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Facile Synthesis of 4-Substituted 3,4-Dihydro-1*H*-2,1,3-Benzothiadiazine 2,2-Dioxides

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ABSTRACT: *A new method for the preparation of 4-substituted 3,4-dihydro-1H-2,1,3-benzothiadiazine 2,2-dioxides is described. Treatment of t-butyl N-phenylsulfamoylcarbamate derivatives (***1***) with different aldehydes afforded the corresponding intramolecular cyclized products* **2** *under trifluoroacetic acid conditions.* © 2011 Wiley Periodicals, Inc. Heteroatom Chem 22:192–197, 2011; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.20670

INTRODUCTION

Among the components of the bicyclic diazine group of heterocyclic compounds [1], benzothiadiazin-*S*,*S*-dioxides are of special interest because of their biological properties. For instance, diazoxide has been shown to produce muscle relaxation [2] and bentazone is a potent herbicide [3]. Other members of this family show antihypertensive and vasodilating properties [4], as well as sedative effects [5]. 4-Substituted-1*H*-2,1,3-benzothiadiazine-2,2-dioxides and 3,4-dihydro analogues are also valuable intermediates in the preparation of disinfectants, bleaching agents, and antiseptics [6].

The usual procedure for the preparation of fused 1*H*-2,1,3-thiadiazine 2,2-dioxides is a two-step approach involving sulfamoylation of ortho-substituted amino derivatives, followed by ring closure [1]. This technique produces 4(3*H*)-oxo [7], 4-amino [8], or 4-phenyl [9] 1*H*-2,1,3-benzothiadiazines from *o*-aminobenzoates, *o*-aminobenzonitriles, or 2-aminobenzophenones, respectively.

Catalytic hydrogenation of 4-substituted-1*H*-2,1,3-benzothiadiazenes yielded the corresponding 3,4-dihydro derivatives. These compounds can be prepared directly by reaction of 2-aminobenzylamines with either sulfuryl chloride [10] or sulfamide [11]. Recently, Pews reported

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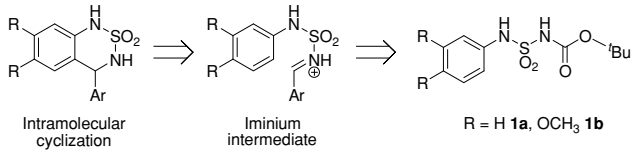


FIGURE 1 Retrosynthetic analysis.

the synthesis of 3-alkyl derivatives by reaction of *N*-alkyl-*N*′-arylsulfamides with trioxane [12]. The scope of these methods is related to the substitution in the benzo moiety; thus, the C-4 position was unsubstituted in almost all the cases.

As 4-substituted-1*H*-2,1,3-benzothiadiazine 2,2-dioxides were required for new drug candidate synthesis, we decided to explore a more straightforward synthesis approach. A simple retrosynthetic analysis led us to recognize that *N*-*t*-butyloxycarbonyl-*N*′-arylsulfamides (**1**) could be a suitable precursor (Fig. 1). So we decided to explore this approach by carrying out, as the key step, the intramolecular cyclization of the corresponding *N*-arylsulfamides with aldehydes to get the iminium ion, which could subsequently be cyclized under trifluoroacetic acid conditions.

A few general methods for the preparation of 4-substituted-3,4-dihydro-1*H*-2,1,3-benzothiadiazine 2,2-dioxides have been reported [13]. We recently demonstrated that intramolecular α-sulfamidoalkylation transformations proceeding through the intermediary of an iminium ion provide an expeditious route for the preparation of cyclic sulfamides [14]. Herein, we report the successful transformation of *N*-*t*-butyloxycarbonyl-*N*′-arylsulfamides (**1**) into 4-substituted-1*H*-2,1,3-benzothiadiazine 2,2-dioxides (**2a**–**j**) via this approach, allowing different substituents at C-4.

