Synthesis and Absolute Configuration of Optically Active 2,3-Disubstituted 2,3-Dihydro-1,3,4-thiadiazoles

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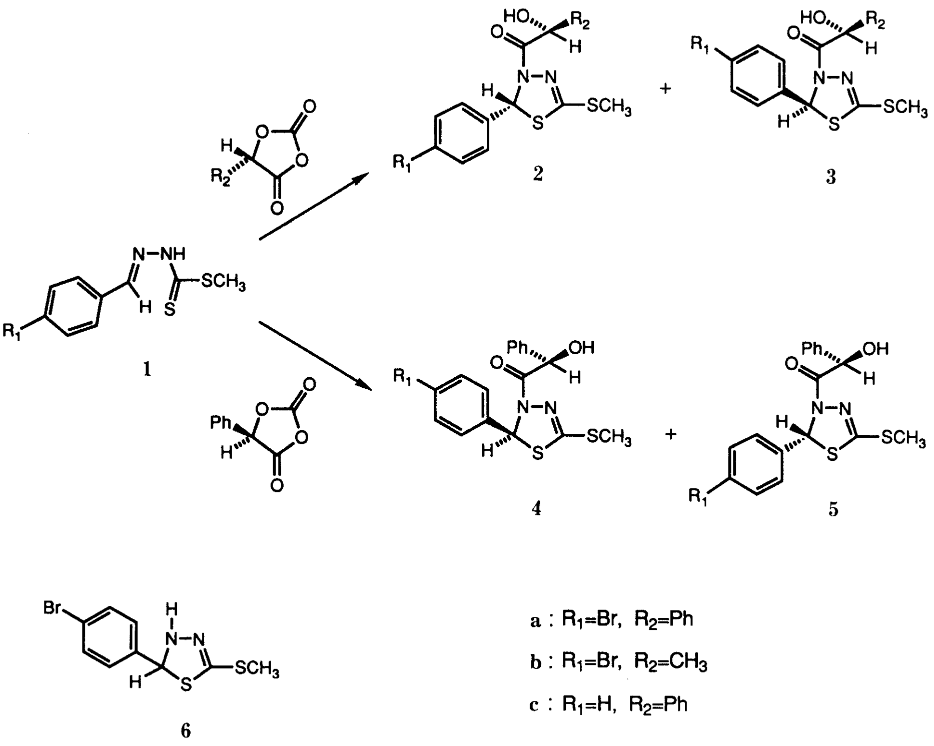
Optically active 3-substituted 2,3-dihydro-1,3,4-thiadiazoles (2—5) were synthesized by the reaction of aldehyde methylthio(thiocarbonyl)hydrazones (1) and chiral 5-substituted 1,3-dioxolane-2,4-diones. The absolute configurations of compounds 2—5 were deduced from their circular dichroism spectra.

Keywords 2,3-dihydro-1,3,4-thiadiazole; absolute configuration; circular dichroism; methylthio(thiocarbonyl)hydrazone; chiral 1,3-dioxolane-2,4-dione; cyclization

Circular dichroism (CD) spectroscopy is one of the generally applicable methods for the analysis of optically active compounds. Among CD techniques, the exciton chirality method[1] is useful for the determination of absolute configurations of organic compounds. Kakimura and co-wokers have applied this method for determining the absolute configuration of asukamycin, having a polyene-amide chromophore.[2]

In a previous communication,[3] we reported that the acylation of 4-bromobenzaldehyde methylthio(thiocarbonyl)hydrazone (**1a**) with chiral 5-phenyl-1,3-dioxolane-2,4-dione gave novel chiral 2-(4-bromophenyl)-3-mandelyl-2,3-dihydro-1,3,4-thiadiazoles (**2a**—**5a**) which have extremely high optical rotations. We determined their absolute configurations by single-crystal X-ray analysis (for compound **2a**) and by analysis of the optical rotations (for **3a**—**5a**). Here we report the application of this new synthetic route to the synthesis of several optically active 3-substituted 2,3-dihydro-1,3,4-thiadiazole analogues and the assignment of their absolute configurations by the CD method.

