SYNTHESIS OF 4H-1,3,2-BENZODITHIAZIN-4-IMINE 1,1-DIOXIDE DERIVATIVES BY OXIDATIVE CYCLIZATION OF 2-(AMINO-SULFONYL)BENZOTHIOAMIDE DERIVATIVES WITH IODINE

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Abstract – An efficient method for the construction of the 4H-1,3,2-benzodithiazine structure utilizing facile experimental operations from readily available starting materials is described. 2-Substituted \((\text{Z})\)-\(N\)-alkyl-4H-1,3,2-benzodithiazin-4-imine 1,1-dioxides can be obtained by the treatment of 2-(aminosulfonyl)benzothioamides, derived from the reaction between \(2,\text{N}\) -dilithio derivatives of readily available secondary benzenesulfonamides and isothiocyanates, with iodine in the presence of two equivalents of triethylamine.

A recent work\textsuperscript{1a} from our laboratory has shown that \((\text{E})\)-\(N\)-substituted 1,2-benzothiazole 1,1-dioxide derivatives (3) can be prepared by treating 2-(aminosulfonyl)benzothioamides (2), derived from the reaction between \(2,\text{N}\)-dilithio derivatives of readily available secondary benzenesulfonamides (1) and isothiocyanates, with thionyl chloride in the presence of two equivalents of pyridine in DMF at 0 \(\degree\)C, as illustrated in Scheme 1. Subsequently, we became interested in constructing 4H-1,3,2-benzodithiazine structure from 2. We therefore envisaged that oxidative cyclization of 2 would yield \((\text{Z})\)-\(N\)-substituted 2-alkyl-4H-1,3,2-benzodithiazin-4-imine 1,1-dioxides (4). Herein, we report the results of our investigation, which provide a convenient method for the first preparation of this class of heterocycles.\textsuperscript{2}

The synthesis of 4 by oxidative cyclization of 2 was accomplished as depicted in Scheme 1 as well. Thus, compounds (2) were allowed to react with an equivalent of iodine in dichloromethane in the presence of two equivalents of triethylamine at 0 \(\degree\)C. The reaction proceeded quickly and cleanly at this temperature and aqueous workup utilizing sodium thiosulfate followed by recrystallization of the crude residual solids.
resulted in the isolation of the desired products (4) in pure forms. The fair to good yields of the products were obtained as compiled in Table 1, which indicates that the size of the substituent R² hardly affects the yields of the products. The substituents on the benzene ring also proved to give no influence on the yields (Entries 8-10).

Table 1. Preparation of (Z)-N-substituted 4H-1,3,2-benzodithiazin-4-imine 1,1-dioxides (4)

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<tr>
<th>Entry</th>
<th>2</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
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<td>Me</td>
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<td>H</td>
<td>Me</td>
<td>Et</td>
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</tr>
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<td>Me</td>
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<td>Me</td>
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</table>

a Yields of isolated products.

The imino thioether structure can be confirmed by their $^{13}$C NMR spectra, which uniformly exhibit the signals due to the imino carbons around $\delta$ 150. The products having a thioamide structure, derived from the N-N coupling, are sure to exhibit signals due to their thiocarbonyl carbons at rather lower magnetic field (around $\delta$ 185). The stereochemistry of the 4-imino moiety is assumed to be Z on the basis of NOESY analyses of the products (4). For example, the NOESY spectrum of 4a did not show interaction between the signal at $\delta$ 8.16 due to 5-H and the signal at $\delta$ 3.39 due to the methyl protons of
4-methylimino group. No interaction was observed between the signals due to the two methyl groups as well. This may exclude the possibility of the product from the N-N coupling. The stereoisomer could not be detected at all in each reaction. As can be seen from Entry 4, N-phenyl derivative 4d was also obtained in a yield comparable to those of N-alkyl derivatives. Unfortunately, however, treatment of N-phenylsulfonamide derivative (2: R¹ = Me, R² = Ph, R³ = Et) with iodine under the same reaction conditions resulted in the formation of the corresponding (E)-N-substituted 1,2-benzothiazol-3-imine 1,1-dioxide derivative (7) in a fair yield as a single stereoisomer,¹a as shown in Scheme 2.

The reaction sequence leading to the production of 4 from 2 is thought to proceed as depicted in Scheme 2. Initially, the reaction of 2 with iodine generates iminosulfonyl iodide intermediate (5) with a help of the first molecule of triethylamine. This is followed by the intramolecular nucleophilic attack of the sulfonamide nitrogen on the sulfenyl sulfur with elimination of hydrogen iodide, which is trapped with the second molecule of triethylamine, to provide 4. For the formation of 7, it is likely that the imidoyl iodide intermediate (6), formed by elimination of sulfur from 5 before the attack of the sulfonamide nitrogen, undergoes intramolecular ring closure. Although the evident reason for the preferable formation of 7 is not clear, it may be ascribed to the less nucleophilicity of the sulfonamide nitrogen toward the sulfur atom in the corresponding intermediate (5).

