

**SYNTHESIS OF NOVEL CHIRAL 2,3-DIHYDRO-1,3,4-THIADIAZOLES WITH
EXTREMELY HIGH OPTICAL ROTATIONS : X-RAY CRYSTAL STRUCTURE OF
(2R)-D-MANDELYL-5-METHYLTHIO-2-PHENYL-2,3-DIHYDRO-1,3,4-
THIADIAZOLE**

Kouhei Toyooka^a, Yoshiyuki Takeuchi^a, Zenei Taira^b, and Seiju Kubota^a

^aFaculty of Pharmaceutical Sciences, University of Tokushima, Sho-machi 1,
Tokushima 770, Japan

^bFaculty of Pharmaceutical Sciences, Tokushima Bunri University, Yamashiro-
cho, Tokushima 770, Japan

Abstract---The reaction of 4-bromobenzaldehyde methylthio(thiocarbonyl)-
hydrazone with chiral 5-phenyl-1,3-dioxolane-2,4-dione in the presence of
trifluoroacetic acid gave chiral 2-(4-bromophenyl)-3-mandelyl-2,3-dihydro-
1,3,4-thiadiazoles with extremely high optical rotations; the absolute
configuration of the 2,3-dihydro-1,3,4-thiadiazole (**2**) was established by
single crystal X-ray analysis.

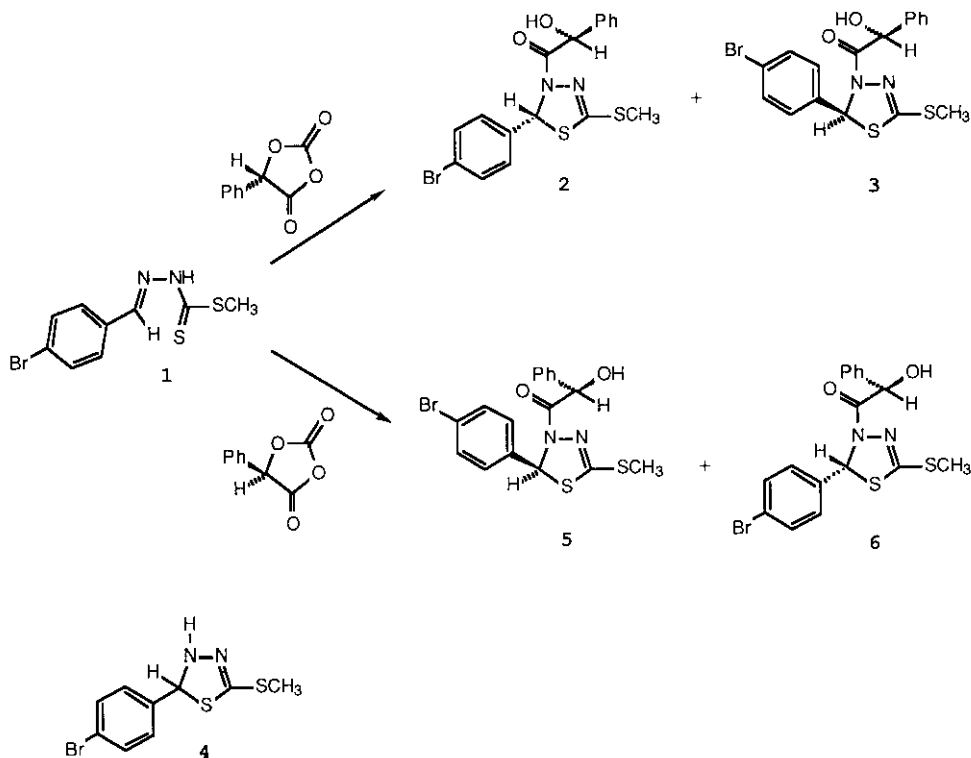
In the previous paper,¹ we described a facile synthesis of 5-substituted 1,3-
dioxolane-2,4-diones as chiral acylating reagents using trichloromethyl chloroformate.
Previously, we have reported that acylation of aldehyde methylthio(thiocarbonyl)-
hydrazones with acetic anhydride or acetyl chloride gave 2-substituted 3-acetyl-5-
methylthio-2,3-dihydro-1,3,4-thiadiazoles in good yields.² To date, no example of
isolation of the chiral 2,3-dihydro-1,3,4-thiadiazole which has an asymmetric
carbon atom in the nucleus has been reported.

