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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

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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.

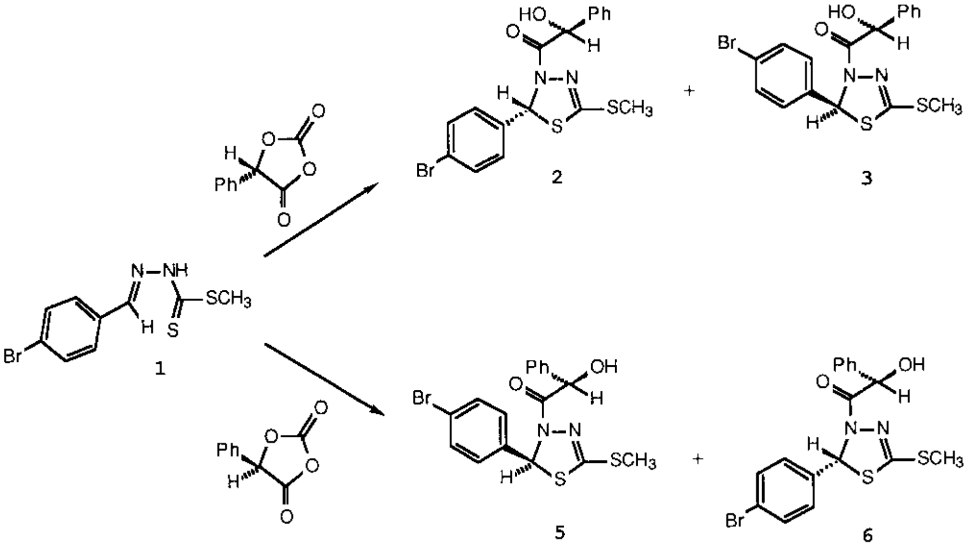
In the previous paper,[1] we described a facile synthesis of 5-substituted 1,3-dioxolane-2,4-diones as chiral acylating reagents using trichloromethyl chloroformate. Previously, we have reported that acylation of aldehyde methylthio(thiocarbonyl)-hydrazones with acetic anhydride or acetyl chloride gave 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.

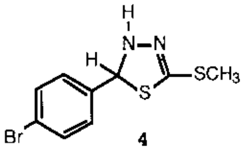
We now extend a novel application of this reaction to the synthesis of chiral 2-substituted 2,3-dihydro-1,3,4-thiadiazoles using chiral 1,3-dioxolane-2,4-diones.

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° (c=1.00, $CHCl_3$) and **3** (66 %), mp 105-106 °C, $[\alpha]_D^{20}$ -426.86° (c=1.00, $CHCl_3$), which showed extremely high optical rotations.[4]

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





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Crystal data for the enantiomer **2**: $C_{17}H_{15}BrN_2O_2S_2$, M=423.342, orthorhombic, space group $P2_12_12_1$, a=8.416(3), b=26.672(7), c=7.768(2) Å, v=1743.6(9) Å^3, Z=4, D_x=1.612g cm^{-3}, F(000)=856, μ(Mo-k_α)=27.42cm^{-1}. The reflection data were collected on a Rigaku AFC-6B diffractometer for $2<\theta<50°$ 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, Rw (w=1.0)=0.051 for 1234 independent reflections $[|F|>6\sigma(|F|)]$. 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**)

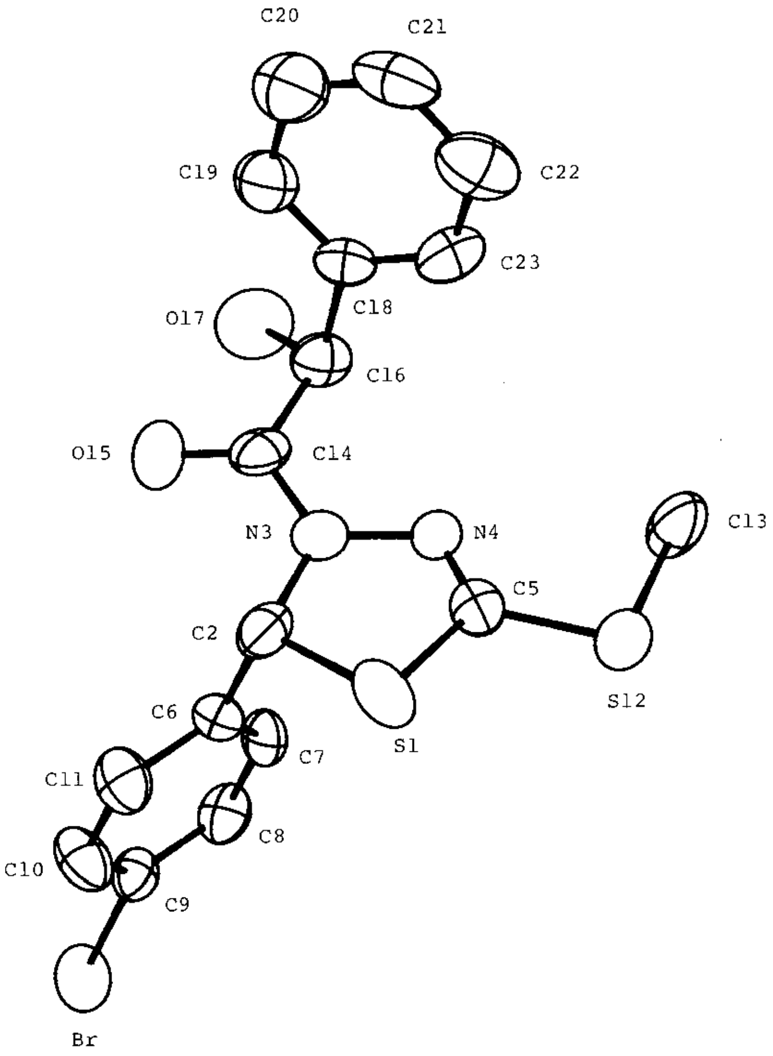

Figure 1 The crystal structure of **2**

(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.

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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}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, C_2-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}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, C_2-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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