In conclusion, we have developed a convenient route leading to 4H-1,3,2-benzodithiazin-4-imine 1,1-dioxide derivatives. The easiness of experimental operations utilizing ordinary reagents under mild conditions and the ready availability of the starting materials makes the present method attractive. The present first general preparation of this class of heterocyclic compounds may make some contributions to both the pharmaceutical and agrochemical industries.
EXPERIMENTAL

All melting points were obtained on a Laboratory Devices MEL-TEMP II melting apparatus and are uncorrected. IR spectra were recorded as KBr disks with a PerkinElmer Spectrum 65 FTIR spectrophotometer. $^1$H and $^{13}$C NMR spectra were recorded in CDCl$_3$ using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 500 and 125 MHz, respectively. High-resolution MS spectra were measured by a Thermo Scientific Exactive spectrometer (DART, positive). Elemental analyses were performed with an Elementar Vario EL II instrument. TLC was carried out on Merck Kieselgel 60 PF$_{254}$. Column chromatography was performed using WAKO GEL C-200E. All of the organic solvents used in this study were dried over appropriate drying agents and distilled prior to use.

Starting Materials. 2-(Aminosulfonyl)benzothioamides (2) were prepared from the respective benzenesulfonamides (1) and isothiocyanates according to the reported procedure.$^{10}$ $n$-BuLi was supplied by Asia Lithium Corporation. All other chemicals used in this study were commercially available.

Typical Procedure for the Preparation of Benzodithiazinimine Dioxides (4). 2,(Z)-$N$-Dimethyl-4H-1,3,2-benzodithiazin-4-imine 1,1-Dioxide (4a). To a stirred solution of 2a (0.24 g, 1.0 mmol) in CH$_2$Cl$_2$ (12 mL) containing Et$_3$N (0.20 g, 2.0 mmol) at 0 °C was added I$_2$ (0.25 g, 1.0 mmol) in several portions. After 5 min, 10% aqueous Na$_2$S$_2$O$_3$ (15 mL) was added and vigorous stirring was continued until the color of iodine had disappeared. The layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na$_2$SO$_4$), and concentrated by evaporation. The residual solid was recrystallized to give 4a (0.18 g, 74%); a pale-yellow solid; mp 107–109 °C (hexane/CH$_2$Cl$_2$); IR 1604, 1350 cm$^{-1}$; $^1$H NMR $\delta$ 3.12 (s, 3H), 3.39 (s, 3H), 7.67–7.73 (m, 2H), 7.91 (dd, $J$ = 7.4, 1.7 Hz, 1H), 8.16 (dd, $J$ = 7.4, 1.1 Hz, 1H); $^{13}$C NMR $\delta$ 38.9, 45.1, 126.4, 127.5, 130.9, 131.4, 132.6, 133.5, 153.2. HR-MS. Calcd for C$_9$H$_{11}$N$_2$O$_2$S$_2$ (M+H): 243.0262. Found: m/z 243.0254. Anal. Calcd for C$_9$H$_{10}$N$_2$O$_2$S$_2$: C, 44.61; H, 4.16; N, 11.56; S, 26.46. Found: C, 44.39; H, 4.19; N, 11.61; S, 26.25.

(Z)-$N$-Ethyl-2-methyl-4H-1,3,2-benzodithiazin-4-imine 1,1-Dioxide (4b): a white solid; mp 68–70 °C (hexane/CH$_2$Cl$_2$); IR 1587, 1348 cm$^{-1}$; $^1$H NMR $\delta$ 3.14 (s, 3H), 1.40 (t, $J$ = 7.4 Hz, 3H), 3.09 (s, 3H), 3.43 (q, $J$ = 7.4 Hz, 2H), 7.64 (dd, $J$ = 8.0, 7.4 Hz, 1H), 7.68 (t, $J$ = 7.4 Hz, 1H), 7.86 (d, $J$ = 7.4 Hz, 1H), 8.18 (d, $J$ = 8.0 Hz, 1H); $^{13}$C NMR $\delta$ 15.7, 15.7, 46.5, 126.3, 127.7, 131.0, 131.3, 132.8, 133.4, 150.8. HR-MS. Calcd for C$_{10}$H$_{13}$N$_2$O$_2$S$_2$ (M+H): 257.0418. Found: m/z 257.0406. Anal. Calcd for C$_{10}$H$_{12}$N$_2$O$_2$S$_2$: C, 48.86; H, 4.72; N, 10.93; S, 25.01. Found: C, 48.61; H, 4.69; N, 11.23; S, 25.04.