We now extend a novel application of this reaction to the synthesis of chiral 2-
substituted 2,3-dihydro-1,3,4-thiadiazoles using chiral 1,3-dioxolane-2,4-diones.

The reaction of 4-bromobenzaldehyde methylthio(thiocarbonyl)hydrazone (**1**) with
(S)-(+)-5-phenyl-1,3-dioxolane-2,4-dione in the presence of trifluoroacetic acid
(TFA) (1.5 equiv.) at 0 °C afforded a diastereomeric mixture of (2R)-(4-bromophenyl)-3-
[(S)-mandelyl]-2,3-dihydro-1,3,4-thiadiazole (**2**) and (2S)-(4-bromophenyl)-3-[(S)-
mandelyl]-2,3-dihydro-1,3,4-thiadiazole (**3**) without epimerization. The hydrazone **1**
presumably exists as an equilibrium mixture with ring form (**4**) under these
reaction conditions.³ The kinetically more preferable product **3** would be formed
predominantly by acylation of the intermediate **4** with (S)-(+)-5-phenyl-1,3-dioxolane-

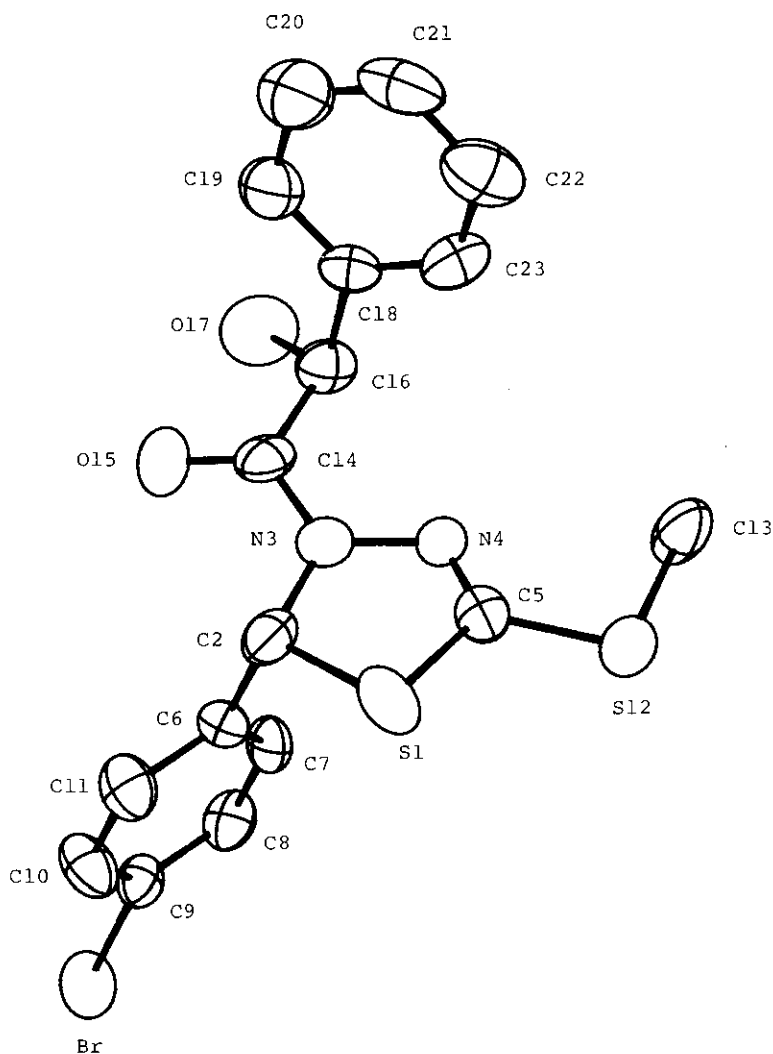
2,4-dione. The mixture was chromatographed on silica gel to give the optical active **2** (19 %), mp 161-162 °C, $[\alpha]_D^{20} +405.18^\circ$ (c=1.00, CHCl₃) and **3** (66 %), mp 105-106 °C, $[\alpha]_D^{20} -426.86^\circ$ (c=1.00, CHCl₃), which showed extremely high optical rotations.⁴

The absolute configuration of the enantiomer **2** was established by single-crystal X-ray analysis (Figure 1).