Reaction of 4-bromobenzaldehyde methylthio(thiocarbonyl)hydrazone (**1a**) and (*S*)-(+)-5-methyl-1,3-dioxolane-2,4-dione[4] in the presence of trifluoroacetic acid (TFA) at room temperature for 3 h gave the optically active compounds **2b** (25%), $[\alpha]_D^{20}$ +437.2°, and **3b** (56%), $[\alpha]_D^{20}$ −511.7° after separation by column chromatography. In view of our previous results,[3] this acylation reaction was assumed to proceed without isomerization at the lactyl moiety.[5] Compounds **2b** and **3b** were both found to be diastereoisomers of 2-(4-bromophenyl)-3-[(*S*)-lactyl]-5-methylthio-2,3-dihydro-1,3,4-thiadiazoles on the basis of the following spectral data. The elemental analyses of both compounds were consistent with the molecular formula $C_{12}H_{13}BrN_2O_2S_2$. The mass spectra (MS) of the 2,3-dihydro-1,3,4-thiadiazoles (**2b** and **3b**) showed the same molecular ion peak at *m*/*z* 362 (M^+ +1). Compounds **2b** and **3b** showed infrared (IR) absorption due to a carbonyl group at 1645 and 1650 cm^{-1}, respectively. The proton nuclear magnetic resonance (^{1}H-NMR) spectra of compounds **2b** and **3b** showed C-2 proton absorptions at δ 6.97 and 7.01 with an upfield shift of 0.83 and 0.79 ppm from



a : R_1=Br, R_2=Ph
b : R_1=Br, R_2=CH_3
c : R_1=H, R_2=Ph

Chart 1

that of the methine proton of the starting material (**1a**), respectively. Those shift values are in good agreement with those reported for 2,3-dihydro-1,3,4-thiadiazole derivatives.[6]

Benzaldehyde methylthio(thiocarbonyl)hydrazone (**1c**) was acylated with (*S*)-(+)-5-phenyl-1,3-dioxolane-2,4-dione[4] in a similar manner to that used for compounds **2b** and **3b** to give the optically active compounds **2c** (17%), $[\alpha]_D^{20}$ +465.2°, and **3c** (47%), $[\alpha]_D^{20}$ −540.2°, after separation by column chromatography. Compounds **2c** and **3c** were both found to be diastereoisomers of 3-[(*S*)-mandelyl]-5-methylthio-2-phenyl-2,3-dihydro-1,3,4-thiadiazoles on the basis of their spectral data. The elemental analyses of both compounds were consistent with the molecular formula $C_{17}H_{16}N_2O_2S_2$. MS of 2,3-dihydro-1,3,4-thiadiazoles (**2c** and **3c**) showed the same molecular ion peak at *m/z* 344 (M^+). Compounds **2c** and **3c** showed IR absorption due to a carbonyl group at 1650 and 1660 cm^{-1}, and the ^{1}H-NMR signal due to the C-2 protons at δ 6.98 and 7.04, respectively.

Similarly, acylation of the methylthio(thiocarbonyl)hydrazone (**1c**) with (*R*)-(−)-5-phenyl-1,3-dioxolane-2,4-dione[4] afforded the optically active compounds **4c** (17%), $[\alpha]_D^{20}$ −456.6° and **5c** (54%), $[\alpha]_D^{20}$ +543.1° as diastereoisomers of 3-[(*R*)-mandelyl]-5-methylthio-2-phenyl-2,3-dihydro-1,3,4-thiadiazoles. The optical purity of the 2,3-dihydro-1,3,4-thiadiazoles (**2c**—**5c**) was confirmed by chiral phase high performance liquid chromatography (HPLC) (CHIRAL OC, EtOH at 0.5 ml/min for compounds **2c** and **4c**, EtOH at 0.05 ml/min for compounds **3c** and **5c**, ultraviolet (UV) detector set at 254 nm) to be >99.9% in each case.

