S}_2$: C, 45.88; H, 4.48; N, 8.91. Found: C, 45.73, H, 4.50, N, 8.84.

(R)-3-[(6-chloro-2*H*-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)thio]-2-methylpropanoic acid methyl ester **2c**

Yield: 84%. m.p.: 187-189°C. $[\alpha]_D^{20} = +66.7$ (c 0.5, methanol). >98% ee by NMR analysis with CSR. $^1\text{H NMR}$ (DMSO- d_6): δ 1.25 (d, $J=7.1$, 3H), 2.90 to 3.00 (m, 1H), 3.26 to 3.45 (m, 2H), 3.67 (s, 3H), 7.29 (d, $J=2.0$, 1H), 7.49 (dd, $J=2.0$, 8.5, 1H), 7.85 (d, $J=8.5$, 1H), 12.64 (s, 1H). IR (Nujol) ν_{max} : 3221, 1731, 1157, 1384 cm^{-1} . Anal. Calcd. for $\text{C}_{12}\text{H}_{13}\text{ClN}_2\text{O}_4\text{S}_2$: C, 41.32; H, 3.76; N, 8.03. Found: C, 41.05, H, 3.85, N, 8.03.

(S)-3-[(6-chloro-2*H*-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)thio]-2-methylpropanoic acid methyl ester **2d**

Yield: 90%. m.p.: 187-189°C. $[\alpha]_D^{20} = -66.7$ (c 0.5, methanol). >98% ee by NMR analysis with CSR. $^1\text{H NMR}$ (DMSO- d_6): δ 1.25 (d, $J=7.1$, 3H), 2.86 to 3.03 (m, 1H), 3.27 to 3.45 (m, 2H), 3.67 (s, 3H), 7.29 (d, $J=2.0$, 1H), 7.49 (dd, $J=2.0$, 8.5, 1H), 7.85 (d, $J=8.5$, 1H), 12.62 (s, 1H). IR (Nujol) ν_{max} : 3219, 1730, 1160, 1384 cm^{-1} . Anal. Calcd. for $\text{C}_{12}\text{H}_{13}\text{ClN}_2\text{O}_4\text{S}_2$: C, 41.32; H, 3.76; N, 8.03. Found: C, 41.17, H, 3.80, N, 8.04.

3-[(2*H*-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)thio]-2-methylpropanoic acids **1a-d**

A solution of the methyl ester **2** (g 0.5) in KOH ethanolic (90% v/v) (5 ml) was kept at room temperature under a nitrogen atmosphere until TLC indicated the disappearance of the starting material. Then the solvent was evaporated under reduced pressure, the residue was dissolved in water and the solution acidified with HCl (2M). The afforded product was filtered, washed with water, dried in vacuo and crystallized from methanol and water.

(R)-3-[(2*H*-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)thio]-2-methylpropanoic acid **1a**

Yield: 84%. m.p.: 248°C. $[\alpha]_D^{20} = +65.6$ (c 0.5, methanol). $^1\text{H NMR}$: (DMSO- d_6) δ 1.32 (d, $J=7.3$, 3H), 2.86 to 2.95 (m, 1H), 3.32 to 3.44 (m, 2H), 7.37 (dd, $J=0.9$, 8.0, 1H), 7.52 (ddd, $J=0.9$, 7.8, 7.7, 1H), 7.77 (ddd, $J=1.4$, 7.7, 8.0, 1H), 7.89 (dd, $J=1.4$, 7.8, 1H), 12.6 (s*, 1H). IR (Nujol) ν_{max} : 3232, 1692, 1156, 1375 cm^{-1} . Anal. Calcd. for $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}_4\text{S}_2$: C, 43.99; H, 4.03; N, 9.33. Found: C, 43.85; H, 4.03; N, 9.34.