RESULT AND DISCUSSION

The starting materials **1** were prepared according to established synthetic protocols [15]. When *t*-butanol was reacted with an equimolar quantity of chlorosulfonyl isocyanate in dichloromethane, followed by the reaction with 2 equimolar quantity of aniline or 3,4-dimethoxybenzenamine, compounds **1** were formed with 80 and 91% yields, respectively. The general synthetic strategy for the preparation of 4-R′-3,4-dihydro-1*H*-2,1,3-benzothiadiazine 2,2-dioxides **2** was developed by the intramolecular cyclization reaction using trifluoroacetic acid conditions in dichloromethane (Scheme 1).

The intramolecular cyclization reaction of **1** with aldehydes or acetal was carried out to obtain the

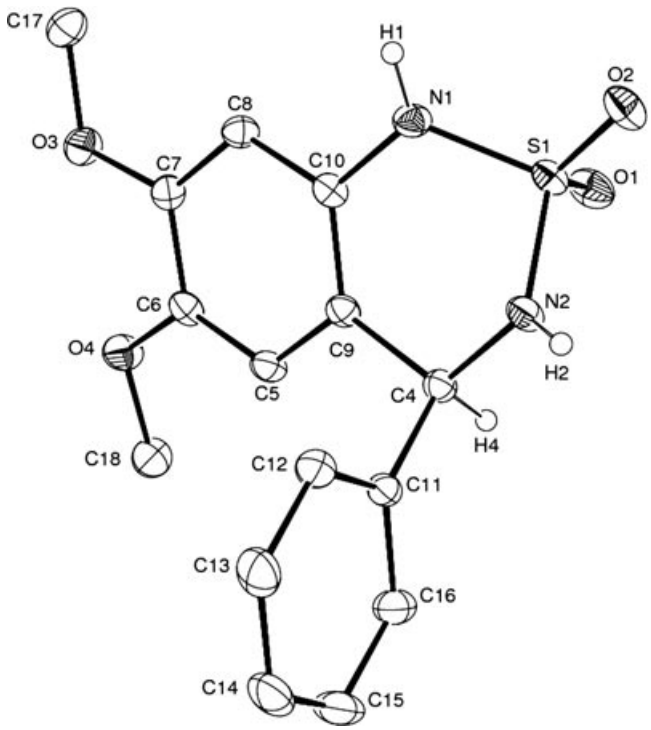
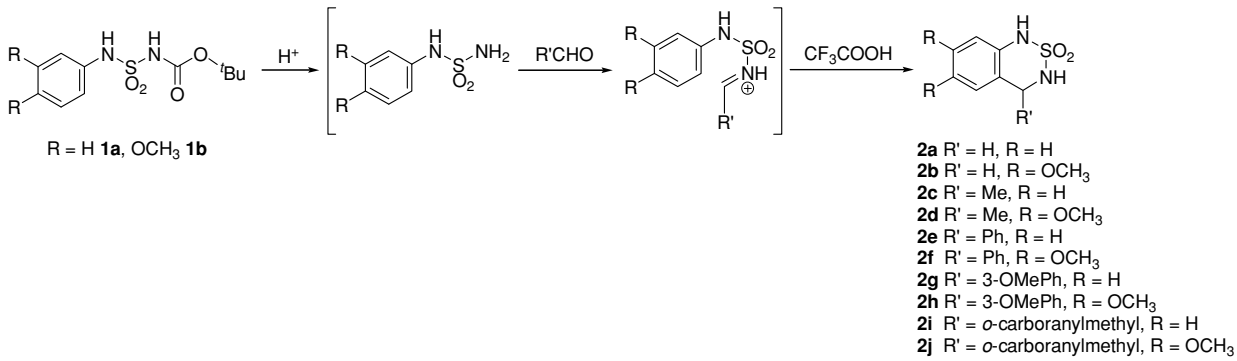


FIGURE 2 Molecular structure of **2f** with thermal ellipsoids drawn at the 30% level and H atoms, except H1, H2, and H4, are omitted for clarity.