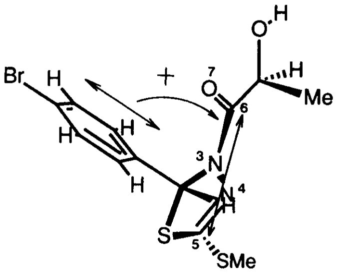


Fig. 1. A Stereochemical View of (+)-**2b**

Table I. UV and CD Data for **2**—**5**

Compound	UV$^{a)}$ λ_{max} nm (ε)	CD$^{a)}$ λ nm ($\Delta\varepsilon$)	Absolute configuration
2a	265 (9500), 235 (17450), 211 (17100)	250 (+40.5), 226 (−46.8)	2*R*
2b	262 (7150), 234 (12100), 208 (9650)	245 (+36.4), 218 (−39.0)	2*R*
2c	269 (10350), 230 (13950), 209 (20450)	245 (+29.6), 219 (−35.1)	2*R*
3a	265 (12800), 235 (21050), 211 (19600)	249 (−32.7), 222 (+40.7)	2*S*
3b	261 (6900), 234 (11600), 208 (9300)	245 (−35.7), 218 (+38.9)	2*S*
3c	266 (7400), 228 (9250), 210 (11600)	248 (−24.3), 220 (+31.3)	2*S*
4a	265 (10600), 235 (19400), 211 (18400)	250 (−40.7), 226 (+46.5)	2*S*
4c	266 (10400), 230 (14050), 209 (21100)	245 (−29.6), 219 (+36.9)	2*S*
5a	265 (14450), 235 (24000), 211 (22300)	249 (+32.4), 222 (−37.9)	2*R*
5c	268 (7000), 228 (8700), 210 (11100)	248 (+24.6), 220 (−31.3)	2*R*

a) Compounds **2**—**5** in EtOH.

The CD spectra of (+)-**2b** and (−)-**3b** were studied as models for 3-acyl-2,3-dihydro-1,3,4-thiadiazoles. The acylhydrazino moiety, O(7)–C(6)–N(3)–N(4)–C(5), of the 3-acyl-2,3-dihydro-1,3,4-thiadiazole nucleus is assumed to be almost planar and the 4-bromophenyl group on C-2 would be located below (α) or above (β) the 2,3-dihydro-1,3,4-thiadiazole ring on the basis of the results of X-ray analysis reported previously.[3,7] If the 4-bromophenyl group is located below (α) the thiadiazole ring, the exciton dipoles should have the directions shown in Fig. 1, and positive induced Cotton effects would be expected, based on exciton chirality method. The CD spectrum of (+)-**2b** exhibited a distinct positive split Cotton effect owing to exciton coupling with a maximum at 245 nm ($\Delta\varepsilon$ +36.4) and a minimum at 218 nm ($\Delta\varepsilon$ −39.0). The positive sign of the longer wavelength peak indicates that the two chromophores have a clockwise helicity (Table I). Therefore, the absolute configuration at C-2 of (+)-**2b** was assigned as *R*. The CD spectrum of (−)-**3b** showed a negative Cotton effect at 245 nm ($\Delta\varepsilon$ −35.7) (Table I), indicating that the two chromophores have a counterclockwise helicity. Therefore, the absolute configuration at C-2 of (−)-**3b** was assigned as *S*. Further support for the absolute configurations of (+)-**2b** and (−)-**3b** was obtained by comparison of the CD spectra with those of similar compounds, (+)-**2a** and (−)-**3a**, having known absolute configurations, respectively. The CD curves of compounds **2b**, **3b** were similar to those of compounds **2a**, **3a** in the sign, shape, and position of the Cotton effect, respectively, reflecting the similarity in their absolute configurations at C-2 (Fig. 2). This result also suggests that the absolute configurations of (+)-**2b** and (−)-**3b** are 2*R* and 2*S*, respectively.

The CD spectra of the two diastereoisomers (+)-(**2c**) and (+)-(**5c**) showed positive Cotton effects while the two diastereoisomers (−)-(**3c**) and (−)-(**4c**) showed negative Cotton effects at longer wavelengths in accordance with (+)-**2b** and (−)-**3b** having 2*R* and 2*S* configurations, respectively (Table I). The CD signs of compounds **2c**—**5c** are also in agreement with those of the similar compounds **2a**—**5a** (Table I) and with the rule described above for compounds **2b** and **3b**.

From our results and the above facts, it was concluded

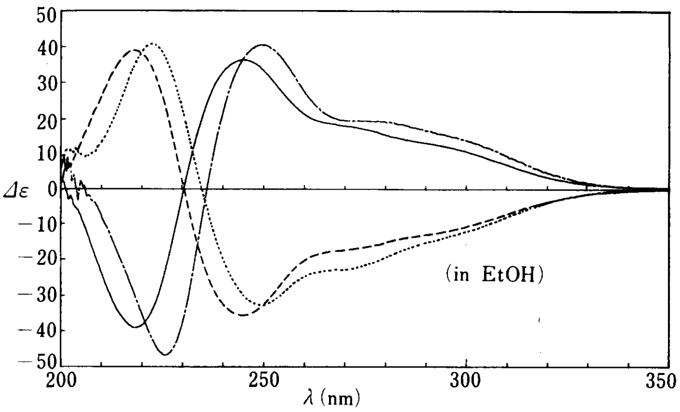


Fig. 2. CD Spectra of 2,3-Dihydro-1,3,4-thiadiazole Derivatives
(+)-**2a**, ———; (+)-**2b**, —; (−)-**3a**, ---; (−)-**3b**, ---.

that the absolute configurations of 3-lactyl- or 3-mandelyl-2,3-dihydro-1,3,4-thiadiazoles can be determined from the CD sign independently of the nature and chirality of the 3-acyl moiety.