(S)-3-[(2*H*-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)thio]-2-methylpropanoic acid **1b**

Yield: 66%. m.p.: 248°C. $[\alpha]_D^{20} = -65.6$ (c 0.5, methanol). $^1\text{H NMR}$: (DMSO_{d6}) δ 1.32 (d, $J=7.1$, 3H), 2.86 to 2.95 (m, 1H), 3.32 to 3.44 (m, 2H), 7.37 (dd, $J=1.0$, 7.8, 1H), 7.52 (ddd, $J=1.0$, 7.6, 7.9, 1H), 7.77 (ddd, $J=1.4$, 7.6, 7.8, 1H), 7.89 (dd, $J=1.4$, 7.9, 1H), 12.6 (s*, 1H). IR (Nujol) ν_{max} : 3234, 1693, 1158, 1375 cm⁻¹. Anal. Calcd. for C₁₁H₁₂N₂O₄S₂: C, 43.99; H, 4.03; N, 9.33. Found: C, 43.97; H, 4.05; N, 9.25.

(R)-3-[(6-chloro-2*H*-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)thio]-2-methylpropanoic acid **1c**

Yield: 75%. m.p.: 242°C. $[\alpha]_D^{20} = +54.6$ (c 0.5, methanol). $^1\text{H NMR}$: (DMSO_{d6}) δ 1.24 (d, $J=7.1$, 3H), 2.74 to 2.92 (m, 1H), 3.19 to 3.40 (m, 2H), 7.29 (d, $J=2.0$, 1H), 7.49 (dd, $J=2.0$, 8.5, 1H), 7.85 (d, $J=8.5$, 1H), 12.61 (s*, 1H). IR (Nujol) ν_{max} : 3214, 1709, 1162, 1390 cm⁻¹. Anal. Calcd. for C₁₁H₁₁ClN₂O₄S₂: C, 39.46; H, 3.31; N, 8.37. Found: C, 39.14; H, 3.28; N, 8.31.

(S)-3-[(6-chloro-2*H*-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)thio]-2-methylpropanoic acid **1d**

Yield: 61%. m.p.: 241°C. $[\alpha]_D^{20} = -54.6$ (c 0.5, methanol). $^1\text{H NMR}$: (DMSO_{d6}) δ 1.24 (d, $J=7.1$, 3H), 2.74 to 2.91 (m, 1H), 3.21 to 3.40 (m, 2H), 7.29 (d, $J=1.9$, 1H), 7.49 (dd, $J=1.9$, 8.5, 1H), 7.85 (d, $J=8.5$, 1H), 12.6 (s*, 1H). IR (Nujol) ν_{max} : 3215, 1710, 1162, 1390 cm⁻¹. Anal. Calcd. for C₁₁H₁₁ClN₂O₄S₂: C, 39.46; H, 3.31; N, 8.37. Found: C, 39.34; H, 3.33; N, 8.45.

Esterification of 1d A 0.1 g (0.3 mmol) amount of **1d** was treated with methanol (3 ml) in the presence of boron trifluoride (3.9 mmol) and the obtained solution was refluxed for 20 minutes. After methanol excess removal under reduced pressure the crude product was triturated with 15 ml of water, filtered, dried and crystallized from methanol and water to obtain **2d**. Yield 67%. m.p.: 187-189°C. $[\alpha]_D^{20} = -66.7$ (c 0.5, methanol). >98% ee by NMR analysis with CSR. $^1\text{H NMR}$: (DMSO_{d6}) δ 1.25 (d, $J=7.1$, 3H), 2.86 to 3.03 (m, 1H), 3.27 to 3.45 (m, 2H), 3.67 (s, 3H), 7.29 (d, $J=2.0$, 1H), 7.49 (dd, $J=2.0$, 8.5, 1H), 7.85 (d, $J=8.5$, 1H), 12.62 (s, 1H). IR (Nujol) ν_{max} : 3219, 1730, 1160, 1384 cm⁻¹. Anal. Calcd. for C₁₂H₁₃ClN₂O₄S₂: C, 41.32; H, 3.76; N, 8.03. Found: C, 41.08; H, 3.71; N, 8.00.

References and Notes

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9. The racemic mixtures of **2a** - **2b** and of **2c** - **2d** were obtained with almost quantitatively yields by reaction of the corresponding 3-mercaptoderivatives with (±) 3-bromo-2-methylpropanoic acid methyl ester in the conditions reported for compounds of **2a** - **2d**. Elemental analyses (± 0.3%) and $^1\text{H NMR}$ spectra are in agreement with the proposed structures.