desired heterocyclic benzothiadiazines **2a**–**j** in good yield (**2a**: 60%; **2b**: 79%; **2c**: 61%; **2d**: 83%; **2e**: 62%; **2f**: 85%; **2g**: 65%; **2h**: 80%; **2i**: 45%; **2j**: 60%). All the new compounds were characterized by ^{1}H and ^{13}C NMR, elemental analysis, and X-ray crystallography. The ^{1}H NMR spectrum of compounds **2a**–**d** showed resonances at around 4.50–4.99 ppm due to the methylene protons in the C*H*R′ (R′ = H, Me), respectively. Peaks at around 46.7–53.3 ppm (*C*HR′) were observed in the ^{13}C NMR spectrum of compounds **2a**–**d**. Spectroscopic characterization of the 4-aryl-1*H*-2,1,3-benzothiadiazine compounds **2e**–**h** showed that the aryl group is linked to the C-4 position in the benzothiadiazine ring. The most significant difference between the ^{1}H NMR spectrum of **2a**–**d** and **2e**–**h** was the downfield shift of signals for the methylene proton of C*H*R′ (R′ = Ph, 3—OMePh). The ^{1}H NMR spectrum of compounds **2e**–**h** showed resonances at around 5.55–6.67 ppm due to the methylene protons in the C*H*R′ unit, respectively. Peaks at around 46.7–62.6 ppm (*C*HR′) were observed the downfield shift of signals of C-4 in the ^{13}C NMR spectrum of compounds **2e**–**h**.

The final structural proof of **2f** was obtained by an X-ray analysis, which was performed on the crystals of **2f** (Fig. 2). Selected bond lengths, bond angles,



SCHEME 1 Synthesis of compounds **2**.

and torsion angles are collected in Table 1. The crystal structure corresponds well with the conformation and configuration derived from the NMR data. All three regions, that is, aryl, heterocyclic ring, and tethered phenyl group of **2f**, can be clearly assigned. The crystal structure of **2f** confirms that the heterocyclic ring exists in a half-chair conformation with an equatorial phenyl substituent. The S1–N1/N2 bond distance 1.6425(13)/1.6139(12) Å is similar to 1.631(4)/1.611(5) Å in 3,4-dihydroisoquinoline-2(1*H*)-sulfonamide [14]. The coordination geometry at the S1 atom is distorted tetrahedrally, with bond angles between 118.23(7) (O1–S1–O2), 109.78(6) (O1–S1–N2), 107.64(7) (O2–S1–N2), 108.13(7) (O1–S1–N1), 110.36(7) (O2–S1–N1), and 101.40(6)° (N1–S1–N2), as shown in Table 1 and Fig. 2. These values are similar to 105.3(3)–119.9(2)° obtained in the 3,4-dihydroisoquinoline-2(1*H*)-sulfonamide [14]. In **2f**, the torsion angles for N1–S1–N2–C4/C10 range from −58.46(11) to 55.87(10)°.

As shown in Scheme 1, the benzothiadiazines **2i** and **2j** containing *o*-carboranyl moiety ($C_2B_{10}H_{11}$, Cab) were prepared from the reaction of sulfamides **1** and *o*-carboranylmethyl diethyl acetal [16]. In the ^{1}H NMR spectra of **2i** and **2j**, diagnostic signals were observed for methylene protons of C*H*CH_2 and CH_2Cab at around 4.48–4.52 and 2.74–3.68 ppm, respectively. Both the **2i** and **2j** yielded ^{1}H NMR signals very similar to those of the **2a**–**d**. Key signals detected in the ^{13}C NMR spectrum of **2i** and **2j** include resonances at 30.7 and 31.2 (*C*H_2Cab), 55.8 and 56.0 (*C*HCH_2), 63.1 and 63.5 (*C*H at carborane), and 74.9 and 74.6 (C_{ipso} at carborane) ppm, respectively.