Experimental

Melting points were determined by the capillary method and are uncorrected. IR spectra were recorded on a Hitachi 215 spectrometer. ^{1}H-NMR spectra were recorded on a JEOL PS-100 spectrometer or a JEOL JNM-FX 200 spectrometer using tetramethylsilane as an internal standard. The optical rotations were measured with a Union Giken PM-201 polarimeter, and CD spectra were measured with a JASCO J-600 spectropolarimeter. UV spectra were recorded with a Shimadzu UV-200 spectrometer. MS were measured with a JEOL D-300 instrument. Column chromatography was performed on silica gel (K-100-S, from Katayama Chemicals). HPLC was performed on a CHIRAL OC column (4.6 i.d. × 250 mm) using an EtOH solvent system.

Aldehyde Methylthio(thiocarbonyl)hydrazones (1) Compounds **1a**[8] and **1c**[9] were prepared by literature methods.

(2*R*)-(4-Bromophenyl)-3-[(*S*)-lactyl]-5-methylthio-2,3-dihydro-1,3,4-thiadiazole (2b) and (2*S*)-(4-Bromophenyl)-3-[(*S*)-lactyl]-5-methylthio-2,3-dihydro-1,3,4-thiadiazole (3b) A solution of (*S*)-(−)-5-methyl-1,3-dioxolane-2,4-dione (322 mg, 2.78 mmol) in CH_2Cl_2 (10 ml) was added to a stirred solution of 4-bromobenzaldehyde methylthio(thiocarbonyl)hydrazone (**1a**) (800 mg, 2.77 mmol) and TFA (0.21 ml, 2.82 mmol) in CH_2Cl_2 (15 ml) at 0 °C. After being stirred at room temperature for 3 h, the reaction mixture was concentrated under reduced pressure. The residue was chromatographed on silica gel with $CHCl_3$–acetone (50 : 1) as the eluent to give two fractions containing diastereomeric products. Evaporation of the first fraction gave a solid, which was recrystallized from isopropyl ether to give **2b** (249 mg, 25%), mp 95—96 °C. $[\alpha]_D^{20}$ +437.2° (*c* = 0.99, $CHCl_3$). IR (KBr): 3100—3600 (OH), 1645 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.40 (3H, d, *J* = 8 Hz, CH_3), 2.62 (3H, s, SCH_3), 2.70—3.15 (1H, br, OH), 4.79 (1H, q, *J* = 8 Hz, CH), 6.97 (1H, s, C_2-H), 7.21 (2H, dd, *J* = 2, 8 Hz, ArH), 7.49 (2H, dd, *J* = 2, 8 Hz, ArH). MS *m/z*: 362 ($M^+ + 1$). *Anal.* Calcd for $C_{12}H_{13}BrN_2O_2S_2$: C, 39.90; H, 3.63; N, 7.75. Found: C, 39.84; H, 3.55; N, 7.54. Evaporation of the second fraction gave a solid, which was recrystallized from isopropyl alcohol to give **3b** (564 mg, 56%), mp 98—99 °C. $[\alpha]_D^{20}$ −511.7° (*c* = 0.983, $CHCl_3$). IR (KBr): 3100—3600 (OH), 1650 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.43 (3H, d, *J* = 8 Hz, CH_3), 2.62 (3H, s, SCH_3), 2.70—3.10 (1H, br, OH), 4.69 (1H, q, *J* = 8 Hz, CH), 7.01 (1H, s, C_2-H), 7.19 (2H, dd, *J* = 2, 8 Hz, ArH), 7.49 (2H, dd, *J* = 2, 8 Hz, ArH). MS *m/z*: 362 ($M^+ + 1$). *Anal.* Calcd for $C_{12}H_{13}BrN_2O_2S_2$: C, 39.90; H, 3.63; N, 7.75. Found: C, 39.84; H, 3.47; N, 7.61.