Crystal data for the enantiomer **2**: C₁₇H₁₅BrN₂O₂S₂, M=423.342, orthorhombic, space group P2₁2₁2₁, a=8.416(3), b=26.672(7), c=7.768(2) Å, v=1743.6(9) Å³, Z=4, D_x=1.612g cm⁻³, F(000)=856, μ(Mo-Kα)=27.42cm⁻¹. The reflection data were collected on a Rigaku AFC-6B diffractometer for 2<θ<50° using graphite monochromated radiation (0.71069Å) with ω scan mode. The structure was solved by direct methods using the MULTAN program and refined by block diagonal least-squares to R=0.049, R_w (w=1.0)=0.051 for 1234 independent reflections [|F|>6σ(|F|)]. The absolute configuration of **2** was determined by the intensity examinations of Bijvoet pairs.

Similarly, the reaction of the methylthio(thiocarbonyl)hydrazone **1** with (R)-(-)-5-phenyl-1,3-dioxolane-2,4-dione in the presence of TFA at 0 °C gave the (2S)- (**5**)

Figure 1 The crystal structure of **2**

(20 %), mp 162-163 °C, $[\alpha]_D^{20}$ -407.18° ($c=1.00$, CHCl_3) and (2R)-(4-bromophenyl)-3-[(R)-mandelyl]-2,3-dihydro-1,3,4-thiadiazole (**6**) (66 %), mp 104-105 °C, $[\alpha]_D^{20}$ +433.13° ($c=1.00$, CHCl_3)⁴.

The optical purities of the 2,3-dihydro-1,3,4-thiadiazoles **2** and **5** obtained here were established by chiral phase hplc (CHIRALCEL OC, EtOH at 0.5 ml/min, 25cm x 4.6mm, uv detector 254 nm) to be >99.9 %, respectively.

REFERENCES

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2. S. Kubota, K. Toyooka, J. Ikeda, N. Yamamoto, and M. Shibuya, *J. Chem. Soc., Perkin Trans. 1*, **1983**, 967.
3. M. Uda and S. Kubota, *J. Heterocyclic Chem.*, 1979, **16**, 1273.
4. Satisfactory spectral and analytical data were obtained for all new compounds :
2 and **5**; Ir(KBr) 3300 (OH), 1640 (C=O) cm^{-1} ; $^1\text{H-nmr}$ (CDCl_3) δ 2.44 (3H, s, SCH_3), 3.95 (1H, d, $J=8$ Hz, OH), 5.60 (1H, d, $J=8$ Hz, CH), 6.91 (1H, s, $\text{C}_2\text{-H}$), 7.19 (2H, dd, $J=2,8$ Hz, ArH), 7.32 (5H, s, ArH), 7.50 (2H, dd, $J=2,8$ Hz, ArH); Ms m/z 424 (M^++1).
3 and **6**; Ir(KBr) 3400 (OH), 1665 (C=O) cm^{-1} ; $^1\text{H-nmr}$ (CDCl_3) δ 2.55 (3H, s, SCH_3), 4.01 (1H, d, $J=8$ Hz, OH), 5.53 (1H, d, $J=8$ Hz, CH), 6.78 (2H, dd, $J=2,8$ Hz, ArH), 6.98 (1H, s, $\text{C}_2\text{-H}$), 7.29 (5H, s, ArH), 7.32 (2H, dd, $J=2,8$ Hz, ArH); Ms m/z 424 (M^++1).

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