Recently, the construction of high boron content molecules has received considerable interest [17]. At the same time, the introduction of carboranes into different types of dendrimeric structures, at the inner region or at the molecular surface, is also being explored [18]. The medicinal chemistry of *o*-carborane, which contains 10 boron atoms, has a clear advantage for its use in boron neutron capture therapy. The biological activities, including the cytotoxicity and intracellular accumulation of the *o*-carboranyl benzothiadiazine derivative, were next investigated. As shown in Table 2, compounds **2i** and **j** exhibited high cytotoxicity in CT26 cells, with IC_{50}

TABLE 1 Selected Bond Lengths (Å), Bond Angles (°), and Torsion Angles (°) of **2f**

	Bond Lengths (Å)		
S(1)–O(1)	1.4242(10)	N(1)–C(3)	1.4327(16)
S(1)–O(2)	1.4381(12)	N(2)–C(4)	1.4883(16)
S(1)–N(2)	1.6139(12)	N(2)–H(2)	0.87(2)
S(1)–N(1)	1.6425(13)	N(1)–H(1)	0.79(2)
	Bond Angles (°)		
O(3)–S(1)–O(4)	118.23(7)	O(3)–S(1)–N(1)	108.13(7)
O(3)–S(1)–N(2)	109.78(6)	O(4)–S(1)–N(1)	110.36(7)
O(4)–S(1)–N(2)	107.64(7)	N(2)–S(1)–N(1)	101.40(6)
	Torsion Angles (°)		
O(1)–S(1)–N(1)–C(3)	171.29(9)	O(1)–S(1)–N(2)–C(4)	−172.65
O(2)–S(1)–N(1)–C(3)	−58.00	O(2)–S(1)–N(2)–C(4)	57.42(12)
N(2)–S(1)– N(1)–C(3)	55.87(10)	N(1)–S(1)–N(2)–C(4)	−58.46(11)

TABLE 2 Effects of *o*-Carboranyl Derivatives (**2i** and **j**) on CT26 Cells Viability and Intracellular Accumulation

Compound	Viability $IC50^a$ (mM)	Accumulated Boron Concentration[b] (ppm)
2i	0.691 ± 0.035	0.465 ± 0.075
2j	0.671 ± 0.017	0.454 ± 0.040
p-Boronophenylalanine (BPA)	4.627 ± 0.404	0.264 ± 0.026

[a]CT26 cells (5×10^3 cells) were incubated for 3 days in the presence of various concentrations of compounds **2i** and **2j** or BPA, and the viability was determined by MTT assay.
[b]CT26 cells (5×10^5 cells) were incubated for 3 h in the presence of compounds **2i** and **2j** or BPA (10 ppm). After three washes, the accumulated boron concentrations were determined by inductively coupled plasma atomic emission spectroscopy (ICP-AES). The values are the mean ± SD from three samples.

values (the half maximal inhibitory concentration) in the 0.671 ± 0.017 mM. However, the accumulated boron concentration of compounds **2i** and **j** was higher than that of *p*-boronophenylalanine (BPA).

CONCLUSION

In conclusion, we found a one-pot synthetic procedure for the formation of the 4-substituted 3,4-dihydro-1*H*-2,1,3-benzothiadiazine 2,2-dioxides **2** based on an intramolecular α-sulfamidoalkylation reaction of *N*-*t*-butyloxycarbonylsulfamides **1** with aldehydes or acetal in an acidic condition.

EXPERIMENTAL

All manipulations were performed under a dry, oxygen-free nitrogen or argon atmosphere using standard Schlenk techniques. Dichloromethane was distilled under nitrogen from P_2O_5. Chlorosulfonyl isocyanate, *t*-butanol, and aniline derivatives were used as received from Aldrich Chemicals (St. Louis, MO). *o*-Carborane was purchased from KatChem (Prague, Czech Republic) and used after sublimation. The starting materials **1** [15] and *o*-carboranyl diethyl acetal [16] were synthesized by literature procedures. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 spectrometer operating at 300.1 and 75.4 MHz, respectively. All proton and carbon chemical shifts were measured relative to internal residual peaks from the lock solvent (99.5% acetone-d_6). IR spectra were recorded on a Biorad FTS-165 spectrophotometer. Elemental analyses were performed with a Carlo Erba instruments CHNS-O EA1108 analyzer. All melting points were taken in open capillaries and are uncorrected.