3-[(*S*)-Mandelyl]-5-methylthio-(2*R*)-phenyl-2,3-dihydro-1,3,4-thiadiazole (2c) and 3-[(*S*)-Mandelyl]-5-methylthio-(2*S*)-phenyl-2,3-dihydro-1,3,4-thiadiazole (3c) A solution of (*S*)-(+)-5-phenyl-1,3-dioxolane-2,4-dione (609 mg, 3.42 mmol) in CH_2Cl_2 (16 ml) was added dropwise to a stirred solution of benzaldehyde methylthio(thiocarbonyl)hydrazone (**1c**) (600 mg, 2.86 mmol) and TFA (0.25 ml, 3.36 mmol) in CH_2Cl_2 (20 ml) at 0 °C. After being stirred at room temperature for 1 h, the reaction mixture was concentrated under reduced pressure. The residue was chromatographed on silica gel with $CHCl_3$–acetone (50 : 1) as the eluent to give two fractions of diastereomeric products. Evaporation of the first fraction gave a solid, which was recrystallized from isopropyl ether to give **2c** (162 mg, 17%), mp 155—157 °C. $[\alpha]_D^{20}$ +465.2° (*c* = 1.01, $CHCl_3$). IR (KBr): 3300—3600 (OH), 1650 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.44 (3H, s, SCH_3), 4.00 (1H, d, *J* = 8 Hz, OH), 5.62 (1H, d, *J* = 8 Hz, CH), 6.98 (1H, s, C_2-H), 7.31 (10H, s, ArH). MS *m/z*: 344 (M^+). *Anal.* Calcd for $C_{17}H_{16}N_2O_2S_2$: C, 59.28; H, 4.68; N, 8.13. Found: C, 59.15; H, 4.47; N, 8.09. Evaporation of the second fraction gave a solid, which was recrystallized from diethyl ether to give **3c** (463 mg, 47%), mp 82—83 °C. $[\alpha]_D^{20}$ −540.2° (*c* = 1.02, $CHCl_3$). IR (KBr): 3150—3550 (OH), 1660 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.54 (3H, s, SCH_3), 4.05 (1H, d, *J* = 8 Hz, OH), 5.56 (1H, d, *J* = 8 Hz, CH), 7.04 (1H, s, C_2-H), 7.28 (5H, s, ArH), 6.84—7.38 (5H, m, ArH). MS *m/z*: 344 (M^+). *Anal.* Calcd for $C_{17}H_{16}N_2O_2S_2$: C, 59.28; H, 4.68; N, 8.13. Found: C, 59.28; H, 4.64; N, 8.12.

3-[(*R*)-Mandelyl]-5-methylthio-(2*S*)-phenyl-2,3-dihydro-1,3,4-thiadiazole (4c) and 3-[(*R*)-Mandelyl]-5-methylthio-(2*R*)-phenyl-2,3-dihydro-1,3,4-thiadiazole (5c) Compounds **4c** and **5c** were obtained from (*R*)-(−)-5-phenyl-1,3-dioxolane-2,4-dione (760 mg, 4.27 mmol), the methylthio(thiocarbonyl)hydrazone (**1c**) (600 mg, 2.86 mmol), and TFA (0.32 ml, 4.31 mmol) in a similar manner to that described for compounds **2c** and **3c**. The minor diastereoisomer (**4c**) (171 mg, 17%) showed the same IR and ^{1}H-NMR spectra as those of **2c**, mp 154—156 °C, $[\alpha]_D^{20}$ −456.6° (*c* = 1.01, $CHCl_3$). MS *m/z*: 344 (M^+). *Anal.* Calcd for $C_{17}H_{16}N_2O_2S_2$: C, 59.28; H, 4.68; N, 8.13. Found: C, 59.14; H, 4.56; N, 8.03. The major diastereoisomer (**5c**) (527 mg, 54%) showed the same IR and ^{1}H-NMR spectra as those of **3c**, mp 83—84 °C, $[\alpha]_D^{20}$ +543.1° (*c* = 0.99, $CHCl_3$). MS *m/z*: 344 (M^+). *Anal.* Calcd for $C_{17}H_{16}N_2O_2S_2$: C, 59.28; H, 4.68; N, 8.13. Found: C, 59.28; H, 4.75; N, 8.09.

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