(Z)-$N$-Ethyl-2,6-dimethyl-4H-1,3,2-benzodithiazin-4-imine 1,1-Dioxide (4c): a white solid; mp 94–96 °C (hexane/CH$_2$Cl$_2$); IR 1588, 1346 cm$^{-1}$; $^1$H NMR $\delta$ 1.43 (t, $J$ = 7.4 Hz, 3H), 2.48 (s, 3H), 3.08 (s, 3H), 3.46 (q, $J$ = 7.4 Hz, 2H), 7.46 (d, $J$ = 8.0 Hz, 1H), 7.78 (d, $J$ = 8.0 Hz, 1H), 7.99 (s, 1H); $^{13}$C NMR $\delta$ 15.7,
21.7, 45.0, 46.5, 126.5, 127.9, 129.9, 130.7, 131.9, 144.4, 151.3. HR-MS. Calcd for C$_{11}$H$_{15}$N$_2$O$_2$S$_2$ (M+H): 271.0575. Found: m/z 271.0562. Anal. Calcd for C$_{11}$H$_{14}$N$_2$O$_2$S$_2$: C, 48.87; H, 5.22; N, 10.36; S, 23.72. Found: C, 48.98; H, 5.25; N, 10.41; S, 23.83.

2,6-Dimethyl-(Z)-N-phenyl-4H-1,3,2-benzodithiazin-4-imine 1,1-Dioxide (4d): a yellow solid; mp 160–162 °C (hexane/CH$_2$Cl$_2$); IR 1589, 1350 cm$^{-1}$; $^1$H NMR $\delta$ 2.52 (s, 3H), 3.07 (s, 3H), 6.97 (d, $J = 8.0$ Hz, 2H), 7.21 (t, $J = 7.4$ Hz, 1H), 7.39 (dd, $J = 8.0, 7.4$ Hz, 2H), 7.55 (d, $J = 8.0$ Hz, 1H), 7.84 (d, $J = 8.0$ Hz, 1H), 8.19 (s, 1H); $^{13}$C NMR $\delta$ 21.7, 44.8, 119.2, 125.8, 126.7, 128.3, 129.4, 130.3, 130.6, 132.9, 144.5, 147.7, 155.3. HR-MS. Calcd for C$_{15}$H$_{15}$N$_2$O$_2$S$_2$ (M+H): 319.0575. Found: m/z 319.0561. Anal. Calcd for C$_{15}$H$_{14}$N$_2$O$_2$S$_2$: C, 56.58; H, 4.43; N, 8.80; S, 20.14. Found: C, 56.20; H, 4.47; N, 8.66; S, 19.92.

2,6-Diethyl-6-methyl-4H-1,3,2-benzodithiazin-4-imine 1,1-Dioxide (4e): a pale-yellow solid; mp 108–110 °C (hexane/CH$_2$Cl$_2$); IR 1584, 1344 cm$^{-1}$; $^1$H NMR $\delta$ 1.20 (t, $J = 7.4$ Hz, 3H), 1.44 (t, $J = 7.4$ Hz, 3H), 2.47 (s, 3H), 3.05 (br, 1H), 3.50 (q, $J = 7.4$ Hz, 2H), 3.65 (br, 1H), 7.43 (d, $J = 8.0$ Hz, 1H), 7.77 (d, $J = 8.0$ Hz, 1H), 7.96 (s, 1H); $^{13}$C NMR $\delta$ 12.8, 15.7, 21.7, 46.5, 51.6, 125.8, 127.9, 131.0, 131.8, 132.0, 144.2, 151.9. HR-MS. Calcd for C$_{12}$H$_{17}$N$_2$O$_2$S$_2$ (M+H): 285.0731. Found: m/z 285.0721. Anal. Calcd for C$_{12}$H$_{16}$N$_2$O$_2$S$_2$: C, 50.68; H, 5.67; N, 9.85; S, 22.55. Found: C, 50.79; H, 5.68; N, 9.89; S, 22.80.