*Synthesis of 4-R′-3,4-Dihydro-1H-2,1,3-benzothiadiazine 2,2-dioxides (**2a**–**j**)*

General Procedure. Aldehydes (2.5 mmol) and excess trifluoroacetic acid were added to a stirred solution of *N*-*t*-butyloxycarbonyl-*N*′-phenylsulfamides **1** (2.0 mmol) in dichloromethane (30 mL) via a cannula through a serum cap at 0°C. The resulting mixture was stirred at room temperature for 24 h. The progress of the reaction was monitored by thin layer chromatography. After completion of the reaction, the removal of the solvent at the rotary evaporator gave a crude product, which was then chromatographed (SiO_2, Hx:EA 2:1) to yield **2a**–**j**.

*Characterization of 4-R′-3,4-dihydro1H-2,1,3-benzothiadiazine 2,2-dioxides (**2a**–**j**)*

2a: Yield: 60% (0.22 g, 1.2 mmol). mp 183–185°C. Elemental Analysis: $C_7H_8N_2O_2S$, Found: C, 45.63; H, 4.40; N, 15.20. Calcd: C, 45.64; H, 4.38; N, 15.21. IR (KBr pellet, cm^{-1}) ν(S=O) 1313, 1171. ^{1}H NMR (acetone-d_6) δ 4.99 (d, J = 15.6 Hz, 2H), 6.67 (t, J = 15.6 Hz, 1H), 6.77 (m, 1H), 7.17–7.41 (m, 3H), 9.23 (s, 1H). ^{13}C NMR (acetone-d_6) δ 46.7 (CH_2), 120.63, 124.9, 126.4, 127.5, 129.1, 129.6 (*Ph*).

2b: Yield: 79% (0.39 g, 1.6 mmol). $C_9H_{12}N_2O_4S$, Found: C, 44.28; H, 4.96; N, 11.45. Calcd: C, 44.25; H, 4.95; N, 11.47. IR (KBr pellet, cm^{-1}) ν(S=O) 1317, 1156. ^{1}H NMR (acetone-d_6) δ 3.74 (s, 6H), 4.50 (d, J = 15.0 Hz, 2H), 6.09 (t, J = 15.0 Hz, 1H), 6.42 (s, 1H), 6.76 (m, 1H), 9.51 (s, 1H). ^{13}C NMR (acetone-d_6) δ 47.7 (CH_2), 55.6, 55.7 (OCH_3), 102.9, 110.4, 111.2, 132.3, 145.3, 149.4 (*Ph*).

2c: Yield: 61% (0.24 g, 1.2 mmol). mp 80–82°C. $C_8H_{10}N_2O_2S$, Found: C, 48.45; H, 5.10; N, 14.10. Calcd: C, 48.47; H, 5.08; N, 14.13. IR (KBr pellet, cm^{-1}) ν(S=O) 1323, 1160. ^{1}H NMR (acetone-d_6) δ 1.68 (d, J = 18.8 Hz, 3H), 4.75–4.79 (m, 1H), 6.18 (d, J = 19.3 Hz, 1H), 6.83 (d, J = 7.8 Hz, 1H), 7.19 (t, J = 15.1 Hz, 2H), 7.27 (d, J = 7.8 Hz, 1H), 9.02 (br s, 1H). ^{13}C NMR (acetone-d_6) δ 19.2 ($CHCH_3$), 53.3 ($CHCH_3$), 117.3, 122.2, 124.8, 126.3, 128.2, 139.0 (*Ph*).

2d: Yield: 83% (0.43 g, 1.7 mmol). mp 108–112°C. $C_{10}H_{14}N_2O_4S$, Found: C, 46.47; H, 5.45; N, 10.88. Calcd: C, 46.50; H, 5.46; N, 10.85. IR (KBr pellet, cm^{-1}) ν(S=O) 1329, 1158. ^{1}H NMR (acetone-d_6) δ 1.65 (d, J = 10.0 Hz, 3H), 3.75 (s, 3H), 3.78 (s, 3H), 4.65–4.70 (m, 1H), 6.03 (d, J = 2.0 Hz, 1H), 6.43 (s, 1H), 6.84 (s, 1H), 8.53 (br s, 1H). ^{13}C NMR (acetone-d_6) δ 28.6 ($CHCH_3$), 53.3 ($CHCH_3$), 55.3, 56.0 (OCH_3), 102.8, 110.6, 116.6, 132.1, 145.3, 149.4 (*Ph*).

2e: Yield: 62% (0.32 g, 1.2 mmol). Mp. 133–135°C. $C_{13}H_{12}N_2O_2S$, Found: C, 60.01; H, 4.66; N,

10.77. Calcd: C, 59.98; H, 4.65; N, 10.76. IR (KBr pellet, cm^{-1}) ν(S=O) 1326, 1164. ^{1}H NMR (acetone-d_6) δ 5.83 (d, $J = 2.0$ Hz, 1H), 6.64 (d, $J = 2.0$ Hz, 1H), 7.08–7.11 (m, 2H), 7.27-7.45 (m, 5H), 7.53-7.56 (m, 1H), 7.65–7.68 (m, 2H), 7.96–7.98 (m, 1H), 9.13 (br s, 1H). ^{13}C NMR (acetone-d_6) δ 62.4 (*C*HPh), 117.6, 118.5, 120.9, 121.9, 128.2, 128.4, 128.7, 129.2, 139.5, 140.3 (*Ph*).

2f: Yield: 85% (0.54 g, 1.7 mmol). mp 160–163°C. $C_{15}H_{16}N_2O_4S$, Found: C, 56.21; H, 5.04, N, 8.77. Calcd: C, 56.24; H, 5.03; N, 8.74. IR (KBr pellet, cm^{-1}) ν(S=O) 1317, 1157. ^{1}H NMR (acetone-d_6) δ 3.40 (s, 3H), 3.70 (s, 3H), 5.55 (d, $J = 2.0$ Hz, 1H), 6.08 (s, 1H), 6.41 (s, 1H), 7.34–7.37 (m, 5H), 7.49 (d, $J = 2.0$ Hz, 2H), 9.94 (brs, 1H). ^{13}C NMR (acetone-d_6) δ 56.1, 56.4 (O*C*H$_3$), 61.9 (*C*HPh), 102.7, 112.2, 114.8, 128.8, 129.0, 129.5, 133.0, 139.8, 144.2, 149.5 (*Ph*).

2g: Yield: 65% (0.35 g, 1.2 mmol). $C_{14}H_{14}N_2O_3S$, Found: C, 57.89; H, 4.85; N, 9.64. Calcd: C, 57.92; H, 4.86; N, 9.65. IR (KBr pellet, cm^{-1}) ν(S=O) 1321, 1159. ^{1}H NMR (acetone-d_6) δ 4.99 (s, $J = 15.6$ Hz, 2H), 6.67 (t, $J = 15.6$ Hz, 1H), 6.77 (m, 1H), 7.17–-7.41 (m, 3H), 9.23 (s, 1H). ^{13}C NMR (acetone-d_6) δ 46.7 (*C*H), 120.63, 124.9, 126.4, 127.5, 129.1, 129.6 (*Ph*).

2h: Yield: 80% (0.56 g, 1.6 mmol). mp 163–164°C. $C_{16}H_{18}N_2O_5S$, Found: C, 54.82; H, 5.19, N, 7.98. Calcd: C, 54.85; H, 5.18; N, 7.99. IR (KBr pellet, cm^{-1}) ν(S=O) 1319, 1155. ^{1}H NMR (acetone-d_6) δ 3.51 (s, 3H), 3.77 (s, 3H), 3.80 (s, 3H), 5.69 (s, $J = 2.0$ Hz, 1H), 6.25 (s, 1H), 6.28 (d, $J = 2.0$ Hz, 1H), 6.51 (s, 1H), 6.93–6.95 (m, 1H), 7.06–7.07 (m, 1H), 7.07–7.08 (m, 2H), 7.31–7.34 (m, 1H), 8.69 (br s, 1H). ^{13}C NMR (acetone-d_6) δ 54.8 (O*C*H$_3$), 55.3, 55.9 (O*C*H$_3$), 62.6 (*C*HPh), 103.0, 114.2, 114.4, 115.1, 121.4, 129.7, 132.8, 141.6, 145.0, 150.0, 160.2 (*Ph*).