2-Butyl-6,6-Diethyl-6-methyl-4H-1,3,2-benzodithiazin-4-imine 1,1-Dioxide (4f): a white solid; mp 76–78 °C (hexane/CH$_2$Cl$_2$); IR 1591, 1344 cm$^{-1}$; $^1$H NMR $\delta$ 0.91 (t, $J = 7.4$ Hz, 3H), 1.32–1.37 (m, 2H), 1.61–1.65 (m, 2H), 2.46 (s, 3H), 2.78 (br, 1H), 3.19 (br, 3H), 7.45 (d, $J = 8.0$ Hz, 1H), 7.78 (d, $J = 8.0$ Hz, 1H), 7.92 (s, 1H); $^{13}$C NMR $\delta$ 13.6, 19.4, 21.7, 29.4, 38.9, 56.4, 126.0, 127.8, 130.9, 131.5, 131.9, 144.3, 154.3. HR-MS. Calcd for C$_{13}$H$_{19}$N$_2$O$_2$S$_2$ (M+H): 299.0888. Found: m/z 299.0880. Anal. Calcd for C$_{13}$H$_{18}$N$_2$O$_2$S$_2$: C, 52.32; H, 6.08; N, 9.39; S, 21.42. Found: C, 52.15; H, 6.23; N, 9.37; S, 21.62.

2-Butyl-(Z)-N-ethyl-6-methyl-4H-1,3,2-benzodithiazin-4-imine 1,1-Dioxide (4g): a white solid; mp 53–56 °C (hexane); IR 1588, 1344 cm$^{-1}$; $^1$H NMR $\delta$ 0.90 (t, $J = 7.4$ Hz, 3H), 1.31–1.36 (m, 2H), 1.43 (t, $J = 7.4$ Hz, 3H), 1.62–1.65 (m, 2H), 2.46 (s, 3H), 2.80 (br, 1H), 3.49 (q, $J = 7.4$ Hz, 2H), 3.65 (br, 1H), 7.43 (d, $J = 8.0$ Hz, 1H), 7.76 (d, $J = 8.0$ Hz, 1H), 7.97 (s, 1H); $^{13}$C NMR $\delta$ 15.6, 45.1, 46.8, 127.7, 128.0, 131.2, 131.4, 132.3, 140.0, 149.8. HR-MS. Calcd for C$_{10}$H$_{15}$ClN$_2$O$_2$S$_2$ (M+H): 291.0028. Found: m/z 291.0017. Anal. Calcd for C$_{10}$H$_{14}$ClN$_2$O$_2$S$_2$: C, 41.31; H,

6-Chloro-2-ethyl-(Z)-N-methyl-4H-1,3,2-benzodithiazin-4-imine 1,1-Dioxide (4i): a white solid; mp 145–147 °C (hexane/CH₂Cl₂); IR 1601, 1352 cm⁻¹; ¹H NMR δ 1.19 (t, J = 7.4 Hz, 3H), 3.06 (br, 1H), 3.40 (s, 3H), 3.70 (br, 1H), 7.58 (dd, J = 8.0, 2.3 Hz, 1H), 7.80 (d, J = 8.0 Hz, 1H), 8.11 (d, J = 2.3 Hz, 1H); ¹³C NMR δ 12.8, 39.1, 51.9, 127.3, 127.6, 131.3, 132.6, 133.0, 139.8, 152.8. HR-MS. Calcd for C₁₀H₁₂ClN₂O₂S₂ (M+H): 291.0028. Found: m/z 291.0023. Anal. Calcd for C₁₀H₁₁ClN₂O₂S₂: C, 41.31; H, 3.81; N, 9.63. Found: C, 41.18; H, 3.79; N, 9.59.

(Z)-N-Ethyl-6-methoxy-2-methyl-4H-1,3,2-benzodithiazin-4-imine 1,1-Dioxide (4j): a white solid; mp 86–88 °C (hexane/CH₂Cl₂); IR 1587, 1342 cm⁻¹; ¹H NMR δ 1.42 (t, J = 7.4 Hz, 3H), 3.09 (s, 3H), 3.46 (q, J = 7.4 Hz, 2H), 3.92 (s, 3H), 7.13 (dd, J = 8.6, 2.9 Hz, 1H), 7.66 (d, J = 2.9 Hz, 1H), 7.82 (d, J = 8.6 Hz, 1H); ¹³C NMR δ 15.6, 45.1, 46.5, 55.8, 111.7, 117.4, 124.9, 128.6, 132.8, 151.0, 163.1. HR-MS. Calcd for C₁₁H₁₄N₂O₃S₂ (M+H): 287.0524. Found: m/z 287.0517. Anal. Calcd for C₁₁H₁₃N₂O₃S₂: C, 46.14; H, 4.93; N, 9.78; S, 22.39. Found: C, 46.12; H, 4.97; N, 9.82; S, 22.40.

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REFERENCES AND NOTES