2i: Yield: 45% (0.3 g, 0.9 mmol). mp 158–160°C. $C_{10}H_{20}B_{10}N_2O_2S$, Found: C, 35.26; H, 5.93, N, 8.24. Calcd: C, 35.28; H, 5.92; N, 8.23. IR (KBr pellet, cm^{-1}) ν(B–H) 2581, ν(S=O) 1321, 1162. ^{1}H NMR (acetone-d_6) δ 3.01–3.04 (m, 1H), 3.35–3.68 (m, 1H), 4.48–4.52 (m, 1H), 5.15 (br s, 1H), 6.85–-7.04 (m, 2H), 7.24–7.30 (m, 1H), 7.50–7.58 (m, 2H), 9.23 (s, 1H). ^{13}C NMR (acetone-d_6) δ 30.7 (*C*H$_2$Cab), 55.8 (*C*HCH$_2$Cab), 63.1 (Cab*C*H), 74.9 (Cab*C*^{ipso}), 118.4, 118.8, 122.0, 128.7, 128.9, 131.8 (*Ph*).

2j: Yield: 60% (0.48 g, 1.2 mmol). mp 162–165°C. $C_{12}H_{24}B_{10}N_2O_4S$, Found: C, 36.02; H, 6.05, N, 7.01. Calcd C, 35.99; H, 6.04; N, 6.99. IR (KBr pellet, cm^{-1}) ν(B–H) 2581, ν(S=O) 1325, 1161. ^{1}H NMR (acetone-d_6) δ 3.13 (m, 1H), 3.31–-3.36 (m, 2H), 3.69 (s, 3H), 3.71 (s, 3H), 4.48–4.52 (m, 1H), 5.19 (br s, 1H), 6.73 (s, 1H), 7.48 (s, 1H), 9.90 (s, 1H). ^{13}C NMR (acetone-d_6) δ 31.2 (*C*H$_2$Cab), 56.0 (*C*HCH$_2$Cab), 56.8, 57.0 (O*C*H$_3$), 63.5 (Cab*C*H), 74.6 (Cab*C*^{ipso}), 102.4, 111.5, 112.4, 132.6, 144.7, 149.6 (*Ph*).

Crystal Structure Determination. Preliminary examination and data collection were performed using a Brucker SMART CCD detector system single-crystal X-ray diffractometer equipped with a sealed-tube X-ray source (40 kV × 50 mA) using graphite-monochromated Mo Kα radiation ($\lambda = 0.7107$ Å). Preliminary unit cell constants were determined with a set of 45 narrowframe (0.3° in ω) scans. The double-pass method of scanning was used to exclude any noise. The collected frames were integrated using an orientation matrix determined from the narrow–frame scans. The SMART software package was used for data collection, and SAINT was used for frame integration [19]. Final cell constants were determined by a global refinement of *xyz* centroids of reflections harvested from the entire data set. Structure solution and refinement were carried out using the SHELXTL-PLUS software package [20].

X-ray Crystal Data for 4-Phenyl-3,4-dihydro-1H-2,1,3-(3,4-dimethoxybenzo)thiadiazine 2,2-dioxide (**2f**). $C_{15}H_{16}N_2O_4S$, M = 320.36, Orthorhombic, space group $P2_12_12_1$, $a = 5.570(1)$ Å, $b = 16.002(3)$ Å, $c = 16.311(3)$ Å, $V = 1453.7(5)$ Å^3, $Z = 4$, $Dc = 1.464$ g/m^3, $F(000) = 672$, $R_1 = 0.0291$, absolute structure parameter = 0.05(5). CCDC no. 789856 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; Fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).

Supporting Information

Supporting Information related to this article containing the experimental data is available from the corresponding author (sangok@korea.ac.kr) on request.

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